EQUINE VETERINARY EDUCATION/AMERICAN EDITION VOLUME 33 NUMBER 4 APRIL 2021

EQUINE VETERINARY EDUCATION

American Edition | April 2021

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The official journal of the American Association of Equine Practitioners, produced in partnership with BEVA.

IN THIS ISSUE:

IN A WORLD OF ITS OWN

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References:
[1] Nogradi N, Couetil LL, Messick J, Stochelski MA, Burgess JA. Evaluation of an Omega-3 Fatty Acid Containing Feed Supplement in the Management of Horses with Chronic Lower Airway Inflammatory Diseases. J Vet Intern Med 2015; 29:299-306.
[2] Couetil LL, Cardwell J.M, Gerber V, Lavoie J.-P, Leguillette R, Richard E.A. Inflammatory Airway Disease of Horses. ACVIM Consensus Statement J of Vet Intern Med 2016; 30:503-515 p. 508-510.

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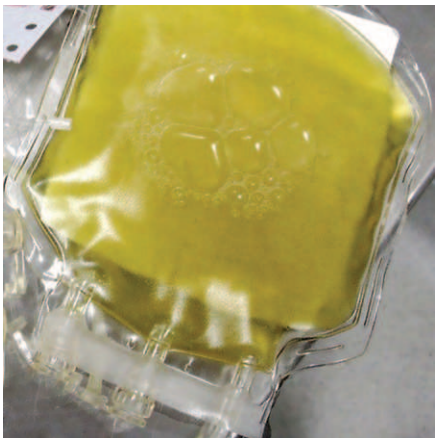

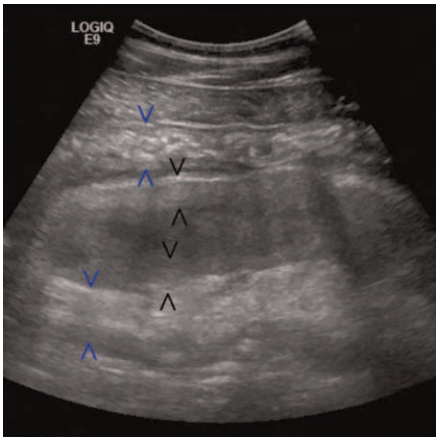

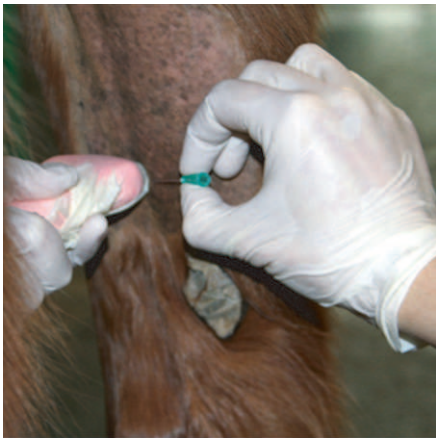

AAEP NEWS In this issue

Cover photo by Dr. Steven Berkowitz.

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AAEP Mission Statement: To improve the health and welfare of the horse, to further the professional development of its members, and to provide resources and leadership for the benefit of the equine industry.

Equine Veterinary Education is a refereed educational journal designed to keep the practicing veterinarian up to date with developments in equine medicine and surgery. Submitted case reports are accompanied by invited reviews of the subject (satellite articles) and clinical quizzes. Tutorial articles, both invited and submitted, provide in-depth coverage of issues in equine practice.

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'We've always done it this way'

By Caitlin O'Shea, DVM, MS, DACVS-LA, CVA

Dr. Caitlin O'Shea

The late United States Navy Rear Admiral Grace Murray Hopper once wisely stated, "The most dangerous phrase in the language is 'We've always done it this way.'" I am reminded of that adage almost daily in teaching bright, inquisitive third-year veterinary students, many of whom have minimal background in the horse world. They challenge me continually with their fresh approach to the world, not only in our discussions of medical diagnostics and treatments, but also in our thought processes as equestrians.

I often ask them, "If it was a dog, what would you do?" and I frequently learn new things about clinical approaches that our colleagues in small animal medicine might employ. But the non-equine-oriented students in particular also do a fantastic job of questioning the status quo, which we who grew up with horses may have unwittingly become complacent to. I like to think that my contribution to them is meaningful in the realm of medical science, but perhaps I am even more grateful to them for the spillover of their enthusiasm and curiosity to my clinical practice.

Just because we've always done something "that way" doesn't mean it is current best practice—knowledge expands, techniques improve, theories fail and times change. The last paragraph of the oath we took when graduating from veterinary school pledges that we will "accept as a lifelong obligation the continual improvement of my [our] professional knowledge and competence" (AVMA, revised 2010).

Lifelong learning is our responsibility and our salvation: critical to the care of our equine friends and paramount to our personal well-being. A curious mindset can be a very effective antidote against the feelings of burnout that many of us struggle with at one time or another during our careers. Medical advances are being made in leaps and bounds, and I try to remind myself from time to time that the degree I received at graduation is really just a license to learn. I continue to learn every time I see a horse or talk to a client or referring veterinarian, and the day I stop doing that should be the day I retire.

I don't believe we should judge owners for not buying Ferrari-level care. They have their constraints, as do we all. But we do have an obligation to explain to them clearly the full extent of our capabilities as a professional team and to be advocates for the horse's well-being. Many are still surprised to learn how much better our diagnostic and treatment capabilities are today than they were even a decade ago. Retraining our clientele to understand that we can now obtain more accurate diagnoses and therefore create targeted treatment plans and achieve better outcomes in some cases, or catch potential problems before they become clinically problematic, is a continuing goal.

In the equine world, best practice and standard of care is fraught with many financial and logistical challenges our human clinical counterparts usually, thankfully, don't have to navigate in the United States. However, great strides can be made by communicating with, and recruiting as teammates, the others involved in our patients' care. When "it takes a village," our up-front workload might be greater, but in the end we're all happier, most importantly the horses.

Just because we've always done something "that way" doesn't mean it is current best practice—knowledge expands, techniques improve, theories fail and times change.

Equine veterinarians largely consider we have each made it to where we are in part because of our tenacity, and most of us are very proud of that. It does take a special type of person—persistent and self-reliant—to survive the rigors of training and practice. However, we can and should learn to redirect our persistence toward building and training a collaborative team, rather than repeatedly pulling all-nighters alone.

For those of you who are unable to mentor students or interns daily, I urge you to avail yourself of those opportunities if they arise; and if you do already, stop to actively listen. At least take a moment right now (and regularly) to really think back and remember yourself as a third-year veterinary student. Why did you embark on this lifelong journey, this vocation? Yes, you have learned much and weathered a lot over the course of your career no matter its duration so far, but would the veterinary student you once were be proud of your work now?

AAEP ETHICAL PRACTICE Every Day-Every Time

Dr. O'Shea is on faculty at Western University of Health Sciences and in private practice in Southern California. She is a member of the AAEP's Professional Conduct and Ethics Committee.

Veterinarians enabled to assist with COVID-19 vaccinations

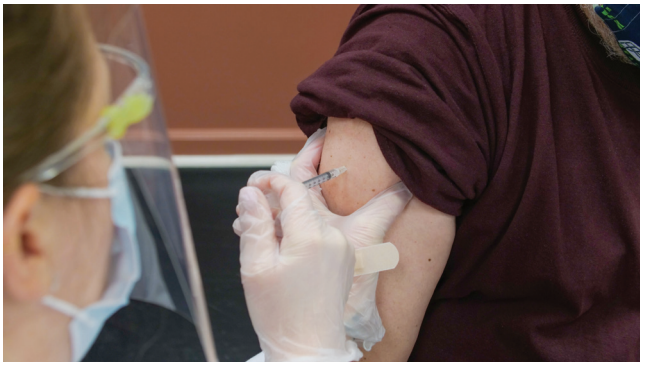
AVMA offers guidance for practitioner participation

The Public Readiness and Emergency Preparedness (PREP) Act has been amended to allow veterinarians licensed in any state to administer COVID-19 vaccines in association with a vaccination effort by a state, local, tribal, or territorial authority or by an institution in which the COVID-19 vaccine is administered.

The AVMA in mid-March issued general guidance about participation requirements and liability protections for veterinarians who administer COVID-19 vaccines in accordance with the amended PREP Act.

Veterinarians will be afforded liability protections through Oct. 1, 2024, provided additional requirements are met, including CPR certification, completion of the CDC COVID vaccination modules, observation period, etc.

Liability outlined in the PREP Act does not apply to willful misconduct, and the federal government does not provide a legal defense in the event you are sued. In addition, your state may have separate liability protections, separate requirements to qualify, and may or may not provide a legal defense. Veterinary malpractice will not likely respond to claims arising from a veterinarian intentionally vaccinating people against COVID.



For more information and additional resources, visit avma.org/blog/veterinarians-covid-19-vaccinators-what-you-need-know.

Equine Parvovirus-Hepatitis Virus Guidelines published

Comprehensive guidelines to educate practitioners about transmission, risk factors, clinical signs and other considerations pertaining to equine parvovirus-hepatitis virus (EqPV-H), a recently discovered virus capable of causing hepatitis in infected horses, are now available on the AAEP website.

Two distinct etiologies of EqPV-H infection are recognized: biologic transmission and non-biologic transmission. Asymptomatic infection is common; only a small percentage of infected horses will develop clinical signs of liver disease.

"Drs. Thomas Divers and Bud Tennant of Cornell University College of Veterinary Medicine discovered that this novel parvovirus was associated with the disease 'serum sickness' in horses who had recently been administered a parvovirus-infected biologic," said guidelines co-author Dr. Piper Norton. "Because of their seminal research and active ongoing research, information will be learned about this virus that will assist in making biologics safer for use in horses and help with diagnosis and treatment of this disease."

EqPV-H is a recently discovered virus and the focus of rapidly evolving research. These guidelines reflect knowledge at the time of writing. Practitioners are encouraged to seek further consultation for questions regarding clinical cases of EqPV-H.

The Equine Parvovirus-Hepatitis Virus Guidelines, available as a PDF file, were authored by Drs. Linda Mittel, Piper Norton, Joy Tomlinson and Thomas Divers. The guidelines were reviewed and approved by the AAEP's Infectious Disease Committee and board of directors. View the guidelines or save them to your mobile device for future reference at https://tinyurl.com/283yt7vf.

In addition to EqPV-H, AAEP guidelines for 21 other equine infectious diseases are available at aaep.org/guidelines/infectious-disease-control. In addition, two foreign animal disease guidelines—for African horse sickness and Glanders—can be found at aaep.org/infectious-disease-control/foreign-animal-disease-guidelines.

It is recommended that veterinarians administer USDA APHIS-licensed and tested biologic products to prevent the spread of EqPV-H.

5 things to know about AAEP this month

1. With the outbreak of equine herpesvirus-neurologic in Europe and parts of the U.S., point your clients to a handy FAQ about the disease at aaep.org/horsehealth/faq-equine-herpesvirus-ehv.
2. View the AAEP's new Equine Parvovirus-Hepatitis Virus Guidelines or save them as a PDF to your mobile device at https://tinyurl.com/283yt7vf.
3. Watch on-demand recordings of previous Virtual Wednesday Round Tables and register for upcoming sessions at aaepanywhere.org.
4. The Virtual CE Summer Series will return in late July with a global perspective on lameness diagnosis and therapeutic approaches. Registration will open soon at aaep.org/meetings.
5. For your convenience, you can now listen to the biweekly Spur of the Moment news bulletin while on the go. Follow the podcast at aaepspur.podbean.com.

AAEP approves position statement on diversity, equity and inclusion

At the recommendation of the Diversity, Equity and Inclusion Task Force, the AAEP board of directors recently approved a position statement on DEI in equine practice. The complete text of the statement follows. It is also available at aaep.org/guidelines/aaep-ethical-and-professional-guidelines/aaep-position-statements/veterinary-practice.

The nine-person task force, formed in 2020, continues to work on development of recommendations for the association that will create a more inclusive profession.

Courtesy Dr. Liara Gonzalez

Position on Diversity, Equity and Inclusion in Equine Practice

The AAEP recognizes the historical lack of diversity within the equine veterinary profession and the importance of representation, inclusion, and mutual respect for our members and stakeholders to thrive. The AAEP commits to creating permanent structural change by providing education, resources, and mechanisms for continual evolution of our leadership and membership to accurately reflect the society in which we live. The AAEP will lead the industry in facilitating improvements in representation, safety, respect, inclusion, and equity to best serve equine industry communities of all backgrounds, identities, and lived experiences.

Nominate a difference maker for an AAEP award

Recognize the excellence of a colleague by nominating that individual for a 2021 AAEP award. The nomination deadline is June 1, and winners will be announced and recognized during the President's Luncheon at the AAEP's 67th Annual Convention in Nashville, Tenn., Dec. 4–8.

Nominations are being accepted in the following categories:

AAEP Research Award
Distinguished Educator – Academic Award
Distinguished Educator – Mentor Award
Distinguished Life Member Award
Distinguished Service Award
George Stubbs Award
Sage Kester Beyond the Call Award
The Lavin Cup (The Equine Welfare Award)

Visit aaep.org/about-aaep/annual-awards for nomination forms as well as additional information about each award and the selection process. You may also request a nomination form from Sue Stivers at sstivers@aaep.org or (859) 233-0147.

Dr. David Wilson, left, accepts the 2019 Distinguished Educator – Academic Award from Dr. Jeff Berk during the 65th Annual Convention in Denver, Colo.

New *EVE* podcast focuses on reproductive tract abnormalities

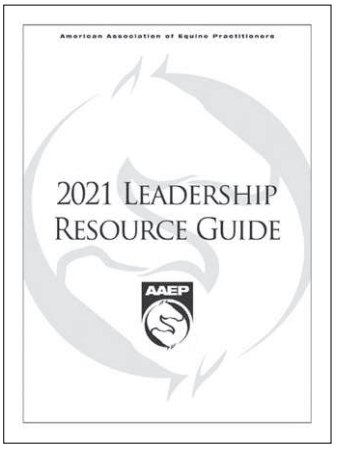
In the latest episode of the *Equine Veterinary Education* podcast, Drs. James Crabtree and Rory Gormley discuss their clinical commentary article, "Female caudal reproductive tract abnormalities." Download or listen to the 56-minute episode at equineveterinaryeducation.podbean.com.

View ethical guidelines and more in Leadership Resource Guide

Acquire the AAEP's Ethical and Professional Guidelines, including position statements updated within the past year pertaining to use of therapeutic medications in racing and performance horses, in the 2021 Leadership Resource Guide available on the AAEP's website and Publications App.

The handy 48-page guide, available as a PDF, also includes listings of the board of directors, councils and committees, staff, award recipients, student chapters and AVMA representation, along with a compendium of equine and veterinary organizations. AAEP's articles of incorporation, bylaws and updated disciplinary procedures are also presented.

The Leadership Resource Guide is accessible at aaep.org/newsroom/publications and on the AAEP Publications App. Download the free app by searching "AAEP Publications" at the App Store or Google Play.



Performance medicine, ethics on tap for May Round Tables

Are you among the hundreds of members taking advantage of the new Virtual Wednesday Round Tables to advance knowledge and engage with subject matter experts on topics pertinent to equine practice?

Available free to all members on the second and fourth Wednesday of every month through October, the Round Tables are live virtual discussions similar to convention Table Topics. There is no cost to participate; simply register in advance through aaepanywhere.org.

Each month's Round Tables feature one clinical and one non-clinical topic. Following is the tentative schedule of sessions through May:

April 28 – Student Debt Relief Strategies
May 12 – Pain Management in Performance Horses
May 26 – Ethics

Members unable to attend a live 90-minute Round Table can watch a recording of the session on-demand through AAEP Anywhere, the association's free-to-members online learning platform. On-demand sessions are

available approximately 48 hours following the live session and include mentioned resources such as PowerPoint slides, images and more. CE credit is not offered for the Round Tables.

The Virtual Wednesday Round Tables are sponsored by Boehringer Ingelheim and CareCredit LLC.

New Practice Life podcast offers tips for hiring, integrating new vets and staff

Every practice would love to hire veterinarians and support staff who possess not only the requisite skills but the drive to succeed and the personality to enhance the culture of the practice. But how do you find, onboard and support them so they reach their potential and become a valuable member of your team?

In the latest episode of the AAEP Practice Life podcast, entitled "Hiring new veterinarians and staff," Dr. Mike Pownall discusses the challenges and opportunities with Dr. Shane Baird, owner of Mobile Veterinary Services, LLC in Golden, Colo.; Dr. Alex Eastman, co-owner and chief operating officer of Steinbeck Peninsula Equine Clinics in Salinas and Menlo Park, Calif; and Dr. Miranda Gosselin, partner in Millbrook Equine Veterinary Clinic P.C. in Millbrook, N.Y.

During a discussion of the importance of personality and fitting in to the practice culture, Dr. Gosselin stressed the importance of trusting your gut. "Sometimes, something feels perfect, and the person seems like they were meant to be part of your team; but if it's not there, I can't say I'm a big proponent of pushing it," she said. "I know how hard we've worked to have the team and culture that we have, and the moment we sacrifice that just to get somebody in the spot, it can blow up the whole situation."

Additional topics explored during the 34-minute episode include finding and retaining veterinarians and support staff, the interview process, references and background checks, wage determination, and training and mentoring for success. Download or listen to the episode at podcast.aaep.org or on iTunes.

The AAEP Practice Life podcast is sponsored by Boehringer Ingelheim.

UHVRC distributes core vaccines for 3,500 horses in need

UHVRC
Unwanted Horse Veterinary Relief Campaign

Blue Rose Ranch, a Springfield, Colo., horse rescue and adoption facility, is among 247 nonprofit equine rescue and retirement facilities to receive free vaccines in 2021 through the Unwanted Horse Veterinary Relief Campaign (UHVRC).

A longstanding partnership between the AAEP and Merck Animal Health, the UHVRC provided 3,500 doses of both Prestige® 5+WNV and Equirab to protect horses from eastern equine encephalitis, western equine encephalitis, equine rhinopneumonitis (EHV-1 and EHV-4), influenza, tetanus, rabies and West Nile Virus. Since its inception, more than 46,000 doses of core vaccines have been distributed to protect horses in need.

"The donation of vaccines from the Unwanted Horse Veterinary Relief Campaign is an enormous help to our organization," said Cheryl Webb, executive director of Blue Rose Ranch, which received 30 doses of both vaccines. "We have between 60-70 horses at a given time. The support of UHVRC providing vaccines enables us to help more horses."

"Blessing," an 18-year-old American Quarter Horse who was found in extremely poor condition on the side of the road in Kansas in November 2020, is among the Blue Rose Ranch residents to receive core vaccines through the UHVRC.

Dr. Rusty Murdock with Boise City Animal Hospital in Boise, Okla., coordinated the facility's application for free vaccines. The annual application deadline is Feb. 1. Learn more at https://tinyurl.com/uhvrc21.

CONTINUING EDUCATION

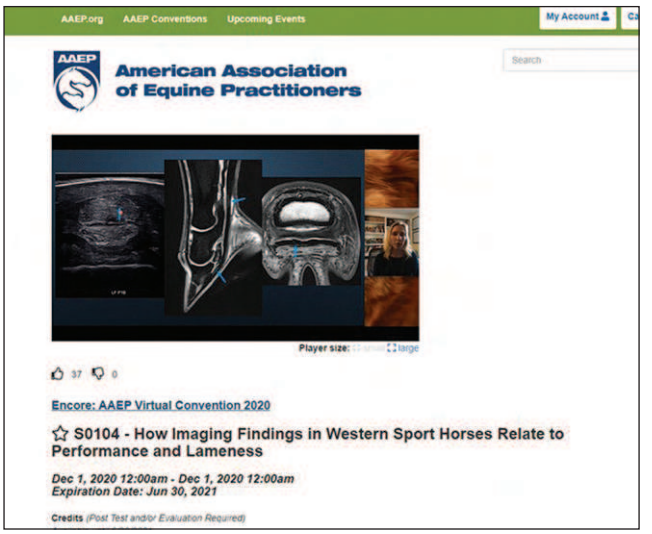
Encore edition of virtual convention now available

If you did not attend the AAEP's Virtual Convention in December 2020, you may now purchase an "Encore" edition of the entire event or a la carte packages of related presentations.

The virtual convention presented 135.5 hours of continuing education across a broad range of clinical topics relevant to all types of practice, including lameness, reproduction, imaging, internal medicine, neonatology and more.

Visit aaep.digitellinc.com/aaep/store/10/index/42 to view the menu of offerings or to purchase one or more presentation packages. Purchases remain available for CE credit through Dec. 31, 2021, enabling you to watch and learn at your convenience.

As a reminder, those who attended the virtual convention in December 2020 have until June 30, 2021, to watch and claim CE credits for on-demand sessions.



WELLNESS

Looking out for and supporting one another

Editor's note: The following is excerpted from a Wellness Committee email to the membership in mid-March.

There is a wave of grief and solidarity within the veterinary community after recent deaths by suicide of colleagues and support staff in the last few weeks. As we reflect on the loss of these colleagues, we want to emphasize that veterinarians are in this TOGETHER.

While mental health issues are complex and there are no easy fixes or simple answers, we can all offer help and hope in some way. We, as veterinarians, provide caring, understanding and compassion to patients and clients in pain every day. We can and must extend these attributes to ourselves and our community.

If you are suffering today, please reach out to a trusted friend, colleague, mentor, professor, family member, co-worker, religious leader, counselor, therapist or physician. You are not alone. You are valuable. You are loved. We see you.

If you or someone you know is in crisis:

- Call the National Suicide Prevention Lifeline at 1-800-273-TALK (8255) or visit suicidepreventionlifeline.org.
- Text TALK to the Crisis Text Line at 741-741 (crisistextline.org)
- Go to the emergency room
- Call 911

Early help and support for yourself and your practice colleagues are signs of strength. For resources to help yourself or a colleague in need, please visit aaep.org/wellness/emotional-social-wellness.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convention.aaep.org

AAEP past president Dr. A. Gary Lavin dies at 87

Dr. A. Gary Lavin, 1994 AAEP president and namesake of the association's equine welfare award, The Lavin Cup, passed away Feb. 27 at the age of 83.

Dr. Lavin received his veterinary degree from the University of Pennsylvania in 1962 and enjoyed a long and esteemed career as a racetrack practitioner and surgeon based in Louisville, Ky. He also spent many years on the Thoroughbred sales inspection team for Keeneland Association and directed the commercial breeding and boarding operation at his family's Longfield Farm in Goshen, Ky.

He mentored generations of veterinarians, racetrack professionals and breeders, and his dedication to the sport of racing and the profession of veterinary medicine included volunteer leadership with many prominent organizations. He served as president of the Kentucky Thoroughbred Association, vice chair of Grayson-Jockey Club Research Foundation, director of Keeneland, and trustee of Breeders' Cup and the Thoroughbred Owners and Breeders Association. In 1994, he became the first veterinarian elected to The Jockey Club and later served as a steward of the organization.

In addition, Dr. Lavin was instrumental in creation of the AAEP's On Call program and served as chair of the Racing and Scientific Program committees as well as a member of the Nominating and Racing Ethics committees.

Dr. A. Gary Lavin

His many accolades include Distinguished Life Member of the AAEP, the Bellwether Medal for Distinguished Leadership from his alma mater, and Honored Guest designation by the Thoroughbred Club of America.

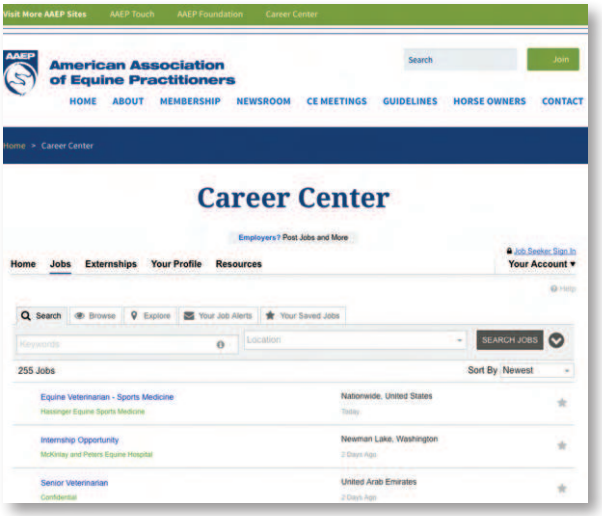
Benefit: Find the perfect position or candidate in the AAEP Career Center

Whether you're an associate seeking a new opportunity or a practice owner seeking qualified candidates for an open position, the AAEP Career Center will help you make a career connection.

The Career Center provides a targeted and cost-effective means for employers to reach qualified candidates, with rates significantly below the mass market job boards. For just a little more, employers can expand the reach of their job post through inclusion in the Veterinary Career Network, which will push their post out to nearly 60 veterinary-related sites like the AVMA, many state VMAs and other VCN participants.

After posting a job opening, employers can proactively search resumes on file in the Career Center using multiple criteria to identify potential candidates. They will also receive email notice when job seekers apply for the posted position.

Job seekers, meanwhile, can view all available openings or narrow their search by location, keyword or other criteria; sign up for job alerts to receive notice when new positions of interest are posted; upload an anonymous resume available for review by employers; and take advantage of resources to assist with their job search



such as assistance with effective resume and cover letter writing, salary negotiation and more.

Post your job opening or your resume in the AAEP's Career Center today at jobs.aaep.org. If you have questions about the Career Center or need assistance crafting a job post, contact Megan Gray, AAEP's member concierge, at mgray@aaep.org.

Members in the News

Dr. John Park appointed to Kentucky Board of Veterinary Examiners

Governor Steve Beshear has appointed Dr. John Park, CEO of Park Equine Hospital in Central Kentucky, as a member of the Kentucky Board of Veterinary Examiners. His term expires in September 2024.

Dr. Park, who received his veterinary degree from Auburn University, established Park Equine Hospital in 2004 following seven years as owner of a mixed practice.

Dr. Robert Monin elected to Tennessee VMA executive board

Dr. Robert Monin has been elected an at-large member of the executive board of the Tennessee Veterinary Medical Association.

Dr. Monin has been with Mountain Empire Large Animal Hospital in Johnson City, Tenn., since 2002, shortly after receiving his veterinary degree from Oklahoma State University.

Dr. Noah Cohen named University Distinguished Professor

Dr. Noah Cohen is among five Texas A&M University scholars recently named University Distinguished Professors, the highest faculty honor. The designation identifies faculty members considered who are considered pre-eminent in their field, have made at least one transformational contribution of substantial intellectual leap forward in their discipline, and have made a major impact in their field.

Conrhod Zonio

Dr. John Park

Dr. Robert Monin

Dr. Noah Cohen

A veterinary graduate of University of Pennsylvania, Dr. Cohen became a faculty member at Texas A&M in 1991 and serves as associate department head, Large Animal Clinical Sciences. Dr. Cohen delivered the 2011 Milne Lecture on the topic of equine epidemiology. He has also served on the AAEP's Infectious Disease and Research committees.

FOUNDATION

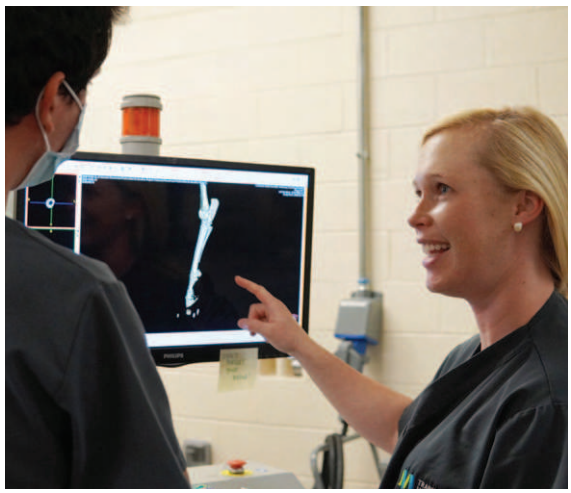
Residents and grad students: Apply for research funding by June 7

The Foundation for the Horse is accepting grant proposals from AAEP-member graduate students, fellows and residents for up to $20,000 in funding for the study of key diseases and disorders affecting equine health. In the program's first two years, The Foundation has awarded a cumulative $194,681 in support of exceptional science conducted by 10 up-and-coming researchers.

Pressing research topics and areas of special interest include musculoskeletal, gastrointestinal and metabolic disease; laminitis; factors to improve racing safety; and development of new technologies (i.e., stall-side tests). However, research applications on any topic will be considered for funding, and all investigators are encouraged to apply.

Pilot studies or preliminary studies that are part of a major study or which will lead to a major project are of particular interest; small stand-alone projects will also be considered.

Grant proposals must be received by June 7. Additional information, including application instructions, requirements and selection criteria, is available at foundationforthehorse.org/graduate-student-fellow-resident-research-grants.



Awarded researchers in 2020 included Dr. Holly Stewart for her project, "Validation of an innovative contrast subtraction technique to detect equine bone marrow lesions using CT."

FOUNDATION

Equine Welfare Data Collective expands submission options

The Equine Welfare Data Collective, a collaborative effort to accumulate, analyze and report data to enhance services for transitioning and at-risk equines, now offers monthly survey data submission in addition to biannual. The EWDC uses surveys to collect national data on equines at risk and in transition from transition centers, adoption centers, rescues, sanctuaries, shelters and other equine welfare organizations. The Foundation for the Horse is a funding partner of the EWDC.

View EWDC reports or contribute data at unitedhorsecoalition.org/ewdc.

INDUSTRY

AAEP Educational Partner Profile: American Regent Animal Health

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EQUINE VETERINARY EDUCATION
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Highlights of recent clinically relevant papers

Aseptic preparation of the equine distal limb

This randomised trial by Aimie Doyle and co-workers in Canada aimed to determine whether ethanol-based antisepsis reduces bacterial counts on the equine distal limb comparable to a current chlorhexidine scrub method and determine the most effective application technique for the product.

Each of the 41 horses in this study had a 5 x 5 cm patch clipped over the distal interphalangeal joint of three limbs. By horse, each limb was randomly assigned to a treatment group: 5 min scrub using 4% chlorhexidine gluconate to a clipped site (CHG); 90 s scrub using 80% ethanol to a clipped site (ETC); 90 s contact with 80% ethanol applied as a spray to a clipped site (ETS); and 90 s scrub using 80% ethanol to an unclipped site (ETUC). Samples were collected pre- and post-treatment and plated in duplicate. Bacterial counts were $\log_{10}$ transformed and averaged between duplicates. Mean $\log_{10}$ CFU/mL reduction was then compared between groups. The cost of each treatment was determined based on the cost of the consumables and the technical time required. A cost- benefit analysis was performed by comparing the mean $\log_{10}$ CFU/mL reduction per dollar cost between CHG and each of the ET groups.

There was no significant difference in mean $\log_{10}$ CFU/mL reduction between CHG and ETC in either fore- or hindlimbs. In forelimbs, there was no significant difference in mean $\log_{10}$ CFU/mL reduction between any groups. In hindlimbs, CHG had significantly greater mean $\log_{10}$ CFU/mL reduction than ETUC and ETS. No significant difference in cost-benefit was found between CHG and ETC. Significant differences were noted between CHG and both ETUC and ETS.

Ethanol-based antisepsis can be used for skin preparation prior to performing immediate, short-duration procedures in horses. A 90 s wet contact time using gauze sponges is recommended. It is important to note that this study did not investigate the efficacy of other alcohol-based antiseptics such as isopropanol or n-propanol.

Occipital condyle defects in foals

This study by Sophie Sage and co-workers in Canada aimed to characterise incidental occipital condyle defects assessed by radiography or computed tomography (CT) and to define the age of complete ossification.

Analyses were made on 121 horses, from 106 radiographic and 19 CT studies showing the occipital condyles of horses less than 5 years of age. The margin of occipital condyles was classified as regular or with defect(s). Neurological signs and outcome were not associated with occipital defects. Horses with regular occipital condyles on radiographs had a median age of 974 days compared with 47 days in the defect group. The odds of finding radiographically regular occipital condyles were 2.6% higher for each additional day of age. In the CT group, univariate analyses demonstrated a significant effect of age on the aspect of occipital condyles. Horses with regular occipital condyles were older (median age 881 days) than horses with a defect (median age 109 days). All horses above 156 days of age on radiographic images and 550 days of age on CT images had regular occipital condyles. This study describes occipital condyle defects as a potential normal finding in young horses and provides guidelines for interpretation of the occipital condyle ossification process.

Strip grazing for ponies

This study by Annette Longland and co-workers in the UK aimed to compare the effects of three restricted grazing regimens on changes in bodyweight (BW) and morphometric measurements.

Twelve mature ponies were individually grazed in 10 m wide, rectangular, electric fenced paddocks. The dry matter (DM) herbage yield of each paddock was determined, and paddock length adjusted on Day 1 to provide 1.5% of individual pony BW as herbage DM daily, for 28 days. There were four ponies per treatment. Treatments were: total paddock area (TA) and strip grazing treatments, SG1 and SG2. TA allowed ponies access to the entire paddock. SG1 had a 'lead' fence spanning the paddock width being moved a set distance along the paddock length daily. SG2 also had a 'back fence' 7–12 m behind the 'lead' fence which was moved the same distance as the lead fence daily. Dry matter intakes, and changes in BW, cresty neck score, body condition score, heart girth, belly girth, and rump width were compared between treatments.

Mean DM intakes in the TA paddock ponies were significantly higher than the two strip grazing groups. Mean percentage BW changes were higher for total paddock ponies as compared to the strip grazing groups, which did not differ significantly from each other. The TA paddock ponies showed significant increases in body condition score, cresty neck score, rump width and belly girth, while the strip grazing groups did not. The SG1 group showed a significant decrease in heart girth and the SG2 group had a significant decrease in belly girth measurements.

Strip grazing is a useful tool to aid management of body weight and condition of pastured ponies. The presence of a back fence did not appear to confer a significant benefit.

Equine headshaking syndrome

This research by Laura Stange and co-workers in Germany aimed to gain an overview of the underlying causes of equine headshaking syndrome to identify effective treatment options, reduce the distress of horses and, potentially, improve therapeutic possibilities for horse owners and veterinarians.

An online survey was designed by experts in the field (researchers and veterinarians) and answered by German horse owners. The questionnaire consisted of 27 questions, which were divided into seven open questions with an associated text field and 20 multiple-choice questions. For some of the multiple-choice questions, multiple answers were permitted. Completed questionnaires were received from 163 owners of headshaking horses. Gender distribution was 64.4% geldings, 33.7% mares and 1.8% stallions. Most horses were German Warmbloods (55.4%). The average age was 12.7 years (range 5–34 years). The most frequently mentioned

clinical sign was vertical movement of the head (75.5%) and stress was reported as the main trigger for headshaking in 18.4% of cases. Additional stereotypical behaviour was reported in 18.4% of cases. Scientifically evaluated therapies were tried by 11.0% of the participants, such as surgical therapy (1.2%) or medical treatment (9.8%). Nose covers to reduce the signs of headshaking syndrome were used by 54.0% of the owners. Alternative therapies were used by a high percentage of owners (84.0%), such as physiotherapy (31.9%), change of equipment (22.7%), or change of riding style (29.4%). Overall, this study provides a useful overview of causes and effective therapies.

Suspensory ligament branch splits

This case series by Natasha Werpy and colleagues in the USA and UK described a non-weight bearing ultrasonographic technique for differentiation of complete and incomplete suspensory ligament branch splits from connective tissue and fibre abnormalities.

Ultrasonographic examination was performed on suspensory ligament branches with the limbs in weight bearing and non-weight bearing positions. Suspensory ligament branch splits were defined as linear regions of decreased echogenicity when imaged with the limb in a weight bearing position that increased in size and became anechoic with the limb in a non-weight bearing position. This appearance was considered an indication of pathologic change in the branch. The study included 62 suspensory ligament branches from 37 horses, with 14 partial splits, 11 intrasubstance splits, and 14 complete splits of which two had extension of fetlock synovial fluid and synovial membrane through the split. Ultrasonographic examinations performed in eight horses up to 14 months after the initial examination demonstrated persistence of the split in two horses, partial resolution in five horses, and complete resolution in one horse.

The non-weight bearing approach proved valuable for increasing the lesion conspicuity as compared to the weight bearing images. Certain abnormalities, such as longitudinal fibre disruption (split) in suspensory ligament branches may only be evident when imaged non-weight bearing. This technique provides a more accurate representation of lesion severity and allows for monitoring over time. A longitudinal study is necessary to determine the clinical relevance of suspensory ligament branch splits.

Foreign bodies in the equine foot

This prospective experimental cadaver study by Nadine Ogden and co-workers in the UK aimed to describe the appearance of five foreign body materials within the equine hoof using computed tomography (CT), magnetic resonance imaging (MRI), and digital radiography (DR) and to compare interrater agreement among three reviewers.

Fifty foreign bodies consisting of five materials were implanted at solar or coronary locations in 25 equine cadaver feet. Three experienced veterinarians, blinded to the material of the foreign body, reviewed the images. Foreign bodies were graded on visibility and appearance. Sensitivity and specificity were calculated to accurately identify the different materials. Interrater agreement was assessed using Fleiss' kappa.

