EQUINE VETERINARY EDUCATION/AMERICAN EDITION
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JUNE 2023

EQUINE VETERINARY EDUCATION

American Edition | June 2023

BEVA

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

IN THIS ISSUE:

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References:
[1] Brendemuehl JP, Kopp K, Altman J. Uterine Inflammatory Response to Frozen Semen is attenuated by Oral Supplementation of a Blend of Omega-3 Fatty Acids (Algal DHA and Flax Seed) in Susceptible and Resistant Mares. Submitted to Theriogenology. [2] Brendemuehl JP, Altman J, Kopp K. Influence of dietary algal N-3 fatty acids on breeding induced inflammation and endometrial cytokine expression in mares bred with frozen semen. J Equine Vet Sci. 2014; 34(1): 123-124. [3] A.M. Adkin, A.V. Muniz, C.J. Mortensen, L.K. Warren. Maternal fatty acid supplementation influences memory and learning ability in yearling and 2-year-old horses. J Equine Vet Sci. 2015; 35: 418-436. [4] A.M. Adkin, L.K. Warren, C.J. Mortensen, J. Kivipelto. Maternal supplementation of docosahexaenoic acid and its effect on fatty acid transfer to the foal (longitudinal study). Equine Vet Sci. 2013; 33: 321-329. t[5] A.M. Adkin, L.K. Warren, and C.A. McCall. Effect of maternal docosahexaenoic acid supplementation on behavior and cognitive development in nursing foals. J Equine Vet Sci. 2013; 33: 321-399.

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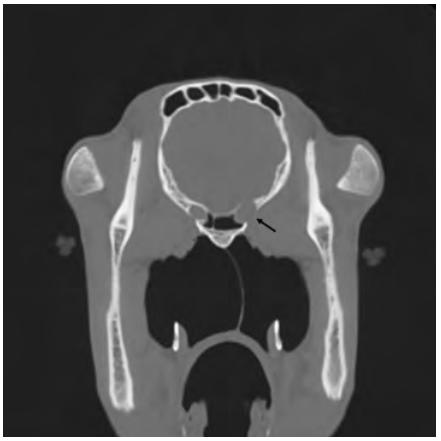

AAEP NEWS In this issue

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American Association of Equine Practitioners
4033 Iron Works Parkway
Lexington, KY 40511
TEL (800) 443-0177 • (859) 233-0147
FAX (859) 233-1968
EMAIL aaepoffice@aaep.org
aaep.org

To access our website, go to aaep.org, select LOGIN, then enter your email and password. If you have difficulty logging in or have forgotten your password, please call or email the office.

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Address advertising inquiries to Dana Kirkland
(859) 233-0147 / dkirkland@aaep.org

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
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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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All manuscript submissions for the journal should be submitted online at http://mc.manuscriptcentral.com/eve. Full instructions and support are available on the site and a user ID and password can be obtained on the first visit. If you require assistance, click the Get Help Now link that appears at the top right of every ScholarOne Manuscripts page.

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From the president: Sowing seeds of change

Dr. Rob Franklin

Howdy, colleagues. Spring is sprung and I trust your days are full and fulfilling. I would like to update you on the illicit xylazine issue, our exciting member assistance program and the pivotal work of the Commission on Equine Veterinary Sustainability.

Xylazine

As you are likely aware from our previous communications on this issue, illicit xylazine has become a serious public health concern. It is frequently mixed in combination with illegal drugs resulting in serious dermatological wounds, non-Narcan-responsive loss of consciousness and even death. Law enforcement personnel currently do not have any legal grounds to prosecute the sale or use of illicit xylazine and are therefore seeking legislation to schedule the drug.

To preserve the lawful use of xylazine in veterinary medicine, the AAEP earlier this year adopted a position that states the association does not support the scheduling of the drug at this time in order to preserve access in daily practice. Thankfully, at the federal level, legislators are listening to the veterinary point of view and are considering a bill that will only criminalize the illicit use of xylazine and keep veterinary (licit) xylazine unscheduled. This position would likely change if veterinary xylazine begins to become diverted and a source for illicit use. There is also interest by some states to go it alone and schedule xylazine independent of any federal law. The biggest veterinary concern is the potential loss of this drug should it become a scheduled product.

The AAEP encourages you to reach out to your state and federal representatives, attend information hearings in your state and support the AVMA PAC to help educate policymakers about the value of xylazine in day-to-day veterinary practice, especially for horses, cattle and sheep.

AAEP Healthy Practice Member Assistance Program

The new Healthy Practice Member Assistance Program has been expanded to allow AAEP members to offer the program's counseling and consultation services to all practice employees at the greatly reduced AAEP program rate. This is an amazing benefit and one that greatly improves your practice culture and your team's well-being. You can learn more about the array of services provided by visiting aaep.org/healthy-practice-member-assistance-program. If you'd like to explore offering the program to all practice staff, contact Sally Baker at sbaker@aaep.org or (859) 705-0434 and she will walk you through the process.

Retention & Recruitment: Transforming Equine Practice

AAEP-member volunteers on the Commission on Equine Veterinary Sustainability are continuing their work to change the numbers in equine practice in five key categories: Compensation, Internships, Practice Culture, Emergency Coverage and Student Recruitment.

Many of the subcommittees have begun to present their findings via webinars, written documents, toolkits and infographics, including:

- The Compensation Subcommittee has determined through the Salary & Lifestyle Survey that total compensation for recent graduates is much better (~$90,000 per annum) than previously reported by the AVMA.
- The Internship and Emergency Coverage groups have hosted webinars recently to share their recommendations for changing how the profession approaches these two critical facets of career longevity.
- The Internship Subcommittee is finalizing several valuable resources (best practices, benchmarks, recommended goals and outcomes) to guide both practices hosting internships as well as new graduates seeking internships.
- The Practice Culture group will soon release resources tied to the seven key areas practitioners and practice owners can target to create a healthy practice life.
- The Student Subcommittee is developing a speakers bureau to increase equine practitioner presence at veterinary school student chapters of the AAEP, as well as surveying AAEP student members to learn about the factors influencing their consideration of equine as a career path.

Study, organize, discover, present and publish, realize change…this is the sequence your association is following to improve equine practice. The overarching goal is to make our profession enjoyable, desirable, fulfilling and fruitful for all who choose this line of work. In doing so, we are confident that more students will choose equine practice and more practitioners will remain in the profession.

However, we should all recognize that no matter how much surveying, meeting, presenting and publishing we do, nothing happens until we create change individually. This is not one person's fault, and it is also not the responsibility of someone else to fix.

We can do it together, but the work starts in your office, in your truck, in your classroom, in your laboratory and in your conversations. I encourage you to tune in to the subcommittees' resources and use them to be the change you seek to find in the profession.

Iron sharpens iron.

5 things to know about AAEP this month

1. Newer practitioners—don't get shut out! Claim one of just 60 spots at the wet labs-focused Foundational Skills in Equine Practice CE meeting by registering at aaep.org/meetings.
2. Mark your calendar for the AAEP's 2023 Annual Convention, which will begin Wednesday, Nov. 29 and conclude Sunday, Dec. 3 in San Diego. Registration opens in July.
3. Submit a short, how-to video of a technique used in patient care for possible inclusion in the AAEP's new microlearning videos library. Learn more at aaep.org/microlearning.
4. Acquire resources to help work with clients and law enforcement to prevent equine abuse and neglect at aaep.org/owner-guidelines/equine-welfare.
5. AAEP-member doctoral or residency students: Apply by Aug. 4 to receive one of three $5,000 research fellows being awarded by The Foundation for the Horse. Learn more at aaep.org/scholarships/research-fellows.

New *EVE* podcast debates standing sedation vs general anaesthesia for fracture repair

In the latest episode of the *Equine Veterinary Education* podcast, Dr. Kate Loomes discusses her clinical commentary, "Is general anaesthesia avoidable for limb fracture repair in horses?"

Dr. Loomes is a European specialist in Veterinary Anaesthesia and Analgesia who practices at Rainbow Equine Hospital in Malton, United Kingdom. Download or listen to the 23-minute episode on iTunes or at equineveterinaryeducation.podbean.com.

Compensation, practice culture in focus on Practice Life podcast

As the five subcommittees of the AAEP's Commission on Equine Veterinary Sustainability make headway on sustainability initiatives, the co-chairs for two of the subcommittees recently joined AAEP Practice Life podcast co-hosts Drs. Jessica Dunbar and Mike Pownall to review early progress and upcoming plans for their respective working groups.

Participating in the discussion were Drs. Travis Boston and Jim Zeliff, co-chairs of the Compensation subcommittee, and Drs. Stacey Cordivano and Kelly Zeytoonian, co-chairs of the Practice Culture subcommittee.

The Practice Culture subcommittee has identified 7 pillars that contribute to a positive veterinary workplace culture and is working to create user-friendly, practical and actionable educational content in support of each individual pillar. Completed and awaiting board approval is a short workbook that walks through development of workplace communication boundaries. By the AAEP Convention, the subcommittee intends to have a formalized booklet working through each pillar, defining what they are, why they are important, and linking to the deliverables created throughout the year so members can begin making changes to enhance the culture within their practice.

The Compensation subcommittee, meanwhile, is creating "small bite" deliverable media messages in the form of email blasts, published articles and infographics spotlighting the positive data from last fall's Equine Medicine Salary and Lifestyle Survey. The subcommittee is also closely examining gender disparities within the compensation data, remediation of which could significantly increase overall compensation; and creating a rubric that will help associates understand the actual dollar value of their benefits package.

AAEP TRANSFORMING EQUINE PRACTICE

"I'm excited that we have made it to the point where we are actually admitting that there's a problem," said Dr. Zeytoonian. "We've been working on this—this has been sort of a passion project for years it feels like—and it finally feels like it's gaining momentum. We're past the tipping point that we really need to have the energy behind it to start making really notable improvements and changes."

Download or listen to the 32-minute episode at podcast.aaep.org or on iTunes.

Survey results correlates salary with job satisfaction

AAEP TRANSFORMING EQUINE PRACTICE

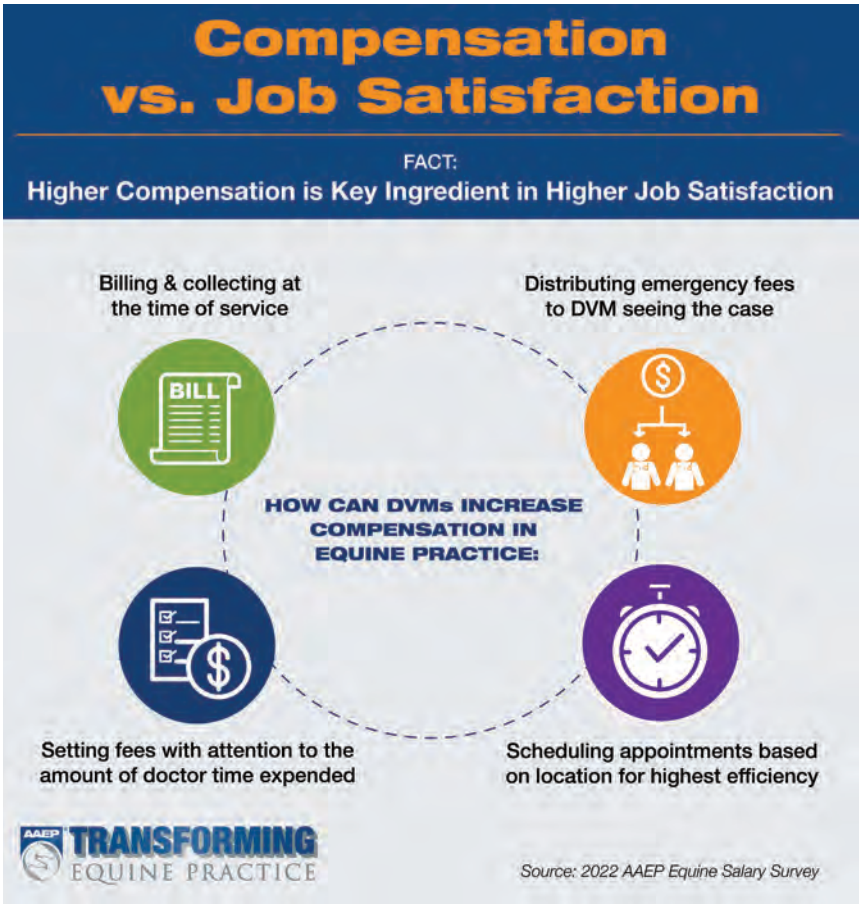
The May issue of *EVE* included a look at several important compensation issues for equine veterinarians based on results of the Equine Medicine Salary and Lifestyle Survey of U.S.-based members conducted by the AAEP in fall 2022. Delving deeper into the survey, a correlation between increasing job satisfaction and increasing salary was found among the respondents:

- Very Satisfied with Job: $193,175
- Somewhat Satisfied with Job: $131,136
- Somewhat Dissatisfied with Job: $116,874
- Very Dissatisfied with Job: $100,556

Higher salary is certainly not the sole reason for increased job satisfaction—salary can be a proxy for other factors—but how can we help to improve this aspect of equine practice?

Tactics for increasing DVM compensation appear in the infographic.

The Compensation Subcommittee of the AAEP's Commission on Equine Veterinary Sustainability is spotlighting key research findings from the survey to assist equine practitioners in developing policies and practices that will fuel financial growth and salaries in equine veterinary practice.



For additional insights gleaned from the 2022 AAEP Equine Medicine & Lifestyle Survey, visit aaep.org/compensation.

ASSOCIATION

Play it again: Watch recordings of prior Virtual Round Table sessions

Since 2021, Virtual Wednesday Round Tables have provided AAEP members with twice monthly opportunities for education and engagement on clinical and non-clinical topics pertinent to practice. If unable to attend a 90-minute live session—held on the second and fourth Wednesdays of each month between March and October—you can access an on-demand recording to watch at your convenience.

The recordings are available through AAEP Anywhere, the association's online learning platform that is free for members. On-demand sessions are generally available 48 hours after the live session and include links to external resources.

The 2023 session topics so far have included:

- Social License to Operate
- Who, What, When, Where, and Why of Orthobiologics and Polyacrylamides
- Emergency Coverage: Client Communication Strategies to Prevent Burnout
- Chronic Management of Gastric Ulcers

- Finding the Right Fit: How to Get the Most Out of an Equine Internship
- Lameness Cases Where Imaging and Blocking Don't Make Sense

Access recordings of previous sessions by going to aaep anywhere.org and selecting "Wednesday Round Tables" in the navigation bar at the top of the page. You will need to log in using your AAEP website credentials to watch recorded sessions.