Computed tomography had higher visibility score, sensitivity/specificity, and interrater agreement for detection of all materials; particularly slate, glass, and dry wood, compared to the other imaging modalities. Soaked wood and plastic had lower sensitivity on CT with a similar attenuation of the two materials. Foreign bodies were often visible on MRI, but with similar appearance and unclear details. On DR, only slate and glass were visible. The interrater agreement for identifying the correct material was almost perfect for slate, glass, and dry wood and poor for plastic and soaked wood on CT. Interrater agreement was poor for all materials on MRI and DR, except for slate on DR (fair) and soaked wood on MRI (moderate).

Positive blood culture in foals

In this retrospective case-control study Martin Furr and Harold McKenzie III aimed to identify factors associated with the risk of positive blood culture in neonatal foals.

Bloodstream infections (BSI) are common in sick foals. Recognition of risk factors for BSI could be an important means to limit their occurrence.

This study included 429 foals <14 days of age (143 cases and 286 controls). Risk of a foal having a BSI was increased in foals with umbilical disease, hypoglycaemia, and the combined presence of umbilical disease and low haematocrit. Prematurity, hypothermia, abdominal disease, diarrhoea, failure of passive transfer, and maternal uterine infection were not found to be risk factors for BSI.

Knowledge of the historical and physical examination findings that increase the risk of foals being blood culture positive at presentation may aid early identification of blood culture status, thus aiding in treatment decisions.

S. WRIGHT
EVE Editorial Office

References

Doyle, A.J., Saab, M.E., Lewis, K.M. and McClure, J.T. (2021) Comparison of chlorhexidine and alcohol-based antisepsis of the distal limbs of horses. *Equine Vet. J*. Epub ahead of print: https://beva.onlinelibrary. wiley.com/doi/epdf/10.1111/evj.13417.

Furr, M. and McKenzie, H. 3rd (2020) Factors associated with the risk of positive blood culture in neonatal foals presented to a referral center (2000–2014). *J. Vet. Intern. Med.* **34**, 2738-2750.

Longland, A.C., Barfoot, C. and Harris, P.A. (2021) Strip-grazing: reduces pony dry matter intakes and changes in bodyweight and morphometrics. *Equine Vet. J*. Epub ahead of print: https://beva.onlinelibrary.wiley.com/doi/abs/10.1111/evj.13416.

Ogden, N.K.E., Milner, P.I., Stack, J.D. and Talbot, A.M. (2020) CT more accurately detects foreign bodies within the equine foot than MRI or digital radiography. *Vet. Radiol. Ultrasound*. Epub ahead of print: https://doi.org/10.1111/vru.12944

Sage, S.E., Olive, J. and Lavoie, J.-P. (2020) Occipital condyle defects assessed by radiography or CT can be a normal finding in foals. *Vet. Radiol. Ultrasound*. Epub ahead of print: https://doi.org/10.1111/vru.12940

Stange, L.M., Krieter, J. and Czycholl, I. (2020) Overview of the current situation in a sample of headshakers and owner assessment of effective therapeutic measures used in Germany. *J. Equine Vet. Sci*. **95**, 103270

Werpy, N., Chapman, K. and Griffith, L. (2021) Non-weight bearing ultrasonographic examination allows the diagnosis of longitudinal fiber disruption (split) in equine suspensory ligament branches not visible on weight bearing examination. *Vet. Radiol. Ultrasound* **62**(**1**), 84-97.

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Case Report

Laryngeal dyskinesia in a horse

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Keywords: horse; laryngeal dysfunction; bilateral laryngeal adduction; upper airway obstruction; exercise endoscopy; exercise spirometry

Summary

A 3-year-old Warmblood gelding was evaluated for intermittent respiratory distress and an inspiratory noise. These signs were mainly observed at exercise but sometimes occurred at rest as well. At the age of 2 months, a severe episode of respiratory distress had necessitated placement of a temporary tracheotomy, which had then healed uneventfully. Clinical examination of the patient and resting endoscopy revealed no structural laryngeal alterations. When the horse was exercised, a mainly roaring and intermittently groaning inspiratory noise was audible occasionally in walk, trot and early phase of canter. Respiratory noise and clinical signs of respiratory distress were most pronounced at the trot. However, when canter was continued, the noise and respiratory distress disappeared rapidly and reoccurred in the cool down period when returned to walk or trot. Resting endoscopy did not reveal any structural pharyngeal or laryngeal abnormalities. Exercise endoscopy at walk revealed that both arytenoid cartilages predominantly remained in a neutral, slightly abducted resting position with full abduction after swallowing. In trot and early phase of canter, active bilateral laryngeal adduction occurred during inspiration. With continuation of canter, full abduction during inspiration was present but when returned to trot intermittent phases of active bilateral laryngeal adduction were observed again. Spirometrically, corresponding impairments of inspiratory airflow were identified. These abnormalities were most pronounced at trot and before the horse was cantering (**Fig 1**). In contrast to horses suffering from recurrent laryngeal neuropathy, the abnormalities observed in this report occurred at lower inspiratory airflow (around 20 L/s) and did not correlate directly with the magnitude of airflow and negative respiratory pressure. Therefore, the diagnosis of a laryngeal dyskinesia characterised by an active bilateral arytenoid adduction during inspiration was made. No specific treatment was implemented. Three years later, the owner reported that the condition was markedly improved and the horse was used for pleasure riding.

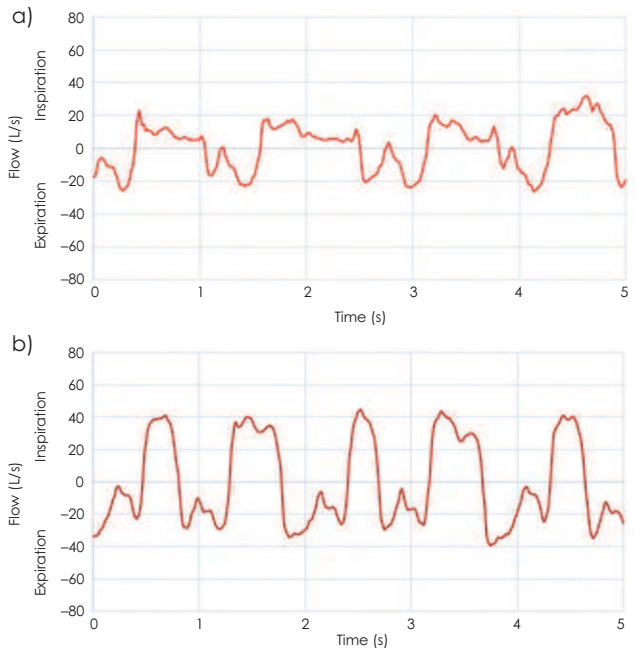

Fig 1: Exercise spirometry: Flow pattern at trot during the incremental exercise test (a) and while cooling down (b). a) Trot 3.5 m/s, 4.5% incline; breathing pattern with LD at inspiration. b) Trot 3.5 m/s, 0% incline; breathing pattern without LD at inspiration.

Key points

- Laryngeal dyskinesia can occur in horses – typical clinical signs are inspiratory noise and respiratory distress at rest or at exercise.
- The condition is characterised by episodes of active bilateral laryngeal adduction leading to impairments in inspiratory airflow.
- Treatment can target trigger factors such as pharyngitis as a locally irritating factor or psychogenic hyperresponsiveness. In human species, inhaled anticholinergics before exercise are described. Our patient shows that even without any treatment, the condition can improve over time and horses can function as riding horses.

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Clinical Commentary

Active or passive laryngeal closure

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Keywords: horse; larynx; glottic; closure; exercise

The intrinsic laryngeal musculature regulates the size of the glottic opening (or rima glottidis) by controlling the position of the corniculate processes of the arytenoid cartilages and the vocal folds. Contraction of the cricoarytenoideus dorsalis muscle widens the glottic opening by abducting the corniculate process of the arytenoid cartilage and tensing the vocal folds. The thyroarytenoideus, arytenoid transversus and cricoarytenoideus lateralis adduct the corniculate process of the arytenoid cartilage, thereby narrowing the glottic opening. The glottic opening is widened during exercise, to permit the increased ventilation required for exercise and is closed during swallowing to prevent aspiration of food.

The purpose of this clinical commentary is to describe laryngeal/glottic closure that occurs during exercise and which is evident during an exercising endoscopy procedure.

Laryngeal hemiplegia or arytenoid cartilage collapse is well described in the horse, where recurrent laryngeal neuropathy results in progressive atrophy of the cricoarytenoideus dorsalis muscle, and failure of, usually the left, arytenoid cartilage to fully abduct during exercise. Bilateral laryngeal paralysis also occasionally occurs in the horse, most commonly secondary to hepatopathy or toxins, resulting in almost complete obstruction of the rima glottidis. These forms of arytenoid cartilage collapse are a 'passive' form of laryngeal closure, due to failure of the abductor muscles to maintain patency in the face of high pressures during exercise.

Also, evident during exercise in some horses is an 'active' closure, that is the horse is capable of arytenoid abduction but there are times when the larynx is closed, presumably resulting from contraction of the adductor muscles rather than failure of the abductor muscles. They are often quick closure manoeuvres. These active laryngeal closures can be seen during swallowing, before snorting, jumping, sprint start and often a change of pace – an example would be a horse doing an extended canter down the long side of the arena. Often a 'grunting' sound can be heard at the time of the glottic closure. For activities such as jumping, riders will often associate the 'grunting' noise when the horse is putting in extra effort at take-off. Active laryngeal closure appears to occur more frequently at lower levels of exercise (walk/trot) or at the start of a pace, it is uncommon to see it during established high-intensity exercise. It is also interesting to note that active laryngeal closure (aside from swallowing) is less often seen during treadmill endoscopy and is more commonly seen during overground endoscopy. Whether this difference relates to differences in the exercise being undertaken or whether the presence of the rider is the cause is at yet unknown. However, it has been noted that if a rider kicks the horse during ridden exercise, a laryngeal closure may be observed, presumably as the horse tries to protect the thorax.

Human patients can also develop forms of exercise-induced laryngeal obstruction (EILO). Whereas currently these forms of obstruction or collapse are considered passive in horses, there is controversy surrounding whether they are active or passive in human patients (Hull *et al.* 2016). In human patients, active adduction is key in activities such as vocalisation, swallowing and coughing. Complete or partial active glottic closure also occurs during breath holds, typical when a person is straining or performing a Valsalva manoeuvre (Mendelsohn and Martin 1993; Orlikoff 2008). In this situation, brief glottic closure allows entrapment and subsequent pressurisation of air that helps stabilise the chest wall. Restraining the collapse of the ribcage, this supportive closure allows the muscles of the trunk and limbs to perform with greater effectiveness. The maintenance of alveolar (and thus intratruncal) pressure during lifting has been shown to not only assist the support of the pectoral girdle but also to alleviate part of the load on the vertebral column. Even moderate levels of physical exertion may be associated with this type of adductory bias (Orlikoff 2008). Laryngeal closure is seen in a variety of activities during maximal effort in human patients. One study investigating upper limb power showed that all the human patients assessed could achieve greater power when the larynx was closed. There was an average of 20% power loss when the larynx remained patent (Naito and Niimi 2000).

It seems likely that active laryngeal closure, as is observed in the horse during sprint starts, jumping and pace change could also be an adaptive process; acting to generate force +/- to provide a stabilising mechanism to create intrathoracic pressure and support during these movements. Accordingly, the data from human patients raises the question as to whether laryngeal surgery (e.g. in the form of tie-back and hobday, which prevents complete glottic closure) could be detrimental for some activities, most likely those requiring generation of explosive power such as jumping.

A further example of how laryngeal closure may be functionally helpful or 'adaptive' is provided in human studies evaluating expiratory phase laryngeal closure. Specifically, in addition to breath-hold manoeuvres, active contraction of the adductor muscles during expiration is thought to provide expiratory 'braking'. There is close neurophysiological coupling between the larynx and diaphragm, and vocal fold adduction is thought to play a role in regulating the time constraints of lung emptying and thus controlling end-expiratory lung volume (Brancatisano *et al.* 1985). This strategy

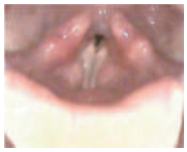
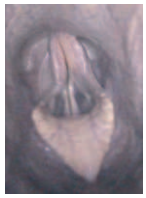
Laryngeal closure/obstruction during exercise		
HUMAN 	Adaptive behaviour Vocalisation Swallowing Coughing Expiratory closure during airflow obstruction	Maladaptive behaviour Exercise-induced laryngeal obstruction Inspiratory paradoxical closure Laryngeal hypersensitivity
HORSE 	Swallowing Coughing Closure on jumping, change of pace, sprint start Asthma?	Arytenoid cartilage collapse Vocal cord collapse Laryngeal dyskinesia

Fig 1: Schematic outlining proposed adaptive and maladaptive responses resulting in laryngeal closure.

appears to be prominent in conditions such as chronic obstructive pulmonary disease (COPD). In the later, a chronic relatively fixed impairment in expiratory airflow often leads patients to utilise a 'pursed-lip' expiratory breathing pattern. It is assumed that this acts to generate a degree of auto positive end-expiratory pressure (PEEP) and thus to optimise intrathoracic pressure and provide flow generation. It is now apparent that this process also occurs at the level of the laryngeal inlet, with the degree of active glottic narrowing directly relating to the severity of COPD (Baz *et al.* 2015; Hull *et al.* 2019). Intervention to increase laryngeal patency, in this setting, has been shown to be associated with a deleterious outcome (Lillie and Fowler 2013).

Likewise, in severe asthma excessive laryngeal closure was apparent in the expiratory phase in 40% of patients, the inspiratory phase in 47% and in both phases in 13% (Hull *et al.* 2019). Laryngeal closure during expiration is proposed to modulate intrathoracic pressure, however, excessive closure particularly during inspiration is considered maladaptive and likely to increase work of breathing (Hull *et al.* 2019). Certainly, these and other studies appear to show that, in human patients, closure of the laryngeal inlet during exertion can involve different anatomical structures/ levels of the larynx. It is thus apparent that the most common form of EILO in human patients involves inspiratory closure of the supra-glottic/arytenoid structures (>80% of cases) whereas in inducible laryngeal obstruction or vocal cord-dysfunction the closure almost exclusively occurs at the glottic level.

An emerging concept in human respiratory medicine is that laryngeal hyperresponsiveness or hypersensitivity may play a role in the development of exercise-induced laryngeal obstruction in some human patients (Hull *et al.* 2016; Nordang *et al.* 2018). As the glottic closure reflex serves to protect the lower airways against aspiration, laryngeal hypersensitivity could lead to an exaggerated tendency to inappropriate reflex closure, that becomes amplified/prominent during exercise. It seems likely that the hyperpnoea of exercise and the heightened upper airway flow may trigger a defensive closure reflex.

In summary, in the exercising horse, laryngeal closure can be passive or active, physiologic or pathologic (**Fig 1**). Brief episodes of apparent active glottic closure are not uncommon during light ridden exercise. They are less commonly seen during high-intensity exercise. When they occur frequently during ridden exercise, the significance is less clear. It is important not to assume that adaptive processes that are amplified are necessarily deleterious. The associated case report is an unusual presentation as the findings were also associated with an obvious respiratory distress (Kühnle *et al.* 2021). When observed during an overground endoscopy procedure, the veterinary surgeon can at that time work with the rider to understand whether alterations in how the horse is ridden influence their occurrence. Veterinary surgeons must also be cautious reviewing exercising endoscopy recordings as interpretation of their significance is likely to be harder without information obtained when observing the horse – such as the actions of the rider, change in pace, etc. Like human patients, an association with equine asthma is also a potential explanation and further investigations of the lower airways should always be considered and evaluated.

Author's declaration of interests

No conflicts of interest have been declared.

Ethical animal research

Not applicable to this clinical commentary which represents a review of the literature and personal clinical experience.

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References

Baz, M., Haji, G.S., Menzies-Gow, A., Tanner, R.J., Hopkinson, N.S., Polkey, M.I. and Hull, J.H. (2015) Dynamic laryngeal narrowing during exercise: a mechanism for generating intrinsic PEEP in COPD? *Thorax* **70**, 251–257.

Continued on page 183

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Case Report

Treatment using cannabidiol in a horse with mechanical allodynia

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Keywords: horse; hyperaesthesia; cutaneous; cannabidiol; allodynia

Summary

A 4-year-old Quarter Horse mare was seen in the field by Colorado State University's Equine Sports Medicine Service for a 5-week history of sensitivity to touch near the withers/shoulder region. At the onset of the clinical signs, the mare had been seen violently bucking and reacting to an unknown stimulus. At the time, it was presumed that she may have been stung by an insect. Shortly thereafter, she displayed a similar episode while being lunged while tacked. Following these episodes, the mare would twitch uncontrollably to touch of the withers/shoulder region, often becoming dangerous in her stall. The mare was treated with two doses of dexamethasone (20 mg i.v. q. 24 h) and started on vitamin E (5000 IU daily per os) 2 weeks prior to presentation, which mildly improved the clinical signs.

On examination, touching near the withers on the right side resulted in a violent reaction consisting of twitching, kicking out behind and striking out in front. She would tolerate firm palpation of the ventral aspect of her neck and brushing/stroking of her neck but would not tolerate any touching of the top of her scapula/withers region. No abnormal soft tissue swellings or any other abnormalities could be appreciated on limited palpation. A dynamic examination did not reveal any overt lameness. Neurological examination included assessment of cranial nerves, static and dynamic tail pulls, small circles and walking with the head elevated. All of these findings were within normal limits. The mare was observed walking over the threshold of her stall multiple times without incident but the facilities did not allow walking over a curb and/or up and down a hill. Lateral radiographs of the cervical spine and withers, including the cranial thoracic spine, were performed and revealed no abnormalities. Ultrasound of the caudal cervical, withers and shoulder region could not be performed safely in the field, even with sedation. Complete blood count and diagnostic profile showed no abnormalities. Differential diagnoses included syringohydromyelia, trauma or idiopathic neuropathic pain leading to cutaneous hyperaesthesia and mechanical allodynia and/or a behavioural component.

The mare was placed on a course of gabapentin (15 mg/kg per os t.i.d. for 5 weeks followed by a 2-week weaning period), which did not result in any improvement in clinical signs. Systemic treatment with prednisolone was then instituted (1 mg/kg per os q. 24 h for 2 weeks, followed by 0.5 mg/kg per os q. 24 h for an additional 2 weeks, and 0.5 mg/kg per os q. 48 h for 2 weeks). This treatment did not result in any improvement in clinical signs. Throughout, the mare continued to be fed a magnesium and Vitamin E (5000 IU daily) supplement with no significant improvement.

Recheck examination was performed approximately 3 months after the initial assessment, with only mild improvement in clinical signs. The mare was moderately to markedly reactive to light touch over the neck, withers and back. She was most reactive near the withers, on the right side. The mare was more tolerant of firm pressure, with no significant trigger points appreciated over the thoracic or lumbar region when firm pressure was used. Reproductive ultrasound was performed, which showed no significant abnormalities. A reproductive hormone panel was also performed, which revealed normal levels of progesterone, testosterone, inhibin B and antimuellerian hormone. The mare was sedated with detomidine and butorphanol i.v. and aquapuncture with Vitamin B12 was performed at acupuncture points around the withers/shoulder region, as well as at points influential for skin hypersensitivity. Options for further diagnostics, including referral for a neurological consultation and nuclear scintigraphy, were declined. Additional treatment options included placing the mare on Regumate (20 mL q. 24 h per os) to further rule out the reproductive tract as a cause of the mare's behaviour or reserpine (2.5 mg b.i.d. per os) to help rule out a purely behavioural cause. The owner elected instead to place the mare on cannabidiol (CBD). The mare was placed on pure crystalline CBD at 250 mg by mouth twice daily. This formulation was fed on grain without any palatability issues.

After 36 h on CBD, the mare exhibited significant improvement in clinical signs, including allowing both light and firm touch over the neck, withers and shoulder region. She was also able to be tacked for lungeing without any evidence of adverse behaviour. After approximately 60 days, the CBD dosage was decreased by half which resulted in recurrence of the clinical signs within one day. The initial dose of 250 mg twice daily was resumed and tapered more gradually over the next 2 months without any subsequent recurrences of clinical signs. The mare is currently maintained on 150 mg per os CBD once daily with the owner reporting a 90% improvement of clinical signs overall.

Key points

- Use of CBD can be considered for use in horses for pain and behaviour modulation, especially in cases that are refractory to more traditional medications.
- CBD may be an alternative treatment option for horses who fail to respond to traditional pain medications.
- Significant research is needed to establish the safety, bioavailability, dosage and drug interactions in equine patients.

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Clinical Commentary

Cannabinoids in veterinary medicine: Is there evidence to support the trend?

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Keywords: horse; pain; cannabinoids; neuropathic pain; veterinary

Introduction

The use of endocannabinoids and marijuana by-products is a trending topic in both human and veterinary medicine, yet few scientific publications are available to back up the increasingly wide therapeutic uses touted by its proponents. In a recent study of veterinary students in Canada, where marijuana has been legalised for general use, 56% of respondents believed that medical marijuana has a potential therapeutic value in animals, based on perceived evidence for the efficacy of medical marijuana in humans (Vogt *et al.* 2019). The case report by Ellis and Contino highlights the potential benefits of modulating the endocannabinoid system and central pain sensitisation with cannabidiol (Ellis and Contino 2021).

Pain sensitisation and endocannabinoid system physiology

Pain sensitisation, such as in this case, is mediated by the production and distribution of pro-inflammatory tissue by-products, such as prostaglandins, cytokines, eicosanoids and leukotrienes (Basbaum *et al.* 2009; Muir 2010). These by-products are then released into the injured area and cause repetitive stimulation of the peripheral sensory nerves, which can lead to the pain state of central sensitisation via summation and production of prolonged action potentials in dorsal horn sensory neurons of the spinal cord (Muir 2010). Central sensitisation is what allows low-intensity stimuli to produce pain, contributing to changes in sensory processing in the spinal cord and changes in the release of inhibitory neurotransmitters from descending pathways of the spinal cord, such as 5-hydroxytryptamine, norepinephrine and endogenous opioids (Muir 2010).

The endocannabinoid (EC) system is present throughout the peripheral nerves and spinal cord, but primarily within central nervous system nociceptive regions (Walker and Hohmann 2005; Alexander and Kendall 2009; Josee and Andrea 2009; Burston and Woodhams 2014; Woodhams *et al.* 2015). The EC system is comprised of endocannabinoids and two G protein-coupled receptors known as cannabinoid type 1 (CB_1) and cannabinoid type 2 (CB_2) (Burston and Woodhams 2014). CB_1 receptors are expressed centrally within the neocortex, cerebellum and limbic systems, where activation can lead to initiation of descending inhibition to spinal cord nociceptive mechanisms, as well as modulation of the emotional aspects of pain in humans (Alexander and Kendall 2009; Burston and Woodhams 2014; Woodhams *et al.* 2015). CB_2 receptors, however, typically have limited neuronal expression and are found mostly on immune system cells (e.g. mast cells, B cells, macrophages, microglial cells and natural killer cells) (Burston and Woodhams 2014). Endocannabinoids, such as cannabidiol, are endogenous or exogenous lipid signalling molecules that are produced via enzymatic cleavage of membrane phospholipids to form a variety of arachidonic acid derivative transmitters (Basbaum *et al.* 2009). These transmitters can be produced on demand and therefore allow for adaptability of the neuronal response to synaptic transmission.

Activation of cannabinoid receptors at the peripheral level has been shown to attenuate central sensitisation of pain responses due to the location of cannabinoid receptors in the dorsal root ganglion cells of the spinal cord, which suppresses C-fibre responses in models of inflammatory and neuropathic pain (Burston and Woodhams 2014). Administration of exogenous endocannabinoids has demonstrated antinociception in tissue injury models of acute and persistent inflammatory pain, as well as neuropathic pain in animal models (Josee and Andrea 2009; Burston and Woodhams 2014). These studies may not reflect the activity of endogenous endocannabinoids as exogenous endocannabinoids have a longer half-life (Woodhams *et al.* 2015). Therefore, the true biologic activity of endogenous endocannabinoids remains unknown.

Major classifications of cannabinoids

The compounds isolated from *Cannabis* spp. are collectively known as cannabinoids. While there are hundreds of cannabinoids known to exist in cannabis cultivars, cannabidiol (CBD) and tetrahydrocannabinol (THC) are the two major compounds known to have a pharmacologic effect. Cannabis cultivars are classified based on the content of THC in the plant, as this is the compound associated with psychoactive effects. Hemp must contain less than 0.2% THC in Europe and 0.3% in North America, while marijuana contains higher percentages of THC (Schluttenhofer and Yuan 2017). While the levels of THC in products are highly regulated in most areas, concentration of CBD is not. A recent study has highlighted the lack of regulation in the manufacture of unapproved CBD products, with CBD levels ranging from below the limit of quantification (<19 μg/g) to 8410 μg/g (Meng *et al.* 2018). The lack of consistency and regulation in the manufacturing processes of these products makes accurate dosing nearly impossible.

Because of the psychoactive potential of some of these compounds, there may be legal consequences associated

with their use in animals. Readers are encouraged to contact authorities in their locale to determine the legalities of cannabinoids, as this is a rapidly changing field and legalities vary based on product, active ingredients (i.e. THC vs. CBD) and the cultivars from which the active ingredient is derived. In terms of competition use, USEF and the FEI medication rules prohibit cannabidiols (CBD) and their metabolites. The Kentucky Horse Racing Commission has approved a 'B penalty' classification for cannabidiols (second highest classification).

Human and basic science research of cannabidiol in neuropathic pain

Cannabidiol is the endocannabinoid that has been most extensively pursued as a therapeutic agent due to its analgesic effects and lack psychotropic activity, although it is used as an anxiolytic and antidepressant which suggests some degree of psychotropism (Viudez-Martínez *et al.* 2019; Vogt *et al.* 2019). Due to their lipophilicity, THC, CBD and other cannabinoids undergo rapid tissue distribution and cross the blood–brain barrier, leading to a prolonged biological half-life. Due to this wide distribution to the CNS and effects on neuronal transmission, endocannabinoids have mainly been studied for CNS disorders and neuropathic pain. Cannabidiol has been granted orphan drug status for 22 different conditions in the USA, and 10 conditions in the EU as of August 2019, and has been investigated for use by clinical trials for 26 different medical conditions in the USA. As of the time of publication, there is only one FDA approved CBD product in the USA, which is a Schedule V drug labelled for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in humans over 2 years of age. In Canada, a 1:1 THC: CBD oromucosal spray is available for the treatment of neuropathic pain associated with multiple sclerosis.

In humans, The Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) published guidelines for the treatment of neuropathic pain in 2015, which do not include the use of cannabinoids (Attal 2019). The NeuPSIG meta-analysis identified nine trials of nabiximols (extracts of *Cannabis sativa* consisting of 27 mg/mL THC and 25 mg/mL CBD) in neuropathic pain, of which only two demonstrated significant findings, with one in multiple sclerosis demonstrating a positive outcome and a second larger study demonstrating a negative outcome. Therefore, the NeuPSIG guidelines concluded that there were weak recommendations against the use of cannabinoids due to negative results and potential for misuse and diversion of THC containing products (Finnerup *et al.* 2015).

Several studies have been performed in mouse models since the NeuPSIG guidelines were published in 2015 which indicate promising utility for CBD in neuropathic pain. In a mouse model, CBD and THC alone were found to be effective in preventing the development of mechanical allodynia in mice treated with chemotherapeutics, and the effects of CBD and THC were synergistic in combination (King *et al.* 2017). Cannabidiol has also been found to attenuate mechanical allodynia in streptozocin-induced diabetic rats at a dose of 0.3–3 mg/kg, which appeared to be at least partially mediated through the serotonergic system (Jesus *et al.* 2019). Yet the mechanism of action for CBD's purported analgesic effects remains incompletely understood, and it should be anticipated that the anxiolytic activity of CBD in human patients has a significant influence on any analgesic effects. Furthermore, the extent of the potential for drug–drug interaction is incompletely elucidated. Since CBD is metabolised via a variety of cytochromes (CYP450 2 C9 and 3A4), any concurrent administration of a CYP450 inhibitors/inducers could lead to toxicity. For more information on CYP450 drug interactions in veterinary species, the reader is referred to an excellent review written by Dr Lauren Trepanier (Trepanier 2006).

Veterinary research of cannabidiol

Up until very recently, cannabinoids were only understood as toxicants in the veterinary profession. Unfortunately, there are no published pharmacokinetic, pharmacodynamic or controlled research studies on cannabinoids in large animals, and therefore extrapolations must be made from limited studies in small animals. Compared with humans, dogs have increased cannabinoid receptors in the brain, resulting in increased sensitivity to the effects of cannabinoids (Freundt-Revilla *et al.* 2017). The comparative brain cannabinoid receptor distribution is unknown in other veterinary species. In dogs, the minimum lethal dose for THC is >3000 mg/kg, resulting in a high morbidity but low mortality rate. The half-life of THC in dogs is approximately 30 h, with 80% of THC excreted within 5 days of administration (Fitzgerald *et al.* 2013). Cannabidiol, however, has a shorter half-life in dogs than THC, ranging from 2 to 4 h depending on the dose (2–20 mg/kg) (Brutlag and Hommerding 2018). Additionally, CBD faces extensive first-pass metabolism, and a study on the bioavailability of different CBD preparations in dogs demonstrated a significantly lower oral bioavailability in capsulated products and highest bioavailability in an oil-based preparation (Bartner *et al.* 2018). Transdermal absorption was also investigated with a relative bioavailability of around 9%. In dogs with naturally occurring osteoarthritis, treatment with CBD oil (2 mg/kg per os q. 12 for 30 days) resulted in a significant decrease in pain (Gamble *et al.* 2018). However, animals in this study were also receiving a variety of chronically administered NSAIDs and supplements, and there was no significant change in the subjective veterinary lameness score and weight-bearing capacity over the course of the study. In two studies, chronic treatment with CBD (2–20 mg/kg/day) resulted in reversible elevation of alkaline phosphatase that appeared to be dose dependent, suggesting hepatic CYP450 induction (Gamble *et al.* 2018; McGrath *et al.* 2018).

A difficulty in veterinary medicine is determining an appropriate dose for CBD, given the lack of pharmacokinetic–pharmacodynamic studies in all species, and variability in CBD concentrations among and within available products. In this case by Ellis and Contino, dosing (0.5 mg/kg tapered to 0.33 mg/kg daily) was based on human recommendations and appears to be in-line with the lower end of dosing used in mouse and rat models of neuropathic pain. The ability of such low dosing of CBD to alleviate the clinical signs in this mare suggests high concentrations of cannabinoid receptors in the skin, as has been demonstrated in cats with hypersensitivity dermatitis (Miragliotta *et al.* 2018). Therefore, further research into cannabinoid pharmacokinetics, pharmacodynamics and receptor distribution is warranted in horses, particularly given clinical reports of success in treating chronic pain states.

Conclusions

Cannabinoid research is a rapidly expanding and developing field that is still limited by the legalities of its use, a lack of regulated products, and inconsistent clinical evidence. Case reports, such as the one published in this edition, highlight the potential benefit for its use in horses and should encourage the conduction of controlled research studies to validate a dose and/or efficacy. Given the public interest in this compound and the potential benefits for its use in neuropathic pain states, further research in horses is warranted.

Authors' declaration of interests

No conflicts of interest have been declared.

Ethical animal research

Not applicable to this clinical commentary.

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All authors contributed to the writing and preparation of the manuscript.

References

Alexander, S.P.H. and Kendall, D.A. (2009) The life cycle of the endocannabinoids: formation and inactivation. In: *Behavioral Neurobiology of the Endocannabinoid System*, Ed: S. Alexander, Springer Berlin Heidelberg, Berlin, Heidelberg. pp 3–35.

Attal, N. (2019) Pharmacological treatments of neuropathic pain: the latest recommendations. *Rev. Neurol.* **175**, 46–50.

Bartner, L.R., McGrath, S., Rao, S., Hyatt, L.K. and Wittenburg, L.A. (2018) Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs. *Can. J. Vet. Res.* **82**, 178–183.

Basbaum, A.I., Bautista, D.M., Scherrer, G. and Julius, D. (2009) Cellular and molecular mechanisms of pain. *Cell* **139**, 267–284.

Brutlag, A. and Hommerding, H. (2018) Toxicology of marijuana, synthetic cannabinoids, and cannabidiol in dogs and cats. *Vet. Clin. North Am. Small Anim. Pract.* **48**, 1087–1102.

Burston, J.J. and Woodhams, S.G. (2014) Endocannabinoid system and pain: an introduction. *Proc. Nutr. Soc.* **73**, 106.

Ellis, K.L. and Contino, E.K. (2021) Treatment using cannabidiol in a horse with mechanical allodynia. *Equine Vet. Educ.* **33**, 176. https://doi.org/10.1111/eve.13168.

Finnerup, N.B., Attal, N., Haroutounian, S., McNicol, E., Baron, R., Dworkin, R.H., Gilron, I., Haanpää, M., Hansson, P., Jensen, T.S., Kamerman, P.R., Lund, K., Moore, A., Raja, S.N., Rice, A.S.C., Rowbotham, M., Sena, E., Siddall, P., Smith, B.H. and Wallace, M. (2015) Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* **14**, 162–173.

Fitzgerald, K.T., Bronstein, A.C. and Newquist, K.L. (2013) Marijuana poisoning. *Top. Companion Anim. Med.* **28**, 8–12.

Freundt-Revilla, J., Kegler, K., Baumgärtner, W. and Tipold, A. (2017) Spatial distribution of cannabinoid receptor type 1 (CB1) in normal canine central and peripheral nervous system. *PLoS ONE* **12**, e0181064–e0181064.

Gamble, L.-J., Boesch, J.M., Frye, C., Schwark, W.S., Mann, S., Wolfe, L., Brown, H., Berthelsen, E.S. and Wakshlag, J.J. (2018) Pharmacokinetics, safety, and clinical efficacy of cannabidiol treatment in osteoarthritic dogs. *Front. Vet. Sci.* **5**, 165.

Jesus, C.H.A., Redivo, D.D.B., Gasparin, A.T., Sotomaior, B.B., de Carvalho, M.C., Genaro, K., Zuardi, A.W., Hallak, J.E.C., Crippa, J.A., Zanoveli, J.M. and da Cunha, J.M. (2019) Cannabidiol attenuates mechanical allodynia in streptozotocin-induced diabetic rats via serotonergic system activation through 5-HT1A receptors. *Brain Res.* **1715**, 156–164.

Josee, G. and Andrea, G.H. (2009) The endocannabinoid system and pain. *CNS Neurol. Disord. Drug Targets* **8**, 403–421.

King, K.M., Myers, A.M., Soroka-Monzo, A.J., Tuma, R.F., Tallarida, R.J., Ward, S.J. and Walker, E.A. (2017) Single and combined effects of Δ9-tetrahydrocannabinol and cannabidiol in a mouse model of chemotherapy-induced neuropathic pain. *Br. J. Pharmacol.* **174**, 2832–2841.

McGrath, S., Bartner, L.R., Rao, S., Kogan, L.R. and Hellyer, P.W. (2018) A report of adverse effects associated with the administration of cannabidiol in healthy dogs. *Vet. Med.* **1**, 6–8.

Meng, Q., Buchanan, B., Zuccolo, J., Poulin, M.-M., Gabriele, J. and Baranowski, D.C. (2018) A reliable and validated LC-MS/MS method for the simultaneous quantification of 4 cannabinoids in 40 consumer products. *PLoS ONE* **13**, 1–16.

Miragliotta, V., Ricci, P.L., Albanese, F., Pirone, A., Tognotti, D. and Abramo, F. (2018) Cannabinoid receptor types 1 and 2 and peroxisome proliferator-activated receptor-alpha: distribution in the skin of clinically healthy cats and cats with hypersensitivity dermatitis. *Vet. Dermatol.* **29**, 316–e111. https://doi.org/10.1111/vde.12658.

Muir, W.W. (2010) Pain: mechanisms and management in horses. *Vet. Clin. North Am. Equine Pract.* **26**, 467–480.

Schluttenhofer, C. and Yuan, L. (2017) Challenges towards revitalizing hemp: a multifaceted crop. *Trends Plant Sci.* **22**, 917–929.

Trepanier, L.A. (2006) Cytochrome P450 and its role in veterinary drug interactions. *Vet. Clin. North Am. Small Anim. Pract.* **36**, 975–985.

Viudez-Martínez, A., García-Gutiérrez, M.S., Medrano-Relinque, J., Navarrón, C.M., Navarrete, F. and Manzanares, J. (2019) Cannabidiol does not display drug abuse potential in mice behavior. *Acta Pharmacol. Sin.* **40**, 358–364.

Vogt, N.A., Sargeant, J.M., Stevens, C.P.G. and Dunn, J.N. (2019) A survey of veterinary student attitudes concerning whether marijuana could have therapeutic value for animals. *PLoS ONE* **14**, 1–11.

Walker, J.M. and Hohmann, A.G. (2005) Cannabinoid mechanisms of pain suppression. In: *Cannabinoids*, Ed: R.G. Pertwee, Springer Berlin Heidelberg, Berlin, Heidelberg. pp 509–554.

Woodhams, S.G., Sagar, D.R., Burston, J.J. and Chapman, V. (2015) The role of the endocannabinoid system in pain. *Handb. Exp. Pharmacol.* **227**, 119–143.

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Case Report

Epiploic foramen entrapment of the large colon in a 9-month-old Thoroughbred filly

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Keywords: horse; colic; epiploic foramen; colon; incarceration

Summary

A 9-month-old Thoroughbred filly presented for evaluation of colic of a few hours' duration, unresponsive to antispasmodic medications. On admission, she appeared quiet with moderately decreased gut sounds, no visible abdominal distension nor gastric reflux. Transrectal palpation was not performed due to the filly's small size. A suspicion of right displacement of the large colon was based on the ultrasonographic absence of a structure compatible with large colon on the left side of the abdomen, and the presence of a relatively amotile large intestinal structure, with discrete wall oedema (4–5 mm thickness), on the right side, obstructing visualisation of the duodenum, right kidney and liver lobe. After an hour of intravenous fluid therapy, the filly displayed more overt signs of colic, unresponsive to administration of a combination of scopolamine and metamizole (0.16 and 20 mg/kg bwt, i.v., Estocelan ND). Exploratory laparotomy was advised and revealed an oedematous and hyperhaemic ascending colon with a purplish serosa, impacted and displaced to the right side of the abdomen. Upon careful palpation, a right to left epiploic foramen entrapment of the large colon was diagnosed. The caeco-colic fold could not be followed freely but was stretched by and towards the EF, while a 5-cm long serosal tear was palpable on the dorsal colon immediately adjacent to the EF. Pelvic flexure enterotomy was performed prior to gentle reduction by right-handed pulling of the caeco-colic junction area and left-handed pushing of the colon through the foramen. Once the colon was completely freed, the foramen was explored and found to easily fit the surgeon's hand; no bleeding occurred and the site of serosal tear was sutured, before replacement of all intestinal structures. The large colon remained amotile throughout the surgery, while the serosal colour normalised.

The filly recovered uneventfully, except for two episodes of pasty faeces treated symptomatically, immediately after surgery and two weeks later. The owners were informed of the risk of recurrent EFE but declined laparoscopic examination and potential closure of what could be considered an abnormally enlarged EF. No recurrence of colic was noted during the 6 months of follow-up and the filly displayed normal body development.

Epiploic foramen entrapment of the colon or caecum is a rare reason for colic in the adult horse and was to our knowledge unreported in foals; however rare, it should be included as a differential diagnosis of large colon displacement, and would have similar palpation and ultrasonographic findings as the much more common right dorsal displacement of the colon (RDDC). While prognosis for medical treatment of suspected RDDC has been reported to be fair to good with a 64% success rate, delaying surgical treatment in the event of an EFE of the large colon or caecum would lead to more vascular damage and a poorer prognosis, as evidenced in the few reported cases. Left to right EFE of small intestinal loops is most commonly found but in the present case, the colon might have taken the more common path of right dorsal displacement before entering the EF from the right side of the abdomen.

Key points

- Epiploic foramen entrapment of the large colon, however rare, may occur in horses of all ages and should be included in the differential diagnoses for large colon displacements.
- Emptying the large colon prior to careful reduction of the entrapment can lead to a successful outcome.
- Displacement of the large colon to the right side of the abdomen might be suspected in the absence of a large intestinal structure compatible with colon on the left side of the abdomen, and the inability to visualise the typical right-sided abdominal structures such as liver, kidney and duodenum.

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Clinical Commentary

Epiploic foramen entrapment colic in horses

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Keywords: horse; epiploic foramen; entrapment; colic

Introduction

The epiploic foramen (EF) is defined as 'the opening from the greater peritoneal sac to the omental vestibule that passes between the caudal vena cava dorsally, the portal vein that is included in the hepatoduodenal ligament ventrally, the caudal lobe of the liver cranially, and the pancreas caudally' (Schaller 2012). This slit-like opening is called the 'Winslow foramen' or 'foramen of Winslow' in human literature, named after the French–Danish doctor and anatomist Jacob alias Jacques-Bénigne Winslow (1669–1760) who first described this enigmatic structure (Bellary *et al.* 2012).

Human literature lacks large case series of intestinal herniation through the foramen of Winslow as this condition is very uncommon in man. Reports of EF herniation in other mammals, besides humans and horses, are even more scarce. Only three cases of small intestinal incarceration in the EF in young calves have been described (Deprez *et al*. 2006). In horses, a herniation through the Winslow foramen is quite common and is called epiploic foramen entrapment (EFE) throughout the veterinary literature.

Large intestinal EFE

In men, the caecum is involved in a large percentage of cases of Winslow foramen herniation (Valenziano *et al.* 1987). This is in contrast to equine EFE, where, except for a few reported cases of herniation of the large colon (Foerner *et al.* 1993; Steenhaut *et al.* 1993; Segura *et al.* 1999) and one recently reported case of herniation of the apex of the caecum (Grzeskowiak *et al.* 2017), all herniations consisted of herniated small intestines. The report of Chambourg *et al.* (2019) adds an additional case of large colon EFE to the equine literature, and they report the first young filly (9 months of age) with this condition. The authors conclude that EFE of the large colon is very rare, but the condition should be included as a differential diagnosis of colon displacement, even in young horses, requiring prompt surgical intervention (Schambourg *et al.* 2021).

Small intestinal EFE

In horses, small intestinal EFE is encountered in about 5% of all surgically treated colic patients (Vachon and Fischer 1995; Archer *et al.* 2004b; Mair and Smith 2005) and is an important differential diagnosis in equine small intestinal colic. This importance of small intestinal EFE contrasts with all other species where this condition is almost never reported. Wind sucking/crib biting has been identified as an important risk factor related to the development of small intestinal EFE (Archer *et al.* 2004a, 2008; van Bergen *et al.* 2019).

Possibly, the combination of the specific funnel-like shape of the equine EF as was recently described (Freeman and Pearn 2015; van Bergen *et al.* 2015), the rhythmic movement of the abdominal wall, diaphragm and liver, and the possible occurrence of pressure differences throughout the abdomen during wind sucking/crib biting (Albanese *et al.* 2013) may be involved in EFE development in horses. This hypothesis warrants further investigation. The funnel-like shape of the equine EF could also be responsible for the almost exclusive left-to-right occurrence of small intestinal EFE (van Bergen *et al.* 2019). The opposite direction of the colon passage through the EF in the exceptional case reported by Schambourg *et al.* (2021) illustrates that the very incidental passage of the colon through the EF is unrelated to the frequent occurrence of small intestinal EFE pathology in horses.

Recurrence of small intestinal EFE has been reported in 2 and 14% of surgically treated horses (Vachon and Fischer 1995; Archer *et al.* 2004b; Freeman *et al.* 2014; van Bergen *et al.* 2019). This relatively low recurrence rates despite the persistence of risk factors may be explained by the spontaneous closure of the EF after EFE due to the induced inflammation and subsequent serosal adhesions at the level of the EF and omental vestibule. Such spontaneous closure of the EF after surgical correction of EFE is reported to occur in about 30–40% of cases (van Bergen *et al.* 2016b).

Prevention of small intestinal EFE in horses

Based on the importance of small intestinal EFE in horses, the severity of the condition with high morbidity and mortality rates (Proudman *et al.* 2002a, 2002b; 2005) and the demonstrated recurrences, several techniques for obliteration of the equine EF were developed.

First a right flank standing laparoscopic technique using 4–10 titanium helical coils to obliterate the EF was described (Munsterman *et al.* 2014). However, the EF was only closed by a tissue fold and closure was inconsistent.

After gathering 3D insights and dimensions of the EF (van Bergen *et al.* 2015), a 3D diabolo-shaped mesh construct was developed that could be introduced into the omental vestibule through the EF during a right flank standing laparoscopic procedure (van Bergen *et al.* 2016a). The laparoscopic technique was first performed on six experimental horses, and consistent closure of the whole EF and omental vestibule with dense fibrous tissue was demonstrated (van Bergen *et al.* 2016a).

Laparoscopic inspection of the abdomen about one month after colic surgery for EFE to verify the state of the EF, and at the same time, to close the EF by means of the

diabolo-shaped mesh construct when the EF appeared open during this inspection, was proposed (van Bergen *et al.* 2016b). This approach could be of particular value in horses that demonstrate crib biting or wind sucking behaviours. Until now the authors performed this laparoscopic procedure in 34 horses without major complications. In 11 (32%) of these cases, the EF was spontaneously closed. In 23 (68%) of the horses, the mesh construct was introduced into the EF.

The laparoscopic experience supported the idea that it should be feasible to apply the 3D diabolo-shaped mesh construct into the EF during the initial colic surgery for EFE through the ventral midline laparotomy. However, concerns were raised in regard to the feasibility of correct mesh introduction without visual control, the stability of the mesh during recovery and the risk of infection when introducing foreign material into the abdomen during a clean-contaminated procedure. The technique was therefore first performed on six experimental horses in which a colic procedure under general anaesthesia was mimicked. Mesh introduction was uneventful, and meshes remained in place resulting in dense closure of the EF and omental vestibule with fibrous tissue, comparable to the laparoscopic technique (van Bergen *et al.* 2018).

The diabolo-shaped mesh construct has been introduced during the initial colic surgery for small intestinal EFE in 15 cases till now and in one case of colon torsion as a preventive measure because the horse displayed wind-sucking/crib-biting behaviour. Four of these horses underwent an end-to-end jejunoileostomy, two an end-to-end jejunojejunostomy, two a side-to-side jejunocaecostomy, four a pelvic flexure enterotomy or typhlotomy, and four horses did not undergo an enterotomy or enterectomy. Eleven of these 16 horses left the hospital and are doing well at the moment. One of them had a second colic surgery 1.5 months later due to adhesions at the side-to-side anastomosis. These were released, and the horse is doing well. Four of the five horses that died in the post-operative period were subjected to euthanasia due to ongoing post-operative reflux unrelated to the mesh (necropsy performed in all cases), and the other was subjected to euthanasia due to a severe radial nerve paralysis 2 days after surgery. This last horse had a very agitated recovery due to the paralysis. Despite this agitated recovery, the mesh construct was still perfectly in place on necropsy giving additional support for the fixation-free 3D meshing technique.

Our current approach for small intestinal EFE is that surgeons comfortable with the technique apply the mesh construct immediately during the initial colic surgery for EFE in horses, whether or not intestinal resection is performed. If the surgeon involved is less comfortable with the technique, or if the specific case bears a less good prognosis, mesh application is postponed and, if the horse survives the post-operative period, a laparoscopic mesh application is proposed about one month after the colic surgery.

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Ethical animal research

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T. van Bergen and A. Martens contributed to the manuscript preparation. All authors have approved the final version of the manuscript.

References

Albanese, V., Munsterman, A.S., DeGraves, F.J. and Hanson, R.R. (2013) Evaluation of intra-abdominal pressure in horses that crib. *Vet. Surg.* **42**, 658–662.

Archer, D., Freeman, D.E., Doyle, A.J., Proudman, C.J. and Edwards, G.B. (2004a) Association between cribbing and entrapment of the small intestine in the epiploic foramen in horses: 68 cases (1991–2002). *J. Am. Vet. Med. Assoc.* **224**, 562–564.

Archer, D., Proudman, C.J., Pinchbeck, G., Smith, J.E., French, N.P. and Edwards, G.B. (2004b) Entrapment of the small intestine in the epiploic foramen in horses : a retrospective analysis of 71 cases recorded between 1991 and 2001. *Vet. Rec.* **155**, 793–797.

Archer, D.C., Pinchbeck, G.K., French, N.P. and Proudman, C.J. (2008) Risk factors for epiploic foramen entrapment colic: an international study. *Equine Vet. J.* **40**, 224–230.

Bellary, S.S., Walters, A., Gielecki, J., Shoja, M.M., Tubbs, R.S. and Loukas, M. (2012) Jacob B. Winslow (1669–1760). *Clin. Anat.* **25**, 545–547.

van Bergen, T., Doom, M., van den Broeck, W., Wiemer, P., Clegg, P.D., Cornillie, P. and Martens, A. (2015) A topographic anatomical study of the equine epiploic foramen and comparison with laparoscopic visualisation. *Equine Vet. J.* **47**, 313–318.

van Bergen, T., Wiemer, P., Bosseler, L., Ugahary, F. and Martens, A. (2016a) Development of a new laparoscopic Foramen epiploicum mesh closure (FEMC) technique in 6 horses. *Equine Vet. J.* **48**, 331–337.

van Bergen, T., Wiemer, P., Schauvliege, S., Paulussen, E., Ugahary, F. and Martens, A. (2016b) Laparoscopic evaluation of the epiploic foramen after celiotomy for epiploic foramen entrapment in the horse. *Vet. Surg.* **45**, 596–601.

van Bergen, T., Rötting, A., Wiemer, P., Schauvliege, S., Vanderperren, K., Ugahary, F. and Martens, A. (2018) Foramen epiploicum mesh closure (FEMC) through a ventral midline laparotomy. *Equine Vet. J.* **50**, 235–240.

van Bergen, T., Haspeslagh, M., Wiemer, P., Swagemakers, M., van Loon, G. and Martens, A. (2019) Surgical treatment of epiploic foramen entrapment in 142 horses (2008–2016). *Vet. Surg.* **48**, 291–298.

Schaller, O. (2012) Splanchnologia. In: *Illustrated Veterinary Anatomical Nomenclature*, 3th edn., Eds: G.M. Constantinescu and O. Schaller, Enke Verlag, Stuttgart. pp 140–233.

Deprez, P., Hoogewijs, M., Vlaminck, L., Vanschandevijl, K., Lefère, L. and van Loon, G. (2006) Incarceration of the small intestine in the epiploic foramen of three calves. *Vet. Rec.* **158**, 869–870.

Foerner, J., Ringle, M., Junkins, D., Fischer, A., MacHarg, M. and Phillips, T. (1993) Transection of the pelvic flexure to reduce incarceration of the large colon through the epiploic foramen in a horse. *J. Am. Vet. Med. Assoc.* **203**, 1312–1313.

Freeman, D.E. and Pearn, A.R. (2015) Anatomy of the vestibule of the omental bursa and epiploic foramen in the horse. *Equine Vet. J.* **47**, 83–90.

Freeman, D.E., Schaeffer, D.J. and Cleary, O.B. (2014) Long-term survival in horses with strangulating obstruction of the small intestine managed without resection. *Equine Vet. J.* **46**, 711–717.

Grzeskowiak, R.M., Barrett, E.J. and Rodgerson, D.H. (2017) Cecal entrapment within the epiploic foramen in a mare. *Can. Vet. J.* **58**, 842–844.

Mair, T.S. and Smith, L.J. (2005) Survival and complication rates in 300 horses undergoing surgical treatment of colic. Part 1: short-term survival following a single laparotomy. *Equine Vet. J.* **37**, 296–302.

Munsterman, A.S., Hanson, R.R., Cattley, R.C., Barrett, E.J. and Albanese, V. (2014) Surgical technique and short-term outcome for experimental laparoscopic closure of the epiploic foramen in 6 horses. *Vet. Surg.* **43**, 105–113.

Proudman, C.J., Smith, J.E., Edwards, G.B. and French, N.P. (2002a) Long-term survival of equine surgical colic cases. Part 1: patterns of mortality and morbidity. *Equine Vet. J.* **34**, 432–437.

Proudman, C.J., Smith, J.E., Edwards, G.B. and French, N.P. (2002b) Long-term survival of equine surgical colic cases. Part 2: modelling postoperative survival. *Equine Vet. J.* **34**, 438–443.

Proudman, C.J., Edwards, G.B., Barnes, J. and French, N.P. (2005) Factors affecting long-term survival of horses recovering from surgery of the small intestine. *Equine Vet. J.* **37**, 360–365.

Schambourg, M., Nodin, M. and Bussy, C. (2021) Epiploic foramen entrapment of the large colon in a 9-month-old Thoroughbred filly. *Equine Vet. Educ.* **33**, 180. https://doi.org/10.1111/eve.13191.

Segura, D., Garzon, N., Nomen, C., Prades, M. and Valls, S. (1999) Entrapment of large colon through the epiploic foramen in a horse. *Equine Vet. Educ.* **11**, 227–228.

Steenhaut, M., Vandenreyt, I. and Van Roy, M. (1993) Incarceration of the large colon through the epiploic foramen in a horse. *Equine Vet. J.* **25**, 550–551.

Vachon, A.M. and Fischer, A.T. (1995) Small intestinal herniation through the epiploic foramen: 53 cases (1987–1993). *Equine Vet. J.* **27**, 373–380.

Valenziano, C., Howard, W. and Criado, F. (1987) Hernia through the foramen of Winslow: a complication of cholecystotomy. A case report. *Am. Surg.* **53**, 254–257.

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Brancatisano, T.P., Dodd, D.S., Collett, P.W. and Engel, L.A. (1985) Effect of expiratory loading on glottic dimensions in humans. *J. Appl. Physiol.* **58**, 605–655.

Hull, J.H., Backer, V., Gibson, P.G. and Fowler, S.J. (2016) Laryngeal dysfunction: assessment and management for the clinician. *Am. J. Respir. Crit. Care Med.* **194**, 1062–1072.

Hull, J.H., Walsted, E.S., Pavitt, M.J., Menzies-Gow, A., Backer, V. and Sandhu, G. (2019) High prevalence of laryngeal obstruction during exercise in severe asthma. *Am. J. Respir. Crit. Care Med.* **199**, 538–542.

Kühnle, C., Kümmerle, J.M., Parente, E.J. and Weishaupt, M.A. (2021) Laryngeal dyskinesia in a horse. *Equine Vet. Educ*. **33**, 172. https://doi.org/10.1111/eve.13182

Lillie, S. and Fowler, S. (2013) Expiratory vocal cord dysfunction – symptom presentation and co-morbidities. *Eur. Resp. J.* **42**, *Suppl.* **57**, 919.

Mendelsohn, M.S. and Martin, R.E. (1993) Airway protection during breath-holding. *Ann. Otol. Rhinol. Laryngol.* **102**, 941–944.

Naito, A. and Niimi, S. (2000) The larynx during exercise. *Laryngoscope* **110**, 1147–1150.

Nordang, L., Norlander, K. and Walsted, E.S. (2018) Exercise -induced laryngeal obstruction – an overview. *Immunol. Allergy Clin. North Am.* **38**, 271–280.

Orlikoff, R.F. (2008) Voice production during a weightlifting and support task. *Folia Phoniatr. Logop.* **60**, 188–194.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Supplementary Item 1: Endoscopic recording during exercise of a horse with left-side arytenoid cartilage collapse. Also evident during the recording are multiple 'active' laryngeal closures.

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Case Report

In-hospital development of an aorto-cardiac fistula in a Warmblood gelding with chronic renal disease

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Keywords: horse; echocardiography; aorto-cardiac fistula; ventricular tachycardia; azotaemia; chronic renal disease

Summary

A 20-year-old Warmblood gelding was presented for evaluation and treatment of ventral oedema and azotaemia of unknown aetiology. On presentation, a diastolic heart murmur was appreciated and echocardiography revealed moderate aortic insufficiency due to chronic degenerative valve disease but was not considered clinically significant (**Fig 1a**). The horse was hospitalised and treated for presumptive acute kidney injury with oral and intravenous fluids and diuretic therapy. The gelding failed to respond to treatment, and the possibility of an acute exacerbation of chronic renal disease was considered likely. Based on his lack of response and otherwise bright attitude, the decision was made to discontinue therapy and monitor prior to discharge. Following discontinuation of all therapies, he became acutely agitated and developed monomorphic ventricular tachycardia. The ventricular tachycardia spontaneously converted to normal sinus rhythm; however, the heart murmur changed in timing to a right basilar continuous murmur and bounding jugular pulses were noted. Repeat echocardiogram was performed at that time and revealed the development of an aorto-cardiac fistula with dissection into the basilar interventricular septum, and left-sided chamber volume overload (**Fig 1b**). Attempts at stabilisation were unsuccessful, and euthanasia was elected following development of acute congestive heart failure and colic. A limited post-mortem examination was performed and confirmed the presence of chronic renal membranous glomerulopathy with interstitial fibrosis of unknown aetiology in addition to an aorto-cardiac fistula originating from the right sinus of Valsalva with subsequent dissection into the basilar interventricular septum. This case is one of the few reports to have a detailed echocardiographic examination just prior to fistula development, systemic blood pressure measurements following fistula development and one of the few documented cases with pre-existing aortic regurgitation.

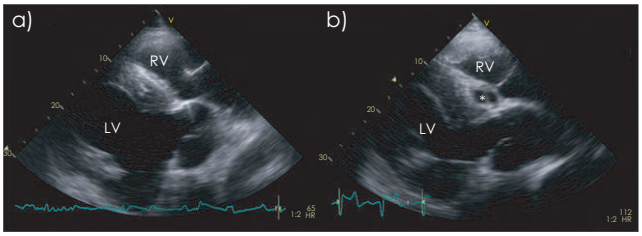

Fig 1: Right parasternal long-axis two-dimensional view of the right ventricle (RV), left ventricle (LV) and the aortic dissection (*). Image a) is from the initial echocardiogram, and image b) is the second echocardiogram. The numerical scale denotes centimetres of depth, and the yellow triangle depicts the focal point.

Key points

- An aorto-cardiac fistula is a rare but life-threatening cardiac abnormality of horses.
- Detailed echocardiography prior to fistula development does not appear to be beneficial in detecting abnormalities that indicate impending fistula development. Its use as a screening tool is likely limited.
- Care should be taken with aggressive intravenous fluid therapy in horses with pre-existing cardiac lesions. Careful evaluation for systemic hypertension prior to initiation of high-volume fluid therapy should be considered.

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Clinical Commentary

Hypertension and aortic root rupture: Cause and effect?

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The case report by Baker *et al*. (2021) describes the unusual development of an aortocardiac fistula (ACF) in a 20-year-old Warmblood gelding while hospitalised for renal failure. The initial echocardiographic examination revealed moderate aortic regurgitation. On Day 6, after discontinuing fluid therapy, the gelding became acutely agitated while turned out. He had a right basilar continuous murmur, marked tachycardia (168 beats/min) and bilateral jugular pulses. An electrocardiogram (ECG) confirmed monomorphic ventricular tachycardia that spontaneously converted. A repeat echocardiogram revealed an ACF. This is the first and only report of the development of an ACF in a hospitalised horse.

The clinical signs of agitation (often mistaken for colic), tachycardia and profound jugular pulses in an older gelding are classic for a horse with ACF. Uniform ventricular tachycardia (VT) is common and is thought to be associated with dissection of blood through the interventricular septum. This dissection into the interventricular septum is painful in some subjects with rupture of the sinus of Valsalva. The VT may also cause agitation, which may disappear with its resolution, as was the case in this gelding.

The right sinus of Valsalva (RSoV) is the most common site to rupture, similar to human subjects (Golzari and Riebman 2004; Fennich *et al*. 2018). In some horses, the RSoV ruptures; in others, there are pre-existing aneurysms (Rooney *et al*. 1967; Roby *et al*. 1986; Reef *et al*. 1990; Lester *et al*. 1992; Marr *et al*. 1998; Cornelisse *et al*. 2000; Sleeper *et al*. 2001; Javsicas *et al*. 2010; Norman *et al*. 2010; Vernemmen *et al*. 2019). Rupture of the RSoV, in the absence of a pre-existing aneurysm, is extremely rare in humans (Fennich *et al*. 2018).

The ACF in this gelding involved the dissection of blood into the interventricular septum, without rupture into the cardiac chambers. This type was well described in the early pathology literature. Since then, the echocardiographic appearance of this type of ACF has been described (Marr *et al*. 1998; Cornelisse *et al*. 2000; Sleeper *et al*. 2001). With increasing pressure from the blood dissecting into the subendocardial region, the endocardium ruptures, creating a communication between the aorta and cardiac chamber, usually the right atria or ventricle (Rooney *et al*. 1967; Lester *et al*. 1992; Marr *et al*. 1998; Sleeper *et al*. 2001; Norman *et al*. 2010; Vernemmen *et al*. 2019). ACF fistulas can also develop from rupture of a RSoV aneurysm (Roby *et al*. 1986; Lester *et al*. 1992; Marr *et al*. 1998; Sleeper *et al*. 2001; Norman *et al*. 2010; Vernemmen *et al*. 2019).

This horse had a larger than expected aortic root. Aortic root enlargement is common in horses with moderate to severe aortic regurgitation (Reef and Spencer 1987; Stadler *et al*. 1995; Marr 2010; Ven *et al*. 2016). While aortic regurgitation is common, rupture of the aortic root and the development of an ACF are rare. Only four other horses with aortic regurgitation have subsequently developed an ACF (Rooney *et al*. 1967; Marr *et al*. 1998; Cornelisse *et al*. 2000; Sleeper *et al*. 2001; Marr 2010). This suggests that there are other factors that contribute to the development of an ACF. One of the reasons that few horses with aortic regurgitation develop an ACF may have to do with haemodynamics. The bounding pulses of moderate to severe aortic regurgitation correlate with a hyperdynamic state and left ventricular volume overload (Reef and Spencer 1987; Reef 1995; Reef *et al*. 2014). While systolic pressure increases, diastolic pressure falls, creating this widened pulse pressure. This wide pulse pressure is an indication of severity and is >60 mmHg in horses with progressively worsening aortic regurgitation (Horn *et al*. 2002). This gelding had a pulse pressure of >100 mm Hg (240 mmHg/137 mmHg; MAP 164 mg). The presumed elevated isolated systolic pressures associated with his moderate aortic regurgitation may have contributed to the severity of his systolic hypertension and subsequent aortic dissection into the interventricular septum. Monitoring blood pressure in horses with aortic regurgitation is an important aid in assessing severity of the regurgitation.

One of the intriguing aspects of this case is the severe hypertension. In this case, the hypertension was increasing after the ACF occurred, prior to the gelding's euthanasia. The cause for the continued increase in blood pressure is most likely severe chronic renal disease. Unfortunately, blood pressure measurements were not obtained prior to the development of the ACF.

The kidney plays an important role in the development of hypertension (Eknoyan 2004). Interestingly, aortic diameter is larger in hypertensive subjects with chronic kidney disease compared to hypertensive human subjects with normal renal function (Mulè *et al*. 2017). Sustained severe hypertension has been documented in two horses with chronic renal disease and hypertensive cardiomyopathy (Navas de Solis *et al*. 2013). While hypertensive cardiomyopathy had not developed in this gelding, his arterial blood pressure was likely elevated at presentation associated with the azotaemia. Post-mortem examination revealed severe renal membranous glomerulopathy with chronic interstitial fibrosis and interstitial nephritis. Measurement of arterial blood pressure is indicated in horses with moderate to severe renal disease.

The authors speculate that fluid overload may have played a role in elevating the arterial blood pressures, and the subsequent aortic root rupture. While RSoV rupture is much more common in males, pregnancy and the associated volume expansion resulting in increased cardiac output is a risk factor for RSoV and aortic dissection in women (Kamel *et al*. 2016; Marroush *et al*. 2018).

The exercise right before the gelding exhibited clinical signs may also have elevated his arterial blood pressures.

Exercise is a common precipitating event in horses that develop an ACF (Rooney *et al*. 1967; Lester *et al*. 1992; Marr *et al*. 1998). Rooney originally postulated that the rupture of the RSoV occurred due to greatly elevated blood pressures during breeding (Rooney *et al*. 1967). Systemic hypertension occurs in exercising horses, even with brief strenuous exercise (Masri *et al*. 1990). Systolic blood pressure increases more than diastolic pressure (Munoz *et al*. 2016). In humans, physical activity also commonly precedes the development of RSoV rupture (Goldberg and Krasnow 1990). The additional elevation of systemic arterial pressure associated with exercise, coupled with the likely pre-existing renal hypertension, fluid overload, moderate aortic regurgitation and an enlarged aortic root may have led to its disruption. This combination may have resulted in elevations of pressure in the enlarged aorta root that it was unable to withstand.

The authors describe marked enlargement of the left atrium that was detected when the gelding demonstrated clinical signs of congestive heart failure (CHF). The acute onset of CHF associated with the RSoV rupture is uncommon (Rooney *et al*. 1967; Roby *et al*. 1986; Vernemmen *et al*. 2019). CHF often develops weeks, months or years later secondary to the chronic volume overload associated with the left to right shunt. New-onset aortic regurgitation or worsening of pre-existing aortic regurgitation can occur with RSoV rupture if the aortic root becomes unstable (Golzari and Riebman 2004; Javsicas *et al*. 2010). Although degenerative aortic valve disease was reported in this gelding, there was no history of any murmur prior to presentation. Once the ACF occurred, no worsening of the aortic regurgitation was reported and there was no increase in left ventricular size. There also was no aortic root disease found at post-mortem examination.

It is likely that the CHF was precipitated by the aggressive fluid administration. RSoV rupture into the interventricular septum, without communication with any cardiac chamber, is not usually associated with the acute CHF (Rooney *et al*. 1967; Marr *et al*. 1998; Sleeper *et al*. 2001). If the ACF caused the CHF, a large shunt between the aorta and one of the cardiac chambers should be present, as was seen in the mare reported by Roby *et al*. (1986). There was no communication between the aorta and any of the cardiac chambers in this case. There was 5 L of pleural fluid in the thoracic cavity consistent with CHF. The arterial hypoxaemia was most likely due to pulmonary oedema that developed from hyperhydration. Unfortunately, the lungs were not examined because the horse had a limited cosmetic necropsy.

It is also interesting to speculate about the role that the prior administration of levothyroxine sodium powder may have had in this case. Elevated doses of levothyroxine sodium administered for 14 days resulted in marked increases in total thyroxine concentrations in horses (Bertin *et al*. 2019). Hypertension is associated with hyperthyroidism in humans and small animals, and this is likely to be the case in the horse. Increased cardiac output is the underlying mechanism for isolated systolic hypertension (Prisant *et al*. 2006). Widened pulse pressures occur with hyperthyroidism associated with decreased peripheral vascular resistance (Prisant *et al*. 2006). Although clinical hyperthyroidism has not been reported in horses supplemented with levothyroxine sodium powder to the author's knowledge, this possibly could have contributed to the horse's systolic hypertension.

The poor outcome was likely due to the combination of renal failure, fluid overload, severe hypertension and the development of CHF. In humans, renal dialysis patients have a poorer outcome when they have concurrent CHF or fluid overload than when those co-morbidities are absent (Banerjee *et al*. 2007). This case is fascinating due to all the co-morbidities that could have contributed to the development of ACF and sheds light on the possible pathophysiology.

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References

Baker, R.E., Schlipf, J.W. Jr, Scollan, K.F., LeBlanc, N.L. and Russell, D.S. (2021) In-hospital development of an aorto-cardiac fistula in a Warmblood gelding with chronic renal disease. *Equine Vet. Educ.* **33**, 184. https://doi.org/10.1111/eve.13163

Banerjee, D., Ma, J.Z., Collins, A.J. and Herzog, C.A. (2007) Long-term survival of incident hemodialysis patients who are hospitalized for congestive heart failure, pulmonary edema, or fluid overload. *Clin. J. Am. Soc. Nephrol.* **2**, 1186-1190.

Bertin, F.R., Eichstadt Forsythe, L. and Kritchevsky, J.E. (2019) Effects of high doses of levothyroxine sodium on serum concentrations of triiodothyronine and thyroxine in horses. *Am. J. Vet. Res.* **80**, 565-571.

Cornelisse, C.J., Schott, H.C. 2nd, Olivier, N.B., Mullaney, T.P., Koller, A., Wilson, D.V. and Derksen, F.J. (2000) Concentration of cardiac troponin I in a horse with a ruptured aortic regurgitation jet lesion and ventricular tachycardia. *J. Am. Vet. Med. Assoc.* **217**, 231-235.

Eknoyan, G. (2004) On the central role of studies on the kidney in the recognition, conceptual evolution, and understanding of hypertension. *Adv. Chronic Kidney. Dis.* **11**, 192-196.

Fennich, H., Doghmi, N., Rim, F., Belhaj, S., Cheikhi, F. and Cherti, M. (2018) Spontaneous rupture of right aortic sinus of Valsalva leading to massive cystic dissection of interventricular septum and complete heart block. *Echocardiography* **35**, 2109-2112.

Goldberg, N. and Krasnow, N. (1990) Sinus of Valsalva aneurysms. *Clin. Cardiol.* **13**, 831-836.

Golzari, M. and Riebman, J.B. (2004) The four seasons of ruptured sinus of Valsalva aneurysms: case presentations and review. *Heart Surg. Forum* **7**, E577-E583.

Horn, J., Marr, C.M., Elliott, J. and Pfeiffer, D.U. (2002) Identification of prognostic factors in equine aortic insufficiency. *J. Vet. Intern. Med.* **16**, 335.

Javsicas, L.H., Giguère, S., Maisenbacher, H.W., Schmidt, M., Frederick, J.D., Conway, J.A. and Estrada, A.H. (2010) Percutaneous Transcatheter Closure of an Aorto-Cardiac Fistula in a Thoroughbred Stallion Using an Amplatzer Occluder Device. *J. Vet. Intern. Med.* **24**, 994-998.

Kamel, H., Roman, M.J., Pitcher, A. and Devereux, R.B. (2016) Pregnancy and the risk of aortic dissection or rupture. *Circulation* **134**, 527-533.

Lester, G.D., Lombard, C.W. and Ackerman, N. (1992) Echocardiographic detected of a dissecting aortic root aneurysm in a Thoroughbred stallion. *Vet. Radiol. Ultrasound.* **33**, 202-205.

Marr, C.M. (2010) Cardiac murmurs: valvular regurgitation and insufficiency. In: *Cardiology of the Horse*, 2nd edn., Ed: C.M. Marr and I.M. Bowen, Saunders Elsevier, London.

Marr, C.M., Reef, V.B., Brazil, T.J., Thomas, W.P., Knottenbelt, D.C., Kelly, D.F., Baker, J.R., Reimer, J.M., Maxson, A.D. and Crowhurst, J.S. (1998) Aorto-cardiac fistulas in seven horses. *Vet. Radiol. Ultrasound.* **39**, 22-31.

Marroush, T.S., Boshara, A.R., Botros, B., Vendittelli, P., Ahmed, Z., Dawood, L. and Rosman, H.S. (2018) Rupture of sinus of Valsalva aneurysm: two case reports and a concise review of the literature. *Heart Lung* **47**, 131-135.

Masri, M., Freestone, J.F., Wolfsheimer, K.J. and Shoemaker, K. (1990) Alterations in plasma volume, plasma constituents, renin activity and aldosterone induced by maximal exercise in the horse. *Equine Vet. J.* **22**, *Suppl.* **9**, 72-77.

Mulè, G., Nardi, E., Morreale, M., Castiglia, A., Geraci, G., Altieri, D., Cacciatore, V., Schillaci, M., Vaccaro, F. and Cottone, S. (2017) The relationship between aortic root size and hypertension: an unsolved conundrum. In: *Hypertension: From Basic Research to Clinical Practice*, Ed: M.S. Islam, Cham, Springer International Publishing. pp 427-445.

Munoz, A., Esgueva, M., Gomez-Diez, M., Serrano-Caballero, J.M., Castejon-Riber, C. and Serrano-Rodriguez, J.M. (2016) Modulation of acute transient exercise-induced hypertension after oral administration of four angiotensin-converting enzyme inhibitors in normotensive horses. *Vet. J.* **208**, 33-37.

Navas de Solis, C., Slack, J., Boston, R.C. and Reef, V.B. (2013) Hypertensive cardiomyopathy in horses: 5 cases (1995-2011). *J. Am. Vet. Med. Assoc.* **243**, 126-130.

Norman, T.E., Achen, S.E., Coleman, M.C. and Schroeder, J.D. (2010) What is your diagnosis? Ruptured right aortic sinus (sinus of Valsalva) aneurysm, valvular endocarditis, and cardiac volume overload with early failure. *J. Am. Vet. Med. Assoc.* **237**, 1371-1372.

Prisant, L.M., Gujral, J.S. and Mulloy, A.L. (2006) Hyperthyroidism: a secondary cause of isolated systolic hypertension. *J. Clin. Hypertens. (Greenwich)* **8**, 596-599.

Reef, V.B. (1995) Heart murmurs in horses: determining their significance with echocardiography. *Equine Vet. J.* **27**, *Suppl.* **19**, 71-80.

Reef, V.B. and Spencer, P. (1987) Echocardiographic evaluation of equine aortic insufficiency. *Am. J. Vet. Res.* **48**, 904-909.

Reef, V.B., Klumpp, S., Maxson, A.D. and Sweeney, R.W. (1990) Echocardiographic detection of an intact aneurysm in a horse. *J. Am. Vet. Med. Assoc.* **197**, 752-755.

Reef, V.B., Bonagura, J., Buhl, R., McGurrin, M.K.J., Schwarzwald, C.C., van Loon, G. and Young, L.E. (2014) Recommendations for management of equine athletes with cardiovascular abnormalities. *J. Vet. Intern. Med.* **28**, 749-761.

Roby, K.A., Reef, V.B., Shaw, D.P. and Sweeney, C.R. (1986) Rupture of an aortic sinus aneurysm in a 15-year-old broodmare. *J. Am. Vet. Med. Assoc.* **189**, 305-308.

Rooney, J.R., Prickett, M.E. and Crowe, M.W. (1967) Aortic ring rupture in stallions. *Pathol. Vet.* **4**, 268-274.