The AAEP thanks its Virtual Wednesday Round Table sponsors: Boehringer Ingelheim, CareCredit a Synchrony solution

CONTINUING EDUCATION

Optimize your foundational skills at small, labs-focused CE event

If you are less than 10 years out of school, acquire the core knowledge, skills and professional relationships to enhance patient care and expand professional possibilities at the AAEP's Foundational Skills in Equine Practice, a wet labs-focused CE event being held Oct. 6–8 at Spy Coast Farm in Lexington, Ky.

With attendance limited to only 60 participants, you'll acquire plenty of hands-on training in key areas. Each afternoon and on the morning of the final day, you'll rotate through three wet labs featuring a low 4:1 participant-to-instructor ratio:

Oct. 6 Wet Labs *(90 minutes each)*
- Neurologic Exam
- Cardiac Evaluation
- Distal Limb Radiography

Oct. 7 Wet Labs *(90 minutes each)*
- Lameness Exam
- Cervical Facet Ultrasound
- Cervical Spine Radiography

Oct. 8 Wet Labs *(60 minutes each)*
- Regional Distal Limb Anesthesia
- Dentistry Exam with Oroscope
- Cervical Interpretation

During morning sessions on the first two days, you'll obtain expert guidance in a how-to format on pertinent medical topics, immediately followed by practical business and wellness advice fundamental to professional success and satisfaction. Meanwhile, social opportunities will facilitate formation of professional friendships with colleagues at a similar stage of practice or skill level.

The meeting is expected to offer 18.5 CE credits. The AAEP-member registration rate is $675. Register for the meeting, view the program and book your hotel room at aaep.org/meetings. The meeting coincides with opening weekend of the Keeneland Fall Meet so registrants are advised to book their hotel room early.

Foundational Skills in Equine Practice is sponsored by: ARENUS ANIMAL HEALTH, CareCredit a Synchrony solution, contura vet, Dechra Veterinary Products, MERCK Animal Health

Convention keynote to help harness the power of resilience to embrace change

Equine veterinary medicine is in the midst of a professional evolution—identifying and implementing changes to increase the sustainability of equine practice for the betterment of both the practitioner and horse. However, change is not easy and often creates feelings of anxiety and fear.


Cassandra Worthy

During her keynote address, "Master the Chemistry of Change: Uncover Your Inner Change Enthusiasm®," Cassandra Worthy will empower you to self-assess your change emotions and redirect anxiety and fears into moments of opportunity. Through a practical and repeatable framework, Worthy will share strategies for transforming workplace culture from surviving change to growing through change.

Worthy is founder and CEO of Change Enthusiasm Global, which she created after nearly two decades as a chemical engineer in the consumer packaged goods industry. Her consulting firm helps organizations disrupt "change as usual" and arms individuals with the means to harness the power of emotion, a resource in infinite supply, to embrace and accelerate change and transformation journeys.

With a client base that spans the Fortune 500 from Procter & Gamble and Allstate to Centene Corporation and WeWork, Worthy helps build organizational resilience and adaptability by invigorating and inspiring organizations, C-suite executives and business associations alike undergoing significant change, disruption and transformation.

Sponsored by MERCK Animal Health

FOUNDATION

Graduate-level researchers: Apply for Foundation fellows

Applications for annual scholarships due August 4

Applications for The Foundation for the Horse Research Fellow, AAEP Past Presidents' Research Fellow and EQUUS Foundation Research Fellow are being accepted until Aug. 4.

The annual $5,000 scholarships reward AAEP-member doctoral or residency students who have made significant progress in the field of equine healthcare research. Recipients will be honored at the AAEP's 69th Annual Convention, Nov. 29–Dec. 3 in San Diego, Calif. Each will receive a $500 stipend to support travel to the convention.

The scholarship application and descriptions are accessible at aaep.org/scholarships/research-fellows.

Dr. Rebecca Bishop receives the AAEP Past Presidents' Research Fellow from 2021 AAEP President Dr. Scott Hay during the 68th Annual Convention.

What is your ethical responsibility when responding to an emergency?

By Barb Crabbe, DVM, MA Bioethics, and Lisa Hanelt, DVM

Dr. Barb Crabbe

Dr. Lisa Hanelt

How many times have you received an emergency call for a horse that you simply couldn't help, either because you were too far away, didn't have the necessary equipment, or were busy working on another horse? How much did it bother you?

If you are a veterinarian who is on call for emergencies, chances are you wrestle with this issue on a regular basis. If you find yourself facing this scenario frequently, it is likely to be causing you distress.

Equine veterinarians have an ethical responsibility to care for the horse. In fact, the Principles of Veterinary Medical Ethics of the AVMA clearly states that "a veterinarian should first consider the needs of the patient to prevent and relieve disease, suffering, or disability." Yet, what happens when the veterinarian faced with an emergency can't respond because they lack the necessary resources, whether that means equipment, facility, skills or simply their own time or emotional energy?

Equine veterinarians have finite resources, including time and emotional energy. Balancing the need to provide emergency services with our duty to ourselves is an increasingly urgent quandary within the profession, as evidenced by the startling statistics related to veterinarians leaving practice. We know 50% of new equine veterinarians leave equine practice within five years. This is not sustainable. We also know emergency availability is a major issue leading to veterinarians electing work without equine on-call responsibilities.

There are numerous discussions of how to set boundaries by pooling resources and working together to create emergency cooperatives that help relieve the burden of providing emergency care. Just as important is helping veterinarians develop the tools they need to justify refusal of care as an ethical choice when circumstances require it. Any veterinarian who offers emergency on call must also occasionally say "no" in order to preserve their ability to get up and fight another day.

There's no question that the decision to refuse care for a horse in need can create a significant source of moral distress for a veterinarian. Moral distress, or the realization that one is constrained from taking an action that one knows is ethically appropriate, is a leading cause of burnout. Statistics tell us that equine veterinarians who experience this type of burnout are likely to leave the profession altogether. Without equine veterinarians, the landscape of equine emergency care shifts dramatically, to the detriment of the care of the horse.

The ethical framework of utilitarianism tells us that finding the answer to an ethical dilemma depends on making the decision that has the most benefit to the greatest number. If we apply this framework to the question of whether we have an ethical responsibility to provide care for "every emergency, every time," we can easily answer no. More damage will be done to horses everywhere if equine veterinarians continue to leave the profession at such a rate that none remain to provide emergency care at all. But what about our duty to the individual horse?

Any equine veterinarian who has experienced on call understands the powerful duty to serve patients and clients, and a majority of equine veterinarians will continue to feel helpless when confronted with an emergency to which they either cannot respond or cannot adequately manage with available resources. We need to understand that our duties as veterinarians expand beyond our patients and their owners. We also owe a duty to ourselves and to our colleagues.

As veterinarians, it's time we recognize our duty to ourselves and begin to understand that it is ethically permissible to create boundaries, even if that means we won't be available for "every emergency, every time." Our mental health depends on it. We also owe a duty to our regular patients and clients to ensure they have access to emergency care. Finally, there is a balance: We must recognize our duty to our colleagues who are likely to experience extraordinary pressure if increasing numbers of equine veterinarians refuse to provide emergency services at all.

The answer to the ethical dilemma surrounding provision of emergency care requires that we work together to find solutions that ensure individual veterinarians feel com-

continued on page XI

AAEP TRANSFORMING EQUINE PRACTICE

AAEP ETHICAL PRACTICE Every Day-Every Time

Dr. Crabbe was a practitioner and the owner of a general equine practice in the Portland, Ore.-area for over 30 years. She is now involved with curriculum development in veterinary ethics and serves on both the AAEP's Professional Conduct and Ethics Committee and the AVMA's Council on Veterinary Services. Dr. Hanelt is an equine veterinarian based in Massachusetts and serves of the AAEP's Professional Conduct and Ethics Committee.

2023 ANNUAL CONVENTION & TRADE SHOW

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OF OPPORTUNITY IN EQUINE PRACTICE

Registration opens in July at

convention.aaep.org

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69th AAEP Annual Convention
San Diego, CA | Nov. 29 - Dec. 3

AAEP HEALTHY Practice MEMBER ASSISTANCE PROGRAM

Services provided by MYgroup McLAUGHLIN YOUNG

The member assistance program is an AAEP-sponsored benefit that offers the support and resources you need to address personal or work-related challenges and concerns. It's confidential and free to you and your household family members. Two types of services are provided: counseling and consultation sessions and online resources.

Accessing Services

Call 800-633-3353 to speak to a qualified clinician, 24 hours a day, 7 days a week. No password or special access information is required to utilize this service.

To access online resources, visit mygroup.com * Click on My Portal Login * Select Work-Life option * Enter Username: aaep & Password: guest

Download MYgroup App

You can also conveniently access services through the MYgroup app, available for download in the Apple and Google Play stores. The login credentials are the same as they are for the mygroup.com website.

Assessment and Counseling

Reasons to use the member assistance program include relationship difficulties, depression or anxiety, stress, grief and loss, parenting concerns, and alcohol and drug abuse and addiction. The program provides short-term, solution-focused therapy.

When an AAEP member or family member calls, you will be offered face-to-face, telephonic, or virtual counseling sessions in which a thorough assessment can be conducted by a licensed, experienced clinician in your area. AAEP members and immediate family can utilize the member assistance program for an unlimited number of issues per year, with up to three counseling sessions offered per issue. There is no cost to you.

Legal Services

- Free telephonic legal advice
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- In most cases, 25% discount on ongoing legal services
- Legal forms available to download on mygroup.com, such as wills, request for death certificate, etc.
- Please note: Legal services through this program do not cover disputes or actions involving the member's employer or issues related to business.

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- Issues addressed include bankruptcy, buying a home, loan repayment and retirement planning.
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- Over 100 streaming audio files and 100 video files covering a range of health topics.
- Savings Center and Relocation Center

ACCESSING SERVICES

Toll-free: 800-633-3353

Website: www.mygroup.com > My Portal Login > Work-Life

Username: aaep
Password: guest

The Member Assistance Program is offered to U.S. and Canadian members only at this time due to variances in available providers outside of North America.

Member benefit: Fill the information gaps with document retrieval services

Dr. Lydia Gray

Without institutional support for accessing veterinary literature, the road to discovery can be expensive and is often paved with detours and dead ends. Whether you're seeking a specific article to assist with a case or simply following a trail of medical curiosity, enlist the help of the AAEP's document retrieval service.

Over 300 members have received more than 600 articles through the service during the past year, including Dr. Lydia Gray of Elburn, Ill. "Not being at a university, it can be expensive to gain access to full scientific journal articles, not just abstracts on PubMed," she said. "I'm thrilled that AAEP is now making it quick, easy and free for its members to request research papers."

Request a mediated database search on a particular veterinary topic by contacting Megan Gray, member concierge, at membership@aaep.org.

For copies of articles, book chapters and conference papers, email membership@aaep.org and include the following required information:

- Journal/Proceedings/Anthology Title *(Do not abbreviate unless your citation is abbreviated)*
- Article Title
- Year
- Volume
- Pages

If available, please also include:

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If possible, please copy and paste the requested information or embed a screenshot of the article citation into the body of the email. The requested item(s), if available, will be delivered to your inbox as a PDF file in 5 to 7 business days. There is no cost for the first 25 articles each year; beyond 25 articles, a fee applies. For more information on this valuable benefit of your membership, email Megan Gray at mgray@aaep.org.

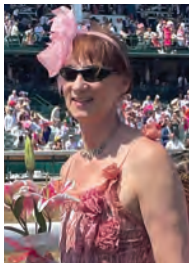
ETHICS

What is your ethical responsibility when responding to an emergency? continued

fortable declining to respond to an emergency by knowing that their patients and clients can find help at the hands of colleagues. Whether this means exploring options for emergency cooperatives or encouraging the establishment of emergency-only practices, one thing is certain: No veterinarian should feel ethically responsible to respond to "every emergency, every time."

EDITOR'S NOTE: The AAEP has two subcommittees within its Commission on Equine Veterinary Sustainability—Emergency Coverage & Practice Culture—that are presently developing tools and other resources to assist members in the area of emergency coverage.

Members in the News



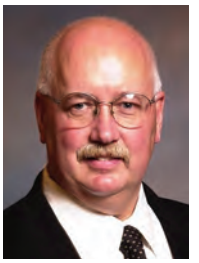
Dr. Dana Westerman

Dr. Dana Westerman selected for Kentucky Oaks Survivors Parade

Dr. Dana Westerman, owner of Professional Equine Therapeutic Services, an ambulatory practice in Monroe, Wash., was among 149 cancer survivors and fighters to march in the Survivors Parade prior to the running of the Longines Kentucky Oaks on May 5 at Churchill Downs.

The parade is a moving tradition that celebrates breast and ovarian cancer survivors and encourages those still fighting their cancer. After being diagnosed in 2012, Dr. Westerman has been cancer free for 11 years.

Dr. Westerman received her veterinary degree from Purdue University. In addition to her ambulatory practice, she worked at Emerald Downs last year assisting staff with the transition to the Horseracing Integrity and Safety Authority rules. Her vacations are often spent in developing countries leading small teams in the care of working horses.



Dr. Larry Bramlage

Dr. Larry Bramlage to receive Dinny Phipps Award

Grayson-Jockey Club Research Foundation will present the 2023 Dinny Phipps Award to noted equine orthopedic surgeon and AAEP past president Dr. Larry Bramlage for his demonstrated dedication to equine health. The presentation will take place in early August in Saratoga Springs, N.Y.

A veterinary graduate of Kansas State University, Dr. Bramlage is a partner at Rood & Riddle Equine Hospital in Lexington, Ky. He was instrumental in the growth and development of the AAEP's award-winning On Call program and his many accolades include the association's 2021 Sage Kester Beyond the Call Award in recognition of his distinguished service to the profession, horse health and community; and the 2019 American College of Veterinary Surgeons Founders Award for career achievement.

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Equine Veterinary Education

RESEARCH HIGHLIGHTS

Highlights of recent clinically relevant papers

VERTICAL HEAD HEIGHT ASYMMETRY

In this study, Susanne Kolding and co-workers in Denmark and the United States aimed to estimate the prevalence of increasing head height asymmetry after a palmar digital nerve (PDN) block and determine if this is associated with the cause of forelimb lameness.