Sleeper, M.M., Durando, M.M., Miller, M., Habecker, P.L. and Reef, V.B. (2001) Aortic root disease in four horses. *J. Am. Vet. Med. Assoc.* **219**, 491-496, 459.

Stadler, P., Hoch, M., Fruhauf, B. and Deegen, E. (1995) Echocardiography in horses with and without heart murmurs in aortic regurgitation. *Pferdeheilkunde* **11**, 373-383.

Ven, S., Decloedt, A., Van Der Vekens, N., De Clercq, D. and van Loon, G. (2016) Assessing aortic regurgitation severity from 2D, M-mode and pulsed wave Doppler echocardiographic measurements in horses. *Vet. J.* **210**, 34-38.

Vernemmen, I., De Clercq, D., Decloedt, A., Schauvliege, S., Taeymans, Y., De Wolf, D. and van Loon, G. (2019) Percutaneous transcatheter closure of an aorto-cardiac fistula in a six-year-old Warmblood mare with atrial fibrillation. *J. Vet. Cardiol.* **24**, 78-84.

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Case Report

Bilateral Morgagni hernia in a donkey

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Keywords: horse; colic; diaphragm; hernia; mesh

Summary

A 2-year-old 150 kg donkey was presented for evaluation of colic. For the last 8 months, the donkey had been showing intermittent colic without a precise diagnosis. Medical treatment was usually sufficient to resolve the colic episodes. This time, signs of colic persisted and the donkey was referred to the clinic. The donkey showed moderate signs of abdominal pain with mild tachycardia (54 beats/min) and tachypnoea (28 breaths/min). Borborygmi were decreased on abdominal auscultation. Abdominal radiography showed a rounded structure of granular opacity within the caudo-ventral part of the thorax, overlapping with and causing border effacement of the cardiac silhouette and diaphragmatic *crus* (**Fig 1**). Those findings were confirmed by trans-parietal abdominal and thoracic ultrasonography. A presumptive diagnosis of diaphragmatic hernia was established and an emergency exploratory laparotomy was performed. Abdominal exploration confirmed the presumptive diagnosis of diaphragmatic hernia with the presence of the sternal and diaphragmatic flexures of the ascending colon as well as the left hepatic lobe in a central diaphragmatic defect. The incarcerated segment of the colon was removed from the diaphragmatic defect and exteriorised. The central tendinous portion of the diaphragm was bilaterally absent. The diaphragm only showed muscular margins around the entire circumference of the thorax. The edges of the defect were smooth and a large hernial sac (Morgagni/retrosternal hernia) was present preventing direct communication between the abdominal and thoracic cavities (**Fig 2**). The size of the defect did not allow closure with sutures, and a polyester mesh was implanted to cover it. The mesh was doubled and laid over the defect, before securing it to the hernia ring using a skin stapler. The greater omentum was resected in order to cover the mesh and was also secured with skin staples. The donkey recovered from anaesthesia without complications.

Afterwards, the donkey returned gradually onto full feed without any significant complications. Post-operative radiographs showed a fluid-filled cavitary lesion at the previous location of the herniated large colon. Ultrasonography confirmed the liquid content of the intrathoracic collection, which was interpreted as fluid-filled dead space of the hernial sac secondary to mesh porosity. There was no recurrence of large colon herniation. Pleural effusion progressively resolved, but the fluid-filled hernial sac remained unchanged. Eight months after discharge, the donkey is still alive and has not developed further signs of abdominal pain since its discharge from the hospital.

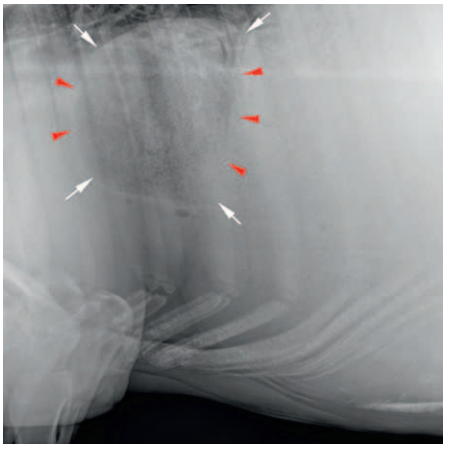

Fig 1: Latero-lateral radiograph of the caudo-ventral thoracic and cranio-ventral abdominal areas. The large granular structure (white arrows) causing border effacement of the diaphragmatic crus and cardiac silhouette (red arrowheads) is the herniated colon.

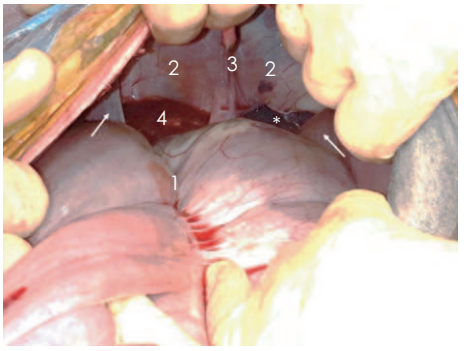

Fig 2: Intraoperative view (after removal of the large intestine) of the large diaphragmatic defect with round margins (arrows), which allowed the partial migration of liver and the sternal and diaphragmatic flexures of the ascending colon from the abdomen into the thorax. Note the presence of the migrated lobe of the liver (white*). 1: Large colon. 2: Hernia sac. 3: Band of hernia sac covering the oesophagus. 4: Fluid accumulated into the hernia sac.

Key points

- Morgagni hernias are rare conditions in equids.
- Clinical signs are often nonspecific but horses usually show intermittent signs of colic.
- Prognosis for Morgagni hernias appears to be favourable.

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Case Report

Removal of a metallic foreign body from the tongue of three horses

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Keywords: horse; tongue; metallic foreign body; laparoscopic instruments; hypersalivation

The presence of a deeply located foreign body in the tongue of a horse is rare because horses usually select their food carefully. The diagnosis and treatment of a foreign body in the tongue can be challenging because of the potentially small size of the object and the possibility of deep penetration without an obvious entry wound. Clinical signs often will include anorexia, a swollen tongue, hypersalivation, transient lingual paralysis, dysphagia, dehydration, halitosis and fever. Differential diagnoses include dental disease, oral soft tissue lacerations or inflammation, sialoadenitis, and fractures of the mandible or maxilla.

This case series describes the clinical presentation, diagnostic evaluation, surgical treatment, post-operative management and outcome of three adult horses with deeply located metallic foreign bodies in the tongue. The horses were presented for evaluation and treatment of dysphagia and marked hypersalivation of 3–5 days duration. Radiographs of the head revealed the presence of a metallic foreign body in the tongue of each horse. The foreign bodies could be precisely localised under general anaesthesia using palpation and lingual ultrasonography and/or lingual radiography in combination with a forceps as a marker. The foreign bodies were successfully removed using laparoscopic instruments, creating minimal soft tissue trauma. The use of long (43 cm) small laparoscopic (5 mm) instruments enabled a precise surgical manoeuvre and good visualisation of the surgical field, providing optimal conditions for successful minimally invasive surgical treatment of horses with foreign bodies in the tongue. The tongue was left unsutured for second-intention wound healing. The three horses made an uneventful recovery and 12 months after surgery were eating normally and could be ridden with a bit as per usual routine. Depending on the suspected location of a foreign body in the tongue, different approaches are described for its removal. It can be removed in the recumbent anaesthetised or in the standing sedated horse, using an intra-oral lingual or a ventral inter-mandibular approach. General anaesthesia allows for a more thorough oral examination, caudal parts of the tongue are more easily accessible, and manipulation of the immobile tongue is easier. When the foreign body is located within the body of the tongue, a lingual approach is preferred (**Fig 1**).

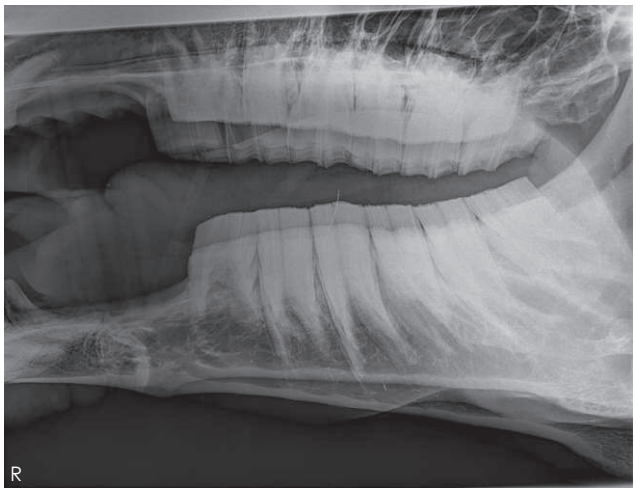

Fig 1: Case 1: Lateral radiograph of the mandibular cheek teeth with the mouth displaced open: an approximately 3.5 cm long sewing needle in the body of the tongue is seen at the level of the 308/408 teeth.

Key points

- Clinical signs of a foreign body in the tongue include anorexia, a swollen tongue, hypersalivation, transient lingual paralysis, dysphagia, dehydration, halitosis and fever.
- Use of long (43 cm) laparoscopic (5 mm) instruments in combination with palpation, ultrasonography and/or radiography allows removal of the foreign body with minimal soft tissue trauma.
- The tongue wound is left unsutured for second-intention wound healing.

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Case Report

Intramural jejunal leiomyoma as a cause of colic

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Keywords: horse; leiomyoma; colic; surgery; sporthorse

A 15-year-old Thoroughbred gelding showjumper was examined in the field for mild colic signs of 4-h duration. He had a previous history of chronic mild colic episodes beginning about 3 months prior to presentation, which occurred every 3 weeks until just prior to presentation when its frequency increased to weekly. He was referred to the authors' clinic after nasogastric intubation with mineral oil and rectal examination revealing dilated small intestines, and due to refractory pain despite numerous sedatives.

On presentation at the referral facility, the gelding was initially quiet, without overt signs of pain. His rectal temperature was 37.9°C, with a heart rate of 40 beats/min and respiratory rate of 16 breaths/min. His mucous membranes were dark pink with a capillary refill time of 1 s. Gastrointestinal sounds were absent on both sides of the abdomen. Rectal examination revealed dilated small intestines and gas distension of the large colon. A nasogastric tube was passed, and no net reflux was obtained. With mild lavage, a small amount of mineral oil and hay material was obtained. Transabdominal ultrasonography revealed moderately dilated (4–5 cm diameter), nonmotile small intestinal loops with frequent sediment lines and an enlarged, fluid-filled stomach suspected to be the previously administered mineral oil. Mural wall thickness was normal throughout, and no other abnormalities of the small intestine were identified. A scant amount of hypoechoic peritoneal fluid was noted.

Haematological evaluation was within normal limits except for a PCV of 40% suggestive of mild haemoconcentration. A biochemistry profile revealed hyperalbuminaemia (33 g/L rr 19–32) and a total protein (TP) of 70 g/L, further supporting concerns for mild haemoconcentration. Blood lactate was normal (0.9 mmol/L), and abdominocentesis yielded grossly normal peritoneal fluid with a lactate of 2.0 mmol/L. There was not enough fluid sample obtained for further analyses. Due to the hemoconcentration and relatively small disparity between abdominal and peripheral lactate levels, rehydration was discussed and elected with serial sampling of blood and peritoneal fluid for comparative lactate monitoring. Four hours after presentation, the gelding became acutely painful and complete ileus was diagnosed on transabdominal ultrasonography. Repeat abdominocentesis at this time identified serosanguineous fluid with a lactate of 4.7 mmol/L and a total protein of 26 g/L. Due to the worsening abdominal lactate and his failure to respond to medical management, an exploratory laparotomy was recommended.

Routine exploration of the abdomen revealed diffusely distended small intestine. Further examination of the small intestine revealed a 15-cm intramural mass in the distal jejunum, approximately 3 m orad to the ileum. A resection and anastomosis were performed to remove the mass with 12 cm margins of grossly normal jejunum orad and aborad to the mass. The abdomen was closed, and the gelding recovered from anaesthesia with no complications. The immunohistochemistry results confirmed the presumptive diagnosis of a gastrointestinal leiomyoma, and the lack of KIT immunoreactivity ruled out a gastrointestinal stromal tumour (GIST).

At one year post-operatively, follow-up with the owner revealed that the patient had returned to normal jumping athletic activities with no further colic signs or complications related to the procedure.

Leiomyomas are benign tumours of mesenchymal origin. They arise from smooth muscle cells and are most common in the uterus and gastrointestinal tract. When located intraluminally, these should only cause signs of severe colic if they grow large enough to obstruct. An intraluminal leiomyoma should be a differential for small intestinal obstruction especially in horses with a history of chronic and recurrent colic.

Key points

- Leiomyomas are benign tumours of mesenchymal origin that can occur throughout the gastrointestinal tract of horses.
- Leiomyomas must be differentiated from gastrointestinal stromal tumours by the lack of KIT immunoreactivity on immunohistochemistry.
- Small intestinal leiomyomas should be a differential for a horse with a history of chronic colic and warrants a thorough ultrasound examination of the gastrointestinal tract.

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Case Report

Caeco-caecal and caeco-colic intussusception in two half-sibling Standardbred horses

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Keywords: horse; caeco-caecal; caeco-colic; intussusception; caecum; caecal dysmotility

Summary

This report describes caecal intussusception in two 2-year-old half-sibling (same dam) Standardbred horses. Both horses had recently been brought into race work during the 6–12 weeks preceding hospital admission. The two siblings presented 12 months apart: both horses demonstrated signs of low-grade abdominal pain that did not resolve with administration of analgesia (flunixin meglumine [1.1 mg/kg bwt i.v.], xylazine [0.5 mg/kg bwt i.v.] and butorphanol [0.01 mg/kg bwt i.v.]). Case 1 (colt) had been showing signs of abdominal discomfort for 36 h prior to presentation to the hospital, and similar signs had intermittently been present for the preceding 6 weeks. Signs of abdominal discomfort in Case 2 (filly) had been present for approximately 2 h at the time of presentation. Sonographic examination of the abdomen in Case 1 identified a 'target sign' lesion, shown in longitudinal section in **Fig 1**, consistent with intussusception of the large intestine and marked mural thickening of the involved segments. Palpation per rectum revealed a firm mass in the right caudal abdomen. Sonographic examination of the abdomen and palpation per rectum in Case 2 did not identify any abnormalities. Both horses remained haemodynamically stable despite ongoing signs of abdominal pain and tachycardia. Exploratory celiotomy was undertaken in both horses due to persistent abdominal pain and a poor response to administration of analgesic medications. Exploration of the abdomen revealed caeco-colic intussusception in Case 1 and caeco-caecal intussusception in Case 2. In both horses, the intussusception was able to be manually reduced without performing a caecotomy or colotomy. The intussusceptum was deemed viable in both cases, negating the need for resection. The horses recovered uneventfully from surgery. At 12 weeks post-surgery, both horses had recovered without development of complications. Approximately 36 and 18 months post-operatively, respectively, Case 1 had won four races from 13 starts and Case 2 returned in training but had not yet raced. At the time of writing, these were the only two cases of caecal intussusception identified by this hospital in 10 years. An underlying cause for caecal dysfunction and subsequent intussusception was not identified in either horse. Quantification of endoparasite burden was not performed in either horse, and information regarding anthelmintic resistance on the farm was not available. Managerial factors including but not limited to diet, exercise regimen and inadequate endoparasite management or the development of anthelmintic resistance on this farm could be responsible for the development of this condition in two closely related animals. However, a familial predisposition, as occurs in human children with intussusceptions, cannot be ruled out given the low prevalence of caeco-caecal and caeco-colic intussusceptions in the current hospital population and over-representation of young Standardbred horses in reports of these conditions.

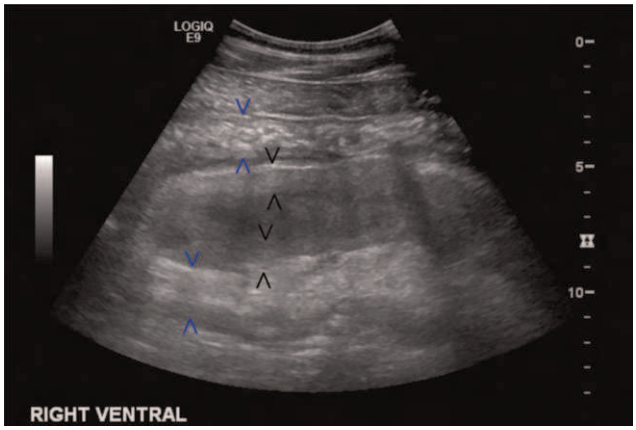

Fig 1: Abdominal sonogram obtained ventrally on the right side from Case 1. Two mural surfaces of an intussusception are present. The blue arrow depicts the mural surface of the intussuscepiens and the black arrow depicts the mural surface of the intussusceptum.

Key points

- A familial predisposition to intussusception involving the caecum, as occurs in human children with intussusception cannot be ruled out.
- The prognosis for return to athletic function is good in cases where manual reduction in the intussusception is successful.
- The signalment of the two horses reported here, being young Standardbreds, is in line with other reports in which young Standardbreds are over-represented.

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Original Article

Trends in the management of horses referred for evaluation of colic: 2004–2017

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Keywords: horse; colic

Summary

The financial crisis of 2008 had effects on veterinary practice, with falling turnovers associated with reluctance of owners to spend money on veterinary care. There were anecdotal reports that fewer horses were undergoing colic surgery. The aims of this study were to document the numbers of horses with colic being referred to, and undergoing surgery and/or euthanasia, at two equine hospitals (a university based equine hospital in the United States [NC State] and a private equine hospital in the UK [Bell Equine]) over a 14-year period (2004–2017). There was a trend of declining total yearly equine accessions at NC State starting in 2009, followed by an increase starting in 2012. At Bell Equine, total accessions showed an increasing trend from 2004 to 2015, followed by a slight decline in 2016 and 2017. The proportion of equine accessions that were colics varied from around 15% to 20% at both hospitals and did not show any notable variations over the time period studied. Both practices showed a trend of decreasing colic admissions undergoing and recovering from surgery starting from 2007 to 2008. The numbers and percentages of colic admissions that were subjected to euthanasia increased from 2004/2005 to 2014/2015 in both hospitals; there was a greater increase in numbers being subjected to euthanasia at surgery at NC State, compared to a greater increase in numbers being subjected to euthanasia without surgery at Bell Equine. At both hospitals, there was a trend of increasing mean invoice totals over the study period. The results show that there has been a trend of decreasing numbers of horses undergoing surgical treatment for colic since 2004/2005. This is likely to be, at least partly, due to the financial crisis of 2008, although other factors, including the high costs of surgery and the ageing equine population may also be important.

Introduction

The financial crisis of 2008 had significant effects on veterinary practice, including the equine veterinary sector, with falling turnovers associated with reluctance of horse-owners to spend money on veterinary care of their animals, including referrals to equine hospitals for surgery (Osborne 2009). The effects of the recession on veterinary practice were recognised for several years until a general improvement in veterinary business was appreciated around 2015 (Moser 2015). Gastrointestinal diseases are common in horses and constitute the commonest reason for emergency admission to equine referral hospitals (Dolente *et al.* 2008). Although there have been significant improvements in the standards of care and survival rates of colic surgery, it remains major and expensive surgery, with significant risks of complications, some of which are life-threatening (French *et al.* 2002; Mair and Smith 2005a,b,c; Moore 2005; Proudman *et al.* 2005; Muñoz *et al.* 2008; Dukti and White 2009). Around the time of the financial crisis of 2008, a number of equine hospitals reported decreasing numbers of horses undergoing colic surgery. This was assumed to have been a direct result of the prevailing economic conditions, although other factors such as an ageing horse population (Brosnahan and Paradis 2003; Wylie *et al.* 2013; Welsh *et al.* 2016) may have influenced the decision of horse-owners to commit to expensive treatments for their animals.

The purpose of this study was to record the numbers of horses undergoing colic surgery at two equine referral hospitals, one a university teaching hospital in the United States (North Carolina State University [NC State]) and one a private equine hospital in the UK (Bell Equine Veterinary Clinic [Bell Equine]). We aimed to document the numbers of horses with colic being referred to, and undergoing surgery and/or euthanasia, at the two equine hospitals over a 14-year period (2004–2017), which included the period of the financial crisis of 2008.

Materials and methods

Caseloads were compared between a university practice in the United States (NC State) and a private referral practice in the UK (Bell Equine). The total number of horses referred yearly (2004–2017) to the hospitals (equine accessions) and the number of horses examined and treated for colic were retrieved from the hospitals' medical records. Horses with colic were assigned to one of four groups: medical colic, surgical treatment with recovery from anaesthesia, surgical exploration with intraoperative euthanasia or euthanasia without surgery. In addition, financial data relating to the total invoice for each case were recorded. Simple descriptive statistics (means) were used to summarise the financial results.

Results

The yearly numbers of equine accessions and colic admissions are summarised in **Table 1** and **Figures 1** and **2**. The yearly equine accessions ranged from 1172 to 1698 for NC State, and 764 to 1045 for Bell Equine. There was a trend of declining total yearly equine accessions at NC State starting in 2009, followed by a trend of increasing numbers of yearly accessions starting in 2012. This trend was not observed at Bell Equine, where total accessions showed a trend of

increasing numbers from 2004 to 2015, followed by a slight decline in 2016 and 2017. The yearly admissions of colics (all groups) ranged from 196 to 301 for NC State, with a trend of decreasing numbers from 2009 to 2010, followed by variable yearly numbers thereafter and a mild increase in 2017 (the year with the lowest total colic admissions was 2015). The total number of colic admissions at Bell Equine showed less variation, ranging from 144 to 184 with the lowest numbers in 2008 and 2012. The proportion of the total equine accessions that were colics varied from around 15%–20% at both hospitals and did not show any notable variations or trends over the time period studied (**Table 2**).

The numbers of medically treated colics varied over the study period at both hospitals with apparent troughs in 2009 and 2015 at NC State; at Bell Equine, there was a trend for increasing numbers of medically treated colics until a peak in 2015. Both practices showed a trend of decreasing colic admissions undergoing and recovering from surgery starting from 2007 to 2008 (**Fig 3**). The maximum and minimum numbers of horses undergoing colic surgery and recovering from anaesthesia were 78 (2006) and 32 (2010) for NC State, and 84 (2004) and 32 (2015) for Bell Equine. The numbers of horses undergoing surgery that were recovered at both hospitals showed a mild increase in 2017, but these numbers were not as high as the numbers at the start of the study period. The percentages of the total colic admissions that underwent surgery and recovered from anaesthesia showed similar trends (**Table 2**). At the start of the study period, the percentage of the total number of colic admissions to NC State that underwent surgery and were recovered was approximately 28–30%, but at the end of the study period this percentage was approximately 18–21%. At Bell Equine, the percentage of the total number of colic admissions that underwent surgery and were recovered was approximately

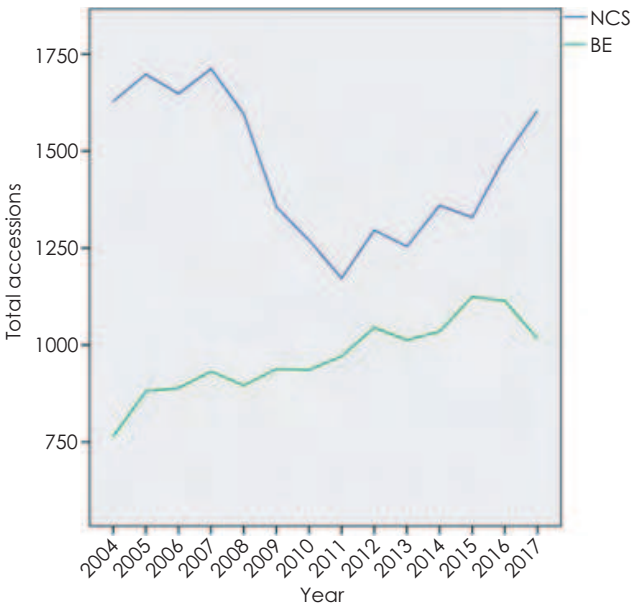

Fig 1: Total numbers of equine accessions at North Carolina State University (NCS) (blue) and Bell Equine Veterinary Clinic (BE) (green) 2004-2017.

TABLE 1: Total number of equine accessions and numbers of horses with colic examined at NC State and Bell Equine 2004–2017

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
NC State														
Total equine accessions	1628	1698	1648	1712	1596	1356	1270	1172	1296	1254	1360	1329	1484	1605
Total number of colic admissions	266	257	301	274	266	228	197	235	238	220	207	196	234	261
Number of colic cases medically managed that were discharged to home	141	121	151	130	143	102	122	115	138	120	106	88	112	154
Number of colic cases treated surgically and recovered from anaesthesia	75	76	78	71	62	65	32	62	38	43	45	53	42	56
Number of colic cases undergoing surgery and subjected to euthanasia during surgery	20	27	34	36	29	42	27	33	39	39	31	28	27	19
Number of colic cases subjected to euthanasia only	30	33	38	37	32	19	16	25	23	18	25	27	53	32
Bell Equine														
Total equine accessions	764	881	889	932	896	938	936	971	1045	1013	1035	1124	1114	1016
Total number of colic admissions	150	162	151	154	133	151	164	163	144	173	158	184	168	173
Number of colic cases medically managed that were discharged to home	52	69	67	77	67	70	83	96	72	92	90	115	105	104
Number of colic cases treated surgically and recovered from anaesthesia	84	80	68	62	52	58	50	34	36	54	37	32	31	38
Number of colic cases undergoing surgery and subjected to euthanasia during surgery	10	10	14	9	7	8	16	12	12	11	8	13	9	10
Number of colic cases subjected to euthanasia only	4	3	2	6	7	15	15	21	24	16	17	24	23	21

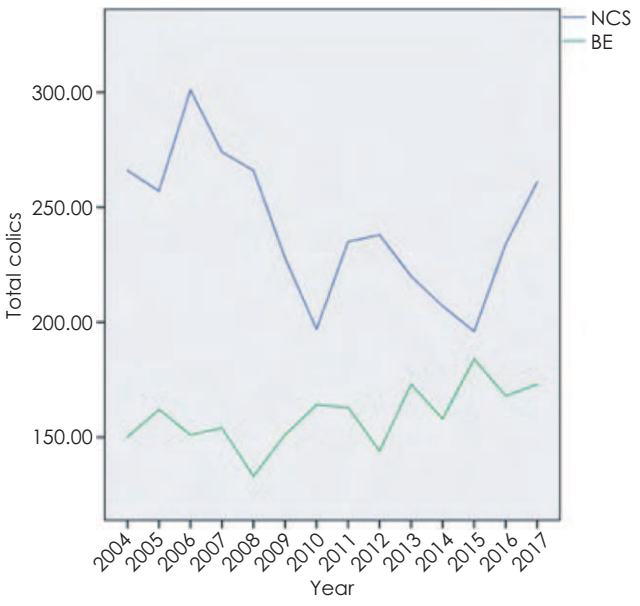

Fig 2: Total number of equine colic admissions at North Carolina State (NCS) (blue) and Bell Equine Veterinary Clinic (green) 2004-2017.

50–56% in 2004-2005, compared to approximately 18–22% in 2016–2017. The percentage of horses that were taken to surgery and subjected to euthanasia under anaesthesia was higher at NC State than Bell Equine in every year of the study period (**Table 2**).

The numbers and percentages of colic admissions that were subjected to euthanasia (either at surgery or without surgery) increased from 2004/2005 to 2014/2015 in both hospitals (**Fig 4**). The number of colics that were subjected to euthanasia peaked in 2016 at NC State (34.1% of total colic admissions were subjected to euthanasia) and 2015 at Bell Equine (27.0% of total colic admissions were subjected to euthanasia). The trends in numbers of horses being subjected to euthanasia were different at the two hospitals, with a greater increase in numbers being subjected to euthanasia at surgery at NC State, compared to a greater increase in numbers being subjected to euthanasia without surgery at Bell Equine. The percentage of the total number of colics being subjected to euthanasia at surgery ranged from 7.5 to 18.4% (NC State) and 5.1 to 9.7% (Bell Equine), and the percentage subjected to euthanasia without surgery ranged from 8.1 to 22.6% (NC State) and 1.3 to 16.7% (Bell Equine) (**Table 2**). At NC State, the percentage of horses that were taken to surgery but subjected to euthanasia under

TABLE 2: Colic admissions to NC State and Bell Equine from 2004 to 2017 expressed as percentages of total equine accessions and percentages of colic admissions

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
NC State %														
Colic admissions as a percentage of total equine accessions	16.3	15.1	18.3	16.0	16.7	16.8	15.5	20.1	18.4	17.5	15.2	14.7	15.8	16.3
Percentage of total colic cases treated medically	53.0	47.1	50.2	47.4	53.8	44.7	61.9	48.9	58.0	54.5	51.2	44.9	47.9	59.0
Percentage of total colic cases treated surgically and recovered from anaesthesia	28.2	29.6	25.9	25.9	23.3	28.5	16.2	26.4	16.0	19.5	21.7	27.0	17.9	21.5
Percentage of total colic cases undergoing surgery and subjected to euthanasia during surgery	7.5	10.5	11.3	13.1	10.9	18.4	13.7	14.0	16.4	17.7	15.0	14.3	11.5	7.3
Percentage of surgical colic cases subjected to euthanasia during surgery	21	24	30	34	22	39	46	55	31	48	41	34	39	25
Percentage of total colic cases subjected to euthanasia without surgery	11.3	12.8	12.6	13.5	12.0	8.3	8.1	10.6	9.7	8.2	12.1	13.8	22.6	12.3
Bell Equine %														
Colic admissions as a percentage of total equine accessions	19.6	18.4	17.0	16.5	14.8	16.1	16.1	16.8	13.8	17.1	15.3	16.4	15.1	17.0
Percentage of total colic cases treated medically	34.7	42.6	44.4	50.0	50.4	46.4	50.1	58.9	50.0	53.2	60.8	62.5	62.5	60.1
Percentage of total colic cases treated surgically and recovered from anaesthesia	56.0	49.4	45.0	40.2	39.1	38.4	30.1	20.8	25.0	31.2	23.4	17.4	18.5	22.0
Percentage of total colic cases undergoing surgery and subjected to euthanasia during surgery	6.6	6.2	9.3	5.8	5.3	5.3	9.7	7.4	8.3	6.4	5.1	7.1	5.4	5.8
Percentage of surgical colic cases subjected to euthanasia during surgery	11	11	23	13	12	12	24	26	25	17	18	29	22	21
Percentage of total colic cases subjected to euthanasia without surgery	2.7	1.8	1.3	3.9	5.3	9.9	9.3	12.9	16.7	9.2	10.8	13.0	13.7	12.1

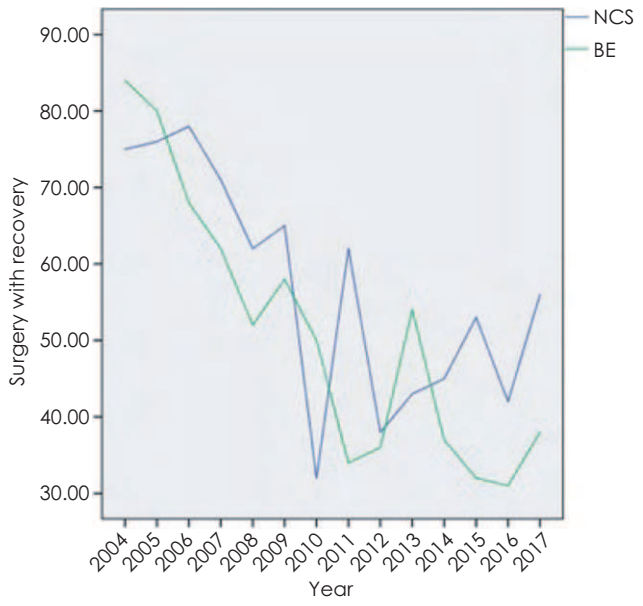

Fig 3: Numbers of horses with colic undergoing surgery and recovering from anaesthesia at North Carolina State University (NCS) (blue) and Bell Equine Veterinary Clinic (BE) (green) 2004-2017.

anaesthesia showed an increasing trend from the start of the study period (21% in 2004), peaking at around 2010-2013 (peak of 55% in 2011), followed by a decreasing trend (25% in 2017). At Bell Equine, the percentage of horses being taken to surgery but subjected to euthanasia under anaesthesia was more variable (11% in 2004 and 2005, followed by a variable increase with a peak of 29% in 2015).

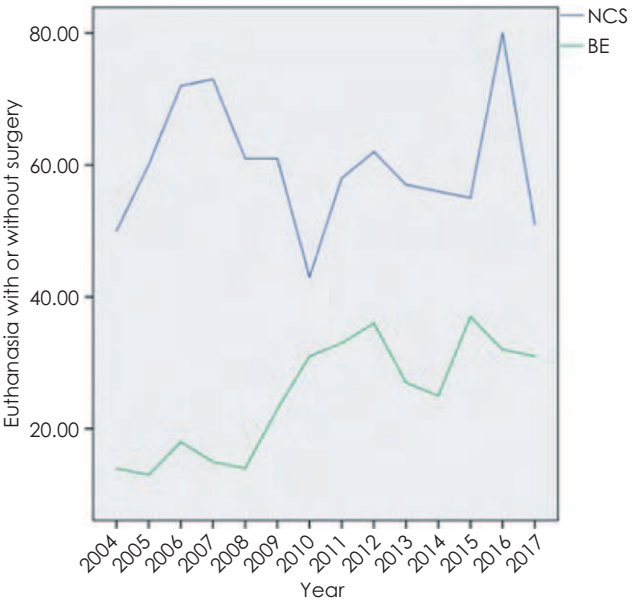

Fig 4: Numbers of horses admitted with colic that were subjected to euthanasia (with or without surgery) at North Carolina State University (NCS) (blue) and Bell Equine Veterinary Clinic (BE) (green) 2004-2017.

Mean invoice totals for colics admitted to the two hospitals over the study period are shown in **Table 3**. For all categories of colic treated at both hospitals, there was a trend of increasing costs over the study period.

Discussion

Although there are differences in the results between the two hospitals, there were similar trends in the numbers of horses with colic undergoing surgery with recovery from anaesthesia, euthanasia during surgery and euthanasia without surgery. The results show that there has been a trend of decreasing numbers of horses undergoing colic surgery and recovering from general anaesthesia since 2004/2005. This is likely to be, at least partly, due to the financial crisis of 2008. In the last year of data collection (2017), a modest increase in the numbers and percentages of horses undergoing surgery that were recovered and a modest decrease in the number of horses with colic being subjected to euthanasia have occurred; however, it is too soon to know whether this trend will continue.

Total numbers of equine accessions and colic examinations showed some differences at the two hospitals. At NC State, the total number of equine accessions to the hospital showed a trend of decreasing numbers starting around 2009, followed by a trend of increasing numbers around 2012. This pattern could have been caused by the financial crisis and resultant reluctance of horse-owners to pay for veterinary treatments. A similar trend was not, however, observed at Bell Equine. A potential explanation for this difference could be the provision of veterinary fees covered by insurance that is commonly taken out by horse-owners in the UK (approximately 60% of horses admitted to Bell Equine have this type of insurance cover) as compared to owners in the United States (approximately 30% for the emergency caseload at NC State).

Interestingly, the trends of decreasing numbers of horses with colic undergoing surgery and being recovered and the increasing numbers of horses being subjected to euthanasia either during surgery or without surgery were evident before 2008 (i.e. before the financial crisis). It is important to speculate why this should be the case. One potential reason could be the ageing general horse population (Brosnahan and Paradis 2003; Wylie *et al.* 2013; Welsh *et al.* 2016), with reluctance or inability of horse-owners to pay for colic surgery in geriatric horses. Although the success rates of colic surgery are equivalent in geriatric and younger horses (Gazzero *et al.* 2015), the financial investment in a geriatric horse may be unattractive to horse-owners. As our results indicate, the costs of veterinary treatments for horses with colic, including the costs of colic surgery, have increased significantly over the past 14 years. This increase in costs is unlikely to have been mirrored by any relative increase in financial value of the horses, even in the younger age groups. With this in mind, clinicians should appraise each case critically regarding the justification for various medical therapies that may be used in the post-operative care of horses following colic surgery and which can significantly escalate the costs. Although a significant proportion of the general horse population in the UK has veterinary fee insurance, the level of insurance coverage is limited for geriatric horses. Even in younger horses with insurance cover, the costs of colic surgery frequently exceed the value of available veterinary insurance. For

TABLE 3: Mean invoice totals for colic cases admitted to NC State ($USD) and Bell Equine (£GBP)

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
NC State ($USD)														
All colics	$2772	$3042	$3388	$3599	$3508	$3928	$3428	$3939	$3379	$3637	$3817	$3590	$3540	$4558
Colic cases medically managed that were discharged to home	$1594	$1847	$1910	$2034	$1933	$2085	$2420	$2187	$2212	$2402	$2377	$2203	$2453	$2704
Colic cases treated surgically and recovered from anaesthesia	$5322	$5483	$6622	$7232	$7614	$8252	$7864	$7968	$7935	$8400	$8166	$6745	$7161	$10,119
Colic cases undergoing surgery and subjected to euthanasia during surgery	$1711	$1364	$1328	$1437	$1374	$1457	$1806	$1291	$1583	$1709	$1522	$1743	$3359	$7873
Colic cases subjected to euthanasia only	$2641	$3180	$4468	$4232	$4521	$4491	$4978	$5504	$5903	$4673	$4937	$3831	$3062	$1779
Bell Equine (£GBP)														
All colics	£1734	£1827	£2116	£1846	£2012	£2057	£1959	£1700	£1904	£2239	£1880	£1848	£1971	£1998
Colic cases medically managed that were discharged to home	£437	£534	£1105	£511	£676	£710	£773	£905	£920	£908	£805	£987	£1050	£1180
Colic cases treated surgically and recovered from anaesthesia	£2683	£3076	£3791	£3745	£3968	£4188	£4464	£4471	£4626	£4750	£4935	£5580	£5895	£5943
Colic cases undergoing surgery and subjected to euthanasia during surgery	£992	£1164	£1249	£1080	£1918	£1419	£1505	£1809	£1850	£2035	£1445	£2120	£2090	£2127
Colic cases subjected to euthanasia only	£505	£487	£288	£518	£361	£450	£666	£788	£801	£1045	£746	£856	£842	£987

horses insured for veterinary fees in the United States, the lower level of major medical insurance coverage is typically $7500, which would not cover the current total cost shown by our data, and there are also limits for geriatric horses, although this varies by insurance company. Furthermore, owners may be reluctant to invest large amounts of money on colic surgery in old horses affected by comorbidities, such as pituitary pars intermedia dysfunction, laminitis, osteoarthritis, etc. In addition to financial constraints and possible unwillingness of horse-owners to pay for colic surgery in geriatric horses, the ageing population of horses might further compound this problem due to the increased prevalence of surgical colics in older horses associated with strangulating lipomas (Blikslager *et al.* 1992; Edwards and Proudman 1994; Freeman and Schaeffer 2001; Garcia-Seco *et al.* 2005).