Head height asymmetry, normalised to expected vertical head displacement, from inertial-sensor data collections of all horses evaluated for forelimb lameness while trotting in a straight line at two different clinics were screened for cases that had an initial PDN block and then another more proximal block in the same limb during the same lameness evaluation. Medical records of the 213 screened cases were evaluated to determine the cause of lameness. Prevalence of increasing head height asymmetry was calculated. Differences in lameness amplitude between groups of cases that remained unchanged (Group 1), that increased (Group 2) and that decreased (Group 3) in head height asymmetry before and after the initial PDN block were compared. Determination of the location of the cause of lameness and final diagnoses of cases were compared between Groups 1 and 2.

The PDN block increased head height asymmetry at a prevalence of 32.5% (95% CI 4.5%–41.5%) and 13.8% (95% CI 7.3%–22.9%), in clinic 1 and 2 respectively. Increasing head height asymmetry after an initial PDN block did not predict localisation of the cause of forelimb lameness or specific diagnosis.

JOINT TREATMENTS

In this study, Danica Wolkowski and co-workers in the United States evaluated the effects of acellular equine liquid amnion allograft (ELAA) injected into healthy equine joints.

One intercarpal joint (ICJ) of each of eight healthy adult horses was randomly assigned to be injected with 1.5 mL of ELAA (treatment) while the contralateral ICJ was injected with 1.5 mL of 0.9% NaCl (control). Subjective lameness evaluation, force plate analysis and synovial fluid analysis, including interleukin-1 receptor antagonist (IL-1ra) analysis, were performed before (day 0) and at days 1, 3, 5 and 10. Synovial fluid analysis was also performed on days 20 and 30.

No difference in subjective lameness and no decrease in peak vertical force or vertical impulse were seen in any limb on any day. Total nucleated cell count (TNCC) was increased in treated joints on days 1 (T: 6039 cells/μL, C: 240 cells/μL) and 3 (T: 1119 cells/μL, C: 240 cells/μL). Log-10 transformed values for IL-1ra were higher in treated joints on days 1 (T: 3553.7 pg/mL, C: 1890.1 pg/mL) and 3 (T: 2283.2 pg/mL, C: 1250.7 pg/mL).

Injection of ELAA into the ICJ caused an increase in synovial fluid but no lameness was observed. IL-1ra was increased on days 1 and 3 after ELAA injection. Intra-articular injection of ELAA into healthy equine joints results in no significant safety concerns. The observed increase in IL-1ra may provide beneficial effects in inflamed joints.

SQUAMOUS CELL CARCINOMA

In this study, Lea Miglinci and co-workers in Austria estimated the prevalence of equine papillomaviruses and gamma-herpesviruses in equine squamous cell carcinoma (SCC).

A series of SCCs from the head-and-neck (HN), (peri-)ocular and genital region, and site-matched controls were screened for equine papillomavirus (EcPV) type 2–5 and herpesvirus DNA using type-specific EcPV PCR, and consensus nested herpesvirus PCR followed by sequencing. EcPV2 DNA was detected in 45.5% of HN lesions, 8.3% of (peri-)ocular SCCs and 100% of genital tumours; all except one control samples from tumour-free horses tested EcPV-negative. Two HN SCCs harboured EcPV5, and an ocular lesion EcPV4 DNA. Herpesvirus DNA was detected in 63.6%, 66.6%, 47.2% and 14.2% of horses with HN, ocular, penile and vulvar SCCs, respectively, and mainly identified as equine herpesvirus 2 (EHV2), 5 (EHV5) or asinine herpesvirus 5 (AsHV5) DNA. In the tumour-free control group, 9.6% of oral secretions, 46.6% of ocular swabs, 47% of penile samples and 14.2% of vaginal swabs were positive for these herpesvirus types. This study highlights the role of EcPV2 as an oncovirus and provides new information on the prevalence of (gamma-)herpesviruses in equine SCCs.

CERVICAL NERVE ROOT INJECTION

This study by Gregoire Fouquet and co-workers in Qatar and the United States described an ultrasound-guided injection of the cervical nerve root C3 to C8, evaluated its accuracy, time and safety and anticipated possible complications on clinical cases.

Under general anaesthesia and with ultrasound guidance, five horses were injected from C3 to C8 with a 1.5 mL mix of contrast and latex. Immediately after euthanasia, the necks were taken for computed tomographic (CT) examination. Dissection was

performed 3 days later. Data regarding the accuracy of injection, the presence of injectate in the nerve root, vertebral vessel or vertebral canal were recorded from both CT and dissection. The time of injection and ability to visualise the nerve root prior to injection were also recorded. Out of 60 intended injections, 55 (CT images) and 57 (dissection) led to injectate deposited within the target zone with direct contact between contrast/latex and cervical nerve roots noted in 76.4% and 73.7% respectively. Presence of contrast/latex injectate within nerves (≤11%), vertebral vessels (<4%) and canal (<4%) were rarely encountered. No variation on success rate or safety was noted based on the site of injection. The technique described has excellent accuracy, with injectate deposition in direct contact (≈75%) or close vicinity (≈25%) of C3–C8 cervical nerve roots. Injectate diffusion is likely to further improve success rate. The rare presence of injectate within nerve/sheath, vertebral vessels/canal along with diffusion warrants caution when performing this procedure in clinical cases.

TARSAL SUBCHONDRAL BONE INJURY

This retrospective study by Virginia Melly and co-workers in the United States aimed to characterise an unreported site of tarsal subchondral bone injury (SBI) in Thoroughbred racehorses.

Tarsal computed tomographic (CT) scans of 108 horses were reviewed for evidence of SBI in the dorsodistolateral calcaneus (DDLC). The association of DDLC SBI with Thoroughbred racehorses compared to other breeds/disciplines was calculated. Nuclear scintigraphic scans of the hindlimbs of Thoroughbreds between 2007 and 2022 were also reviewed for increased radiopharmaceutical uptake (IRU) suggestive of DDLC SBI.

The dorsodistolateral calcaneus SBI was identified in tarsal CT scans of 8/108 (7.3%) horses. All lesions were found in racing Thoroughbreds and in 20% (8/40) of racing Thoroughbreds that underwent tarsal CT. DDLC SBI was determined to be the primary cause of lameness in 3/8 animals. Third tarsal bone fracture was considered the primary cause of lameness in a further 3/8 horses. A total of 1663 nuclear scintigraphic scans of 1603 Thoroughbred horses were reviewed. Increased IRU in the DDLC was present in 13 horses (0.9%).

The DDLC is a previously unreported site of SBI in the Thoroughbred racehorse and can cause clinically relevant lameness.

ENLARGEMENT OF THE EPIPLOIC FORAMEN

In this study, Meghan Wanstrath and co-workers in the United States assessed the safety and efficacy of a method for digitally enlarging the caudal aspect of the epiploic foramen (EF).

This study included 14 healthy horses and three clinical cases of EF entrapment (EFE). Through a ventral midline celiotomy under general anaesthesia, the EF was enlarged by digital separation of the caudal attachments of the caudate lobe of the liver from right dorsal colon, right kidney, gastropancreatic fold and pancreas. Healthy horses were euthanised under anaesthesia, and the enlarged EF was measured at necropsy.

No clinically relevant haemorrhage was observed at necropsy (14 horses) or by vital parameters under anaesthesia in all horses. In clinical cases, EFE was reduced following enlargement of the EF, with no intraoperative complications. In one clinical case, necropsy at 30 days confirmed partial closure of the enlarged EF.

This method enlarged the EF safely and effectively and could be considered in selected cases of EFE in which manual reduction is difficult or protracted.

Sue Wright

EVE Editorial Office
Email: sue@evj.co.uk

ORCID

Sue Wright https://orcid.org/0000-0002-5513-8571

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Equine Veterinary Education

CASE REPORT

Invasive squamous cell carcinoma causes trigeminal nerve dysfunction in a horse

Amie Wilson[1] | **Emanuele Ricci**[2] | **Alison Talbot**[1] | **Fernando Malalana**[1]

[1]Department of Equine Clinical Science, Institute of Veterinary and Ecological Sciences, University of Liverpool, Neston, UK

[2]Department of Veterinary Anatomy, Physiology and Pathology, Institute of Veterinary and Ecological Sciences, University of Liverpool, Neston, UK

Correspondence: Amie Wilson
Email: a.wilson3@liverpool.ac.uk

SUMMARY

Cranial nerve dysfunction can result in severe clinical signs such as loss of vision, hearing or balance. There are multiple potential causes of cranial nerve dysfunction, and they can become damaged either at the level of the brainstem or as they course across the head and neck. An equine case series of facial nerve dysfunction found that this was mostly caused by trauma, though multiple other aetiologies were described (inflammatory conditions, idiopathic and iatrogenic) with only one case of neoplasia. There are scarce reports detailing neoplastic cranial nerve dysfunction in the horse.

This case describes the acute onset of trigeminal nerve dysfunction. The clinical findings directed the advanced imaging. CT identified enlargement of the rostral alar foramen and neurovascular bundles, with osseous lysis, suggestive of neoplasia. Following euthanasia, postmortem findings demonstrated the mass to be a squamous cell carcinoma that likely originated from the oral or respiratory mucosa.

This report highlights the need for accurate clinical assessment of cranial nerve function alongside guided cross-sectional imaging to identify the lesion. Histopathology remains essential to confirm the diagnosis.

KEYWORDS
horse, neoplasia, tumour, neuropathy, CT, cranial

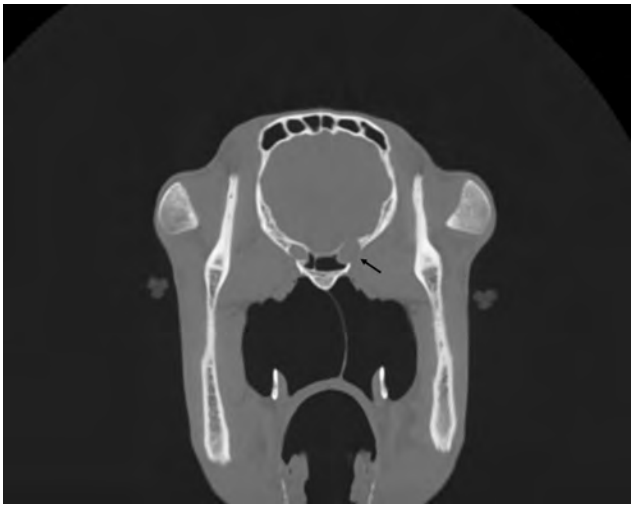

FIGURE 1 Transverse CT image demonstrating the enlargement of the rostral alar foramen and bone thinning, consistent with enlargement of the neurovascular bundle

Key points

- Thorough cranial nerve assessment can aid lesion localisation.
- Squamous cell carcinoma is a rare cause of cranial nerve dysfunction in the horse.
- Computed tomography is a useful modality to identify neoplasia of the head, although histopathology is essential to confirm the diagnosis.

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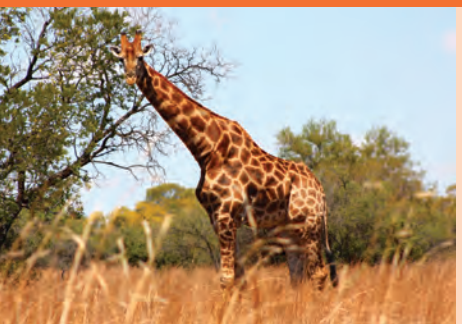

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1 Data on file.

2 Adequan® i.m. Package Insert, Rev 1/19.

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Equine Veterinary Education BEVA AAEP

CASE REPORT

Treatment of mandibular ameloblastoma with surgical resection in combination with radiation therapy in a 15-year-old Hanoverian gelding

Johanna Will[1] | Encarnación Muñoz[1] | Souel Maleh[1] | Achim Gruber[2] | Lisa Coco[1] | Holger Fischer[1]

[1]Tierärztliches Kompetenzzentrum für Pferde Grosswallstadt Altano GmbH, Grosswallstadt, Germany

[2]Freie Universität Berlin Fachbereich Veterinärmedizin, Institute of Veterinary Pathology, Berlin, Germany

Correspondence: Encarnación Muñoz
Email: nani25es@yahoo.es

SUMMARY

A 15-year-old Hanoverian gelding was admitted for evaluation of a firm mass on the right mandible. Radiographs showed a multicavitary calcified mass with areas of sclerosis and lysis in the region of teeth 406–408. Tooth 407 was loose and was extracted. Treatment with tiludronic acid was performed. Due to persistent growth, CT examination of the head was performed standing. The mass had the appearance of a mandibular bone cyst. There was a stress fracture in the right mandible. Differential diagnosis included osteogenic neoplasia of the mandible and osteomyelitis, although the signs of inflammation characteristic of osteomyelitis were absent. Surgery for en bloc resection was performed, where a broad 4.5 locking compression plate (LCP) with 14 holes was placed over the defect as a 'bridge'. The defect was filled with Cerasorb M. The mass was submitted for histological examination, which revealed a locally invasive and, therefore, principally malignant ameloblastoma with secondary fibrosis and osteolytic destruction of adjacent pre-existing lamellar bone. The resection margins were devoid of any tumour cells, suggesting complete excision.

Six weeks after surgery, radiation therapy was started in a radiation oncology centre with a protocol consisting of 10 radiation sessions and a total dose of 42 Gy using volumetric modulated arc therapy (VMAT). All treatments were administered with the patient positioned in Vac-Lok cushion under general anaesthesia. The horse tolerated the treatments well. One year after the last treatment, the horse was re-examined. Radiographs showed a smooth contour of the ventral aspect of the mandible with no periosteal reaction and no signs of resorption around the plate. The original defect was filled with trabecular bone. Multiple biopsies of the area were taken and showed no evidence of tumour cells or inflammation.

KEYWORDS
horse, ameloblastoma, computed tomography, resection, radiation therapy

FIGURE 1 3D reconstruction of CT scan from the right side of the head, showing the mandibular mass and associated fracture (black arrow)

Key points

- Ameloblastomas of the jaw can rapidly threaten the survival of a horse if left untreated, although they very seldom metastasize.
- Surgical excision of large masses in the mandible of the horse can have a good cosmetic and functional outcome.
- Radiation therapy as an adjuvant treatment of aggressive mandibular ameloblastomas in horses can give a very good prognosis in a long-term basis.