In other companion animals, age has been shown to affect owners' responses to illness. Old dogs, for example, receive less medical assistance (Marinelli *et al.* 2007). Old age, coupled with disease and costs of treatment, have been shown to be major influences on the decision to perform euthanasia in both dogs and cats (Gates *et al.* 2017). Age has also been shown to be a strong determinant of euthanasia decisions in animal shelters (Kass *et al.* 2001). Increasing age is negatively associated with quality of life, and the commonest reasons for euthanasia in geriatric horses include musculoskeletal disorders or lameness, colic, and nonspecific chronic diseases (Ireland *et al.* 2011; McGowan and Ireland 2016). In one study in the UK, colic was the reason for euthanasia being undertaken in 21% of geriatric horses (>15 years of age); colic was the second most common reason for euthanasia being performed (after lameness in 24%) in this group of horses. The decision to euthanise a horse is frequently difficult, and perceived effects of major surgery on the animal's quality of life are likely to be major factors that influence owners' decisions to undertake euthanasia. However, in the study of Ireland *et al.* (2011), veterinary advice was found to be an important factor in owner decision-making regarding cases of colic. The influence of veterinary advice on owners' decisions to perform euthanasia in the horses in this study is unknown but was likely to have been considerable. However, one

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interesting aspect of the results was the differences in the proportion of horses being subjected to euthanasia either before or during surgery at the two hospitals, with more horses being subjected to euthanasia during surgery at NC State. This may relate to a fee structure developed in response to the 2008 financial crisis at NC State in which initial surgery fees required to explore the abdomen were reduced to allow a definitive diagnosis at surgery. The exact reasons why many owners opt to undertake euthanasia either without surgery or during surgery are likely to be multifactorial and require further investigation. In view of the published results of colic surgery in horses of all ages, including both short-term and long-term outcomes, it is likely that a proportion of the horses that were subjected to euthanasia would have made a satisfactory recovery if surgery had been completed.

Another potential reason for the reluctance of horse-owners to undertake colic surgery on their horses may be a widespread pessimism among horse-owners about the outcomes of colic surgery and a popular belief that horses undergoing colic surgery never return to normal function and often suffer from distressing complications and reduced quality of life. Despite evidence from numerous published studies of short- and long-term follow-up of horses after colic surgery (Gazzero *et al.* 2015), it has been the authors' experiences that 'bad news' stories of horses that have unsuccessful outcomes or serious post-operative complications are commonly spread among horse-owners by word of mouth and through social media. However, data from NC State would support the fact that most horses undergoing colic surgery return to their expected level of performance. For example, 76% of horses were being used for their intended performance by 1 year following colic surgery, and 66% were performing at or above their pre-operative level in a study of 195 cases from 2003 to 2010 (Davis *et al.* 2013). Therefore, giving owners accurate information on survival, cost and expected long-term outcome may be helpful to owners during decision-making for colic patients.

Authors' declaration of interests

No conflicts of interest have been declared.

Ethical animal research

Ethical review not required.

Authorship

Both authors contributed fully to all aspects of the paper.

References

Blikslager, A.T., Bowman, K.F., Haven, M.L., Tate, L.P. and Bristol, D.G. (1992) Pedunculated lipomas as a cause of intestinal obstruction in horses – 17 cases (1983–1990). *J. Am. Vet. Med. Assoc.* **201**, 1249–1252.

Brosnahan, M.M. and Paradis, M.R. (2003) Demographic and clinical characteristics of geriatric horses: 467 cases (1989–1999). *J. Am. Vet. Med. Assoc.* **223**, 93–98.

Davis, W., Fogle, C.A., Gerard, M.P., Levine, J.F. and Blikslager, A.T. (2013) Return to use and performance following exploratory celiotomy for colic in horses: 195 cases (2003–2010). *Equine Vet. J.* **45**, 224–228.

Dolente, B.A., Lindborg, S., Russell, G. and Southwood, L.L. (2008) Emergency case admissions at a large animal tertiary university referral hospital during a 12-month period. *J. Vet. Emerg. Crit. Care* **18**, 298–305.

Dukti, S. and White, N. (2009) Surgical complications of colic surgery. *Vet. Clin. North Am. Equine Pract.* **24**, 515–534.

Edwards, G.B. and Proudman, C.J. (1994) An analysis of 75 cases of intestinal obstruction caused by pedunculated lipomas. *Equine Vet. J.* **26**(**1**), 18–21.

Freeman, D.E. and Schaeffer, D.J. (2001) Age distributions of horses with strangulation of the small intestine by a lipoma or in the epiploic foramen: 46 cases (1994–2000). *J. Am. Vet. Med. Assoc.* **219**, 87–89.

French, N.P., Smith, J., Edwards, G.B. and Proudman, C.J. (2002) Equine surgical colic: risk factors for postoperative complications. *Equine Vet. J.* **34**, 444–449.

Garcia-Seco, E., Wilson, D.A., Kramer, J., Keegan, K.G., Branson, K.R., Johnson, P.J. and Tyler, J.W. (2005) Prevalence and risk factors associated with outcome of surgical removal of pedunculated lipomas in horses: 102 cases (1987–2002). *J. Am. Vet. Med. Assoc.* **226**, 1529–1537.

Gates, M.C., Hinds, H.J. and Dale, A. (2017) Preliminary description of aging cats and dogs presented to a New Zealand first-opinion veterinary clinic at end-of-life. *N. Z. Vet. J.* **65**, 313–317.

Gazzero, D.M., Southwood, L.L. and Lindborg, S. (2015) Short-term complications after colic surgery in geriatric versus mature non-geriatric horses. *Vet. Surg.* **44**, 256–264.

Ireland, J.L., Clegg, P.D., McGowan, C.M., Platt, L. and Pinchbeck, G.L. (2011) Factors associated with mortality of geriatric horses in the United Kingdom. *Prev. Vet. Med.* **101**, 204–218.

Kass, P.H., New, J.C. Jr, Scarlett, J.M. and Salman, M.D. (2001) Understanding animal companion surplus in the United States: Relinquishment of nonadoptables to animal shelters for euthanasia. *J. Appl. Anim. Welf. Sci.* **4**, 237–248.

Mair, T.S. and Smith, L.J. (2005a) Survival and complication rates in 300 horses undergoing surgical treatment of colic. Part 1: short-term survival following a single laparotomy. *Equine Vet. J.* **37**(**4**), 296–302.

Mair, T.S. and Smith, L.J. (2005b) Survival and complication rates in 300 horses undergoing surgical treatment of colic. Part 2: short-term complications. *Equine Vet. J.* **37**, 303–309.

Mair, T.S. and Smith, L.J. (2005c) Survival and complication rates in 300 horses undergoing surgical treatment of colic. Part 3: long-term complications and survival. *Equine Vet. J.* **37**, 310–314.

Marinelli, L., Adamelli, S., Normando, S. and Bono, G. (2007) Quality of life of the pet dog: influence of owner and dog's characteristics. *Apl. Anim. Behav. Sci.* **108**, 143–156.

McGowan, C.M. and Ireland, J.L. (2016) Welfare, quality of life, and euthanasia of aged horses. *Vet. Clin. North Am. Equine Pract.* **32**, 355–367.

Moore, J.N. (2005) Five decades of colic: a view from thirty-five years on. *Equine Vet. J.* **37**, 285–286.

Moser, S.A. (2015) Veterinary economy may be bouncing back. *DVM News Magazine* **46**, 10.

Muñoz, E., Argüelles, D., Areste, L., San Miguel, L. and Prades, M. (2008) Retrospective analysis of exploratory laparotomies in 192 Andalusian horses and 276 horses of other breeds. *Vet. Rec.* **162**, 303–306.

Osborne, M. (2009) Equine veterinarians affected yet resilient in sour economy. *J. Am. Vet. Med. Assoc.* **234**, 1103–1104.

Proudman, C.J., Edwards, G.B., Barnes, J. and French, N.R. (2005) Factors affecting long-term survival of horses recovering from surgery of the small intestine. *Equine Vet. J.* **37**(**4**), 360–365.

Welsh, C.E., Duz, M., Parkin, T.D.H. and Marshall, J.F. (2016) Prevalence, survival analysis and multimorbidity of chronic diseases in the general veterinarian-attended horse population of the UK. *Prev. Vet. Med.* **131**, 137–145.

Wylie, C.E., Ireland, J.L., Collins, S.N., Verheyen, K.L.P. and Newton, J.R. (2013) Demographics and management practices of horses and ponies in Great Britain: a cross-sectional study. *Res. Vet. Sci.* **95**, 410–417.

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Original Article

Ex vivo COX-1 and COX-2 inhibition in equine blood by phenylbutazone, flunixin meglumine, meloxicam and firocoxib: Informing clinical NSAID selection

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Keywords: horse; NSAIDs; analgesia; anti-inflammatory; COX-2

Summary

Newer cyclo-oxygenase-2 (COX-2) selective nonsteroidal anti-inflammatory drugs (NSAIDs), such as firocoxib, are proposed to reduce inhibition of cyclo-oxygenase-1 (COX-1) and avoid undesirable side effects, while continuing to inhibit inflammation associated with COX-2. However, COX selectivity is typically based on *in vitro* testing, which may not provide sufficient information critical for treatment selection. This study investigated the pharmacokinetics and *ex vivo* COX-1 and COX-2 inhibition of phenylbutazone, flunixin meglumine, meloxicam and firocoxib. Horses (n = 3) were administered one of the four drugs, in a randomised cross-over design, with 3-week washout periods. For each drug, three doses were given and sampling performed. Drug plasma concentrations, thromboxane B_2 (TXB_2) and prostaglandin E_2 (PGE_2) were determined. After one dose, TXB_2 and PGE_2 levels were significantly higher in horses administered firocoxib compared to flunixin meglumine. Following the third dose, TXB_2 levels in horses administered firocoxib and meloxicam were significantly higher compared to flunixin meglumine or phenylbutazone; all drugs reduced PGE_2 to a similar degree. The mean plasma half-lives were 5.97 ± 0.47, 4.74 ± 0.14, 8.24 ± 3.74 and 47.42 ± 7.41 h for phenylbutazone, flunixin meglumine, meloxicam and firocoxib, respectively. Firocoxib and meloxicam exhibited significantly less COX-1 inhibition compared to flunixin meglumine and phenylbutazone; all drugs inhibited COX-2. The plasma half-life of firocoxib was longer than the other NSAIDs, including meloxicam. Data from this study have important clinical relevance and should be used to inform practitioners' drug selection of a COX-1 sparing or traditional NSAID and dose selection and to provide knowledge of the duration for the four NSAIDs studied.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first choice for most clinicians when treating a horse in pain, or for preventing post-operative pain and inflammation. Within the NSAID category of medications, equine clinicians now have the choice of traditional NSAIDs, such as flunixin meglumine or phenylbutazone, or a COX-2 selective NSAID, such as firocoxib or meloxicam (the latter not available for large animal use in the United States). Selection of the most appropriate NSAID for a clinical case can be difficult, especially when treating a foal, a geriatric horse or a horse with significant dehydration prior to fluid administration or referral. However, an understanding of the mechanism of traditional and COX-2 selective NSAIDs, based on data using medications commonly employed in clinical practice, can help clinicians select the most appropriate NSAID for an individual case.

Traditional, or nonselective, NSAIDs have commonly been administered to horses to treat pain and inflammation associated with musculoskeletal disease and colic. However, their use has been associated with adverse effects including gastrointestinal ulceration and renal injury (Ziegler *et al.* 2017). As depicted in **Figure 1**, the cyclo-oxygenase isoform known as COX-2 is an inducibly expressed enzyme responsible for the prostanoids that trigger pain and inflammation in response to injury. Conversely, cyclo-oxygenase-1 (COX-1) is a constitutively expressed enzyme responsible for maintaining protective and reparative mechanisms, such as the production of mucus on gastrointestinal mucosal surfaces, coagulation and renal homeostasis. There is thought to be some cross-over in the function of COX-1 and COX-2 (Warner and Mitchell 2002). Nonetheless, the adverse effects of nonselective NSAIDs such as flunixin meglumine are thought to be the result of COX-1 inhibition and impairment of normal physiological organ functions. Meloxicam and firocoxib are NSAIDs designed to more specifically target the COX-2 isoform to avoid undesirable gastrointestinal side effects. Firocoxib is a recently developed COX-2 selective NSAID shown to have a very high degree of COX selectivity *in vitro* (Cook *et al.* 2009; Cuniberti *et al.* 2012). **Fig 2** depicts molecular configurations of the enzyme active sites and NSAIDs, to illustrate how traditional and COX-2 selective drugs interact with these active sites on the COX enzymes. The COX-1 active site has a relatively simple linear configuration, compared to the larger active site with a hydrophobic side-pocket found on the COX-2 isoform. Traditional NSAIDs have a linear molecular structure and can readily bind to COX-1 and COX-2 active sites. COX-2 selective medications are

designed to more specifically match the larger size of the COX-2 active site with its hydrophobic side-pocket, which then limits the drug from easily entering and binding to the linear COX-1 active sites. This is the method by which firocoxib avoids the COX-1 inhibition experienced with traditional NSAIDs such as flunixin. Meloxicam has a less pronounced change in configuration, compared to the coxibs, and as such is less selective for the COX-2 active site. Meloxicam is categorised as a COX-2 preferential, rather than COX-2 selective, NSAID.

There is an ongoing need for further studies evaluating the effect of NSAIDs at clinically relevant doses on COX-1 and COX-2 to help inform equine clinical practice. This is because the COX selectivity of NSAIDs as well as the type and severity of side effects seem to be species- and dose-dependent (Warner and Mitchell 2002). Additionally, COX selectivity is often based on *in vitro* studies which may not accurately predict COX selectivity of NSAIDs *in vivo* (Beretta *et al.* 2005; Cuniberti *et al.* 2012; Bruno *et al.* 2014). Therefore, as part of our assessment of the present status of NSAIDs in equine practice, we performed a study in which phenylbutazone, flunixin meglumine, meloxicam and firocoxib were administered to horses at clinically relevant doses, accompanied by *ex vivo* COX selectivity assays.

Materials and methods for *in vivo* NSAID study

Horses (n = 3) were administered one of four drugs, in a randomised cross-over design. For each drug, three consecutive intravenous (i.v.) doses were given and sampling

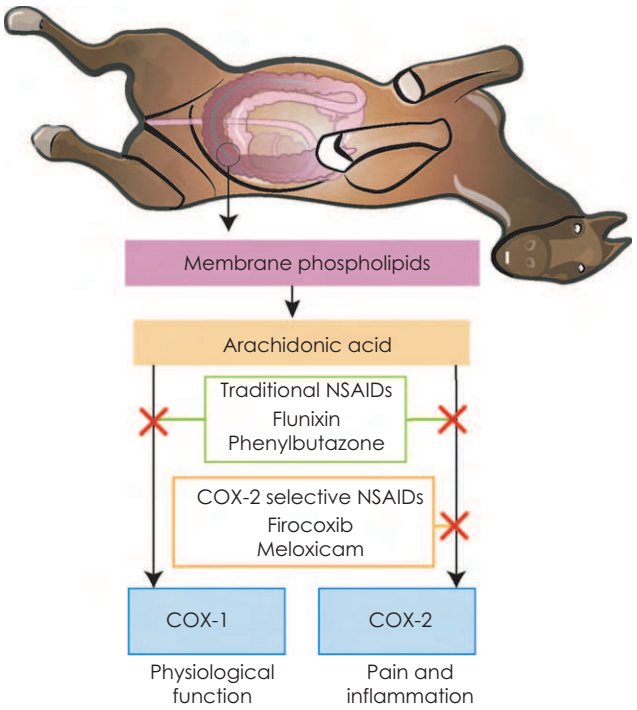

Fig 1: The actions of traditional NSAIDs to block both COX-1 and COX-2 pathways are depicted above. The figure also depicts the COX-2 selective NSAIDs selective blockade of COX-2 pathways responsible for pain and inflammation, while sparing COX-1 pathways, for maintenance of important physiological functions.

was performed, with a 3-week washout period between treatments. Doses and dosing intervals were as follows: phenylbutazone (ButaJect®)[1] 2.2 mg/kg bwt every 12 h, flunixin meglumine (Banamine®)[2] 1.1 mg/kg bwt every 12 h, meloxicam (Metacam®)[3] 0.6 mg/kg bwt every 24 h and firocoxib (Equioxx®)[4] 0.1 mg/kg bwt every 24 h. An intravenous jugular catheter was used for drug administration, and a second intravenous jugular catheter in the contralateral jugular vein was used for sampling. Blood was drawn from each horse prior to drug administration, and 0, 1, 12 h after the first dose of drug and at 0, 1, 2, 4, 8, 16, 24 and 48 h after the third dose. Thromboxane B_2 (TXB_2) and prostaglandin E_2 (PGE_2) were used as surrogate markers for detection of COX-1 and COX-2 activity, respectively, as described in previous studies (Little *et al.* 2007; Holland *et al.* 2014).

TXB_2 quantification

Briefly, a 500 µL aliquot of blood was allowed to coagulate for 1 h before centrifugation and 100 µL of serum was harvested. The serum was then added to 400 µL of methanol to precipitate proteins before centrifugation. A 50 µL sample of supernatant was diluted with 150 µL of EIA buffer and frozen at −70°C until further analysis was performed. The concentrations of TXB_2, the stable metabolite of thromboxane A_2, were determined as a surrogate for COX-1 activity using a commercially available competitive enzyme immunoassay[5].

PGE_2 quantification

A 1000 µL sample of blood was heparinised following collection and divided into two 500 µL aliquots. One aliquot was stimulated with LPS (100 µg/mL) for 24 h at 37°C after which it was centrifuged, and a 100 µL aliquot of plasma was harvested. The second aliquot was not stimulated with LPS and served as a negative control. Each plasma sample was added to 400 µL of methanol to precipitate proteins before centrifugation. A 50 µL sample of supernatant was diluted with 150 µL of EIA buffer and frozen at −70°C until further analysis was performed. The concentrations of serum PGE_2 were determined as a surrogate for COX-2 activity using a commercially available kit[5].

Statistical methods

Data were initially evaluated for normality, and non-normally distributed data were analysed using ANOVA on ranks. Significant differences among the data sets from the four drug treatments were obtained via repeated measures ANOVA on ranks (Friedman Analysis), followed by post hoc Tukey's tests to perform pairwise comparisons when the initial ANOVA was significant. The level of significance was set at $P<0.05$. Scatter plots of PGE_2 and TXB_2 concentrations measured at all time points after the first dose but before the second dose of drug were constructed. Scatter plots of PGE_2 and TXB_2 concentrations at all time points after the third and final dose of drug were also constructed. For **Fig 3a**, a single data point in the firocoxib measurement exceeding 8× the median was removed from analysis as it was most likely a spurious reading. SigmaPlot software was used for analysis and column graphs[6], and scatter plots were constructed using JMP[7].

Drug analysis

Plasma concentrations of each NSAID and its metabolite (where applicable) were determined by liquid

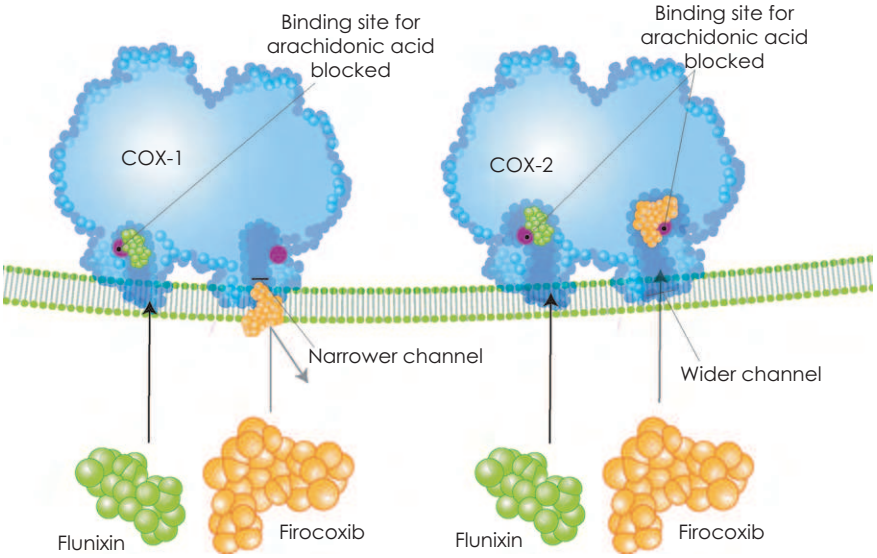

Fig 2: This depicts the structural differences between traditional and COX-2 selective drugs, which allow for binding to both COX-1 and COX-2 active sites in the case of traditional NSAID medications. The relatively narrower channel of the COX-1 active site and the nonlinear configuration of the COX-2 selective drug seen in the figure above do not allow significant binding of the COX-2 selective medications in the COX-1 active sites. These structural features provide the selectivity of the COX-2 selective NSAIDs.

chromatography. Reference standards were obtained from Sigma-Aldrich Corp. (USA) for each compound except OH flunixin meglumine which was obtained from Toronto Research Chemicals (Canada). All solvents and reagents used were HPLC Grade.

Validation of each assay was determined based on calibration curves being linear with a coefficient of determination (r^2) of >0.99 and calibration samples back-calculated to be within ± 15% of the true concentration. The lower limit of quantification (LLOQ) was based on the lowest concentration on a linear regression line from the calibration curve. Accuracy of each HPLC assay was <15% of the true value, and precision was <15% of the mean at relevant low, medium and high concentrations. The plasma concentrations of firocoxib and meloxicam were determined using previously reported assays developed for equine plasma in our laboratory (Little *et al.* 2007; Holland *et al.* 2014). The LLOQ was 0.0025 ng/mL and 0.01 µg/mL for firocoxib and meloxicam, respectively.

The plasma concentrations of phenylbutazone and oxyphenbutazone were determined by high-performance liquid chromatography with ultraviolet detection at 240 nm (Alliance 2695, Waters Corporation, USA). Briefly, 500 µL of sample was added to 500 µL of acetonitrile (ACN), vortexed and then centrifuged. The supernatant was then transferred to a glass tube and evaporated under compressed nitrogen for 35 min at 40°C. After evaporation, the sample was reconstituted in 250 µL of mobile phase (55% 0.05 M ammonium acetate buffer and 45% ACN). Fifty µL of processed sample was then injected onto the HPLC and separated using a C8 column (XBridge 150 × 4.6 mm, 3.5 µm, Waters Corporation, USA) and guard column. Column temperature was maintained at 40°C, mobile phase flow rate was 1 mL/min, and run times were 12 min. The LOQ for both phenylbutazone and the metabolite was 0.5 µg/mL using this method.

The plasma concentrations of flunixin meglumine and 5-OH flunixin were determined by ultra-high-performance liquid chromatography with tandem mass spectrometry detection. Sample preparation and drug detection were performed as previously described (Howard *et al.* 2014) with the exception of a flow rate of 0.4 mL/min and sample temperature maintained at 10°C. The injection volume was 0.5 µL for concentrations ranging between 1–50 µg/mL and 5 µL for concentrations between 0.0025–1 µg/mL, to prevent saturation of detection at the higher concentrations. The limit of quantification for both flunixin meglumine and the metabolite was 0.0025 µg/mL using this method.

Pharmacokinetic analysis

Pharmacokinetic parameters for all NSAIDs and their metabolites (where applicable) were calculated using noncompartmental analysis with a log/linear trapezoidal model. Commercially available pharmacokinetic software (Phoenix WinNonlin, Version 6.3.0)[8] was used to determine the terminal half-life ($T½$) based on the slope of the terminal phase (λz), and area under the curve extrapolated to infinity ($AUC_{0-\infty}$) using the trapezoidal rule. Volume of distribution (Vd), clearance (Cl) and concentration at time zero (C_0) were additionally determined for the parent compounds. The maximum concentration (C_{max}) and time to maximum concentration (T_{max}) were determined directly from the plasma concentrations of oxyphenbutazone and 5-OH flunixin meglumine. Data are reported as mean ± s.d.

Results

In the 12 h following administration of the first dose (**Fig 3a**), flunixin meglumine administration resulted in a significantly lower TXB_2 concentration compared to firocoxib administration (P<0.001). No significant differences were detected between the levels of TXB_2 in horses administered meloxicam, flunixin meglumine or phenylbutazone after the first dose. In the 48 hours following the third dose (**Fig 3b**), TXB_2 levels in horses administered flunixin meglumine or

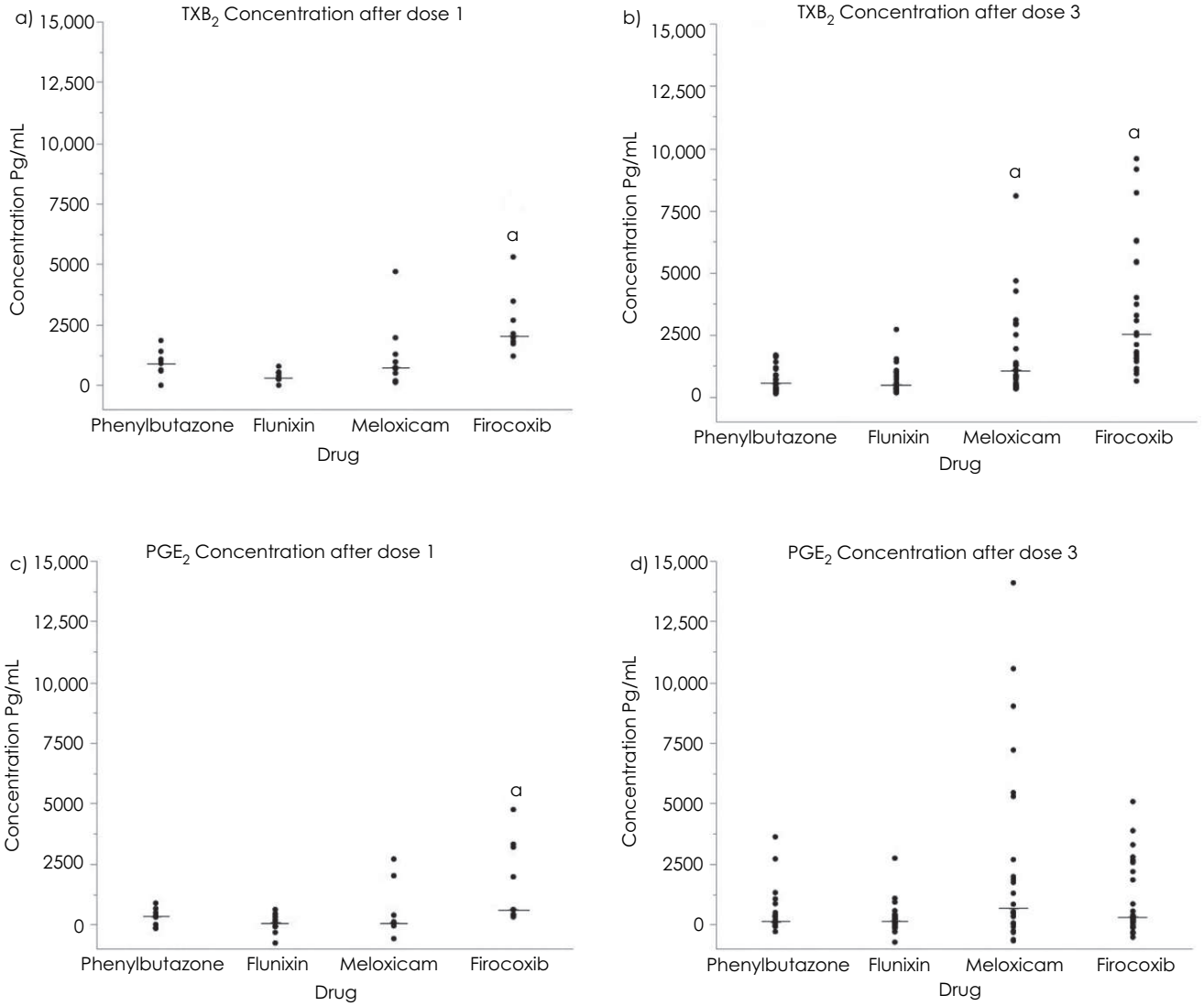

Fig 3: a) Scatter plot of TXB_2 for three horses measured at all time points after the first dose, but prior to the second dose of drug. Dots represent individual measurements from three time points, horizontal line indicates the median value, and the lower case a indicates significant difference ($P \leq 0.05$) between TXB_2 concentrations in horses administered flunixin meglumine and those administered firocoxib. b) Scatter plot of TXB_2 for three horses measured at all time points after the third and final dose of drug. Dots represent individual measurements from eight time points, horizontal line indicates the median value, and the lower case a indicates a significant difference ($P \leq 0.05$) in TXB_2 concentrations between samples from horses administered flunixin meglumine or phenylbutazone and those administered meloxicam or firocoxib. c) Scatter plot of PGE_2 for three horses measured at all time points after the first dose, but prior to the second dose of drug. Dots represent individual measurements from three time points, horizontal line indicates the median value, and the lower case a indicates a significant difference ($P \leq 0.05$) in PGE_2 concentrations between samples from horses administered flunixin meglumine and those administered firocoxib. d) Scatter plot of PGE_2 for three horses measured at all time points after the third and final dose of drug. Dots represent individual measurements from eight time points, and the horizontal line indicates the median value. No significant differences were seen between drugs.

phenylbutazone were significantly lower than samples from horses administered meloxicam or firocoxib ($P<0.001$). However, no significant differences were observed in TXB_2 concentrations in horses administered flunixin meglumine or phenylbutazone, or in horses administered firocoxib or meloxicam.

In the 12 h following administration of the first dose (**Fig 3c**), PGE_2 concentrations in samples from horses administered flunixin meglumine were significantly lower compared to PGE_2 concentrations in samples from horses administered firocoxib ($P = 0.027$). PGE_2 levels were not significantly different in horses administered meloxicam, flunixin meglumine or phenylbutazone. In the 48 h following the third labelled dose (**Fig 3d**), no significant differences were observed among PGE_2 levels in horses administered flunixin meglumine, phenylbutazone, firocoxib or meloxicam.

TXB_2 trough analysis (postdosing intervals)

The median and 25% interquartile range for TXB_2 levels at one dosing interval after the third dose of phenylbutazone, flunixin

meglumine, meloxicam and firocoxib were 368.57 ± 604.57, 341.9 ± 268.62, 820.16 ± 852.05 and 2530.89 ± 4105.92 pg/mL respectively. The median and 25% interquartile range for TXB_2 at two dosing intervals after the third dose of phenylbutazone, flunixin meglumine, meloxicam and firocoxib were 721.53 ± 1243.20, 991.62 ± 536.47, 3033.69 ± 3081.16 and 2417.10 ± 5262.07 pg/mL, respectively. The dose interval was 12 h for phenylbutazone and flunixin meglumine, 24 h for meloxicam and firocoxib. The ~2- to 3-fold increases noted in median TXB_2 levels over the two postdosing intervals for phenylbutazone, flunixin meglumine and meloxicam were notable but not significant, whereas TXB_2 levels were notably higher for firocoxib after the first postdosing interval without any apparent increase over the second postdosing interval.

PGE_2 trough analysis (postdosing intervals)

The median PGE_2 levels with interquartile range, measured at one dosing interval after the third dose of drug, for phenylbutazone, flunixin meglumine, meloxicam and firocoxib were 114.84 ± 401.26, 98.08 ± 483.73, 418.65 ± 1541.49 and 186.28 ± 1409.21 pg/mL, respectively. The median PGE_2 and interquartile range, measured at two dosing intervals after the third dose of drug for phenylbutazone, flunixin meglumine, meloxicam and firocoxib, were 417.76 ± 2325.98, 403.64 ± 1149.74, 6335.79 ± 5861.39 and 2017.65 ± 2720.74 pg/mL, respectively. The dose interval was 12 h for phenylbutazone and flunixin meglumine, 24 h for meloxicam and firocoxib. Over the course of the two postdosing intervals, median PGE_2 concentrations rose for of all NSAIDs, but there were no statistical differences between drugs or between postdosing intervals.

Pharmacokinetic profiles of NSAIDs

Figure 4a–d represents the plasma concentrations of phenylbutazone, flunixin meglumine, meloxicam and firocoxib, respectively, after the last dose (Dose 3) of drug was administered. Plasma concentrations of firocoxib and flunixin meglumine plus metabolite were detected for 48 h after the last dose in 3 out of 3 horses. Plasma concentrations after the last dose of meloxicam were detected for 24 h in one horse and for 48 h in the other two horses. Plasma concentrations of phenylbutazone and oxyphenbutazone were detected for 24 h in 3 out of 3 horses. Noncompartmental analysis yielded pharmacokinetic values similar to those previously reported for each drug (Kvaternick *et al.* 2007; Little *et al.* 2007; Letendre *et al.* 2008; Lees and Toutain 2013; Knych *et al.* 2014; Holland *et al.* 2014; Howard *et al.* 2014). The relevant parameters are summarised in **Table 1**. **Table 2** summarises the mean ± s.d. plasma concentrations for phenylbutazone, flunixin meglumine, meloxicam and firocoxib at 24 and 48 h following the final dose administered for comparison to reported EC50.

Discussion

In the 12 h after the first dose of drug (**Fig 2a**), TXB_2 concentrations in horses administered firocoxib were greater than TXB_2 concentrations in horses administered flunixin meglumine, indicating the COX-2 selectivity (or COX-1 sparing activity) of this drug in horses. However, meloxicam, another purported COX-2 preferential NSAID in horses (Beretta *et al.* 2005), did not yield significantly different TXB_2 concentrations when compared to flunixin meglumine or phenylbutazone. This likely relates to the degree of selectivity for each of these drugs. Selectivity of an NSAID is often measured *in vitro* by the inhibitory concentration required to inhibit 50% of the enzyme (IC_{50}) for COX-1/IC_{50} COX-2. Firocoxib is a highly selective COX-2 inhibitor, with an inhibitory ratio of 263–643 in the horse (Kvaternick *et al.* 2007), compared to a ratio of only 3.8 for meloxicam (Beretta *et al.* 2005). Alternatively, individual variability in response to NSAIDs may explain the lack of selectivity (Bruno *et al.* 2014). An additional unexpected finding was the lack of a significant difference between the TXB_2 levels between horses treated with firocoxib and those treated with phenylbutazone. Since both flunixin meglumine and phenylbutazone are considered nonselective COX inhibitors, it was expected that they would have equal effects on TXB_2 and that a difference would therefore have also been detected between firocoxib and phenylbutazone. However, Beretta *et al* (2005) did demonstrate that *in vitro*, phenylbutazone is a less potent COX-1 inhibitor than flunixin meglumine at both the IC_{50} and the IC_{80}, which may explain the lack of significant findings between firocoxib and phenylbutazone.

TXB_2 levels in the 48 h following the third dose (**Fig 2c**) of firocoxib and meloxicam are significantly higher than TXB_2 concentrations in horses administered either flunixin meglumine or phenylbutazone. Following multiple doses, the COX-1-sparing properties exhibited by meloxicam and firocoxib in this study are as predicted and are similar to results of a previous study investigating the in vitro COX selectivity of meloxicam, flunixin meglumine and phenylbutazone (Beretta *et al.* 2005). The COX-1-sparing effect is seen with clinically relevant doses of meloxicam and firocoxib, which supports selection of one of these drugs for an equine patient when maintenance of the normal physiological homeostatic and repair mechanisms for the gastrointestinal and renal systems is critical. In a study of volume-depleted horses, however, renal responses were similar for the COX-2 preferential NSAID, meloxicam, and the traditional nonselective NSAID, phenylbutazone (Raidal *et al.* 2014). Horses suffering from systemic inflammatory response syndrome secondary to gastrointestinal disease, with pre-existing or concurrent renal compromise, may benefit from selection of a COX-2 selective NSAID, rather than a traditional or COX-2 preferential NSAID.