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Equine Veterinary Education

CASE REPORT

Successful removal of a functional parathyroid adenoma using a radio-guided parathyroidectomy technique with a hand-held gamma detector and technetium Tc 99m sestamibi scintigraphy in a horse

Shannon S. Connard | **Elizabeth A. Hodge** | **Jolie A. Demchur** | **Kathryn B. Wulster** | **Amy L. Johnson** | **Michael W. Ross** | **David G. Levine**

Department of Clinical Studies, New Bolton Center, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence
David G. Levine
Email: dglevine@vet.upenn.edu

Summary

This clinical case report details the use of a radio-guided parathyroidectomy technique using a hand-held gamma detector and technetium Tc 99m sestamibi scintigraphy for detection and removal of a functional parathyroid adenoma in a horse. An 18-year-old Arabian gelding was diagnosed with primary hyperparathyroidism based on persistent hypercalcaemia and increased parathyroid hormone concentration. Single gland disease was suspected after technetium Tc 99m sestamibi scintigraphy showed focal increased radiopharmaceutical uptake (IRU) at the thoracic inlet. Ultrasonography failed to identify a discrete mass in the region of IRU. Surgical excision was recommended; however, due to unreliable preoperative localisation, a radio-guided parathyroidectomy technique was elected. A radio-guided parathyroidectomy technique was performed under general anaesthesia using a hand-held gamma detector and technetium Tc 99m sestamibi scintigraphy to identify the parathyroid adenoma, which was subsequently excised. The horse recovered from the procedure without complication. Successful removal of the parathyroid adenoma was confirmed based on histopathological and serum bioch findings. Following the procedure, the horse showed no evidence of hyperparathyroidism and returned to light pleasure riding. Three years postoperatively, the gelding died of unrelated natural causes; a post-mortem examination was not performed. This radio-guided parathyroidectomy technique was effective in facilitating the removal of a parathyroid adenoma in this gelding and might be useful in other equids that have primary hyperparathyroidism IRU on technetium Tc 99m sestamibi scintigraphy, particularly if a discrete mass cannot be identified ultrasonographically.

KEYWORDS
horse, endocrine, nuclear medicine, primary hyperparathyroidism, radio-guided parathyroidectomy

INTRODUCTION

Primary hyperparathyroidism is a well-characterised endocrinopathy in which chief cells within the parathyroid gland produce and secrete an excessive amount of parathyroid hormone (PTH), ignoring physiological negative feedback mechanisms. This results in clinically significant electrolyte derangements, specifically hypercalcaemia and hypophosphataemia, which can lead to anorexia, weight loss, osteodystrophia fibrosa of the facial bones, osteopenia and lameness (Bringhurst et al., 2008; Cottle et al., 2016; Frank et al., 1998;

Peauroi et al., 1998; Villagrán et al., 2014; Wong et al., 2004). Primary hyperparathyroidism (PHPT) occurs as a result of hyperplasia or neoplasia of the parathyroid gland itself and can involve single or multiple glands (Bringhurst et al., 2008). In humans, single gland disease is much more common than multiple gland disease, occurring at a rate of 80%–90% (Jangjoo et al., 2017; Kakuta et al., 2002; Norman & Chheda, 1997; Urkan et al., 2019). A recent multicentre retrospective study reviewing 17 horses with PHPT showed that single gland disease was also more common in horses; with 10 horses diagnosed with single gland disease, 2 horses with multiple gland disease, and in 5 horses it was undetermined (Flynn et al., 2000).

Horses have two pairs of parathyroid glands which, unlike in other mammalian species, can be variably positioned. The cranial glands are located craniodorsal to the cranial pole of the thyroid gland or are embedded within the thyroid gland itself, while the caudal glands are located at the thoracic inlet adjacent to the distal third of the trachea or at the bifurcation of the bicarotid trunk (Krook & Lowe, 1964; Toribio, 2004). Diagnosis of PHPT is made using a combination of clinical and laboratory findings, ultrasound, technetium 99m Tc sestamibi scintigraphy, dynamic contrast-enhanced multi-dimensional computed tomography (CT), and magnetic resonance imaging (MRI). In human medicine, ultrasonography and scintigraphy are routinely used together, with a reported sensitivity of 97.4% in patients whose PHPT is due to a single adenoma (Casara et al., 2001). Sensitivity is lower in more complicated cases in which patients have small or ectopic parathyroid glands, multigland disease, or conditions causing delayed washout from the thyroid such as goitre and nonadenomatous morphological changes to the parathyroid (Cron et al., 2017). In dogs with PHPT, ultrasonography was effective in identifying a nodule in 96% of cases (Gear et al., 2005). Gorenberg et al. (2020) found the overall diagnostic sensitivity of ultrasonography was significantly lower compared to scintigraphy, at 54% and 90%, respectively, in horses diagnosed with PHPT. Scintigraphic identification did not guarantee successful surgical identification, especially when the uptake was not in a single location at the thoracic inlet. The decreased diagnostic sensitivity of ultrasound in horses compared to humans and dogs was attributed to the variable anatomical location of the caudal parathyroid glands and the difficulty differentiating them from other local structures, such as lymph or thyroid tissue or cases of multigland disease. Their findings suggest that both ultrasonography and scintigraphy should be used in conjunction for highest diagnostic accuracy in horses with PHPT (Gorenberg et al., 2020).

In addition to sestamibi and ultrasonographic imaging, dynamic contrast-enhanced multi-dimensional CT has been used in human medicine with increasing frequency with a reported sensitivity of 89.4% (Cheung et al., 2012). Contrast-enhanced CT has improved diagnostic accuracy and is more cost-effective compared to the combination of ultrasound and scintigraphy in both single-gland and multigland disease (Cheung et al., 2012). While there are currently no published case reports of contrast-enhanced CT in equids, it has been performed at this institution on a Miniature Horse with PHPT. Three-phase CT was used successfully to confirm the localisation of aberrant parathyroid gland tissue adjacent to the left thyroid lobe following ultrasonography and sestamibi nuclear scintigraphy (Colmer et al., 2022). With the exception of standing robotic and large gantry CT systems, CT and MRI have diagnostic limitations in large animals. Most systems have a fixed gantry diameter generally ranging from 50 to 85 cm, capable of accommodating the head and proximal neck of an average size horse, but not the caudal neck and chest. Moreover, conventional CT and MRI systems require general anaesthesia resulting in increased cost and associated risks. While early application of MRI has poor parathyroid detection, it is gaining traction as it avoids use of radioactive substances compared to scintigraphy and contrast-enhanced CT (Strauss et al., 2021).

Medical management, percutaneous ultrasound-guided ethanol ablation and surgical excision have been described for treatment of PHPT, with surgical excision being the treatment choice with the highest success rate of 90%–95% across species in cases of complete removal of all autonomously functioning tissue (Karstrup et al., 1990; Rasor et al., 2007; Walker & Silverberg, 1992). There are many factors which contribute to surgical failure including the presence of multi-gland disease and misidentification of abnormal tissue on ultrasonography, scintigraphy, or intraoperatively. In an attempt to mitigate these risks, a minimally invasive radio-guided parathyroidectomy (MIRP) technique has been described with a reported success rate of 98.6% in humans (Flynn et al., 2000; Goldstein et al., 2003; Norman & Chheda, 1997; Urkan et al., 2019). This case report describes successful application of a radio-guided parathyroidectomy technique using a hand-held gamma detector and low-dose technetium 99m Tc sestamibi scintigraphy for resection of a parathyroid adenoma in a horse with PHPT.

MATERIALS AND METHODS

Clinical case

An 18-year-old, 352-kg (775-lb), Arabian gelding was referred to New Bolton Center for treatment of PHPT. The horse was previously diagnosed with PHPT based on persistently high total (3.63–4.15 mmol/L; reference range 2.70–3.38 mmol/L) and ionised serum calcium (2.2 mmol/L; reference range 1.58–1.90 mmol/L) concentrations with concurrently increased serum parathyroid hormone (PTH) concentration (215.00 ng/L; reference range 5.66–103.73 ng/L), and lack of evidence of renal failure (serum creatinine concentration, 150.28 μmol/L; reference range 70.72–194.48 μmol/L) or paraneoplastic syndrome (thymidine kinase type 1 [TK1], 2.0 U/L; reference range ≤ 3.3 U/L). Two weeks prior to presentation, he was evaluated for signs of colic, which resolved following medical management by the primary care veterinarian. Elective biochemical analysis incidentally identified hypercalcaemia (total serum calcium concentration, 3.63 mmol/L; reference range 2.60–3.23 mmol/L), which prompted further investigation. The gelding had no reported lameness episodes; however, the horse-owner had recently noted increased

tripping when the horse was exercised on a lunge line. No treatment for hypercalcaemia was initiated prior to referral.

On presentation, the gelding was bright and alert, with a normal rectal temperature (37.4°C), mild tachycardia (48 beats/min), and respiratory rate (16 breaths/min). Body condition score was 4/9 with visible ribs and decreased musculature over his back. Visual assessment and palpation of the limbs and skull did not reveal any skeletal abnormalities. The gelding did not show overt lameness or signs of musculoskeletal discomfort. Polyuria and polydipsia were not evident.

Diagnostic evaluation

Packed cell volume (37%, reference range 32%–52%) and total solids (70 g/L, reference range 46–69 g/L) did not reveal any significant derangements. A serum biochemistry profile disclosed hypercalcaemia (total calcium concentration, 3.94 mmol/L; reference range 2.67–3.35 mmol/L) and mild hypophosphataemia (0.55 mmol/L; reference range 0.61–1.74 mmol/L). Serum creatinine (106.08 μmol/L; reference range 53.04–159.12 μmol/L) was within the normal reference range. Free catch urine specific gravity (1.027, reference range 1.025–1.060) and in-house urine dipstick results were normal with pH 8.5 (reference range 7.5–8.5), trace protein, trace urobilinogen, and negative results for glucose, bilirubin, ketones, blood, nitrogen and leucocytes.

No evidence of osteopenia was identified on radiographs of the third metacarpal and metatarsal bones. Ultrasonography of the thyroid region, ventral neck and thoracic inlet did not identify any lesions. Abdominal ultrasonography was performed at the request of the owner due to his recent history of colic and revealed no significant findings. Laboratory analysis performed prior to presentation identified normal TK1 and increased PTH as a cause for the hypercalcaemia; therefore, parathyroid hormone–related protein (PTHrP) was not measured as it was unlikely to be abnormal and an unrewarding expenditure. Nuclear scintigraphy of the neck and thoracic inlet using 200 millicuries (mCi) of technetium Tc 99m sestamibi IV was performed from the ramus of the mandible to the heart base. Lateral and ventral images of the neck and thoracic inlet were acquired using a large field-of-view scintillation camera with a low-energy, all-purpose collimator (Technicare Omega 500, Diagnostix Plus, Inc.; Software: NuQuest by Alphanuclear, MEDX, Inc.). Images were obtained at 10 min, 2.5 h, 5.5 h and 24 h after Tc99m sestamibi injection. Images were acquired without lemon juice, which can be used to stimulate the salivary glands to drain via their ducts into the mouth in order to remove theTc-99m–MIBI from the salivary glands and oesophagus prior to late phase imaging. Marked, focal uptake was identified in the thoracic inlet just ventral to the point of the shoulder, slightly left parasagittal to midline (Figure 1a,b). The lesion was not visualised on the lateral image; therefore, exact location in the dorsal-ventral plane was unknown. The late phase at 24 h showed a small amount of uptake remaining at this abnormal location.

Based on the scintigraphic findings, and increased PTH in the presence of hypercalcaemia, PHPT was confirmed and single gland disease was suspected. Repeat ultrasonography of the thoracic inlet in the location of the abnormal increased radiopharmaceutical uptake again did not identify any obvious masses. Surgical removal was the treatment of choice; however, due to unreliable preoperative localisation, a radio-guided parathyroidectomy technique was recommended. A miniaturised hand-held gamma probe could not be obtained due to the cost-prohibiting expense and declined requests to borrow from local human hospitals; therefore, it was elected to perform a radio-guided parathyroidectomy technique using a non-miniaturised hand-held gamma detector. Perianaesthetic haematology including fibrinogen (3.12 g/L, reference range 1.50–3.75 g/L) and complete blood count did not reveal any significant derangements.

Surgical technique

Anaesthesia

All surgeons, anaesthesia and operating room staff exposed to the case wore lead aprons and radiation monitoring badges. Approximately 2 h prior to surgery, 100 mCi of technetium Tc 99m sestamibi was administered intravenously (IV). An indwelling catheter was placed in a jugular vein, and the gelding was premedicated with trimethoprim sulfamethoxazole (30 mg/kg PO) and phenylbutazone (2.2 mg/kg IV). The horse was sedated with xylazine (1 mg/kg IV) and butorphanol (0.02 mg/kg IV), and anaesthesia was induced with ketamine (2 mg/kg IV) and midazolam (0.05 mg/kg IV). An endotracheal tube was placed, and anaesthesia was maintained with desflurane. The horse was positioned in dorsal recumbency with his head and neck extended. A urinary catheter was placed to safely collect and dispose of urine containing decayed radionucleotide.