In the 12 h following the first dose of drug (**Fig 2b**), PGE_2 levels in horses administered firocoxib were significantly greater than in horses administered flunixin meglumine. This can be explained by the fact that firocoxib does not reach steady-state concentrations until 5–7 doses have been administered (Letendre *et al.* 2008). Additionally, drug accumulation occurs due to a dosing interval that is less than the half-life, and the plasma concentration needed for 80% inhibition of COX-2 is not necessarily reached following the first dose. This is the reason a loading dose of 0.3 mg/kg bwt is now recommended for a more rapid anti-inflammatory effect (Cox *et al.* 2013). The reported therapeutic concentration of 103–110 ng/mL (Barton *et al.* 2014; Holland *et al.* 2014) was not reached after the first dose of firocoxib; however, it was reached after the third dose in all three horses in the present study. Without the loading dose, the results of this study indicate that flunixin meglumine, and to a lesser extent meloxicam and phenylbutazone, reach concentrations that are more effective at inhibiting COX-2

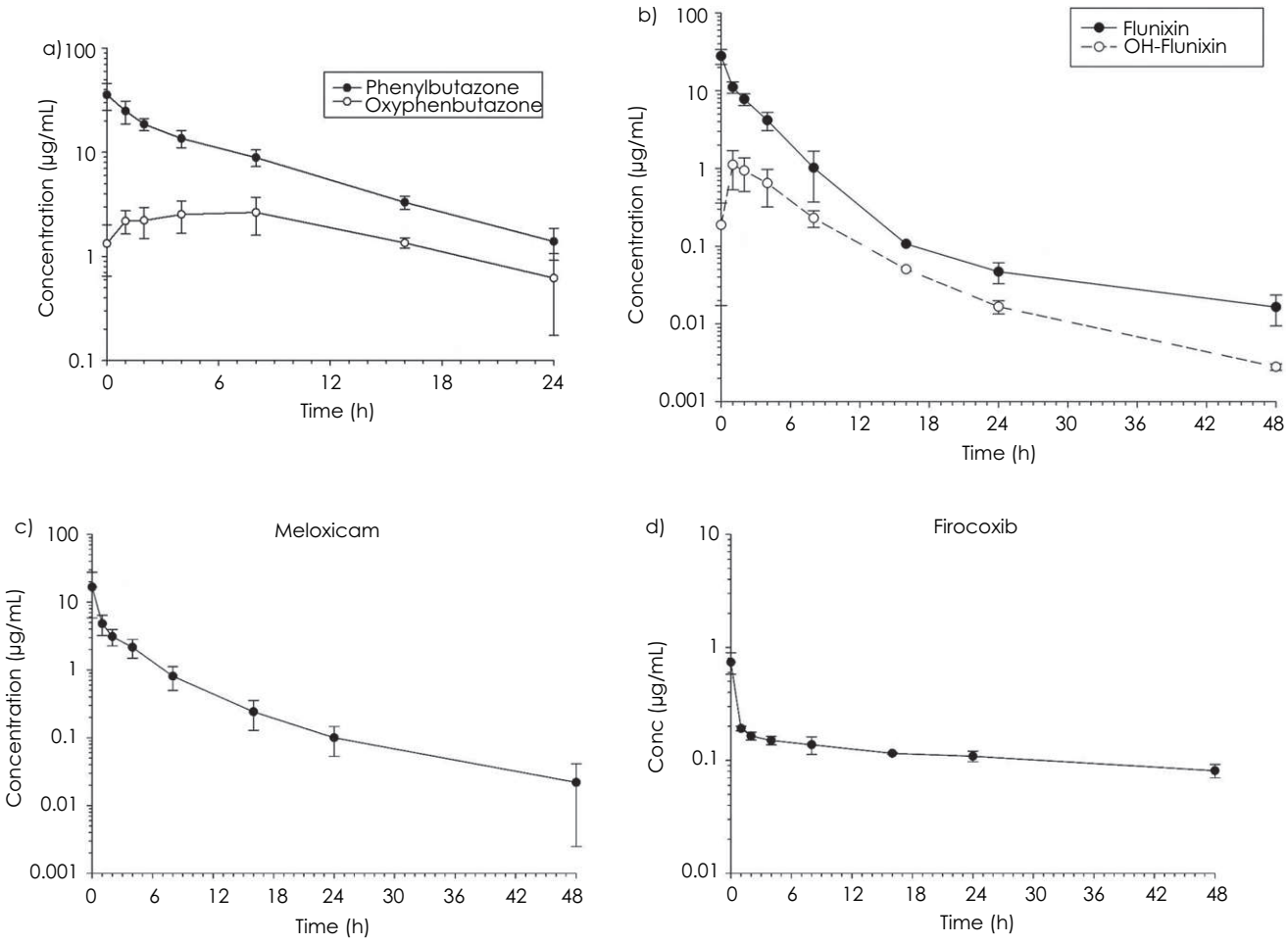

Fig 4: a–d) Pharmacokinetic profiles of phenylbutazone, flunixin meglumine, meloxicam and firocoxib, respectively, after administration of third labelled dose. Data reported as median and range. a) has no 48-hour time point because phenylbutazone and its metabolite were below the limit of quantification by 48 h.

after a single dose than firocoxib. When selecting firocoxib, the loading dose is recommended to achieve drug concentrations for effective anti-inflammatory and analgesic properties while retaining the COX-1 sparing physiology functions. In horses recovering from surgery for small intestinal strangulation, firocoxib (0.3 mg/kg bwt loading dose, followed by 0.1 mg/kg bwt labelled dose q. 24 h) provided analgesia comparable to flunixin, while sparing COX-1 homeostatic processes necessary for renal and gastrointestinal repair (Ziegler *et al.* 2019).

In the 48 h following the third dose of drug (**Fig 2d**), no significant differences in PGE_2 were observed among the four treatments. This likely indicates similar COX-2 inhibition by the four drugs and demonstrates that the reportedly COX-2 selective NSAIDs, firocoxib and meloxicam, exhibit equivalent levels of COX-2 inhibition compared to the traditional, nonselective NSAIDs, flunixin meglumine and phenylbutazone. The similar levels of COX-2 inhibition would predict similar analgesic and anti-inflammatory efficacy for all four drugs. Findings from recent experimental studies revealed similar analgesic efficacy for firocoxib, phenylbutazone and flunixin meglumine (Doucet *et al.* 2008; Cook *et al.* 2009), which is contrary to some veterinarians' clinical impression of inferior analgesia with firocoxib compared to traditional nonselective NSAIDS. Interestingly, the levels of COX-2 inhibition at 48 h following the last dose were also similar, despite very low to undetectable concentrations of phenylbutazone and flunixin meglumine.

Toutain *et al*. (1994) reported the concentrations that would produce 50% of the maximal effect (EC50) at 0.2–0.9 µg/mL and 1.5–4.3 µg/mL for flunixin meglumine and phenylbutazone, respectively. In that study, the concentrations of the metabolites were not measured. The reported EC50 for meloxicam is 0.13–0.195 µg/mL (Toutain and Cester 2004) and 0.027 µg/mL for firocoxib (Holland *et al.* 2014). The EC50 represents the affinity of a drug for binding to the receptor. This would imply that, of the four NSAIDs studied, firocoxib has the highest affinity for its receptor, followed by meloxicam, flunixin meglumine and phenylbutazone. This interpretation should be made with caution, however, as the reported therapeutic values for firocoxib are based on COX-2 inhibition alone, whereas those for the other NSAIDs are based on experimental models of lameness. Based on these values, the plasma concentrations of drug corresponding to the trough concentrations following the final dose of flunixin meglumine, meloxicam and

TABLE 1: Noncompartmental pharmacokinetic parameters

	Phenylbutazone	Oxyphenbutazone	Flunixin meglumine	5-OH Flunixin	Meloxicam	Firocoxib
λz (h^{-1})	0.12 (0.11–0.13)	0.10 (0.077–0.116)	0.145 (0.142–0.151)	0.124 (0.119–0.123)	0.068 (0.065–0.176)	0.014 (0.013–0.018)
T½ λz (h)	6.01 (5.48–6.42)	6.87 (5.98–9.01)	4.77 (4.87–4.59)	5.61 (5.18–5.81)	10.15 (3.93–10.64)	48.7 (39.5–54.1)
C_0 (µg/mL)	29.73 (29.71–47.74)	–	25.64 (25.63-23.23)	–	10.95 (9.94-29.22)	0.67 (0.92-0.62)
C_{max} (µg/mL)	–	2.16 (2.10–3.86)	–	0.80 (0.752–1.787)	–	–
T_{max} (hr)	–	4 (1–8)	–	1	–	–
$AUC_{0-\infty}$ (h * µg/mL)	205.44 (175.61–270.95)	40.57 (37.49–80.46)	59.12 (47.37–73.39)	6.12 (4.84–10.40)	34.47 (20.51–44.52)	10.6 (10.4–12.9)
Cl (mL/kg/min)	0.178 (0.135–0.208)	–	0.310 (0.386–0.249)	–	0.29 (0.225–0.488)	0.141 (0.117–0.144)
Vd (L/kg)	0.093 (0.075–0.099)	–	0.128 (0.163–0.099)	–	0.197 (0.166–0.267)	0.546 (0.493–0.593)

Data reported as median (range).
λz, slope of the terminal phase; $T_{½}λz$, half-life of terminal phase; C_0, calculated concentration at time 0; C_{max}, maximum concentration; T_{max}, time to maximum concentration; $AUC_{0-\infty}$, area under the concentration–time curve extrapolated to infinity; Cl, total body clearance; Vd, volume of distribution.

phenylbutazone are all below the reported EC50 values. Firocoxib remains above the EC50 out to 48 h. Despite this, both flunixin meglumine and phenylbutazone displayed more PGE_2 and TXB_2 suppression compared to the firocoxib and meloxicam at 24 h after the final dose. It is possible that the metabolites of these drugs contribute to the anti-prostaglandin properties (**Table 2**). The addition of oxyphenbutazone to phenylbutazone results in combined concentrations within the therapeutic range. However, the addition of 5-OH flunixin to flunixin meglumine still results in concentrations less than the EC50. This may indicate that flunixin meglumine is more potent than previously reported, or it may indicate that concentration of drug associated with COX inhibition does not necessarily correlate with analgesic effects.

Most published reports of NSAIDs in horses have not evaluated the concentrations of metabolites. Firocoxib is metabolised mainly by dealkylation and glucuronidation to two inactive metabolites (Kvaternick *et al.* 2007). Multiple metabolites of meloxicam have also been described in horses, with all of them thought to be biologically inactive (Tevell Aberg *et al.* 2009). Little is known about the pharmacokinetics of 5-OH flunixin in the horse, although the detection of a hydroxylated metabolite in plasma and urine has been previously described (Jaussaud *et al.* 1987). It is unclear whether this metabolite is active or not; however, since it represents only 10.6% of the total AUC in the horses in this study, it is unlikely to contribute significantly to the overall drug efficacy. Oxyphenbutazone is an active metabolite and may contribute significantly to the overall efficacy of phenylbutazone in the horse (Lees *et al.* 1986). In this study, it represents approximately 20% of the total AUC and the half-life of oxyphenbutazone is longer than its parent compound.

Although there are numerous reports of the pharmacokinetics of NSAIDs in horses, this is the first study that reports the pharmacokinetics of four different drugs in the same horses. The results are similar to those found in other studies. As expected, firocoxib has the longest half-life and the largest volume of distribution. It also appears to be the most potent, with calculated concentration at time 0 (C_0) 22–48 times lower than the other drugs studied following the third dose. However, there are several limitations to this study, including a small sample size and high variability in data. As a result, significant differences in the data may not have been detected because of reduced statistical power. The variability of the COX inhibition data may have also played a part in an inability to detect differences. This variability may be secondary to variability in the model, or it may indicate a different response to individual NSAIDs within individual horses. It is unlikely to be due to pharmacokinetic differences among horses, however, given the lack of variability in the reported pharmacokinetic parameters and the similarity seen between this study and previous reports of the pharmacokinetics of NSAIDs in horses.

The results of this study indicate that in the 12 h following administration of a single labelled dose, flunixin meglumine inhibits COX-1 and COX-2 activity to a significantly greater extent than does firocoxib, with no significant differences in the COX inhibition levels of the other drugs. However, in the 48 h following the third labelled dose, firocoxib and meloxicam inhibit COX-1 to a significantly lesser extent that do flunixin meglumine and phenylbutazone, while COX-2 inhibition levels are similar among all four drugs. After multiple

TABLE 2: Mean ± s.d. plasma concentrations for each NSAID studied at 24 and 48 h following the final dose administered

	Reported EC50 [17,7]	24 h	48 h
Phenylbutazone, μg/mL	1.5–4.3	1.28 (0.976–1.91)	ND
Phenylbutazone plus metabolite, μg/mL		0.69 (1.30–3.03)	ND
Flunixin meglumine, μg/mL	0.2–0.9	0.041 (0.037–0.063)	0.013 (0.012–0.025)
Flunixin meglumine plus metabolite, μg/mL		0.057 (0.055–0.079)	0.016 (0.015–0.027)
Meloxicam, μg/mL	0.13–0.195	0.118 (0.046–0.135)	0.033 (0.029–0.037)
Firocoxib, μg/mL	0.027	0.107 (0.98–0.121)	0.076 (0.073–0.094)

Data reported as median (range).

doses, the reduced COX-1 inhibition of firocoxib, and meloxicam to a lesser extent, may indeed reduce unwanted side effects in clinical patients; and the COX-2 inhibition results support similar analgesic efficacy for all four drugs. Evidence in rodent models suggests that the role of the COX isoenzymes may depend on the specific painful condition, which could alter the expected analgesic efficacy for traditional, COX-2 preferential or COX-2 selective NSAIDs (Zhu *et al.* 2005). Additional studies are needed to determine whether this is true for the horse. Comparative pharmacokinetics revealed that half-life, volume of distribution and maximum concentrations are similar between flunixin meglumine, phenylbutazone and meloxicam. As expected, firocoxib has a longer half-life and larger volume of distribution. Inhibition of COX may persist after plasma concentrations of the drug have decreased below the expected effective concentration.

Informing clinical practice

Monitoring bloodwork

Prescribing or administering a NSAID medication to an equine patient is a frequent, even daily, occurrence for many veterinary surgeons. Traditional NSAIDs, such as flunixin and phenylbutazone, can be appropriate choices for a short-term preoperative analgesic in a healthy mature horse. Bloodwork is ideal, even in the healthy horse, to evaluate the renal function and albumin as indicators of possible subclinical renal disease and gastrointestinal ulceration, respectively. If renal disease or gastrointestinal ulceration is confirmed through diagnostic evaluation, NSAID administration, traditional or COX-2 selective, is contraindicated, and an alternative class of analgesic medication should ideally be considered. In cases with renal or gastrointestinal disease where an alternative class of analgesic drug is not an option, a COX-2 selective NSAID is likely a better choice so that COX-1 physiological processes are less likely to be disrupted. In cases where renal disease or gastrointestinal ulceration is not present, but may occur secondary to the disease process or may occur secondary to prolonged NSAID administration, a COX-2 selective medication such as firocoxib would be an ideal choice. During and after treatment with any NSAID, serial bloodwork monitoring is recommended.

Dehydration and NSAIDs

The dehydrated horse is a common scenario in which NSAID administration can be harmful. The adverse effects of NSAIDs on renal homeostasis may be potentiated by dehydration (Chiarugi *et al.* 2017).

Dehydration should be corrected prior to NSAID usage via enteral or intravenous fluid administration. If that is not an option for a specific case, fluids should be administered concurrently with the NSAID and serial monitoring of renal function and albumin levels should be performed. In horses with persistent or worsening azotaemia, NSAID administration should be discontinued and alternative medications for pain relief used instead of NSAIDs.

Long-term analgesia

If a patient's analgesic plan necessitates long-term NSAID administration, a COX-2 selective NSAID should be considered. The lack of COX-1 inhibition with use of meloxicam or firocoxib may promote better homeostatic gastrointestinal and renal function, while providing effective long-term pain relief. Labelled dose regimens of these analgesics should be used, as increasing the dose or decreasing the dosing interval may negate the safety benefits provided by these drugs. As with previous case examples, serial monitoring of renal function and albumin levels is critical to identify horses that are not tolerating NSAID administration and allow for selection of an alternative category of analgesic medication.

Firocoxib loading dosage

At labelled dosages, firocoxib achieved target therapeutic concentrations after the third, but not the first dose. Firocoxib's COX-2 inhibition was similar to the nonselective NSAIDs, after the third, but not after the first, labelled dose. Therefore, clinicians should consider utilising the loading dosage of firocoxib, 0.3 mg/kg bwt, to achieve clinically significant analgesia after one dose of drug, similar to what one might expect with phenylbutazone or flunixin.

Administration of intravenous firocoxib

Firocoxib has some important practical considerations when administering intravenously that are not encountered with administration of other NSAIDs. When administered through an intravenous extension set, the intravenous formulation of firocoxib can turn the tubing white. To prevent discoloration of the line, inject the drug directly into the catheter, or use an extension set that has an additional port immediately adjacent to the catheter and administer the firocoxib only through the adjacent port. Alternatively, the drug can be administered via direct venepuncture. Additionally, firocoxib injection is a nonaqueous solution and may precipitate when administered with aqueous solutions, including saline (0.9% NaCl). To prevent crystallisation when administering through a catheter or intravenous fluid line, occlude the fluid line, aspirate blood back into the line prior to firocoxib administration and flush with either blood from the patient, or a small amount of 25% DMSO solution prior to flushing with saline.

Possible post-treatment effect in traditional NSAIDs

In this study, COX inhibition was monitored for 48 h after the third dose of drug for all four drugs. At that time point, COX-2 inhibition was similar for all drugs, despite the very low to undetectable concentrations of phenylbutazone and flunixin. COX-1 inhibition was still present for phenylbutazone and flunixin. Therefore, in horses administered a nonselective NSAID, clinicians should be aware of the possibility of adverse gastrointestinal or renal effects, well beyond the predicted 12 h of therapeutic drug concentration. These data confirm the need for a washout period when switching from a nonselective to a COX-2 selective NSAID. The length of the washout period would likely need to be tailored to the individual drug and related to the duration of dosing. A washout period of 48 h would likely be sufficient for meloxicam and firocoxib, whereas longer periods would be necessary for flunixin meglumine and phenylbutazone. The effects seen here with multiple doses suggest that the longer the animal is on the drug, the longer the washout period would need to be. It should be noted that this applies to animals that are being switched from one NSAID to another due to lack of efficacy. If the switch is being made due to development of adverse effects, the animal would require a washout period equal to the time it takes for the adverse effects to be effectively treated.

NSAIDs and analgesic efficacy

Some veterinarians have expressed doubts about the analgesic efficacy of COX-2 selective NSAIDs, firocoxib in particular. The similar levels of COX-2 inhibition found in this ex vivo study predict similar analgesic and anti-inflammatory efficacy for all four drugs. Findings from recent experimental studies in horses experiencing pain also revealed similar analgesic efficacy for firocoxib, phenylbutazone and flunixin meglumine (Doucet *et al.* 2008; Cook *et al.* 2009). Meloxicam provided adequate analgesia in a synovitis model and was effective for control of post-operative orthopaedic pain in a placebo-controlled clinical trial (Walliser *et al.* 2015; UCVM C/O 2016 *et al.* 2017). Firocoxib and flunixin provided equivalent analgesia in a recent clinical trial in horses recovering from colic surgery (Ziegler *et al.* 2019). Practitioners should feel comfortable selecting a drug of either category for effective treatment of pain, as well as prevention of pain. Practitioners should also be aware that the type of painful condition may dictate which COX isoenzyme, COX-1 or COX-2, plays the more primary role. If the analgesic response is not as expected, a change in class of NSAID or providing analgesia through a different medication class altogether should be considered.

Authors' declaration of interests

No conflicts of interest have been declared.

Ethical animal research

This study was approved by the Institutional Animal Care and Use Committee of North Carolina State University, IACUC ID# 09-161-O.

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Authorship

C. Fogle, J. Davis and A. Blikslager contributed to study design, study execution, data analysis and interpretation, and preparation of the manuscript. J. Marshall contributed to study design. B. Yechuri and K. Cordle contributed to study execution and data analysis. All authors gave their final approval of the manuscript.

Manufacturers' addresses

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[5]Cayman Chemical, USA.
[6]Systat Software Inc., USA.
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[8]Pharsight Corporation, USA.

References

Barton, M., Paske, E., Norton, N., King, D., Giguère, S. and Budsberg, S. (2014) Efficacy of cyclo-oxygenase inhibition by two commercially available firocoxib products in horses. *Equine Vet. J.* **46**, 72-75.

Beretta, C., Garavaglia, G. and Cavalli, M. (2005) COX-1 and COX-2 inhibition in horse blood by phenylbutazone, flunixin meglumine, carprofen and meloxicam: an in vitro analysis. *Pharmacol. Res.* **52**, 302-306.

Bruno, A., Tacconelli, S. and Patrignani, P. (2014) Variability in the response to non-steroidal anti-inflammatory drugs: mechanisms and perspectives. *Basic Clin. Pharmacol. Toxicol.* **114**, 56-63.

Chiarugi, A., Boner, A., Montini, G. and Ginaluigi, L. (2017) Working towards an appropriate use of ibuprofen in children: an evidence-based appraisal. *Drugs* **77**, 1295-1311.

Cook, V.L., Meyer, C.T., Campbell, N.B. and Blikslager, A.T. (2009) Effect of firocoxib or flunixin meglumine on recovery of ischemic-injured equine jejunum. *J. Am. Vet. Med. Assoc.* **70**, 992-1000.

Cox, S., Villarino, N., Sommardahl, C., Kvaternick, V., Zarabadipour, C., Siger, L., Yarbrough, J., Amicucci, A., Reed, K., Breeding, D. and Doherty, T. (2013) Disposition of firocoxib in equine plasma after an oral loading dose and a multiple dose regimen. *Vet. J.* **198**, 382-385.

Cuniberti, B., Odore, R., Barbero, R., Cagnardi, P., Badino, P., Girardi, C. and Re, G. (2012) In vitro and ex vivo pharmacodynamics of selected non-steroidal anti-inflammatory drugs in equine whole blood. *Vet. J.* **191**, 327-333.

Doucet, M., Bertone, A., Hendrickson, D., Hughes, F., Macallister, C., McClure, S., Reinemeyer, C., Rossier, Y., Sifferman, R., Vrins, A.A., White, G., Kunkle, B., Alva, R., Romano, D. and Hanson, P.D. (2008) Comparison of efficacy and safety of paste formulations of firocoxib and phenylbutazone in horses with naturally occurring osteoarthritis. *J. Am. Vet. Med. Assoc.* **232**, 91-97. [Abstract].

Holland, B., Fogle, C., Blikslager, A.T., Curling, A., Barlow, B.M., Schirmer, J. and Davis, J.L. (2014) Pharmacokinetics and pharmacodynamics of three formulations of firocoxib in healthy horses. *J. Vet. Pharmacol. Ther.* **38**, 249-256.

Howard, J.T., Baynes, R.E., Brooks, J.D., Yeatts, J.L., Bellis, B., Ashwell, M.S., Routh, P., O'Nan, A.T. and Maltecca, C. (2014) The effect of breed and sex on sulfamethazine, enrofloxacin, fenbendazole and flunixin meglumine pharmacokinetic parameters in swine. *J. Vet. Pharmacol. Ther.* **37**, 531-541.

Jaussaud, P., Courtot, D., Guyot, J. and Paris, J. (1987) Identification of a flunixin meglumine metabolite in the horse by gas chromatography-mass spectrometry. *J. Chromatogr.* **25**, 123-130.

Knych, H.K., Stanley, S.D., Arthur, R.M. and Mitchell, M.M. (2014) Detection and pharmacokinetics of three formulations of firocoxib following multiple administrations to horses. *Equine Vet. J.* **46**, 734-738.

Kvaternick, V., Pollmeier, M., Fischer, J. and Hanson, P.D. (2007) Pharmacokinetics and metabolism of orally administered firocoxib,

a novel second generation coxib, in horses. *J. Vet. Pharmacol. Ther.* **30**, 208-217.

Lees, P. and Toutain, P.L. (2013) Pharmacokinetics, pharmacodynamics, metabolism, toxicology and residues of phenylbutazone in humans and horses. *Vet. J.* **196**, 294-303.

Lees, P., Taylor, J., Higgins, A. and Sharma, S. (1986) Phenylbutazone and oxyphenbutazone distribution into tissue fluids in the horse. *J. Vet. Pharmacol. Ther.* **9**, 204-212.

Letendre, L.T., Tessman, R.K., McClure, S.R., Kvaternick, V.J., Fischer, J.B. and Hanson, P.D. (2008) Pharmacokinetics of firocoxib after administration of multiple consecutive daily doses to horses. *Am. J. Vet. Res.* **69**, 1399-1405.

Little, D., Brown, S.A., Campbell, N.B., Moeser, A.J., Davis, J.L. and Blikslager, A.T. (2007) Effects of the cyclooxygenase inhibitor meloxicam on recovery of ischemia-injured equine jejunum. *Am. J. Vet. Res.* **68**, 614-624.

Raidal, S., Hughes, K., Charman, A.-L., Nielsen, S., Phillips, J. and Noble, G. (2014) Effects of meloxicam and phenylbutazone on renal responses to furosemide, dobutamine, and exercise in horses. *Am. J. Vet. Res.* **75**, 668-679.

Tevell Aberg, A., Olsson, C., Bondesson, U. and Hedeland, M. (2009) A mass spectrometric study on meloxicam metabolism in horses and the fungus Cunninghamella elegans, and the relevance of this microbial system as a model of drug metabolism in the horse. *J. Mass Spectrom.* **44**, 1026-1037.

Toutain, P.L., Autefage, A., Legrand, C. and Alvinerie, M. (1994) Plasma concentrations and therapeutic efficacy of phenylbutazone and flunixin meglumine in the horse: pharmacokinetic/pharmacodynamic modelling. *J Vet Pharmacol Ther.* **17**(**6**), 459-469.

Toutain, P. and Cester, C. (2004) Pharmacokinetic-pharmacodynamic relationships and dose response to meloxicam in horses with induced arthritis in the right carpal joint. *Am. J. Vet. Res.* **65**, 1533-1541.

UCVM Class of 2016, Banse, H. and Cribb, A. (2017) Comparative efficacy of oral meloxicam and phenylbutazone in 2 experimental pain models in the horse. *Can. Vet. J.* **58**, 157-167.

Walliser, U., Fenner, A., Mohren, N., Keefe, T., Vries, F. and Rundfeldt, C. (2015) Evaluation of the efficacy of meloxicam for postoperative management of pain and inflammation in horses after orthopaedic surgery in a placebo controlled clinical field trial. *BMC Vet. Res.* **11**, 113.

Warner, T. and Mitchell, J. (2002) Cyclooxygenase-3 (COX-3): filling in the gaps toward a COX continuum? *Proc. Natl. Acad. Sci. USA* **99**, 13371-13373.

Zhu, X., Conklin, D. and Eisenach, J. (2005) Preoperative Inhibition of Cyclooxygenase-1 in the spinal cord reduces postoperative pain. *Anesth. Analg.* **5**, 1390-1393.

Ziegler, A., Blikslager, A. and Fogle, C. (2017) Update on the use of cyclooxygenase-2-selective nonsteroidal anti-inflammatory drugs in horses. *J. Am. Vet. Med. Assoc.* **250**, 1271-1274.

Ziegler, A., Freeman, C., Fogle, C., Burke, M., Davis, J., Cook, V., Southwood, L. and Blikslager, A. (2019) Multicentre, blinded, randomized, clinical trial comparing the use of flunixin meglumine with firocoxib in horses with small intestinal strangulating obstruction. *Equine Vet. J.* **51**, 329-335.

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Original Article

Ultrasonographic guided block of the median nerve

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Keywords: horse; ultrasonographic guided injection; diagnostic analgesia; median nerve

Summary

Median nerve anaesthesia is sometimes indicated in the diagnosis of forelimb lameness in the horse in conjunction with the ulnar nerve block, but the localisation of the nerve to perform a precise deposition of the anaesthetic solution around and close to the nerve is difficult to achieve using the conventional blind technique. The objectives of this paper are to describe the ultrasonographic anatomy of the median nerve and the technique for performing an ultrasound-guided anaesthetic block of the nerve. The median nerve is imaged using a microconvex (or linear) probe in transverse section performed proximally to the chestnut on the medial aspect of the forearm. Distribution of the anaesthetic solution around the nerve is done by initially inserting the needle caudally and then cranially to the nerve and injecting 4–6 mL at each site. Control of the needle penetration avoids erroneous intravascular or intramuscular injections or sudden horse reaction. Ultrasound-guided injection has the potential to safely and accurately block the median nerve.

Introduction

Ultrasonographic guided injections (USGI) are currently widely used for treating joint disease (Denoix 2006; Carnicer *et al.* 2008) as well as neck, back and pelvic conditions in horses (Denoix and Heitzmann 2005). Growing interest for the use of these techniques is related to the rapid advances in ultrasound technology and the availability of compact portable machines with adequate image quality and resolution to perform USGI. Use of USGI for blocking nerves is rarely reported in equine medicine (Denoix and Audigié 2011; Denoix *et al.* 2020) but is widespread in other species (Shilo *et al.* 2010; Campoy *et al.* 2010; Echeverry *et al.* 2010) and in human medicine (Gray 2006; Marhofer and Chan 2007). Indeed, preliminary results indicate that the use of ultrasound can improve block success rate and decrease complications (Marhofer and Chan 2007). Diagnostic nerve blocks are an essential step to identify the source of pain in lameness evaluation of the horse. Unfortunately, many pitfalls are reported leading to false negative and false positive responses. Amongst them, inappropriate placement and diffusion of the anaesthetic solution are one of the most common complications (Denoix and Tapprest 1992; Nagy *et al.* 2009; Davidson 2018). The use of an ultrasound-guided technique for nerve blocks should assist in avoiding or reducing such complications. Median nerve anaesthesia in practice is often considered in the diagnostic approach of forelimb lameness using a conventional blind technique (Dyson 1984; Denoix 1991; Denoix and Tapprest 1992; Denoix 1995; Bassage and Ross 2003; Fürst 2012). Whilst the anatomical landmarks for blocking superficial nerves in the distal limb, metacarpus and metatarsus can easily be identified (Dyson 1984; Denoix 1991; Denoix and Tapprest 1992), the exact location of deep nerves such as the median nerve is more difficult to determine, which enhances the interest of using USGI to anaesthetise this nerve.

To perform an optimal ultrasound-guided (USG) nerve block, the targeted nerve should be clearly identified, and the needle and the spread of the anaesthetic solution around the nerve should be tracked in real time (Marhofer and Chan 2007; Denoix *et al.* 2020). The objective of this paper is to describe the ultrasonographic anatomy of the median nerve and the technique to perform USG block of this nerve.

Anatomy of the median nerve

The median nerve is the biggest nerve of the forearm (Ghoshal and Getty 1968; Barone and Simoens 2010). It runs

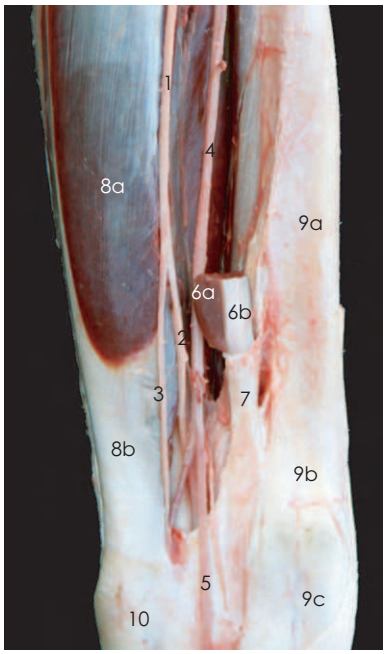

Fig 1: Medial aspect of the dissected antebrachium: superficial structures.* Vessels and nerves: *1 – median nerve; 2 – medial palmar nerve; 3 – Ramus communicans with ulnar nerve (lateral palmar nerve); 4 – median artery; 5 – distal radial artery.* Muscles and tendons: *6 – flexor carpi radialis muscle, 6a – muscle body, 6b – distal tendon; 7 – tendon sheath of the flexor carpi radialis distal tendon; 8 – flexor carpi ulnaris muscle, 8a – body, 8b – distal tendon. Bones: 9 – radius; 9a – body; 9b – distal metaphysis, 9c –styloid process; 10 – accessory carpal bone.

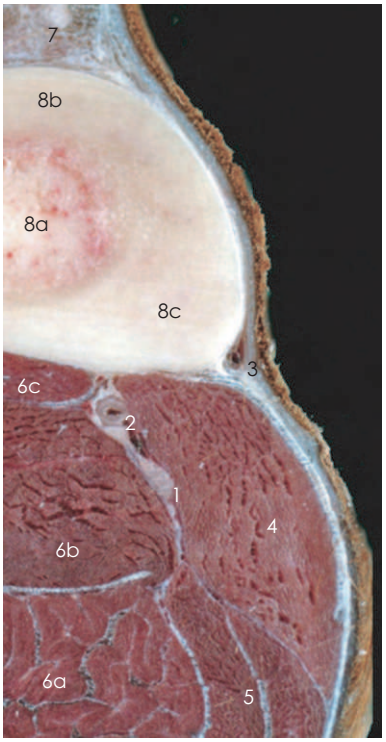

Fig 2: Transverse anatomical section of the antebrachium made at its mid-level (adapted from Denoix 2019). **Vessels and nerves:** ***1 – median nerve; 2 – median artery and veins (collapsed); 3 – cephalic vein (collapsed).*** **Muscles and tendons:** ***4 – flexor carpi radialis muscle; 5 – flexor carpi ulnaris muscle; 6 – deep digital flexor muscle, 6a – caudal part of the humeral head (fused with the superficial digital flexor muscle body), 6b – cranial part of the humeral head, 6c – radial head; 7 – extensor carpi radialis musculotendinous junction.*** **Bones:** ***8 – radius, 8a – medullary cavity, 8b – cranial cortex, 8c – medial cortex.***

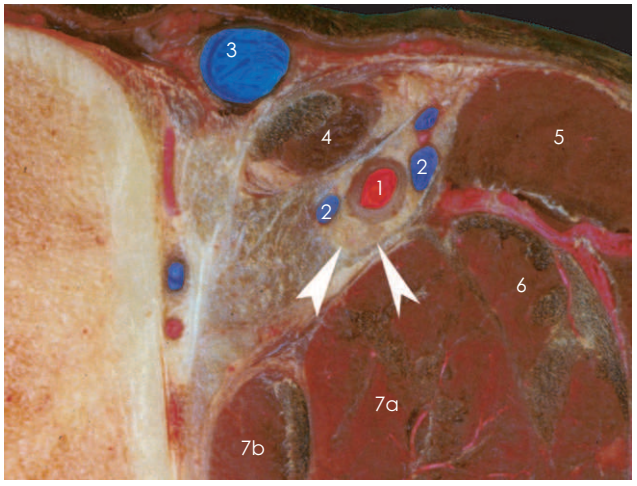

Fig 3: Transverse anatomical section of the antebrachium made just proximal to the chestnut and focused on the median nerve. Arrowheads: median nerve; 1 – median artery; 2 – median veins; 3 – cephalic vein; 4 – flexor carpi radialis musculotendinous junction; 5 – flexor carpi ulnaris muscle; 6 – superficial digital flexor muscle; 7a and 7b – deep digital flexor muscle.

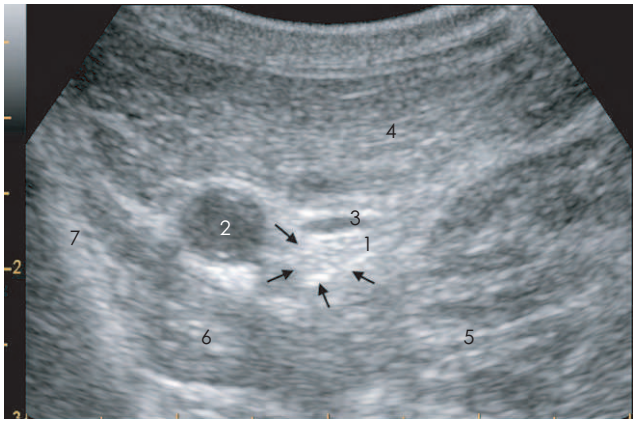

Fig 4: Transverse ultrasound image of the middle forearm using a medial approach with a 7.5 MHz microconvex probe: focused on the median nerve (arrows). Cranial is to the left. 1 – Median nerve; 2 – median artery; 3 – median vein (collapsed); 4 – flexor carpi radialis muscle; 5 – humeral head of the deep digital flexor muscle; 6 – radial head of the deep digital flexor muscle; 7 – radius (caudal aspect).

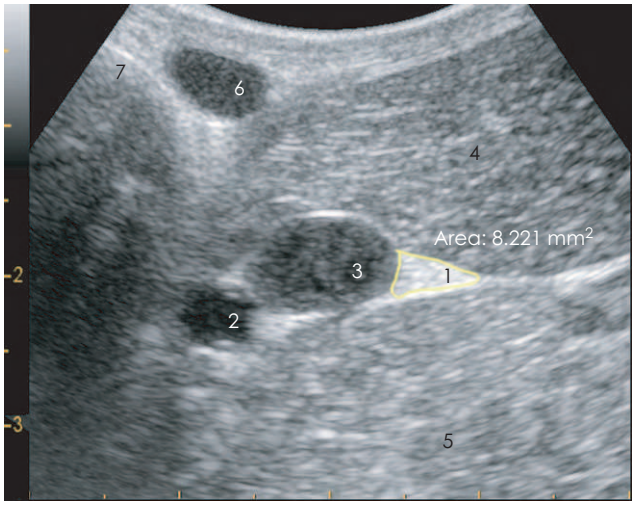

Fig 5: Triangular cross-sectional shape and area of the median nerve at the middle forearm. Cranial is to the left. 1 – Median nerve (cross-sectional area 8.2 mm²); 2 – median artery; 3 – median vein; 4 – flexor carpi radialis muscle; 5 – humeral head of the deep digital flexor muscle; 6 – cephalic vein; 7 – radius.

caudally to the radius and deep to the flexor carpi radialis. It is closely related to the median artery (**Fig 1**). In the proximal forearm, it provides strong muscle rami for the deep and superficial digital flexor muscles and for the flexor carpi radialis muscle (Barone 2000; Barone and Simoens 2010). In the middle forearm, it is located approximately 2 cm deep and 2 cm caudal to the radius and is then deep and caudal to the median artery and veins (**Fig 2**) (Denoix 2019). In the distal forearm, it can be found deep (lateral) or caudal to the median artery and veins (**Fig 3**)

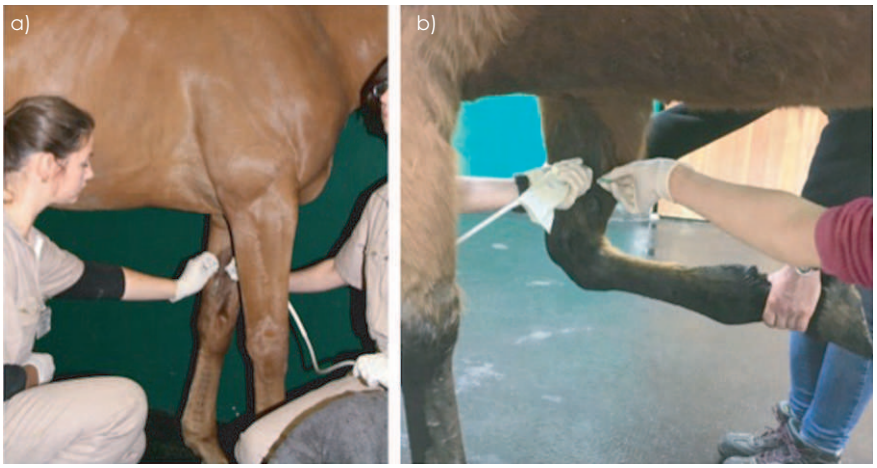

Fig 6: Positioning of the operators for injecting the median nerve using a caudal approach. a)* On the weightbearing. *A twitch is placed on the upper lip of the horse. The probe operator places the probe passing cranially to the opposite forelimb. The needle operator is approaching the injected limb caudomedially; b)* on the flexed limb with a third operator. *The operators' positions are the same, but a third operator is necessary to pull the injected limb caudally. This positioning is safer to avoid sudden flexion of the carpus of the weightbearing limb and the risk of fall.

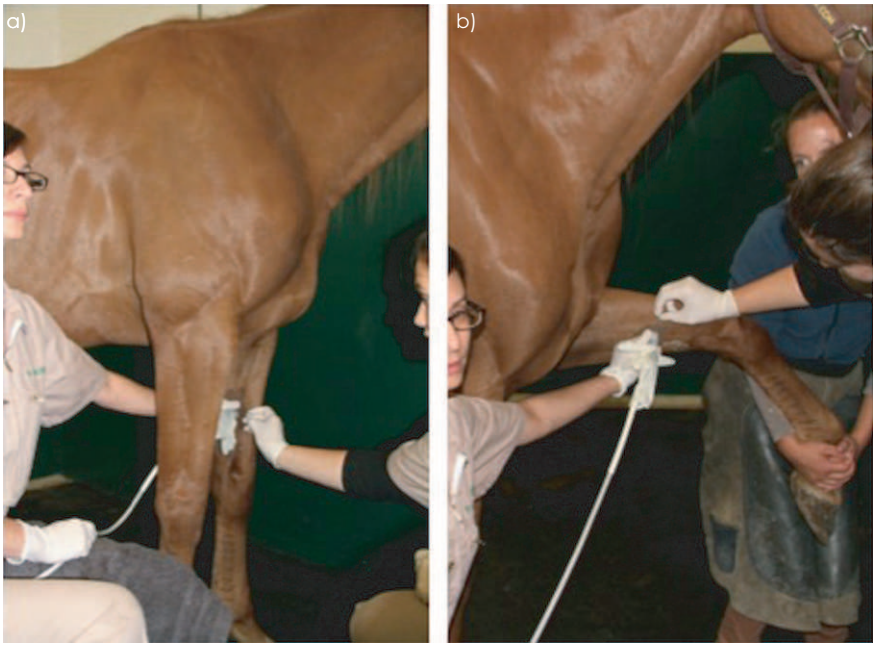

Fig 7: Positioning of the operators for injecting the median nerve using a cranial approach. a)* On the weightbearing. *A twitch is placed on the upper lip of the horse. The probe operator places the probe passing caudally to the opposite forelimb. The needle operator is approaching the injected limb craniomedially, after careful evaluation of the horse behaviour; b)* On the flexed limb with a third operator. *The third operator pulls the injected limb cranially and keeps it stable.

and finishes approximately at the distal quarter of the forearm at a bifurcation that produces two rami just above the accessory ligament of the superficial flexor muscle (Barone and Simoens 2010). One of them (lateral palmar nerve) joins the palmar ramus of the ulnar nerve and participates in the constitution of the lateral palmar common digital nerve. As for the main ramus (medial palmar nerve), it runs in the carpal canal and continues in the metacarpus as the medial common digital palmar nerve. The median nerve, together with the ulnar nerve, provides all deep sensitivity and the main part of skin sensitivity of the carpus, metacarpus (including bones and tendons) and distal limb (fetlock, pastern and foot) (Denoix 1995; Bassage and Ross 2003; Barone and Simoens 2010).

Indications for performing an USG block of the median nerve include the following:

- Diagnosis of the site of pain of a lame horse when a proximal metacarpal nerve block is negative or partially positive (Denoix 1991).

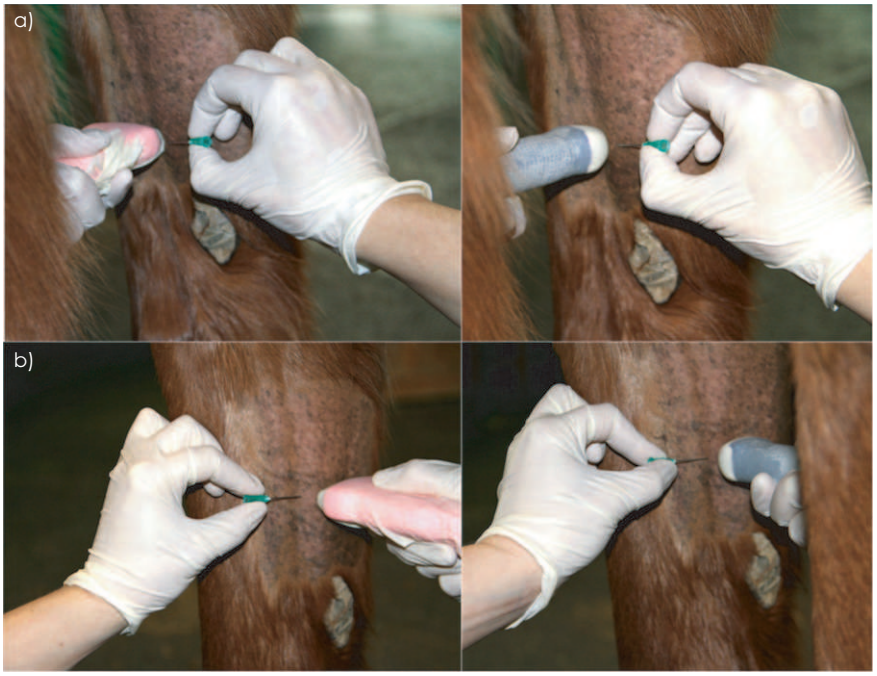

Fig 8: Positioning of the probes for injecting the median nerve. a) Linear and microconvex probes for the caudal approach; b) linear and microconvex probes for the cranial approach.

- Suspicion of subchondral carpal bone pain that does not respond to intra-articular analgesia of the carpus (Bassage and Ross 2003).
- Suspicion of lameness arising from the carpal canal (Bassage and Ross 2003).
- Exclusion of any distal or middle forelimb cause of pain when a proximal forelimb lameness is suspected (Denoix 1995).
- Standing surgery on the carpus or proximal metacarpus. For example, this block can be performed to facilitate lavage of the carpal joints or carpal canal or to perform regional limb perfusion of antimicrobials in standing horses (Bassage and Ross 2003).

Usually an ulnar nerve block is done in conjunction with the median nerve block to induce complete anaesthesia of the distal limb (carpus, metacarpus and digital area).

Ultrasonographic anatomy of the median nerve in the middle forearm

On a transverse ultrasound section performed proximally to the chestnut using a medial approach, the median nerve is imaged as an echogenic structure close to the median artery and veins. This neurovascular bundle is deep to the flexor carpi radialis muscle body, medial to humeral head of the deep digital flexor muscle (DDFM) body and caudal to the radial head of DDFM (**Fig 4**). As mentioned previously, it can be found deep or caudal to the median artery. Its cross-sectional shape can vary from triangular to oval depending on its location. Its cross-section is approximately between 8 and 10 mm^2 in a 550 kg horse (**Fig 5**). It is usually 20–25 mm deep to the skin (Alexander and Dobson 2003) and 20–22 mm caudal to the caudal cortex of the radius (Denoix 1995). On high detailed ultrasonographic images, its fascicular architecture can be seen (**Fig 4**) (Alexander and Dobson 2003; Denoix and Audigié 2011).

Technical data for performing an ultrasonographic guided block of the median nerve

Equipment and preparation

The basic equipment to perform an USG block of the median nerve includes a 25 mm 21-gauge needle and a 6–10 MHz microconvex probe. A linear probe can also be used but adequate positioning is required to improve ultrasonographic image quality (Whitcomb 2009) and to facilitate visualisation and guidance of the needle. The adequate positioning will be described and illustrated in the next paragraph describing the USGI technique. The use of an epijet (Venipuncture Set) may help to avoid repositioning the needle if the horse moves (Denoix et al., 2020). If an epijet is used, it is important to flush the extension set to avoid injecting gas which can cause acoustic shadowing and comet artefacts, making it more difficult to visualise the nerve (Zekas and Forrest 2005).

If too long, the hair is clipped from the chestnut to 5 cm proximal at the medial aspect of the forearm. The skin is prepared aseptically. A sterile glove is placed over the microconvex probe.

Horse restrain and operator(s) positioning

The median nerve can either be blocked on the weightbearing or on the flexed limb. In our experience, it is safer to block the median nerve on the flexed limb as the horse may flex the limb and fall down if the needle touches the nerve. However, the flexed procedure requires three operators. A twitch is placed on the upper lip of the horse, and both operators (one holding the probe, and one placing the needle) are approaching the medial aspect of the

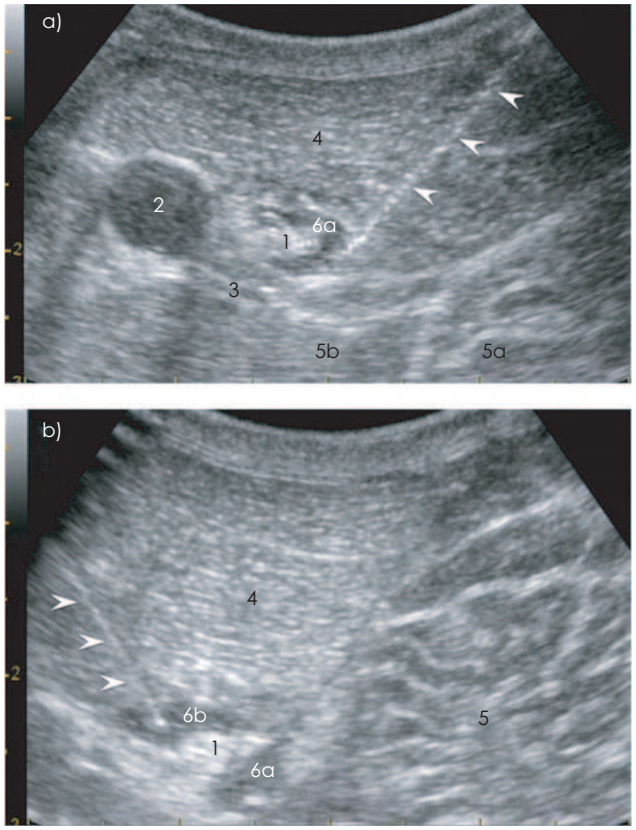

Fig 9: Ultrasonographic guided perineural injection of the median nerve – transverse ultrasound image of the medial part of the middle forearm with a microconvex probe. Cranial is to the left. a) Caudal approach; b) cranial approach. 1 – Median nerve; 2 – median artery; 3 – median vein; 4 – flexor carpi radialis muscle; 5 – humeral head of the deep digital flexor muscle, 5a – caudal part of the humeral head, 5b – cranial part of the humeral head; 6a – anaesthetic solution injected in the conjunctive tissue at the caudal aspect of the nerve, 6b – anaesthetic solution injected in the conjunctive tissue at the cranial aspect of the nerve. Arrowheads: needle.

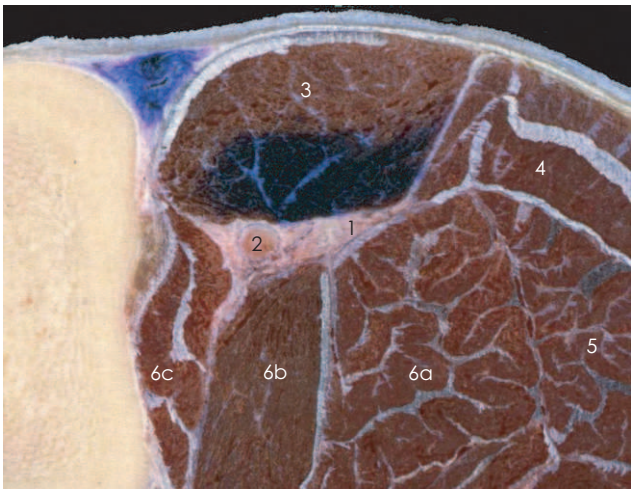

Fig 10: Erroneous perineural injection of the median nerve made with methyl violet on a isolated thoracic limb. Transverse anatomical section of the medial part of the middle forearm (adapted from Denoix 1995). The coloured solution has been injected in the deep and lateral part of the flexor carpi radialis muscle impairing diffusion to the nerve. **Vessels and nerves:** ***1 – median nerve; 2 – median artery and veins (collapsed).*** **Muscles and tendons:** ***3 – flexor carpi radialis muscle; 4 – flexor carpi ulnaris muscle; 5 – superficial digital flexor muscle; 6 – deep digital flexor muscle, 6a – caudal part of the humeral head (fused with the superficial digital flexor muscle body), 6b – cranial part of the humeral head, 6c – radial head.***

injected limb from the opposite side of the horse for ergonomic and safety reasons (**Figs 6** and **7**). To achieve a complete and efficient block of the median nerve, it is best to combine injection of local anaesthetic solution caudally and cranially to the nerve.

Injection of the caudal aspect of the median nerve on the weightbearing limb is performed with the guide operator imaging the nerve from the cranial aspect of the opposite forelimb, and the needle operator is operating from the caudal aspect of this limb (**Figs 6a** and **8a**). On the flexed limb, the operators' positions are the same but a third operator is necessary to hold the injected limb in a retracted position (**Fig 6b**). The operators' positions are reversed for injecting the cranial aspect of the median nerve (**Figs 7a** and **8b**). On the flexed limb, the third operator holds the injected limb in protraction (**Fig 7b**).

Ultrasonographic guided injection technique

Caudal approach

The probe is placed transversally at the medial aspect of the forearm over the flexor carpi radialis muscle body, proximal to the chestnut and up to 5 cm proximally to it (**Fig 6a,b**). The median nerve is imaged close to the median artery. If a linear probe is used, it must be shifted cranially to facilitate adequate positioning of the needle (**Fig 8a**). The 25 mm long needle is placed in the ultrasound beam, caudally to the probe and directed to the caudal aspect of the median nerve (**Fig 9a**). Injection of 4–6 mL of mepivacaine[1] or lidocaine hydrochloride[2] is made in the loose connective tissue embedding the neurovascular bundle to avoid touching the nerve. Once anaesthetic fluid is seen close to the nerve, the needle is approached closer to it to complete the injection.

Cranial approach

The probe is placed transversely at the same level but moved slightly caudally to open enough space between its surface and the radius (**Fig 7a,b**). If a linear probe is used, it must be shifted caudally to facilitate adequate positioning of the needle (**Fig 8b**). A 25 mm long needle is placed cranially to the probe and directed to the cranial aspect of the median nerve (**Fig 9b**). As soon as the tip of the needle is seen in the perineural connective tissue, injection is performed. Once anaesthetic fluid is seen close to the median nerve, the needle can be placed closer to the nerve and injection of 4–6 mL of anaesthetic solution is made again.

Results of the ultrasonographic guided injections

The objective of performing both cranial and caudal approaches is to distribute the anaesthetic solution all around the nerve, achieving a complete troncular anaesthesia (Denoix *et al.* 2020). Erroneous intramuscular (**Fig 10**) (Denoix

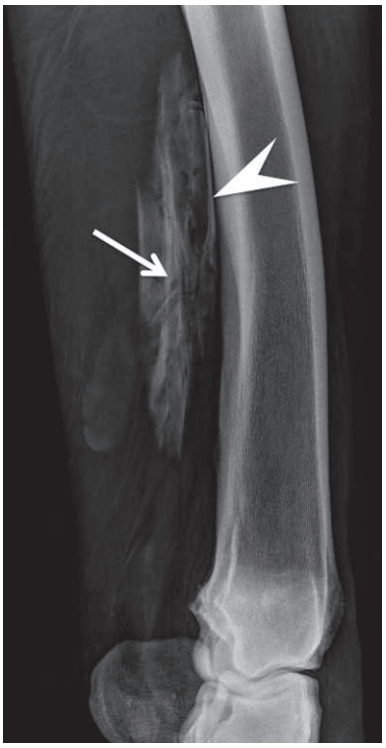

Fig 11: Lateromedial radiograph of the forearm after ultrasonographic guided injection of a total volume of 12 mL of diluted contrast material cranially and caudally to the median nerve. The radiograph was taken 10 min after injection. Note, the proximal diffusion of contrast material deep to the flexor carpi radialis (arrowhead) and the perivascular diffusion around the median nerve and vessels (arrow).

1995) and intravascular injections (Denoix and Tapprest 1992) must be avoided. As for every other nerve block (Nagy *et al.* 2009; Denoix *et al.* 2020), a proximo-distal diffusion of the anaesthetic solution in the perinervous connective tissue is expected and can be imaged using ultrasonography or documented using contrast radiography (**Fig 11**). Proximal diffusion in the connective tissue along the neurovascular bundle (median artery, veins, nerve) may block the lateral palmar nerve that joins the ulnar nerve and may induce partial anaesthesia of the muscle rami of the median nerve arising in the proximal antebrachium. No correlated adverse reactions on the horse gait have been noted following block of the median nerve. Five to ten minutes after injection, successful anaesthesia of the medial heel of the injected forelimb must be checked to assess reliability of the median nerve block (Dyson 1984). The horse can then be re-examined to assess changes in lameness from 5 min after injection. Many horses improve between 5 to 10 min after the block. If improvement is partial, further examinations up to 30 min after injection can be performed (Dyson 1984; Denoix and Tapprest 1992; Denoix 1995; Bassage and Ross 2003) but specificity for blocking exclusively distal or local pain decreases.

Discussion

In our experience, USGI is an easy and rewarding method for median nerve anaesthesia because of direct visualisation of the nerve and diffusion of anaesthetic solution. In the study of Alexander and Dobson (2003), the success rate in identifying the median nerve with ultrasound was 100% on living horses. Five ultrasound examinations were also performed on cadaveric limbs including two USGI of methylene blue. After dissection, the methylene blue was well distributed around the median nerve on both specimens and ultrasonography was then considered to be potential interesting tool for identification of peripheral nerves, evaluation of nerve damage or to perform specific local anaesthesia. Ultrasonographic guidance was also reported to enable a real-time positioning of the needle and a correct distribution of anaesthetic solution (Marhofer and Chan 2007; Strakowski 2016). As the position of the nerve varies along the forearm, anaesthetic solution infusion can indeed be adjusted given the depth and position of the nerve with respect to the median artery. Control of the needle penetration is also crucial to avoid touching the median nerve and experience sudden horse reaction (Fürst 2012). Puncturing and intraneural injections of peripheral nerves did however not result in neurological damage in a human study (Bigeleisen 2006). USGI therefore appears to be more reliable and safer than the conventional blind technique that is based on external anatomical landmarks. Furthermore, for safety reasons, injection on the flexed limb is preferred to avoid sudden flexion of the carpus and the risk of fall. However, this technique requires the intervention of an additional operator.

USGI procedure has the potential to improve the accuracy of the median nerve block. For example, intramuscular injection in the flexor carpi radialis muscle or humeral head of the deep digital flexor muscle reduces diffusion in the adjacent connective tissue containing the median nerve. This erroneous injection is difficult to avoid using a blind technique. A review from Marhofer and Chan (2007) reports positive outcomes in human case series with improvement of success rates, faster onset of effect and longer duration of anaesthesia when using USGI technique compared to conventional techniques. Another study indicates that lower doses of anaesthetic solution can be injected when using USGI, reducing the occurrence and speed of diffusion of the anaesthetic solution (Eichenberger *et al.* 2009). Median nerve block is expected to induce complete analgesia of the medial aspect of the carpus and lower limb, and partial analgesia of its lateral aspect as median nerve fibres are joining the lateral common digital nerve through the ramus communicans crossing the palmar aspect of the flexor tendons in the metacarpus (Denoix and Tapprest 1992; Barone and Simoens 2010). Recent investigations have shown that some fibres coming from the lateral common digital nerve can run in a reverse direction to the ramus communicans to the medial common digital nerve (Schumacher *et al.* 2013). This could explain incomplete analgesia and skin anaesthesia of the medial aspect of the distal limb when the median nerve is anaesthetised alone. A complete analgesia of the deep structures of limb distal to the site of the block requires simultaneous blocks of the median and ulnar nerves (Denoix and Tapprest 1992; Bassage and Ross 2003).

The USGI technique described in this paper appears safer and more accurate than the blind technique to anaesthetise the median nerve. It can be performed easily with any portable ultrasound machine equipped with a microconvex or linear probe.

Authors' declaration of interest

No conflicts of interest have been declared.

Ethical animal research

Not applicable to this article.

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Authorship

A. Beaumont was responsible for the study design. All authors contributed to the study execution and image acquisition. A. Beaumont and L. Bertoni prepared the manuscript. All authors gave their final approval of the manuscript.

Manufacturers' addresses

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[2]CEVA Sante Animale, Libourne, France.

References

Alexander, K. and Dobson, H. (2003) Ultrasonography of peripheral nerves in the normal adult horse. *Vet. Radiol. Ultrasound* **44**, 456-464.

Barone, R. (2000) Anatomie comparée des Mammifères domestiques. In: *Tome second Arthrologie et Myologie*, Ed: R. Barone, Editions Vigot, Paris. pp 773-791.

Barone, R. and Simoens, P. (2010) Anatomie comparée des mammifères domestiques. In: *Tome seventh Neurologie II*. Ed: R. Barone, Editions Vigot, Paris. pp 187-198.

Bassage, L.H. II and Ross, M.W. (2003) Diagnostic analgesia. In: *Diagnosis and Management of Lameness in the Horse*, Eds: M.W.Ross and S.J.Dyson, Elsevier, St Louis. pp 93-123.

Bigeleisen, P.E. (2006) Nerve puncture and apparent intraneural injection during ultrasound-guided axillary block does not invariably result in neurologic injury. *Anesthesiology* **105**, 779-783.

Campoy, L., Bezuidenhout, A.J., Gleed, R.D., Martin-Flores, M., Raw, R.M., Santare, C.L., Jay, A.R. and Wang, A.L. (2010) Ultrasound-guided approach for axillary brachial plexus, femoral nerve, and sciatic nerve blocks in dogs. *Vet. Anaesth. Analg.* **37**, 144-153.

Carnicer, D., Coudry, V. and Denoix, J.-M. (2008) Ultrasonographic guided injection of the scapulohumeral joint in horses. *Equine Vet. Educ.* **20**, 103-106.

Davidson, E.J. (2018) Lameness evaluation of the athletic horse. *Vet. Clin. N. Am. Equine Pract.* **34**, 181-191.

Denoix, J.-M. (1991) Anesthésies sémiologiques des régions proximales des membres chez le cheval, In: *Proceedings International Conference Equine Surgery*, Geneva. p 82.

Denoix, J.-M. (1995) Anesthésie sémiologique nerveuse antébrachiale chez le cheval. *Rec. Med. Vet.* **171**, 747-756.

Denoix, J.-M. (2006) Ultrasonographic guided injections of joints in horses. In: *Proceedings 9th World Equine Veterinary Association (WEVA) Congress*, Marrakech.

Denoix, J.-M. (2019) *Essentials of Clinical Anatomy of the Equine Locomotor System*, CRC Press, Boca Raton. p 46.

Denoix, J.-M. and Audigié, F. (2011) Diagnosis of peripheral nerve injuries in horses. In: *Proceedings 7th MRI User Meeting*, Bern.

Denoix, J.-M. and Heitzmann, A.G. (2005) Apport des injections échoguidées pour les traitements locaux et intra-articulaires. In: *Proceedings of the Association Vétérinaire Équine Française (AVEF) Congrès*, Montpellier. pp 24-27.

Denoix, J.-M. and Tapprest, J. (1992) Anesthésies sémiologiques nerveuses tronculaires dans le diagnostic des boiteries chez le cheval : 2e partie. *Point Vet.* **24**, 259-273.

Denoix, J.-M., Beaumont, A. and Bertoni, L. (2020) Ultrasonographic guided block of the tibial nerve. *Equine Vet. Educ*. **32**, 372-377.

Dyson, S. (1984) Nerve blocks and lameness diagnosis in the horse. *In Practice* **6**, 102-107.

Echeverry, D.F., Gil, F., Laredo, F., Ayala, M.D., Belda, E., Soler, M. and Agut, A. (2010) Ultrasound-guided block of the sciatic and femoral nerves in dogs: a descriptive study. *Vet. J.* **186**, 210-215.

Eichenberger, U., Stöckli, S., Marhofer, P., Huber, G., Willimann, P., Kettner, S.C., Pleiner, J., Curatolo, M. and Kapral, S. (2009) Minimal local anesthetic volume for peripheral nerve block: a new ultrasound-guided, nerve dimension-based method. *Region. Anesth. Pain Med.* **34**, 242.

Fürst, A.E. (2012) Diagnostic anesthesia. In:*Equine Surgery*, Eds: J.A. Auer and J.A. Stick, Elsevier, St Louis. pp 998-1015.

Ghoshal, N.G. and Getty, R. (1968) A comparative morphological study of the somatic innervation of the antebrachium and manus of the domestic animal (Bos taurus, Ois aries, Capra hircus, Sus scrofa domesticus, Equus caballus). *Iowa State J. Sci.* **42**, 283-296.

Gray, A.T. (2006) Ultrasound-guided regional anesthesia current state of the art. *Anesthesiology* **104**, 368-373.

Marhofer, P. and Chan, V.W.S. (2007) Ultrasound-guided regional anesthesia: current concepts and future trends. *Anesth. Analg.* **104**, 1265.

Nagy, A., Bodo, G., Dyson, S.J., Szabo, F. and Barr, A.R.S. (2009) Diffusion of contrast medium after perineural injection of the palmar nerves: an in vivo and in vitro study. *Equine Vet. J.* **41**, 379-383.

Schumacher, J., Taintor, J., Schumacher, J., Degraves, F., Schramme, M. and Wilhite, R. (2013) Function of the *ramus communicans* of the medial and lateral palmar nerves of the horse: Function of the *ramus communicans* of the palmar nerves. *Equine Vet. J.* **45**, 31-35.

Shilo, Y., Pascoe, P.J., Cissell, D., Johnson, E.G., Kass, P.H. and Wisner, E.R. (2010) Ultrasound-guided nerve blocks of the pelvic limb in dogs. *Vet. Anaesth. Analg.* **37**, 460-470.

Strakowski, J.A. (2016) Ultrasound-guided peripheral nerve procedures. *Phys. Med. Rehabil. Clin. N. Am.* **27**, 687-715.

Whitcomb, M.B. (2009) Review of ultrasonographic techniques to improve musculoskeletal image quality. *AAEP Proc.* **55**, 431-437.

Zekas, Lisa J. and Forrest, Lisa J. (2005) Effect of perineural anesthesia on the ultrasonographic appearance of equine palmar metacarpal structures. *Vet. Radiol. Ultrasound* **44**, 59-64.

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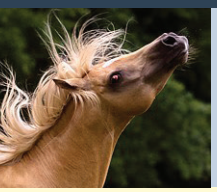

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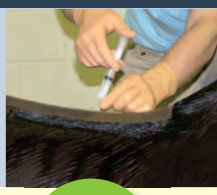

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Original Article

Safety and efficacy of subcutaneous alpha-tocopherol in healthy adult horses

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Keywords: horse; vitamin E; alpha-tocopherol

Summary

Vitamin E is essential for neuromuscular function. The primary treatment, oral supplementation with natural ('RRR') α-tocopherol, is not effective in all horses. The objectives of this pilot study were to evaluate the safety and efficacy of a subcutaneously administered RRR-α-tocopherol preparation. Horses were randomly assigned in a cross-over design to initially receive RRR-α-tocopherol (5000 IU/450 kg of 600 IU/mL) subcutaneously (n = 3) or orally (n = 3) or were untreated sentinels (n = 2). Tissue reactions following injection in Phase I of the study necessitated adjustment of the preparation with reduction of the RRR-α-tocopherol concentration to 500 IU/mL in Phase 2. Following an 8-week washout period, horses received the reciprocal treatment route with the new preparation (5000 IU/450 kg of 500 IU/mL). Serum, CSF and muscle α-tocopherol concentrations were determined by high-performance liquid chromatography over a 14-day period during each phase. Serum and CSF α-tocopherol concentrations increased significantly postinjection only when the 500 IU/mL product was administered (P<0.0001). There was no significant difference in the muscle concentration of α-tocopherol following either treatment. All eight horses had marked tissue reaction to subcutaneous injection, regardless of product concentration. Whilst we have demonstrated that this route may be a useful alternative to oral supplementation, the marked tissue reaction makes use of such products limited at this time to only the most refractory of cases.

Introduction

Horses appear to be particularly susceptible to vitamin E deficiency mediated neurological and muscular degeneration (Finno and Valberg 2012). Horses at risk of deficiency, most commonly due to dry-lot management, or with diagnosed deficiency (serum α-tocopherol <2 μg/mL) are typically supplemented with RRR- α-tocopherol, the most potent enantiomer of vitamin E and the natural form found in lush pasture (Finno and Valberg 2012). However, there are anecdotal reports of horses administered appropriate doses and formulations of oral α-tocopherol failing to respond clinically, with serum concentrations not increasing as expected. Recently, malabsorption of orally administered α-tocopherol secondary to eosinophilic enteritis has been implicated in the aetiology of equine motor neuron disease (Díez de Castro *et al.* 2016). Currently, there are no parenteral α-tocopherol products approved for use in horses. Whilst E-Se® contains alpha-tocopherol, it is in the synthetic formulation and has been demonstrated not to affect serum alpha-tocopherol concentrations in foals (Finno *et al.* 2015). Administration by parenteral routes is routinely performed in food producing species with apparent efficacy (Hidiroglou and Karpinski 1991). The objective of this study was to provide preliminary safety and efficacy data for the subcutaneous administration of α-tocopherol formulated for injection. We hypothesised that subcutaneous administration of RRR-α-tocopherol would increase serum, cerebrospinal fluid and muscle concentrations in vitamin E-deficient horses.

Materials and methods

Animals

Eight adult mixed breed horses (mares n = 4; geldings n = 4), weighing 547.7 ± 47.7 kg and aged 3 to 12 years were used in this study. Based on a noninferiority power analysis for a cross-over design with an $\alpha = 0.05$, $\beta = 0.8$ and $\delta = 0.4$, a sample size of three animals would be necessary.

All horses were housed at the same facility on dry lots. All horses were fed twice daily with grass hay at ~2% bodyweight per day and underwent annual routine husbandry such as dental exams and core vaccinations. No animals in this study were provided with an oral α-tocopherol supplement prior to the study. The Institutional Animal Care and Use Committee at the University of California, Davis approved the study design.

Study design

Initially, a balanced cross-over design was employed with horses randomly assigned to receive the same α-tocopherol preparation once by subcutaneous injection (n = 3) or orally (n = 3). Horses were administered a total dose of 5000 IU (i.e. 10 IU/kg) α-tocopherol by either route. Following an 8-week washout period, animals received the reciprocal treatment. The washout period was determined from previously

published data (Brown *et al.* 2017). All subcutaneous injections were performed after aseptic preparation of the skin over the left pectoral area. The α-tocopherol product was sterilely filtered via a 170- to 250-μm blood component filter (Y-type blood solution set)[1] prior to administration. Due to marked tissue reactions with the original 600 IU/ml formulation (customised preparation, Phase 1)[2], a 500 IU/ml preparation (Vital-E)[2] was used for Phase 2 in an attempt to mitigate the swelling associated with the injection. However, the total dose (5000 IU per horse) remained unchanged for both phases. Two animals (one mare, one gelding; aged 7 and 11 years, respectively) served as environmental sentinels for the entire study period, with only serum samples collected from these animals. The University of California Animal Use and Ethics Committee approved all procedures.

Cerebrospinal fluid (CSF) was collected on day 0 of the experiment. A jugular catheter was placed in all horses. Horses were premedicated with xylazine (1.1 mg/kg bwt i.v.), and general anaesthesia was induced with ketamine hydrochloride (2.2 mg/kg bwt i.v. and midazolam (0.05 mg/kg bwt i.v.). Horses were placed in right or left lateral recumbency and CSF fluid collected in sterile fashion by atlanto-occipital (AO) centesis using an 8.9-cm 18 gauge spinal needle. CSF was collected again in a similar fashion on day 7 post α-tocopherol administration. AO centesis was performed under general anaesthesia in preference to standing collection techniques in order to obtain a higher volume sample with less risk of blood contamination. Samples were collected into plain light-protected plastic vials and kept on ice. Samples were centrifuged at 4°C within 3 h of collection, and the supernatant stored at −80°C until analysis. The same sampling protocol was followed for the reciprocal treatment in phase 2 of the experiment.

Serum was collected immediately before anaesthesia on day 0 into plain light-protected vacutainer tubes. Further serum samples were collected 24, 48, 96 h, 7 and 14 days following α-tocopherol administration. All samples were centrifuged within 3 h of collection and stored at −80°C until analysis. The same sampling protocol was followed for the reciprocal treatment in phase 2 of the experiment.

Muscle was sampled from the gluteus medius whilst the horses were anaesthetised on days 0 and 7. An additional sample was collected on day 14 understanding sedation (xylazine 0.4 mg/kg bwt). Muscle samples were aseptically collected using a Bergström biopsy needle as previously described (Snow and Guy 1976). The sample site was alternated for each sample. All samples were flash-frozen in liquid nitrogen immediately at collection and stored in plastic, light-protected vials at −80°C until analysis. The same sampling protocol was followed for the reciprocal treatment in phase 2 of the experiment.

Serum, CSF and muscle α-tocopherol concentrations were measured at the Iowa State Veterinary Laboratory. Additionally, both injectable products were subjected to independent α-tocopherol quantification. All samples and both injectable products were analysed by HPLC as previously described (Finno *et al.* 2015).

Data analysis

Data were analysed by commercial software (GraphPad Prism 7.4)[3]. Due to small sample size, baseline samples for serum, CSF and muscle were evaluated by Kruskal–Wallis test for each treatment phase. There was no significant difference between baseline measurements; therefore, the washout period was considered appropriate. Serum, CSF and muscle tissue α-tocopherol concentrations were then evaluated by two-way repeated measures ANOVA, with time and experimental group as fixed factors and horse as the random effect. Post hoc testing was performed using Sidak's multiple comparison test. Significance was set at $P<.05$.