Surgical procedure

In the interest of minimising operating time and maintaining an aseptic surgical field, no shielding was used for hands. Prior to creating an incision, the surgery site over the thoracic inlet was assessed using a hand-held gamma detector (Integrated Frisker Model 26-1, Ludlum Measurement Inc.) and a gamma reading of 8–10 milliroentgens per hour (mr/h) was obtained. Briefly, a 15 cm incision was made along ventral midline just cranial to the thoracic inlet and just caudal to the point of the shoulder, where that focal IRU had been previously identified on scintigraphy. Blunt dissection through the subcutaneous tissue and underlying musculature was performed to reveal the ventral aspect of the trachea. The area just to the left of the trachea was assessed using the gamma detector, which showed a gamma reading of 10–13 mr/h. Several masses within the area, ranging from 1 × 1 × 1 cm to 2 × 2 × 2 cm, were identified, excised and assessed ex vivo using the hand-held

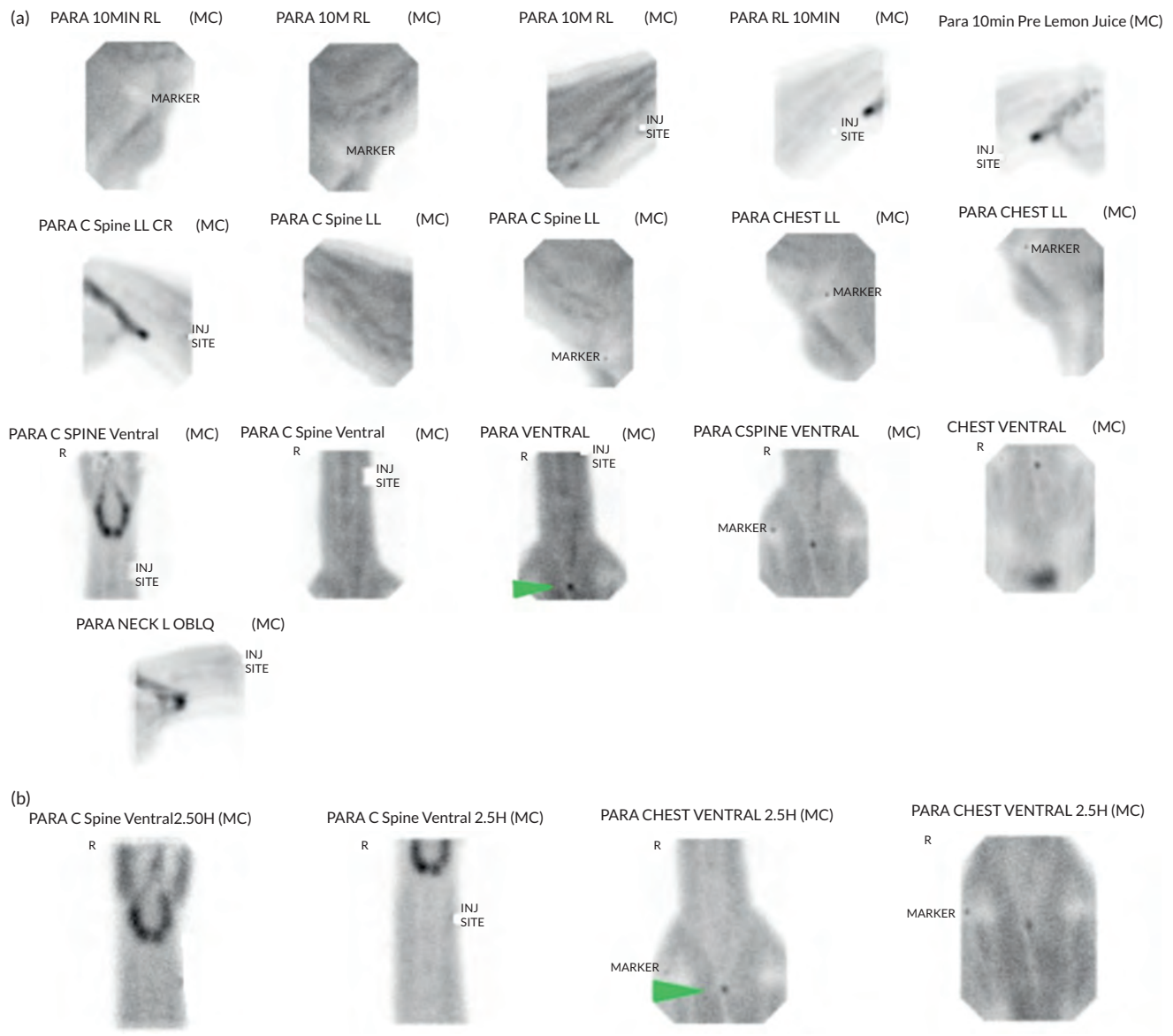

FIGURE 1 Serial technetium Tc 99m sestamibi scintigraphy images at (a) 10 min and (b) 2.5 h post injection of the neck and thoracic inlet of an 18-year-old Arabian gelding with a parathyroid adenoma. (a) Ventral and lateral images from the ramus of the mandible to the thoracic inlet and cranial images of the thoracic inlet are shown 10 min after injection. Marked, focal uptake in the thoracic inlet just ventral to the point of the shoulder, slightly left parasagittal to midline (arrowheads) represents the parathyroid adenoma. A marker was used to show the point of the shoulder in relation to the parathyroid adenoma. (b) Repeat ventral image from the ramus of the mandible to the thoracic inlet and cranial images of the thoracic inlet are shown 2.5 h after injection with similar uptake of the parathyroid adenoma (arrowheads)

gamma detector. The smaller masses (1 × 1 × 1 cm) gamma readings were <1 mr/h; however, the largest mass (2 × 2 × 2 cm) had a gamma reading of 6 mr/h. Following removal of this mass, the gamma reading for the surgery site remained 10–13 mr/h. Serum PTH concentrations measured preoperatively (397.95 ng/L; reference range 5.66–103.73 ng/L) and intraoperatively 20 min after removal of the mass (46.21 ng/L; reference range 5.66–103.73 ng/L) demonstrated an 88% decrease. Vitamin D concentration at the time of surgery was within normal reference ranges (25-Hydroxyvitamin D, 23 nmol/L; reference range 11–24 nmol/L). The incision was closed with absorbable suture and the gelding recovered from general anaesthesia without complication.

RESULTS

Aftercare

Following surgery, the gelding was maintained on trimethoprim sulfamethoxazole (30 mg/kg PO every 12 h), trazodone (2 mg/kg PO every 12 h) and a tapering course of phenylbutazone (2.2 mg/kg PO every 12 h). Approximately 24 h postoperatively, horse developed mild muscular stiffness. Profound hypophosphataemia (<0.13 mmol/L; reference range 0.61–1.74 mmol/L) and decreases in total and ionised calcium (total calcium concentration, 3.94 mmol/L preoperatively to 2.98 mmol/L postoperatively;

reference range 2.67–3.35 mmol/L; iCa, 2.22 mmol/L preoperatively to 1.71 mmol/L postoperatively; reference range 1.45–1.75 mmol/L) were detected, while his magnesium (0.78 mmol/L; reference range 0.66–1.03 mmol/L) remained stable. A combination of intravenous and enteral electrolyte supplementation was used to correct the electrolyte imbalances. Intravenous supplementation was initiated with phosphorus (sterile Fleet enema, [phosphorus] = 1.38 mmol/ml, 0.04 mmol/kg/h) in addition to maintenance potassium (potassium chloride 0.03 mEq/kg/h). Oral supplementation was initiated with calcium and vitamin D (Osteo-Form, calcium 20 mg/kg PO every 12 h), magnesium oxide (Milk of magnesia, magnesium 50 mg/kg PO every 24 h), and potassium phosphate (K_2HPO_4 50 mg/kg PO every 12 h). Intravenous supplementation was tapered over 72 h and oral supplementation successfully maintained electrolyte concentrations within normal limits. Complete correction of the phosphorous concentration was achieved within 48 h.

The gelding was discharged from the hospital 8 days after parathyroidectomy with trimethoprim sulfamethoxazole (30 mg/kg PO every 12 h), trazodone (2 mg/kg PO every 12 h), and a tapering course of electrolyte supplements including calcium and vitamin D (Osteo-Form, calcium 20 mg/kg PO every 12 h) and magnesium oxide (Milk of magnesia, magnesium 50 mg/kg PO every 24 h).

Histopathology

Microscopic examination confirmed the diagnosis of parathyroid adenoma. The excised mass consisted of a well-demarcated and partially encapsulated neuroendocrine neoplasm with a thin, compressed rim of normal parathyroid gland tissue along the margin (Figure 2a,b). The neoplastic cells were arranged in lobules separated by thin fibrovascular septa, with areas of haemorrhage and cystic degeneration. Individual neoplastic cells were polygonal with pale eosinophilic finely granular cytoplasm and an ovoid nucleus that contained one to two prominent nucleoli. Pleomorphism was mild and mitotic figures were rarely detected. In conjunction with the clinical findings and response to surgical removal, the histopathological features of the excised mass were consistent with parathyroid adenoma.

Long-term follow-up

At examination 2 weeks after surgery, the horse-owner reported the gelding to be bright with an excellent appetite with no signs of fatigue or stiffness while on stall rest. He was receiving trimethoprim sulfamethoxazole (30 mg/kg orally every 12 h), calcium and vitamin D supplement (Osteo-Form, calcium 10 mg/kg orally every 12 h), and magnesium oxide supplement (Milk of magnesia, magnesium 12.5 mg/kg orally every 24 h). The incision healed without complication and the remaining sutures were removed at that time. The trimethoprim sulfamethoxazole and supplements were discontinued.

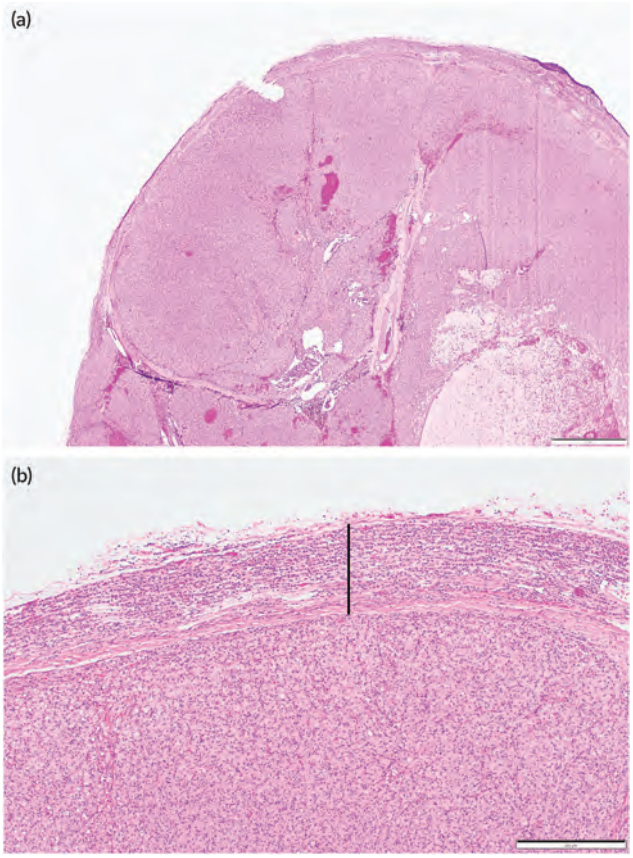

FIGURE 2 (a) Low (20×) and (b) higher (100×) magnification haematoxylin and eosin photomicrographs of the excised parathyroid gland. (a) A multilobulated, well-demarcated neoplastic proliferation of neuroendocrine cells expanded the parathyroid gland. The neoplasm had areas of haemorrhage and cystic degeneration. (b) A fibrous capsule separated the neoplastic cells from the adjacent compressed normal parathyroid gland tissue (black line). The neoplastic cells were arranged in thin cords and had eosinophilic, finely granular cytoplasm with round to ovoid nuclei.

He began small paddock turnout and a gradually increasing exercise rehabilitation program.

Approximately 6 weeks after surgery, serum electrolytes including total calcium (2.60 mmol/L; reference range 2.70–3.38 mmol/L), phosphorus (0.81 mmol/L; reference range 0.65–1.65 mmol/L) and magnesium (0.95 mmol/L; reference range 0.55–1.15 mmol/L) remained stable with no significant derangements. The gelding continued to gain weight and remained sound. He had returned to training as a low-level hunter jumper.

At 7 months postoperatively, the gelding's total calcium (2.83 mmol/L; reference range 2.60–3.38 mmol/L) was normal and ionised calcium (0.36 mmol/L; reference range 0.40–0.49 mmol/L) was mildly decreased. At 18 months after surgery, his ionised calcium (0.34 mmol/L; reference range 0.36–0.43 mmol/L) remained mildly decreased. At 24 months after surgery, via telephone communication, the owner reported complete satisfaction with the radioguided parathyroidectomy technique and would have the procedure performed again. Three years postoperatively, the gelding was

found deceased out on pasture of natural causes. A post-mortem examination was not performed.

DISCUSSION

Across species, PHPT treatment is limited to medical management, percutaneous ultrasound-guided ethanol ablation and surgical excision. Medical management is aimed at mitigating the side effects of PHPT, primarily derangements in calcium and phosphorus, and is frequently unsuccessful for long-term management (Cottle et al., 2016; Gorenberg et al., 2020; Tomlinson et al., 2001; Villagrán et al., 2014). Percutaneous ultrasound-guided ethanol ablation has been described in humans, dogs and horses; however, it is regarded as a second-choice treatment with limited advantages over surgery. Current recommendations for ethanol ablation are for use in cases with a solitary parathyroid tumour with major contraindications for surgical treatment, as there are increased risk of morbidities including recurrent laryngeal nerve damage secondary to extravasation of ethanol and difficulty of subsequent surgical dissection due to development of peritumoural fibrosis (Colmer et al., 2022; Gear et al., 2005; Karstrup et al., 1990). Surgical management is the only curative treatment; however, there are many factors which may contribute to surgical failure including the presence of multi-gland disease, misidentification of abnormal tissue on ultrasonography or scintigraphy, and misidentification of adenomatous tissue at surgery (Goldstein et al., 2003; Gorenberg et al., 2020; Jangjoo et al., 2017; Norman & Chheda, 1997).

In human medicine, surgical techniques include bilateral neck exploration or selective, minimally invasive, video-assisted, endoscopic, or radio-guided removal (Rubello et al., 2003). With the introduction of Tc-99m-sestamibi scintigraphy parathyroid adenomas could be identified and located preoperatively in 80%–90% of cases (Rubello et al., 2003). Shortly thereafter, MIRP was developed by injecting technetium Tc 99m sestamibi 2–4 h before the operation and using an intraoperative miniaturised hand-held gamma probe to facilitate localisation of the abnormal parathyroid tissue (Rubello et al., 2003). This technique has been shown to improve surgical success and decrease time, hospital stay, and cost of surgery (Fujii et al., 2011; García-Talavera et al., 2011; Rubello et al., 2003; Tardin et al., 2011). The original MIRP technique used full dose, 20–25 mCi, technetium Tc 99m sestamibi; however, due to concern for radiation exposure to the case and surgical staff, multiple low-dose protocols, as low as 1 mCi, have been investigated to minimise radiation exposure and found to have similar success rates (Cremonesi et al., 1999; García-Talavera et al., 2011; Goldstein et al., 2003; Jangjoo et al., 2017; Rubello et al., 2003; Tardin et al., 2011). Typically, in horses, a standard dose of 200 mCi technetium Tc 99m sestamibi is used for preoperative diagnosis. In this case report, a low-dose of 100 mCi technetium Tc 99m sestamibi was used to perform a radio-guided parathyroidectomy successfully. Further cases are needed to identify the lowest dose of technetium Tc 99m sestamibi that can be used with comparable success rates while minimising radiation exposure.

A radio-guided parathyroidectomy technique was successfully performed in this case using a non-miniaturised hand-held gamma probe that was available at our hospital by placing it in a sterile plastic cover. There are many design features of gamma detection probes with improved flexibility of utilisation compared to the gamma probe available in our hospital. The ideal probe for MIRP is wireless, pencil-thin, lightweight with angulation of the detector head for better access to desired locations. While pencil-thin probes offer higher spatial resolution, they yield a lower sensitivity than larger-sized detector probes and can limit the degree of attainable shielding and collimation, as thicker shielding and/or longer collimation increase the overall weight and size-dimensions of the gamma detection probe. Moreover, an audible signal and digital display of the gamma detection control unit could provide critical output information to the surgeon as to the localisation of the radionuclide within the area of interest (Povoski et al., 2009). Additional cases are needed to explore the benefits offered by a more technologically advanced, miniaturised, hand-held gamma probe, comparable to those used in human medicine, to achieve the maximum minimally invasive benefit of this technique.

The authors found this radio-guided parathyroidectomy technique helpful in identifying and confirming complete excision of the parathyroid adenoma in this horse. Without this technique, the procedure would have been more difficult, with increased risk of partial or complete excisional failure. The radio-guided parathyroidectomy technique has the potential to significantly decrease surgery time, which is directly correlated with the development of incisional infections. Furthermore, it aids in minimising unnecessary dissection and iatrogenic damage to local tissue, vasculature, nerves and lymphatics.

In a recent retrospective case series evaluating the diagnosis and treatment in horses with PHPT by Gorenberg et al., there was an overall 50% cure rate after attempted surgical excision of parathyroid adenoma, but 100% cure rate for surgical excision of single gland adenomas at the thoracic inlet. The vast majority of surgical failures were attributed to inadequate identification of abnormal tissue (Gorenberg et al., 2020). In order to evaluate excisional success, intraoperative circulating PTH assay may be performed. A 50% decrease between pre- and post-excision PTH levels has been shown to indicate with 90% certainty that the abnormally secreting gland had been removed (Irvin et al., 1991). Human hospitals have access to quick intraoperative PTH assays, which yield results in less than 15 min (Goldstein et al., 2003). Our hospital, along with many other veterinary hospitals, does not have access to in-house stat impression smear, cryosection histology or PTH assays, which makes real-time evaluation of intraoperative excisional success using serum PTH concentrations impractical.

An additional advantage of using a radio-guided parathyroidectomy technique is that it provides further means of investigating surgical success by providing the option to assess the radioactivity of the mass ex vivo using a hand-held gamma probe. In human medicine, there is

a proposed "20% rule" indicating resected parathyroid glands with radioactivity of 20% or greater than that of the surgical field background can be diagnosed as adenoma with a reported 100% accuracy (Murphy & Norman, 1999; Norman & Chheda, 1997). Goldstein et al. (2003) evaluated the outcome of MIRP using intraoperative radioactivity of the mass ex vivo without intraoperative PTH measurements and found equivalent success rates. By using the radio-guided parathyroidectomy technique, we were able to evaluate the mass ex vivo, which demonstrated a radioactivity of 46%–60% compared to the surgical field, suggesting successful removal of a primary adenoma according to the 20% rule. Of note, in this case report, there was no decrease in the gamma reading intraoperatively prior to and following removal of the mass. The authors hypothesise this could be due to the increased radiopharmaceutical uptake by the adjacent soft tissues, specifically the myocardium, as technetium Tc 99m sestamibi is lipophilic and cationic and has a predilection for tissues with high mitochondrial content and negative plasma membrane potentials (Rizk & Nagalli, 2022).

In this horse, postoperative complications consisted of mild muscular stiffness and mild-to-moderate electrolyte derangements, which have been described in several species, including horses (Garrahy et al., 2016; Gorenberg et al., 2020; Peauroi et al., 1998; Tomlinson et al., 2001; Wong et al., 2004). While it is routine to serially monitor serum biochemistry postoperatively and initiate treatment as needed, the postoperative management in this case was based on the current published literature (Tomlinson et al., 2001). A recent study in humans that underwent total thyroidectomy found that prophylactic supplementation of calcium prevented early postoperative hypocalcaemia (Ravikumar et al., 2017). Pre-emptive supplementation with calcium and/or magnesium in our veterinary cases might be beneficial; these practices are currently being evaluated in human medicine (Tabriz et al., 2022).

This is the first reported case of successful removal of a parathyroid adenoma using a radio-guided parathyroidectomy technique in an equid with technetium Tc 99m sestamibi and a hand-held gamma detector. Further exploration is warranted to evaluate the success rate using lower doses of Tc 99m sestamibi and more technologically advanced hand-held gamma probes.

AUTHOR CONTRIBUTIONS

S. Connard, E. Hodge, A. Johnson, K. Wulster, J. Demchur, M. Ross, and D. Levine each contributed to manuscript preparation and gave final approval of the manuscript.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest have been declared.

DATA AVAILABILITY STATEMENT

No data were used in this study. Clinical laboratory findings and diagnostic imaging can be made available upon request.

ETHICS STATEMENT

As a case report, no research or client-owned animals were used for study.

INFORMED CONSENT

In this study, the horse-owner of this case gave consent to submit this case report.

ORCID

Shannon S. Connard https://orcid.org/0000-0002-8509-9470
Kathryn B. Wulster https://orcid.org/0000-0003-0857-9363
David G. Levine https://orcid.org/0000-0001-6281-2766

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Botu-*what?*

Botupharma (bo|too|farma ~ bɒtʃu:fɑ:mə) combines Botucatu, a city in the State of Sao Paulo, where the company's Headquarters is located, and its specialty Pharmaceuticals.

What is Botupharma's history and background?

Founded about 20 years ago by three equine veterinarians and researchers from the State University of Sao Paulo (UNESP), Botupharma has pioneered several products that, over time, have become an industry standard for semen and embryo collection, manipulation, transport, and cryopreservation. As a team, the equine veterinarians and university researchers took part in developing the new reproductive discipline "ART" (Assisted Reproductive Technologies). Today, Botupharma is globally known for its top-performing semen extenders for manipulation, transport, and cryopreservation. But Botupharma didn't stop there; they continued to develop products needed for ART, such as embryo manipulation, artificial vaginas, sperm filter, and its very successful line of supplements that have proven, time and again, their effectiveness in enhancing reproductive performance in stallions and broodmares, boosting athletic performance horses such as Thoroughbred racehorses to reach peak-performance, aid in the quick recovery after events, as well as supplements to support growth, health, well-being in general, and specifically digestive, joint, and hoof health of foals and older horses.

How is Botupharma different from the numerous pharma companies that cater to the equine industry?

As a company, Botupharma exists due to the team effort of veterinarians, researchers, and trainers that have an in-depth understanding of equine nutritional demands. Working together, this team effort has allowed Botupharma to develop effective products using science and day-to-day practice experience. Thus, Botupharma products are not just simply based on science, as so often claimed by suppliers, but Botupharma, in fact, is the science behind its products. All products are rigorously lab-and field tested by trainers and veterinarians. Combining science and first-hand results, Botupharma products are continuously evolving and improving. We only use the purest and highest quality ingredients in our products, and our strict quality assurance program includes testing every batch for every product before it eventually arrives to the end user--Horsemen. And more importantly, all of Botupharma's supplements are "No-Doping"!

Does Botupharma treat health problems diagnosed by a veterinarian?

In the United States, Botupharma products are classified as supplements. They support, aid, promote, and encourage improved athletic and reproductive performances and the overall health of horses. We do not treat horses with health problems diagnosed by a veterinarian, nor are our products considered medication. Nevertheless, based on tests and feedback from horsemen who use our products, we are very confident our supplements aid in the recovery of your horse while promoting the highest level of well-being in any equine discipline, reinforcing their nutritional demand to reach their full potential on the racetrack and in the sales ring.

Is a Prescription from a Veterinarian Needed to Purchase Botupharma Products?

Our product line in the United States is classified as supplements, not as pharmaceuticals. Therefore, anyone can purchase. NO veterinarian prescription is needed. We do recommend, however, consulting

with your veterinarian about all nutritional decisions made for your horses.

What are the testing protocols you go through to bring a product to market?

Botupharma implemented several quality control steps, starting by assuring our prime materials come from trusted sources and are pure and clean when delivered; from there, it goes on to the production line, where modern equipment and highly-trained staff follow the manufacturing protocols until the finish line, where the products go through more inspections before being shipped. Furthermore, and a significant difference to many other manufacturers, every batch produced is tested before being liberated for sale. Trust is a critical decision-maker regarding which supplier and product to put your confidence in! Botupharma has proudly built this trustful relationship with its worldwide clients over the last two decades. Unfortunately, one must do their homework when it comes to choosing the right supplier and product because it's a known fact that several manufacturers are making false claims on their labels about the number and concentration of key ingredients, not to mention the lack of competent understanding of equine nutrition. Not just providing the advertised performance, but even more dangerous, may cause severe health problems and even death.

Are there any withdrawal times (pre-race) for any of your products? And - Are all your products steroid free?

Excellent questions and imperative to choose your horse's nutritional means. For all Botupharma products, there is no reason to interrupt your feeding protocol. All products are strictly developed, respecting the HISA Prohibited Substances List and Controlled Medications, and free of steroids and any substance considered doping.

What are the top three products you offer for the young racehorse?

Well, starting with the newborn foal, Botupharma offers "NEWBORN," an oral paste supplement that offers superior nutritional support for the newborn and nursing foal. It contains a potent adsorbent that removes the toxins produced by infectious agents and boosts the immune system while preventing gastrointestinal disorders. After the initial phase, "Botumix Revitalize" aids foals under stressful situations, such as weaning, diet change, and diarrhea, given together with "Botumix Foal" (to be launched soon), will provide all the nutritional demands, stimulating muscle mass growth, especially for high-performance horses, to get them as close as possible to their maximum potential. After that, the supplement choice depends on the horse's specific needs. For example, does an animal suffer from anemia? We provide "RedUp," stimulating the production of red blood cells and recovery of the animal's energy and vitality after intensive training. Alternatively, perhaps, the horse is with diarrhea; Botupharma's "Entrin" offers complete nutritional support to assist gastrointestinal disorders in horses. The formulation combines prebiotics, toxins adsorbents, and glutamine to improve intestinal immunity and promote enterocyte recovery. For horses with joint problems, "Athroplus" for maximum mutual support, which we will add shortly to our supplement product line.

Botupharma's equine supplement line.

How long will it take to see a result once using your products?

Also, a great question, and of course, we need to consider first that the results vary from individual to individual, as well as the environment and daily training routine. Having said that, we know from many experiences and tests that the first effects occur within the first week of administration.

So what's the next step? How can readers learn more about your product range and whom should they contact?

Botupharma entered the US market about five years ago to be hands-on and available for our North American customers due to the constant demand for our products. Headquartered in Phoenix, Arizona, our desire and commitment are to continue growing as a leading biotech for essential consumables for Assisted Reproductive Technology and the #1 choice for equine supplements, contributing to health, performance, and reproductive success. The reason for our growth is simple: Once customers have tried our product, – they will stay with Botupharma! As we are very enthusiastic and devoted to animal well-being and very confident about the outstanding performance of our products, proven time and again, we offer free samples for the ones who are sincerely interested in testing our products. Our Webpage: *www.botupharmausa.com*, is a good source for more information about the company and its products. Please, feel free to contact *sales@botupharmausa.com* to learn more about it.

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CLINICAL COMMENTARY

Primary hyperparathyroidism in horses: What can we learn from human medicine?

Philip J. Johnson | **Kile S. Townsend**

Veterinary Health Center, University of Missouri, Columbia, Missouri, USA

Correspondence
Philip J. Johnson
Email: johnsonpj@missouri.edu

Summary

Equine primary hyperparathyroidism is rare compared with the condition in human medicine where it is often encountered and represents the most common explanation for hypercalcemia in the outpatient setting. Primary hyperparathyroidism results from a hyperfunctioning parathyroid gland and surgical treatment (parathyroidectomy) is typically curative. Successful surgical removal of a diseased parathyroid gland can be challenging in horses as both normal and hyperfunctioning glands are difficult to localise. Identification of surgical targets using ultrasonography and/or Technetium-99 m sestimibi scintigraphy are useful for this purpose in both the human and equine contexts. However, these localisation approaches are not always effective. Moreover, not all patients are candidates for general anaesthesia and surgery and the costs associated with diagnostic localisation and parathyroidectomy may be prohibitive for some owners. This commentary presents information about primary hyperparathyroidism in the event that it is not treated and strives to review aspects of the disease when left untreated from the human medical context.

In the Case Report in this issue Connard and co-workers have described an innovative and helpful method for the identification and surgical excision of an abnormal parathyroid gland that was identified at the thoracic inlet using a combination of pre- and intraoperative Technetium-99 m sestimibi scintigraphy but that could not be visualised with ultrasonography (Connard et al., 2023). Whereas the clinical diagnosis of primary hyperparathyroidism (PHPT) in horses is usually straightforward and based on documentation of hypercalcaemia, hypophosphataemia and normal or elevated serum PTH concentrations, the positive identification of the location of an abnormal (hyperfunctioning) parathyroid gland can be very challenging.

Confounding explanations for hypercalcaemia that must be routinely considered and ruled out in the human, but not ordinarily equine, medical context include pseudohypercalcaemia and treatment with some pharmaceutical agents. Fictitious total hypercalcaemia (pseudohypercalcaemia) may be present when hyperalbuminaemia is identified because approximately 45% of the calcium in the serum is bound to protein (usually albumin). If hyperalbuminaemia is present, the 'true' calcium concentration is determined using the following formula: corrected calcium = measured calcium + (40 − measured albumin × 0.02) (units for calcium concentrations: mmol/L; units for measured albumin concentration: g/L). A similar correction formula for horses has not been reported and measurement of ionised calcium concentration in serum should allow the diagnostician to rule out pseudohypercalcaemia. Pseudohypercalcaemia may also occur in the presence of calcium-binding paraproteins and, following blood collection, through release of intracellular calcium by platelets in thrombocythaemic states. Treatment with lithium may elevate both circulating plasma parathyroid hormone and calcium concentrations. Hypercalcaemia may also result from treatment with thiazide diuretics (such as hydrochlorothiazide), which enhance renal calcium reabsorption. When applicable, reassessment of calcium and parathyroid hormone levels should be undertaken at least 3 months following discontinuation of these medications (Al-Azem & Khan, 2011; Dandurand et al., 2021).