Results

Serum α-tocopherol

For oral α-tocopherol administration, no time or treatment phase interaction was detected. Therefore, all oral α-tocopherol supplementation data were subsequently combined. A significant time treatment interaction ($P<0.0001$) was detected for the first versus the second subcutaneous injection, and therefore, these data were analysed separately. The majority of variation was derived from treatment (44%). Baseline serum concentrations of α-tocopherol were not significantly different between treatment groups or between phases (**Fig 1**). All animals were considered vitamin E deficient at the beginning of the trial (mean ± s.d.; 1.2 ± 0.07 μg/mL; reference range 2-4 μ/mL) (Finno and Valberg 2012). Serum concentrations were significantly increased at 24 h (18.1 ± 12.05 $P\leq0.0001$), 48 h (16.53 ± 2.04 $P\leq0.0001$) and 72 h (11.6 ± 3.08 $P<0.05$), postadministration only for the 500 IU/mL subcutaneous injection in Phase 2. By days 7 and 14, subcutaneous administration in Phase 2 was not significantly different compared to oral, Phase 1 injection or baseline concentrations.

CSF α-tocopherol

CSF α-tocopherol baseline concentrations were not significantly different between treatment groups. Similar to serum, there was a significant time treatment interaction (<0.0001), with treatments analysed separately. The majority of variation arising from time period (43.2%). All horses were considered vitamin E deficient in the CSF at the beginning of the trial (4.3 ± 1.6 ng/mL; reference range ≥10 ng/mL) (Finno

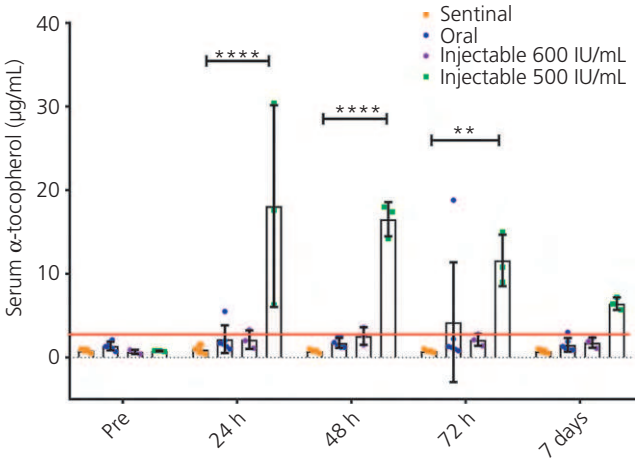

Fig 1: Serum α-tocopherol concentrations with individual animals plotted by treatment group. Significant increase in concentration in 500 IU/mL injection compared to sentinel, oral and 600 IU injections at 24 h (P<0.0001), 48 h (P<0.0001) and 72 h (P<0.05). Red line denotes the serum normal threshold 2 μg/mL

et al. 2015), injection with the 500 IU/mL preparation resulted in significantly higher CSF α-tocopherol at day 7 (15.27 ± 0.95 ng/mL, $P \leq 0.0001$) compared to the 600 IU/mL injection (6.7 ± 0.99 ng/mL), oral administration (6.66 ± 4.23 ng/mL) and baseline (**Fig 2**).

Muscle α-tocopherol

Muscle concentrations were highly variable between animals (range; 0.1-4.3 μg/g). Whilst there was a modest trend towards increased concentrations at 14 days post-subcutaneous administration in Phase 2, this was not significant.

Tissue reaction

All animals developed marked swelling at the injection site, regardless of concentration of the α-tocopherol formulation. For seven of eight animals, this tissue reaction was self-limiting. One horse had persistent swelling and eventual drainage requiring surgical intervention. Histology of the area was consistent with a sterile granuloma (**Fig 3**).

Independent assessment of product α-tocopherol concentrations

Each of the products was independently verified using HPLC (Finno *et al.* 2015). The product in Phase I contained 336 mg/mL (equivalent to 672 IU/mL), with the product in Phase 2 containing 290 mg (equivalent to 580 IU/mL).

Discussion

Currently, there are no labelled parenteral vitamin E preparations suitable for use in treatment or prevention of horses with existing or recurrent deficiencies in vitamin E. Additionally, with reports of malabsorptive conditions leading vitamin E deficiency, a need exists for a safe and efficacious parental means of supplementing horses (Finno and Valberg 2012).

Despite the importance of vitamin E as a potent antioxidant, the exact mechanisms of its biokinetics in horses are poorly understood and extrapolated from studies in other species (Finno *et al.* 2011, 2015). The primary route of absorption of vitamin E is alimentary and is closely associated with fat absorption requiring appropriate pancreatic, biliary and small intestinal function (Desmarchelier and Borel 2018). A specific mechanism for malabsorption in horses has not been evaluated. Speculatively, it is likely that perturbation of small intestinal function plays a role, and however, this is yet to be substantiated. Horses require a constant dietary supply to maintain appropriate serum concentrations of vitamin E, with serum levels falling quickly in the absence of supply (Stuart *et al.* 2010; Brown *et al.* 2017). Horses in the current experiment demonstrate this, with all animals considered deficient at the beginning of the trial, presumably subsequent to dry-lot management (Stuart *et al.* 2010). Despite this deficiency, no horses demonstrated any clinical signs of neuromuscular disease throughout this trial. Further, horses in this experiment appeared to have normal intestinal absorption of α-tocopherol, with an expected approximate doubling of serum concentrations 24 h after oral administration (Lodge *et al.* 2004; Stuart *et al.* 2010). Whilst this increase was not statistically significant, it was a biologically appropriate response and indicates both a normal ability to absorb and also to distribute α-tocopherol (Finno and Valberg 2012).

Vitamin E is fat-soluble and as such may also be absorbed by nonenteric routes. Following subcutaneous, intramuscular or intraperitoneal injection in other species, α-tocopherol is primarily taken up by lymphatics, before rapidly equilibrating between plasma and the cell membrane of erythrocytes (Lodge *et al.* 2004). Distribution to tissues rarely results in accumulation of vitamin E to toxic levels, reflecting a highly regulated and active process (Lodge *et al.* 2004). This process may also take place in the absence of major transport proteins found in the liver (Irías-Mata *et al.* 2018). As such, the tissue-specific absorption remains tightly regulated and is able to utilise nonalimentary α-tocopherol.

Injectable formulations of α-tocopherol have been investigated in a number of domestic species (Knight and

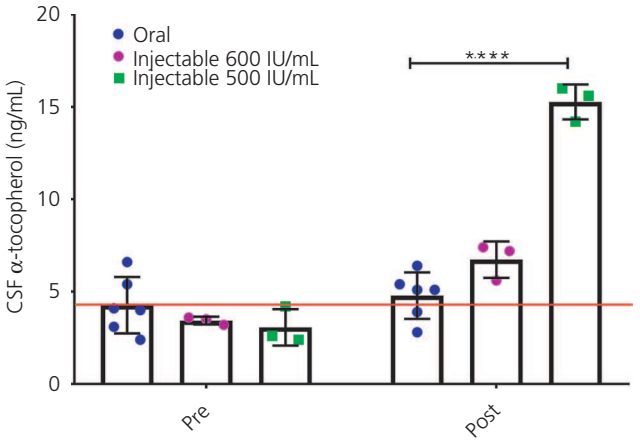

Fig 2: CSF α-tocopherol concentrations pre- and 7-day post-administration with individual animals plotted by treatment group. Significant increase in concentration in 500 IU/mL injection compared to oral and 600 IU injections at 7 days (P<0.0001). Redline denotes the CSF normal threshold 4 ng/mL

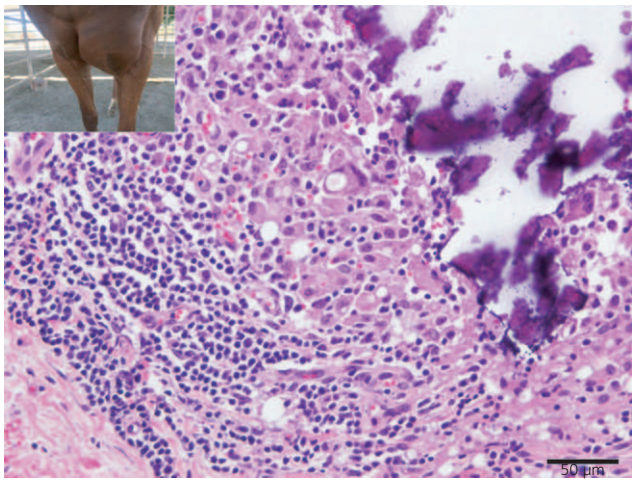

Fig 3: Histological section at 200× magnification showing granulomatous inflammation surrounding a mineralised core and surrounded by a rim of lymphoplasmacytic inflammation and fibrosis. Numerous macrophages are multinucleated and often contain clear, distinct vacuoles consistent with lipid. Clinical image of gross tissue reaction 24 h postinjection (inset)

Roberts 1985; Hidiroglou and Karpinski 1987,1988). Administration by this route appears to effectively and efficiently increase serum α-tocopherol concentrations. In contrast, parenteral administration in horses has not been well studied and there are currently no approved products for use in this species. As mentioned previously, products containing synthetic vitamin E and selenium (such as E-Se®) are commonly administered parenterally to neonatal foals, and however, these products provide insufficient amounts and minimally bio-potent vitamin E to be used to treat deficiency mediated diseases (Finno *et al.* 2015).

Following subcutaneous administration with the 500 IU/mL preparation, supra-physiological α-tocopherol concentrations in the serum and CSF were attained. Very low levels of α-tocopherol administered parenterally are required to maintain erythrocyte stability in deficient horses (Stowe 1968). Administration by this route circumvents both alimentary losses as well as liver-mediated regulation and may account for the large difference in serum and CSF concentrations. Subcutaneous administration demonstrates an opportunity to rapidly increase nervous tissue concentrations, the main target of treatment for vitamin E-mediated neurological diseases. Oral administration of suitable formulations may take up to 14 days to increase CSF concentrations, and therefore, parenteral preparations may be more suitable for early treatment of vitamin E deficient neurological disease (Hidiroglou and Karpinski 1991).

Administration of the 600 IU/mL preparation did not result in the same robust increase in α-tocopherol serum and CSF concentrations. The primary difference between the preparations was concentration, with equipotent doses administered. Local inflammation has previously been recognised as a source of variation for absorbance of nonaqueous preparations administered subcutaneously to horses (Alvinerie *et al.* 1998). Given the variability in individual local inflammatory responses and the small number of animals available in this study, the disparity of absorbance between products may represent the spectrum in local reactions of individual horses. That is to say that horses with more marked tissue reaction (like those in the Phase 1) would have reduced absorbance as reflected by lower serum and CSF concentrations.

Muscle α-tocopherol concentrations were not significantly different pre- and post-supplementation. Muscle concentrations of α-tocopherol are affected by the amount of lipid within the muscle (Ronéus *et al.* 1986). Adipose tissue is a main storage site for α-tocopherol, and therefore, muscle with increased amounts inter-fascicle fat will have increased concentrations of α-tocopherol. The amount of adipose tissue was not standardised in the current experiment, with whole tissue submitted for evaluation. Additionally, as these animals were deficient prior to the study, there was likely preferential distribution to adipose tissue over muscle (Lodge *et al.* 2004).

The tissue reaction observed in the current experiment was marked and affected all animals. The rapidity by which reactions occurred may indicate large scale degranulation of tissue-resident mast cells, leading to marked oedema in the region of injection (Krystel-Whittemore *et al.* 2016; Jørgensen *et al.* 2018). Whilst the tissue reaction was self-limiting in 7 of 8 horses and required no further intervention, the degree of tissue reaction makes use of this product in horses limited only to situations where the benefit of treatment outweighs the development of complications.

In conclusion, parenteral administration of α-tocopherol via the subcutaneous route effectively increases serum and CSF α-tocopherol concentrations. Preparations that circumvent alimentary absorption provide a novel area of investigation for more efficacious and long-term preparations of α-tocopherol. However, the current trial demonstrated that the tested product is not safe for use in horses due to local tissue reaction and as such cannot be recommended for clinical use at this time.

Authors' declaration of interests

R. Stuart is the director and owner of Stuart Products which produces nutritional products.

Ethical animal research

Ethical approval by the University of California-Davis Institutional Animal Care and Use Committee (Protocol number 2009).

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Stuart Products, Bedford, Texas, USA.

Authorship

C. Donnelly, C. Finno and R. Stuart contributed to study design, sample collection and data analysis. E. Burns, S. Katzman and C. Easton-Jones assisted with sample collection. S. Cook assisted with histopathology interpretation. All authors contributed to the manuscript.

Manufacturers' addresses

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[2]Stuart Products, Bedford, Texas, USA.
[3]GraphPad, San Diego, California, USA.

References

Alvinerie, M., Escudero, E., Sutra, J.F., Eeckhoutte, C. and Galtier, P. (1998) The pharmacokinetics of moxidectin after oral and subcutaneous administration to sheep. *Vet. Res.* **29**, 113-118.

Brown, J.C., Valberg, S.J., Hogg, M. and Finno, C.J. (2017) Effects of feeding two RRR-α-tocopherol formulations on serum, cerebrospinal fluid and muscle α-tocopherol concentrations in horses with subclinical vitamin E deficiency. *Equine Vet. J.* **49**, 753-758. https://doi.org/10.1111/evj.12692.

Desmarchelier, C. and Borel, P. (2018) Bioavailability of Vitamin E. Physiology of the Gastrointestinal Tract: Sixth Edition (Sixth Edition, Vol. 2–2). Elsevier Inc. https://doi.org/10.1016/B978-0-12-809954-4.00052-9.

Díez de Castro, E., Zafra, R., Acevedo, L.M., Pérez, J., Acosta, I., Rivero, J.L.L. and Aguilera-Tejero, E. (2016) Eosinophilic enteritis in horses with motor neuron disease. *J. Vet. Intern. Med.* **30**, 873-879. https://doi.org/10.1111/jvim.13944.

Finno, C.J. and Valberg, S.J. (2012) A Comparative review of vitamin E and associated equine disorders. *J. Vet. Intern. Med.* **26**, 1251-1266. https://doi.org/10.1111/j.1939-1676.2012.00994.x.

Finno, C.J., Higgins, R.J., Aleman, M., Bannasch, D.L., Ofri, R., Hollingsworth, S.R., Reilly, C.M. and Madigan, J.E. (2011) Equine Degenerative Myeloencephalopathy in Lusitano Horses. *J. Vet. Intern. Med.* **25**, 1439-1446. https://doi.org/10.1111/j.1939-1676.2011.00817.x.

Finno, C.J., Estell, K.E., Katzman, S., Winfield, L., Rendahl, A., Textor, J., Bannasch, D.L. and Puschner, B. (2015) Blood and cerebrospinal

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For additional information, see brief summary of prescribing information on the following page.

References: 1. Zimeta® (dipyrone injection) [package insert], Rev. 12/2020. **2.** Morresey PR, et al. Randomized blinded controlled trial of dipyrone as a treatment for pyrexia in horses. *Am J Vet Res.* 2019;80(3):294-299.

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fluid α-tocopherol and selenium concentrations in neonatal foals with neuroaxonal dystrophy. *J. Vet. Intern. Med.* **29**, 1667-1675. https://doi.org/10.1111/jvim.13618.

Hidiroglou, M. and Karpinski, K. (1987) Vitamin E kinetics in sheep. *Br. J. Nutr.* **58**, 113-125. https://doi.org/10.1079/bjn19870075.

Hidiroglou, M. and Karpinski, K. (1988) Pharmacokinetic disposition in sheep of various vitamin E preparations given orally or intravenously. *Br. J. Nutr.* **59**, 509-518. https://doi.org/10.1079/bjn19880060.

Hidiroglou, M. and Karpinski, K. (1991) Disposition kinetics and dosage regimen of vitamin E administered intramuscularly to sheep. *Br. J. Nutr.* **65**, 465-473. https://doi.org/10.1079/bjn19910105.

Irías-Mata, A., Sus, N., Flory, S., Stock, D., Woerner, D., Podszun, M. and Frank, J. (2018) α-Tocopherol transfer protein does not regulate the cellular uptake and intracellular distribution of α- and γ-tocopherols and -tocotrienols in cultured liver cells. *Redox. Biol.* **19**, 28-36. https://doi.org/10.1016/j.redox.2018.07.027.

Jørgensen, E., Lazzarini, G., Pirone, A., Jacobsen, S. and Miragliotta, V. (2018) Normal microscopic anatomy of equine body and limb skin: A morphological and immunohistochemical study. *Ann. Anat.* **218**, 205-212. https://doi.org/10.1016/j.aanat.2018.03.010.

Knight, M.E. and Roberts, R.J. (1985) Tissue vitamin E levels in newborn rabbits after pharmacologic dosing. Influence of dose, dosage form, and route of administration. *Dev. Pharmacol. Ther.* **8**, 96-106.

Krystel-Whittemore, M., Dileepan, K.N. and Wood, J.G. (2016) Mast cell: A multi-functional master cell. *Front. Immunol.* **6**, 1-12. https://doi.org/10.3389/fimmu.2015.00620.

Lodge, J.K., Hall, W.L., Jeanes, Y.M. and Proteggente, A.R. (2004) Physiological factors influencing vitamin E biokinetics. *Ann. N. Y. Acad. Sci.* **1031**, 60-73. https://doi.org/10.1196/annals.1331.006.

Ronéus, B.O., Hakkarainen, R.V.J., Lindholm, C.A. and Työppönen, J.T. (1986) Vitamin E requirements of adult Standardbred horses evaluated by tissue depletion and repletion. *Equine Vet. J.* **18**, 50-58. https://doi.org/10.1111/j.2042-3306.1986.tb03537.x.

Snow, D.H. and Guy, P.S. (1976) Percutaneous Needle Muscle Biopsy in the Horse. *Equine Vet. J.* **8**, 150-155. https://doi.org/10.1111/j.2042-3306.1976.tb03327.x.

Stowe, H.D. (1968) A-Tocopherol Requirements for Equine Erythrocyte Stability. *The American Journal of Clinical Nutrition* **21**, 135-142.

Stuart, R.L., Kane, E., Puschner, B., Pusterla, N., Collier, J. and Steidl, S. (2010) α-tocopherol concentrations in equine serum and cerebrospinal fluid after vitamin E supplementation. *Vet. Rec.* **166**, 366-368. https://doi.org/10.1136/vr.b4802.

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Critically Appraised Topic

Antimicrobial regional limb perfusion: Does it really fight infection?

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Keywords: horse

Summary

Over the last decades the use of antimicrobial regional limb perfusion (A-RLP) has increased and A-RLP is nowadays commonly used to treat orthopaedic infections by many equine practitioners. There have been a large number of studies published on the use of A-RLP, many of which describe regional drug pharmacokinetics and clinical safety of the administration of different antimicrobials by A-RLP. A limited number of studies describe the clinical use of A-RLP as prophylactic or therapeutic treatment. However, despite being in use for 30 years there is still limited evidence about the efficacy of A-RLP as a means to prevent and treat orthopaedic infections in horses.

PICO question

In horses undergoing orthopaedic procedures or being treated for orthopaedic infections, has administration of A-RLP changed the incidence of post-operative infection or the successful outcome of horses treated for established orthopaedic infections?

Search strategy

CAB direct, Scopus, Google Scholar and PubMed NCBI search engines were used. There was no date restriction and English and German language were accepted. The following terms were used: equine, horse, IVRLP, IVRP, RLP, RP, IORLP, IORP, antimicrobial, antibiotic, limb, perfusion, infection, arthritis, synovitis, osteomyelitis, bone and joint.

Discussion

In total, 112 papers were selected that met the criteria. From those, 59 were experimental papers describing the regional pharmacokinetics of antimicrobials or the technical aspects of A-RLP in clinically healthy animals. Two studies described experimental case–control studies of A-RLP on horses and 9 publications were tutorials, editorials or literature reviews.

Forty-two other papers described the clinical use of A-RLP in horses with different conditions; however, the reasons for using A-RLP were not consistent throughout the cases included in the studies and, when used, A-RLP was an adjunct therapy to other treatments, including systemic administration of antimicrobials in the majority of cases. From these 42 studies, there were only three studies in which all horses received A-RLP while three studies included a case series where some horses received A-RLP as part of the treatment plan and the use of A-RLP was statistically analysed.

From the 59 papers on pharmacokinetics and description of the technique, no conclusions can be drawn with regard to the efficacy of A-RLP to prevent or resolve infections because all of these studies were experimental and performed on healthy animals without orthopaedic infections or undergoing orthopaedic surgery. However, there was substantial variability of regional antimicrobial concentrations which questions the efficacy of the tourniquet in a proportion of cases. Careful correct technique when applying the tourniquet and injection techniques are key to a successful A-RLP (Grice *et al.* 1986).

From the three studies where all horses were treated with A-RLP, the following can be concluded. Kelmer *et al.* (2012) reported on 44 horses with synovial injuries without differentiating synovial contamination or infection. All horses were treated with A-RLP and most horses (31/44) received antimicrobials systemically. Overall, 87% of the cases survived and the presence of osteomyelitis was associated with a lower likelihood of the infection resolving. In another retrospective study, 174 horses with synovial injuries were all treated with systemic and local antimicrobials via A-RLP (Rubio-Martinez *et al.* 2012). In this study, synovial infection was differentiated from acute synovial contamination based on detailed cytology results and examination findings. Fresh extra- and intrasynovial lacerations were associated with 94% and 91.9% survival rates at hospital discharge and long term, respectively. Synovial involvement in these fresh injuries did not have an effect on survival rates. Horses with established synovial infections had a survival rate of 71.9% at hospital discharge and 53.43% at long term follow-up. Although the overall survival rate was fair to good, it is difficult to compare with previous studies reporting on treatment of synovial infections. Historical retrospective studies on treatment of orthopaedic infections without using A-RLP have reported survival rates for cases with synovial involvement between 62–92% in adults and 42–85% in foals (Schneider *et al.* 1992a,b; Steel *et al.* 1999; Meijer *et al.* 2000; Smith *et al.* 2004; Wereszka *et al.* 2007). Differences in inclusion criteria, definition of synovial involvement or synovial infection, lack of randomisation, different treatment regimens and combination of systemic and local antimicrobials limit drawing conclusions about effectiveness of A-RLP as a treatment for synovial infection.

Neil *et al*. (2007) reported on 22 foals that underwent surgical debridement of septic pedal osteitis. All foals received a single A-RLP treatment with gentamicin at the time of surgery and all received antimicrobials systemically. Bacterial culture and susceptibility results in 15 foals indicated that the initial A-RLP therapy with gentamicin was not effective against infective bacteria. Twelve foals required

TABLE 1: Clinically relevant reports illustrating clinical features, outcomes and limitations in horses treated with A-RLP as a prophylactic and/or therapeutic technique.

Authors	Study type	No. horses	Type of cases	A-RLP use	Systemic antimicrobials	Outcome	Key result	Study limitations
Kelmer and Tatz (2012)	Retrospective clinical case series	44 adults and foals	Synovial contamination/ infection	All received 3–21 A-RLP (median 7)	All received	Survival: 87%	A-RLP can be applied as an adjunct therapy with limited complications and overall good results	Degree of synovial involvement not clear (synovial contamination and infection not differentiated). No comparison between systemic and A-RLP possible.
Rubio-Martinez *et al*. (2012)	Retrospective clinical case series	174 adults and foals	96 synovial infections 50: acute intrasynovial lacerations	All received 1–19 A-RLP (median 5)	All received	Survival: Synovial sepsis: 72% (long term 53.43%). Acute intrasynovial lacerations: 94% (long term 91.9%)	A-RLP associated with low incidence of complications, intravenous much lower than intraosseous RLP	All horses received antimicrobials systemically and A-RLP. No comparative conclusion possible.
Neil *et al*. 2007	Retrospective clinical case series	22 foals	Foals with septic pedal osteitis	All received. 1 A-RLP at surgery with gentamicin (400–600 mg)	All received	Survival 86%	Only one does of gentamicin and many infections not sensitive to gentamicin. Antimicrobial impregnated PMMA also used	No efficacy of A-RLP can be concluded.
Ahern *et al*. 2010	Retrospective clinical case series	192 foals and adults	Long bone fractures or arthrodesis treated by internal fixation	162 (84%) received post-operatively	Number unknown	Post-operative surgical site infection: 28% (53)	Weak trend ($P = 0.07$) for increased hospital discharge of POI not treated with A-RLP	Unknown/ undefined: Number of horses treated with A-RLP Case selection for A-RLP Description of A-RLP A-RLP Length of A-RLP treatment
Curtiss *et al*. (2019)	Retrospective clinical case series	155 foals and adults	Long bone fractures or arthrodesis treated by internal fixation	All	56.8% (88 cases)	Lower SSI: 14.2% Prophylactic A-RLP associated with increased risk of SSI	A-RLP was associated with increased risk of SSI.	Unknowns: Same as above Surgeons' choice of cases for A-RLP Experience

TABLE 1: Continued

Authors	Study type	No. horses	Type of cases	A-RLP use	Systemic antimicrobials	Outcome	Key result	Study limitations
Wright *et al*. 2003	Retrospective clinical case series	121 foals and adults	Synovial contamination or infection	20 cases at the surgeon's discretion	All received	Survival: 90%	A-RLP statistically associated with: Nonsurvivors Reduced post-op performance	Degree of synovial involvement not clear (synovial contamination and infection not differentiated). No randomisation.
Whitehair *et al*. 1992	Experimental case–control	7 adults	Radiocarpal joint infection with *Staphylococcus aureus*	3 (IV gentamicin 2.2 mg/kg)	4 (A-RLP gentamicin 1g). (RLP technical failure in 1 case)	A-RLP group: 2/3 culture negative Systemic group: 0/3 culture positive	A-RLP more effective than systemic gentamicin to eradicate infection	Only 3 horses per group Sõystemic dose of gentamicin is 2.2 mg/kg q.i.d.
Freeland *et al*. (2017)	Experimental case–control	4 adults	Full thickness skin wounds infection with *Staphylococcus aureus*	All in one limb.	None	No difference in bioburden (bacterial growth)	No good tissue perfusion from cephalic vein – tourniquet failure?	A-RLP through cephalic vein may not effectively concentration amikacin within a wound bed on the dorsal metacarpal area

prolonged antimicrobial therapy after discharge for a median of 19 days (4–42 days) to eradicate the infection.

Whitehair *et al*. (1992) created experimental septic arthritis of the radiocarpal joint with *Staphylococcus aureus*. Gentamicin was only administered systemically to three horses and only via intraosseous RLP to the remaining three horses. At the end of the study, two of the A-RLP-treated horses had negative bacterial culture from synovial fluid collected from the infected joint, whereas all three horses in the systemic treatment group had positive cultures. This study provided evidence of A-RLP being effective and more successful than systemic antimicrobial using the same drug; however, the dose used for systemic treatment (2.2 mg/kg q.i.d.) was not the currently recommended dose (6.6–8 mg/kg s.i.d.). In a more recent experimental study, wounds were created on the distal limb of horses and contaminated with *Staphylococcus aureus*. In this study, A-RLP with amikacin did not have an effect on the wound bioburden, and the authors therefore questioned the effectiveness of RLP to concentrate amikacin in the wound bed (Freeland *et al.* 2017). However, amikacin concentrations in the wound tissue were not investigated.

Wright *et al*. (2003) reported on 121 cases with synovial contamination or infection treated endoscopically. In this retrospective study, use of A-RLP was associated with reduced survival and post-operative performance. However, A-RLP was used only in 20 horses and was given once at the end of the surgery. The lack of randomisation therefore precludes strong conclusions, and it is plausible that A-RLP was selected in cases offering a worse prognosis. Treatment with A-RLP was based on the individual surgeon's preference for the specific cases and was performed preferentially in horses with infections of navicular bursa, distal interphalangeal joint and/or digital flexor tendon sheath. Synovial infections involving bursae, and bone have been associated with poorer survival (Walmsley *et al.* 2011; Findley *et al.* 2014; Milner *et al.* 2014).

Ahern *et al*. (2010) published a retrospective study on 192 hoses undergoing long bone fracture fixation and arthrodesis. They reported a 28% incidence of surgical site infections. Among the data retrieved and statistically investigated, the use of A-RLP was one of the variables. All horses with post-operative orthopaedic infections were treated with systemic antimicrobials. A-RLP was used as an adjunct therapy to systemic antimicrobials and other treatments for some cases. Those horses with surgical site infections that were treated with A-RLP post-operatively had a weak trend ($P = 0.07$) for increased rate of hospital discharge compared with those with surgical site infections not treated with A-RLP. However, the details and protocol for A-RLP were not reported and the selection of cases for A-RLP was based on the individual case and attending surgeon's preference. The same clinician group from the same equine hospital have subsequently produced another similar retrospective study, recently (Curtiss *et al*. 2019), where they retrospectively reviewed the records of 155 cases undergoing internal fixation. They found a post-operative orthopaedic infection rate of 14.2%, which was much lower than in the previous study. In this study, A-RLP was associated with an increased risk of surgical site infections. Although this may indicate that A-RLP was not protective but actually increased the risk of infection, the use of A-RLP was not randomly assigned to cases. The treatment of cases was based on the subjective discretion of the surgeon managing the case. Therefore, a sound conclusion about the protective or nonprotective value of the A-RLP cannot be made from this study as it may have been that A-RLP was subjectively selected and applied to those cases of higher severity or with higher risk of surgical site infections (**Table 1**).

Clinical conclusions

From reviewing the peer-reviewed literature, A-RLP can provide high levels of antimicrobials in regional tissues; however, the characteristics of the studies have limitations that preclude evidence-based conclusions on the efficacy of A-RLP as a means to treat or prevent orthopaedic infections. The wide variability of regional antimicrobial concentrations observed in healthy horses may also occur in horses with orthopaedic infections or suffering from other conditions such as fractures. A-RLP is commonly used as an adjunct therapy, which precludes drawing any conclusions regarding its efficacy in preventing or fighting infection. The reported A-RLP protocols are not standard, and dosages, volumes and other technical details vary among studies. The antimicrobials administered by RLP are often different to those given systemically, and the dosages, time courses, administration routes and perfusate volumes are not standard among studies. In conclusion, although A-RLP is an overall safe technique, and has been in use for 30 years (first report on horses by Dietz and Kehnscherper (1990), there is lack of evidence that the use of A-RLP has made a difference in the prophylaxis or treatment of equine orthopaedic infections.

Greater evidence of the efficacy of A-RLP is available in human medicine. In a retrospective study that included 15 human patients suffering from chronic osteomyelitis unresponsive to treatment for the duration of 3 months to 38 years (Finsterbush and Weinberg 1972), bone infection was cleared in all these patients after treatment with A-RLP. Use of A-RLP has been associated with improved outcome in people treated for diabetic and ischaemic nonhealing pedal ulcers in comparison with systemic antimicrobial administration (Seidel *et al.* 1994; Agarwal *et al*. 2005). The use A-RLP has also been successfully used prophylactically on people undergoing total knee arthroplasty (Lazzarini *et al.* 2003).

Authors' declaration of interests

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Ethical animal research

Not applicable.

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References

Agarwal, P., Agrawal, P.K., Sharma, D. and Baghel, K.D. (2005) Intravenous infusion for the treatment of diabetic and ischaemic non-healing pedal ulcers. *J. Eur. Acad. Dermatol. Venereol.* **19**, 158–162.

Ahern, B.J., Richardson, D.W., Boston, R.C. and Schaer, T.P. (2010) Orthopedic infections in equine long bone fractures and arthrodeses treated by internal fixation: 192 cases (1990–2006). *Vet. Surg.* **39**, 588–593.

Curtiss, A.L., Stefanovski, D. and Richardson, D.W. (2019) Surgical site infection associated with equine orthopedic internal fixation: 155 cases (2008–2016). *Vet. Surg.* **48**, 685–693.

Dietz, O. and Kehnscherper, G. (1990) Intravenöse Stauungsantibiose bei pyogenen Infektionen der distalen Gliedmassenabsnitte des Pferdes. *Der Praktische Tierarzt* **8**, 30–33.

Findley, J.A., Pinchbeck, G.L., Milner, P.I., Bladon, B.M., Boswell, J., Mair, T.S., Suthers, J.M. and Singer, E.R. (2014) Outcome of horses with synovial structure involvement following solar foot penetrations in four UK veterinary hospitals: 95 cases. *Equine Vet. J.* **46**, 352–357.

Finsterbush, A. and Weinberg, H. (1972) Venous perfusion of the limb with antibiotics for osteomyelitis and other chronic infections. *J. Bone Joint Surg. Am.* **54**, 1227–1234.

Freeland, R.B., Morello, S.L., DeLombaert, M. and Rajamanickam, V. (2017) Influence of intravenous regional limb perfusion with amikacin sulfate on *Staphylococcus aureus* bioburden in distal limb wounds in horses. *Vet. Surg.* **46**, 663–674.

Grice, S.C., Morell, R.C., Balestrieri, F.J., Stump, D.A. and Howard, G. (1986) Intravenous regional anesthesia: evaluation and prevention of leakage under the tourniquet. *Anesthesiology* **65**, 316–320.

Kelmer, G., Tatz, A. and Bdolah-Abram, T. (2012) Indwelling cephalic or saphenous vein catheter use for regional limb perfusion in 44 horses with synovial injury involving the distal aspect of the limb. *Vet. Surg.* **41**, 938–943.

Lazzarini, L., Novelli, A., Marzano, N., Timillero, L., Fallani, S., Viola, R. and de Lalla, F. (2003) Regional and systemic prophylaxis with teicoplanin in total knee arthroplasty: a tissue penetration study. *J. Arthroplasty* **18**, 342–346.

Meijer, M.C., van Weeren, P.R. and Rijkenhuizen, A.B. (2000) Clinical experiences of treating septic arthritis in the equine by repeated joint lavage: a series of 39 cases. *J. Vet. Med. A. Physiol. Pathol. Clin. Med.* **47**, 351–365.

Milner, P.I., Bardell, D.A., Warner, L., Packer, M.J., Senior, J.M., Singer, E.R. and Archer, D.C. (2014) Factors associated with survival to hospital discharge following endoscopic treatment for synovial sepsis in 214 horses. *Equine Vet. J.* **46**, 701–705.

Neil, K.M., Axon, J.E., Todhunter, P.G., Adams, P.L., Caron, J.P. and Adkins, A.R. (2007) Septic osteitis of the distal phalanx in foals: 22 cases (1995–2002). *J. Am. Vet. Med. Assoc.* **230**, 1683–1690.

Rubio-Martinez, L.M., Elmas, C.R., Black, B. and Monteith, G. (2012) Clinical use of antimicrobial regional limb perfusion in horses: 174 cases (1999–2009). *J. Am. Vet. Med. Assoc.* **241**, 1650–1658.

Schneider, R.K., Bramlage, L.R., Mecklenburg, L.M., Moore, R.M. and Gabel, A.A. (1992a) Open drainage, intra-articular and systemic antibiotics in the treatment of septic arthritis/tenosynovitis in horses. *Equine Vet. J.* **24**, 443–449.

Schneider, R.K., Bramlage, L.R., Moore, R.M., Mecklenburg, L.M., Kohn, C.W. and Gabel, A.A. (1992b) A retrospective study of 192 horses affected with septic arthritis/tenosynovitis. *Equine Vet. J.* **24**, 436–442.

Seidel, C., Buehler-Singer, S., Tacke, J. and Hornstein, O.P. (1994) Therapeutische Überlegenheit regionaler retrograd-venöser Antibiotika-Druckperfusionen versus systemisch-venöser Infusionen bei Diabetikern mit infizierten neuropathischen Plantarulcera. *Der Hautarzt* **45**, 74–79.

Smith, L.J., Marr, C.M., Payne, R.J., Stoneham, S.J. and Reid, S.W. (2004) What is the likelihood that Thoroughbred foals treated for septic arthritis will race? *Equine Vet. J.* **36**, 452–456.

Steel, C.M., Hunt, A.R., Adams, P.L., Robertson, I.D., Chicken, C., Yovich, J.V. and Stick, J.A. (1999) Factors associated with prognosis for survival and athletic use in foals with septic arthritis: 93 cases (1987–1994). *J. Am. Vet. Med. Assoc.* **215**, 973–977.

Walmsley, E.A., Anderson, G.A., Muurlink, M.A. and Whitton, R.C. (2011) Retrospective investigation of prognostic indicators for adult horses with infection of a synovial structure. *Aust. Vet. J.* **89**, 226–231.

Wereszka, M.M., White, N.A. 2nd and Furr, M.O. (2007) Factors associated with outcome following treatment of horses with septic tenosynovitis: 51 cases (1986–2003). *J. Am. Vet. Med. Assoc.* **230**, 1195–1200.

Whitehair, K.J., Bowersock, T.L., Blevins, W.E., Fessler, J.F., White, M.R. and Van Sickle, D.C. (1992) Regional limb perfusion for antibiotic treatment of experimentally induced septic arthritis. *Vet. Surg.* **21**, 367–373.

Wright, I.M., Smith, M.R., Humphrey, D.J., Eaton-Evans, T.C. and Hillyer, M.H. (2003) Endoscopic surgery in the treatment of contaminated and infected synovial cavities. *Equine. Vet. J.* **35**, 613–619.

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