In human medicine, familial hypocalciuric hypercalcaemia (FHH) must also be considered in the differential diagnosis of hypercalcaemia, particularly in younger patients (<20 years of age); acquired PHPT is more common in older human and equine individuals. Although not, to our knowledge, described in horses, FHH is

an inherited condition (autosomal dominant transmission) in which the calcium-sensing receptor is inactivated because of a gene mutation. Elevated levels of both serum calcium and parathyroid hormone (or inappropriately normal parathyroid hormone levels in the face of hypercalcaemia) are also identified in FHH, thus mimicking PHPT. The FHH mutation also affects the kidneys; hypocalciuria results from increased renal tubular calcium resorption. Diagnosis of FHH is additionally based on demonstration of a very low urinary clearance ratio of calcium to creatinine and genetic studies. Although it must be considered as an explanation for incidental hypercalcaemia in asymptomatic (human) patients, identified on routine screening, FHH is an otherwise benign condition that does not require surgical treatment (parathyroidectomy) (Al-Azem & Khan, 2011; Carral et al., 2021).

It has been suggested that, when PHPT is identified in horses with comorbid thyroid gland neoplasia, phaeochromocytoma and pituitary *pars intermedia* dysfunction, it may be similar to the situation in human medicine in which PHPT is sometimes identified as a component of multi-endocrine neoplasia (MEN) syndromes. Multiple endocrine neoplasia is defined by simultaneous neoplasia and hyperplasia of multiple endocrine tissues and has an inherited basis in humans (Bringhurst et al., 2008; Hoff et al., 2000; Miedlich et al., 2002). In one horse with PHPT the surgical removal of an abnormal parathyroid gland failed to resolve hypercalcaemia and elevated serum PTH levels. In that case, it was suggested that there might have been other unidentified parathyroid tumours or that the horse was affected by a MEN-like syndrome (Villagrán et al., 2014). A multiendocrine neoplasia syndrome has also been reported to (rarely) cause hypercalcaemia in horses (De Cock & MacLachlan, 1999; Germann et al., 2006). Both normal and abnormal parathyroid glands are inherently difficult to locate in horses (including at post-mortem examination). Type 2a MEN (Sipple's syndrome), characterised by the co-existence of medullary thyroid carcinoma, hyperparathyroidism and phaeochromocytoma in the same individual, should be considered with this finding in horses, even if an affected parathyroid gland cannot be located (Luethy et al., 2016).

Similar to the situation in other domestic animal species, horses are invested by two pairs of parathyroid glands; the anatomical location of the caudal pair of glands is especially variable being located anywhere along the length of the carotid arteries from the cranial cervical region to the thymus (Tomlinson et al., 2014; Wong et al., 2004). Technetium-99 m sestimibi parathyroid scintigraphy is a nuclear medicine procedure that is performed to localise parathyroid adenoma (hyperfunctioning parathyroid glands absorb the radionuclide faster than normal glands) (Gotway et al., 2002). As with the case described here, overactive parathyroid glands can sometimes be identified using sestimibi scanning; radionuclide uptake by abnormal parathyroid gland cells correlates with the number and activity of their mitochondria. Normal parathyroid glands in the same patient are not identified by sestimibi uptake because they are inhibited through normal negative feedback mechanisms. Sensitivity of sestimibi scanning for the purpose of abnormal parathyroid gland localisation has been improved in human medicine through the introduction of single-photon emission computed tomography (SPECT) (Neumann et al., 2008). Obviously, this technology is not currently available in the equine diagnostic setting. Even using the sophisticated imaging technology that is available to human medical diagnosticians, false-negative outcomes are reported for between 5%–38% of human PHPT cases with sestimibi scanning. Numerous different factors that are related to the absence of uptake in sestimibi scintigraphy in PHPT patients have included young age, female gender, ectopic or upper location, high body mass index, low oxyphilic cell content, small adenoma size (<500 mg), patient motion, ectopy, number of adenomata and coexistence with nodular thyroid gland disease (Carral et al., 2021; Greenspan et al., 2012; Nichols et al., 2008).

Although the sensitivity of Tc-99 m sestimibi nuclear medicine scans for detecting parathyroid adenomas in horses is unknown, it has been reported to be approximately 90% in humans (Hillyar et al., 2022) and 17% in dogs (Matwichuk et al., 2000). In addition to the report in this issue (Connard et al., 2023), Tc-99 m sestimibi scintigraphic scanning has been reported to be effective in 13 of 16 (81%) previously published cases (Colmer et al., 2022; Cottle et al., 2016; Gorenberg et al., 2020; Tomlinson et al., 2014; Wong et al., 2004).

Three quarters of human patients are asymptomatic and do not exhibit symptoms that are explained by PHPT, the clinical course of which has been described as being rather benign (Miedlich et al., 2002). In contrast to the situation in equine medicine in which it is regarded as rare, primary PHPT is a much more common endocrine condition in people, affecting approximately 0.86% of the USA population (Dandurand et al., 2021; Khan et al., 2017). It is the most common explanation for hypercalcaemia in the outpatient setting (Dandurand et al., 2021). Hypercalcaemia associated with PHPT results from the influence of elevated circulating PTH levels causing increased renal tubular calcium reabsorption, enhanced bone resorption through stimulated osteoclasis and increased renal $1,25(OH)_2D_3$ synthesis (which stimulates both calcium and phosphate absorption in the intestine) (Dandurand et al., 2021).

In the past, PHPT was recognised clinically when affected individuals developed complications of osteopenia and bone fragility or evidence of renal disease (Minisola et al., 2018). In more recent years, the inclusion of plasma calcium concentration as a component of routine health assessments in Western society has led to earlier recognition of subclinical PHPT. Asymptomatic PHPT is commonly encountered in people and does not necessarily necessitate surgical treatment. In these cases, the patients are monitored and treated conservatively. Early clinical signs of PHPT in equine patients are often very nonspecific and include lethargy, loss of bodily condition, reduced appetite or anorexia, ill-defined, shifting lameness and stiffness (Darby et al., 2020; Gorenberg et al., 2020; Schwarz et al., 2019; Tomlinson et al., 2014; Villagrán et al., 2014). A number of considerations from the human medical context that may be relevant to some of the signs seen in equine PHPT include the fact that bone pain is described in people with high calcium concentrations (Khosla, 2014; Miedlich et al., 2002). Additionally, people affected

with hypercalcaemia commonly report depression, headache, fatigue, exhaustion and cognitive dysfunction (Miedlich et al., 2002; Shane & Irani, 2006). Other self-reported symptoms in the human context include weakness, constipation forgetfulness and lack of interest (Brown & Macleod, 2001; Hall, 2011).

There has been increasing recognition of the fact that mild/asymptomatic PHPT in people may be present for many years before specific and overt clinical problems arise, affecting principally skeletal structures and the kidneys. Hyperparathyroidism is often discovered incidentally because most affected equids do not exhibit clinical signs over the course of several years (Roussel & Thatcher, 1987). If surgical treatment (parathyroidectomy) is not undertaken (or unsuccessful), the clinical course for (human) patients with mild or asymptomatic PHPT appears to be quite stable. Circulating plasma calcium and parathyroid hormone levels and bone density may remain stable for up to 10 years (Bilezikian et al., 2009), following which time bone density may begin to decrease (Al-Azem & Khan, 2011). This observation is important to consider from the equine perspective because PHPT may have been present in affected horses for at least several years with an absence of radiographic or histopathological evidence of osteopenia (stimulated osteoclasis) (Connard et al., 2023; Schwarz et al., 2019).

Human patients with asymptomatic mild primary hyperparathyroidism that are not surgical candidates are monitored and treated with calcimimetic agents when osteoporosis or declining bone mineral density are identified (Dandurand et al., 2021). Moreover, pharmacological treatment of PHPT is also advocated for the management of inherited (familial) forms of hyperparathyroidism, following surgical failure, and for those patients who refuse surgery.

Although (human) patients with mild asymptomatic PHPT may be medically managed for some time without resort to parathyroidectomy, the onset of renal dysfunction (with diminished glomerular filtration rates) and osteoporosis (based on monitored densitometric criteria) will eventually warrant consideration of parathyroidectomy because of the increased risk of pathological (fragility) fracture. Poor bone mineral density (BMD) as may arise in cases of PHPT is associated with elevated risk of fracture. Therefore, the assessment of BMD is routinely undertaken for human patients using, for example dual-energy X-ray absorptiometry (DEXA). In addition to PHPT, other conditions that warrant DEXA scanning in people include age (women after 65 years and men after 70 years of age), eating disorders, employment of androgen deprivation treatments for management of prostate cancer, long-term glucocorticoid treatment and other bone conditions. Although assessment of BMD in horses is somewhat in its infancy, there have been some post-mortem studies (dissected bones) employing DEXA that have demonstrated correlation between BMD and the force needed to break the third metacarpal in vitro (Junge et al., 2011; Tóth et al., 2014). Assessment of BMD has also been reported for living horses using a radiographic bone aluminium equivalence method (Maher et al., 2020; Nielsen et al., 2017). Deprivation of osteoid from bones (osteopenia) as a result of osteoclast-mediated bone resorption leads to bone fragility and increased risk for fracture.

Historically, diagnosis of late-stage PHPT was commonly based on the identification of characteristic radiographic changes that include salt-and-pepper skull appearance, distal clavicle tapering, subperiosteal bone resorption, bone cysts and brown tumours (collectively referred to as osteitis fibrosa cystica) (Dandurand et al., 2021). Encounters with pathological fracture and *osteitis fibrosa cystica* are now much less commonly reported in developed countries because earlier diagnosis of PHPT is facilitated through routine blood testing during annual medical examinations. Whereas clinical evidence of bone fragility and radiographic osteopenia have been reported in some PHPT-affected horses, these abnormalities are not evident in all cases. Results from a 15-year observational study that evaluated 57 human patients with asymptomatic PHPT showed that worsening hypercalcaemia did not occur until Year 13 and that other measured outcomes (including serum PTH levels) were stable throughout (Rubin et al., 2008). Moreover, whereas vertebral BMD remained unchanged there was a significant bone loss in the distal radius by Year 8. These observations point to the fact that, in many (human) cases, clinically important osteoid depletion occurs over a long period of time and that progressive loss of BMD differs between bones at different locations. Using DEXA scanning, it has been shown that reduction in BMD is most evident in the radius (mostly cortical bone) and much less evident in lumbar vertebrae (rich in trabecular bone) (Miller & Bilezikian, 2002; Syed & Khan, 2000).

The extent to which PTH-induced loss of BMD affects different bones in the equine condition has not been much explored and might be examined prospectively as veterinarians encounter new PHPT cases in the future. Of specific interest and reported more commonly in horses affected with secondary hyperparathyroidism (SHPT) (from nutritional etiologies), horses under the influence of elevated PTH may develop *osteodystrophia fibrosa* of the facial bones in addition to osteopenia at other skeletal locations. In their recent retrospective study of 17 PHPT-affected horses, Gorenberg et al. (2020) reported that skull and limb radiography (or both) was undertaken in 8 horses to screen for bony changes. Abnormalities that were identified in those cases included osteopenia of the limbs or skull (five cases), dystrophic mineralisation (two cases), laminitic changes of unknown cause (one case) and focal loss of the *lamina dura* of the first molars (one case). Radiographic evidence of diminished BMD is somewhat insensitive in that it requires at least 30% loss (Toribio, 2011). When successful, surgical treatment of people affected with PHPT (parathyroidectomy) provides skeletal protection and reverses the risk of pathological fractures associated with increased bone fragility (Dandurand et al., 2021).

In the human condition, PHPT is also associated with the development of kidney stones, nephrocalcinosis and renal insufficiency (Dandurand et al., 2021). Kidney stones are identified more frequently in asymptomatic PHPT patients than in the unaffected population; stone formers are more likely to be hypercalciuric than nonstone formers (Lila et al., 2012). The risk of further stone formation is lowered following parathyroidectomy but remains higher than that seen in the euparathyroid population.

Even though PTH stimulates renal calcium resorption, the primary determinant of the amount of calcium excreted into the urine per day is the ionised calcium concentration in plasma. In PHPT, the daily quantity of calcium excreted in the urine is increased in spite of high circulating PTH levels, because hyperparathyroidism results in hypercalcaemia, thus increasing the urinary calcium concentration (hypercalciuria). Nephroliths are often one of the first signs of PHPT in people, especially when it is considered that hypercalciuria is accompanied by enhanced urinary phosphate excretion (through the action of increased PTH); calcium and phosphate concentrations in the tubular fluid may exceed their solubility product and form precipitate as calcium phosphate stones.

Renal functional impairment is also identified in approximately 17% of asymptomatic human PHPT patients and is associated with the severity and duration of hypercalcaemia (Tassone et al., 2015). When identified, impaired renal function leads to recommendation for surgical intervention. Parathyroidectomy prevents worsening renal dysfunction in PHPT cases. Nephrocalcinosis is identified via CT in approximately 10% of asymptomatic PHPT patients. Risk factors for nephrocalcinosis have not been identified in these PHPT cases and it does not respond to parathyroidectomy.

Clinically evident renal complications of PHPT are not reported (hitherto) in horses, but acute kidney injury may arise following parathyroidectomy (Gorenberg et al., 2020). The reason for post-operative azotaemia in these circumstances is unknown, but all of those patients responded favourably to fluid therapy. Histopathological changes are sometimes reported in the kidneys of PHPT-affected horses post-mortem and have included deposition of calcium salts in the form of granules in the lumen and lining of collecting tubules and in adjacent interstitial tissue (Schwarz et al., 2019). Close attention to the kidneys and renal function in horses affected with PHPT is clearly warranted.

Unless an abnormal hyperfunctioning parathyroid gland can be identified and its location defined, surgical removal (parathyroidectomy) or chemical ablation with ethanol may not be possible (Colmer et al., 2022). Whereas surgical treatment (parathyroidectomy) is recommended and curative for patients with both clinical disease and asymptomatic disease in the absence of comorbidities, medical treatment can be employed. Medical treatments are used in cases in which PHPT-affected individuals are not suitable candidates for general anaesthesia or surgery, surgical treatment is declined, or for those cases in which previous surgical treatment has failed. Medical treatment may be explored further for equine PHPT patients because preoperative localisation of an abnormal parathyroid gland (using sestimibi scintigraphy and ultrasonography) may be unsuccessful, and the costs associated with scintigraphy and surgical treatment may be prohibitive.

Medical management of PHPT was partially successful in only 2 of 7 equids in which it was attempted. (Gorenberg et al., 2020). Although dietary restriction of calcium was undertaken in 5/7 cases in that retrospective study, it should be noted that calcium restriction is not recommended in human PHPT patients because it may drive further PTH release and worsen bone resorption (Dandurand et al., 2021; Marcocci et al., 2014). Whereas surgical treatment for PHPT in dogs is also often recommended, the short-term management of severe hypercalcaemia may include administration of IV fluids (for diuresis), bisphosphonates and glucocorticoids, especially if either or both azotaemia or a high plasma calcium-phosphorus product are identified (Schaefer & Goldstein, 2009).

Bisphosphonates, acting through inhibition of osteoid degradation by osteoclasts, are the most commonly prescribed group of drugs for the treatment of osteoporosis in human medicine. These drugs are also used for the medical management of human PHPT in nonsurgical cases. Modest increases in BMD have been documented when bisphosphonates are used for mild PHPT in people (Dandurand et al., 2021). Tiludronate was administered to one horse with PHPT in which a mild but incomplete improvement in hypercalcaemia status was reported (Gorenberg et al., 2020). In another report, tiludronate ameliorated clinical signs (but not laboratory abnormalities) associated with nutritional SHPT (Lacitignola et al., 2018).

The calcimimetic agent, cinacalcet, acts through allosteric activation of calcium-sensing receptors at the surface of chief cells in the parathyroid glands where it increases their sensitivity, reducing PTH secretion and reducing plasma calcium levels (Khan et al., 2015, 2017). Cinacalcet is primarily indicated for the management of SHPT in people affected with chronic renal disease. It is also approved for the management of PHPT in people for whom surgery is not indicated or possible and in whom surgical treatment has not been successful. Although cinacalcet treatment for PHPT leads to improvements in both PTH and plasma calcium levels, it does not afford skeletal protection. However, treatment using a combination of cinacalcet, and a bisphosphonate improves skeletal health. To our knowledge, treatment of horses affected with hyperparathyroidism using cinacalcet has not been reported at this time.

The authors noted that the diagnosis of PHPT had been appropriately based on identification of hypercalcaemia and an elevated serum PTH level. Two other important explanations for hypercalcaemia in the equine species, chronic renal failure and hypercalcaemia of malignancy, were further ruled out based on normal plasma creatinine and thymidine kinase-1 levels in blood, respectively. Paraneoplastic hypercalcaemia has been previously recognised in horses affected with lymphoma, multiple myeloma, ameloblastoma, mesenchymal ovarian cancer, squamous cell carcinoma, gastric carcinoma and adrenocortical carcinoma (Axiak & Johnson, 2012; Barton et al., 2004). Demonstration of elevated levels of circulating cancer biomarkers for the purpose of affirming or ruling out the presence of neoplasia would represent a helpful advance in cancer diagnosis for all species (Tivey et al., 2022). It is unlikely that a solitary, ideal biomarker will apply in all cases because the importance of various biomarkers depends on the type of cancer. Moreover, the extent to which cancer biomarkers have been investigated in horses is very limited. Elevated levels of PTH-related peptide (PTH-rP) were reported in one horse affected with multiple myeloma (Barton et al., 2004). Although elevated serum thymidine kinase-1 (TK1) levels have been proposed

as useful diagnostic indicators of lymphoma in horses (Larsdotter et al., 2015), later studies yielded conflicting results (Moore et al., 2021; Wang et al., 2021). Although the authors concluded that a paraneoplastic explanation for hypercalcaemia could be ruled out based on a normal TK1 level in their patient, caution in that regard is recommended until better cancer biomarkers with improved positive and negative predictive values have been evaluated and validated for both equine and human medicine.

Although this commentary has been centred on the subject of PHPT, the fact that horses also develop secondary hyperparathyroidism (SHPT) should not be overlooked. The equine veterinary literature contains many excellent and well-illustrated references to SHPT resulting from historical and contemporary nutritional factors. For review of SHPT in horses, readers are encouraged to review a recent paper in which SHPT resulted from the ingestion of soursob weeds (Herbert & Dittmer, 2017). Whereas SHPT is most commonly recognised in the context of renal disease in people, this phenomenon (renal SHPT) does not appear to occur in horses. In almost all cases, equine SHPT can be traced back to the ingestion of nutritional factors that interfere with the oral bioavailability of calcium from the diet (excessive bran, dietary feeding errors, plants that contain high levels of oxalate, etc.).

AUTHOR CONTRIBUTIONS

P. Johnson and K. Townsend prepared the manuscript.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest have been declared.

ETHICS STATEMENT

None.

ORCID

Philip J. Johnson https://orcid.org/0000-0002-8180-7601
Kile S. Townsend https://orcid.org/0000-0001-8418-7842

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CASE REPORT

Masseter myodegeneration in the horse: Suggested approach to diagnosis and treatment

Amie Wilson[1] | **Alison Talbot**[1] | **Hayley Crosby-Durrani**[2] | **Fernando Malalana**[1]

[1]Department of Equine Clinical Science, Institute of Veterinary and Ecological Sciences, University of Liverpool, Neston, UK

[2]Department of Veterinary Anatomy, Physiology and Pathology, Institute of Veterinary and Ecological Sciences, University of Liverpool, Neston, UK

Correspondence
Amie Wilson
Email: a.wilson3@liverpool.ac.uk

Summary

A descriptive case report of the management of a miniature pony presenting to a UK equine veterinary hospital with marked trismus and increased masseter muscle size. Diagnosis of masseter myodegeneration (MM) was aided by the use of computed tomography and excisional biopsy. Hyperlipaemia was diagnosed as a sequelae of MM. Treatment included nonsteroidal anti-inflammatories, parenteral nutrition and fluid therapy in addition to supportive care. The gelding was discharged from the hospital 30 days after admission, having made a full recovery. MM in the horse is a rare condition that appears to be physiologically distinct from canine masticatory muscle myositis which is primarily immune mediated.

KEYWORDS
horse, masseter, muscle, myodegeneration, myositis, trismus

INTRODUCTION

This case report summarises the main diagnostic findings in a pony with suspected masseter myodegeneration (MM) and an approach to treatment. MM has been described in horses, but it remains a challenging disease to definitively diagnose (Conwell, 2010; Pearson et al., 2005). This case report provides an updated approach to diagnosis with the use of advanced imaging.

Diseases affecting the masseter muscles have been described in dogs. Canine masticatory muscle myositis (CMM) is an immune-mediated disease with 64% of dogs having antibodies against masticatory muscle (type 2 M) fibres (Evans et al., 2004).

The use of cross-sectional imaging has been used in the diagnosis of CMM, with characteristic contrast enhancement of the temporalis, masseter and pterygoid muscles (Reiter & Schwarz, 2007). This has not been previously described in horses with MM. In addition, CT imaging can be utilised to exclude other diagnoses such as mandibular fractures as well as assisting the selection of sites for diagnostic muscle biopsy.

CLINICAL PRESENTATION

An 8-year-old miniature Shetland gelding presented with a 24-h history of swelling of the masticatory muscles with marked reduction in range of movement of the mandible, resulting in an inability to prehend food due to trismus (Figure 1). The gelding was dull, depressed and tachycardic (80 beats/min).

On admission, routine blood analysis identified severe hypertriglyceridaemia (triglyceride: 24.96 mmol/L, normal range 0.12–0.77 mmol/L), and the plasma was opaque following centrifugation (McKenzie, 2011). Muscle enzymes including creatine kinase (CK), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) exceeded the analyser's capacity for interpretation. It is noted that neither AST nor LDH levels are specific for muscle disease, but as the other liver enzymes were within normal range and given that there was a high CK level present, these abnormalities were considered most likely to be due to muscle damage. The gelding had an elevated systemic lactate concentration (7.0 mmol/L, range 0.–2.0 mmol/L). The appearance of the urine was dark brown, consistent with

FIGURE 1 Gelding 24 h following admission, note the marked masseter swelling

pigmenturia for the first 48–72 h of hospital admission but no azotaemia on daily serum creatinine measurement. Pigmenturia was considered to be due to myoglobinuria on the basis of the raised CK/AST/LDH levels, in the absence of red blood cells on urine sedimentation and normal haemoglobin levels.

The gelding was administered intravenous fluid therapy with lactated Ringer's solution, in addition to a 2.5% glucose solution infusion. The lactated Ringer's solution and glucose solution were both initially started at a maintenance rate (2 ml/kg/h) although this was continuously reassessed based on hydration status and blood glucose concentration. Nonsteroidal anti-inflammatory therapy was administered using 1.1 mg/kg bwt IV flunixin meglumine. Soaked feed was offered, though the pony showed no interest in feeding.

DIAGNOSIS

Computed tomography

The gelding underwent CT imaging of its head, with plain and contrast-enhanced studies performed. The gelding was anaesthetised for the imaging due to its size compared with the position of the scanner, which prevented the procedure being performed with standing sedation. The nonenhanced CT images showed diffuse hypertrophy of the masseter and temporalis muscles, with no obvious traumatic pathology to the skull or mandible (Figure 2). The intravenous contrast study, utilising Ioversol (Optiray 300) 636 mg/kg bwt, demonstrated very mild diffuse homogenous increased attenuation of all muscle bellies, consistent with contrast material in the local capillary vessels (Figure 3).

FIGURE 2 Transverse images of the head displayed in a soft tissue window (window level, 35 Hounsfield units; window width, 350 Hounsfield units) at the level of the orbit, prior to the administration of intravenous contrast. There is marked diffuse swelling of the left and right masseter muscle.

FIGURE 3 Transverse image of the head displayed in a soft tissue window (window level, 35 Hounsfield units; window width, 350 Hounsfield units) at the level of the orbit, following use of intravenous contrast. There is diffuse subtle increase in the attenuation of all the tissue of the masseter muscles consistent with intravenous contrast in the local capillaries.

Muscle biopsy

A wedge excision biopsy measuring 13 × 10 mm from the affected region of the left masseter muscle was performed under general anaesthesia (following CT). The tissue was fixed in formalin and submitted for histopathological analysis. Diffuse severe subacute myofibre necrosis with dystrophic mineralisation and early signs of regeneration was identified. The abnormality appeared to be monophasic, with all muscle fibres at the same stage of injury (Figure 4). No periodic

acid-Schiff (PAS) positive material was identified, suggesting the myodegeneration seen was unrelated to polysaccharide storage.

Further testing

Serum lactate dehydrogenase (LD) isoenzymes measurement showed significant elevation in LD5 concentration (34.3% normal range 1%–7%) with total LD 22,129 iu/L (normal range 225–700 iu/L), suggesting isolated skeletal muscle damage without cardiac muscle damage. Serum cardiac troponin I measurement supported an absence of cardiac injury (<0.02 ng/ml [normal range < 0.2 ng/ml]).

Serum vitamin E levels were within normal limits (8.5 μmol/L [normal range 3.0–20.0 μmol/L]). Plasma glutathione peroxidase levels were at the low end of the normal range (14.9 μ/ml, normal >15 μ/ml). Serum hypoglycin-A and methylenecyclopropylacetic acid (MCPA)—carnitine levels were below the limit of detection. These results were not supportive of either a nutritional cause of myodegeneration or recent toxin ingestion.

Basal serum insulin testing was low (0 μIU/ml) although further dynamic testing may have been beneficial to exclude underlying equine metabolic disease.

TREATMENT

Fluid therapy

Intravenous fluid therapy with lactated Ringer's solution with 2.5% glucose was initiated on presentation. The rate was initially started at a maintenance rate (2 ml/kg/h) though this was continuously reassessed based on hydration status and blood glucose concentration. In light of persistent hyporexia, the gelding was initiated on partial parental nutrition with a continuous rate infusion of amino acids and glucose, in addition to maintenance fluid therapy with lactated Ringer's solution on Day 5 following its admission. The partial parenteral nutritional requirements were calculated based on a weight of 93 kg and a daily energy requirement of 30 kcal/kg, resulting in 1.5 L of 50% dextrose, mixed with 1 L of 15% amino acid solution (Aminoven® 15, Fresenius Kabi) administered at a rate of 104 ml/h. This rate was used as a guide and altered according to the gelding's blood glucose measurement. As the gelding began to eat, the infusion was tapered.

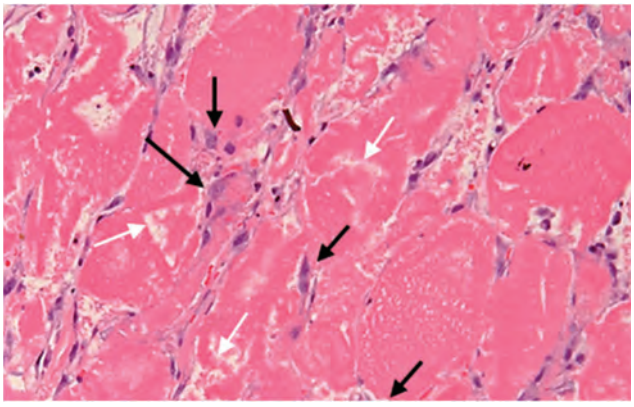

FIGURE 4 Masseter muscles demonstrating signs of myofibre degeneration and necrosis with myofibre splitting (white arrows). Activation of satellite cells demonstrating regeneration (black arrows). All myofibres appeared at a similar stage of injury and repair, haematoxylin and eosin stain, 200×.

Analgesia and anti-inflammatory therapy

Anti-inflammatory initial therapy included flunixin meglumine (1.1 mg/kg bwt) IV BID for 24 h, then dexamethasone 0.1 mg/kg bwt IV SID for 9 days. At this point, flunixin meglumine (1.1 mg/kg bwt IV BID) was reinitiated for 2 days, then halved to 0.55 mg/kg bwt IV BID for 10 days. In addition, paracetamol was administered (20 mg/kg bwt PO BID) for 18 days.

Enteric feeding

Initially, the gelding was anorexic. As the anorexia continued, he was tried with a variety of soaked food to stimulate his appetite. He appeared to show a relatively increased interest in grass, however, showed difficulty prehending the stems and masticating.

Long fibre was withheld initially due to concerns of dysphagia and perceived risk of oesophageal obstruction. This was gradually reintroduced under close observation, as he began to demonstrate an improved appetite and increased range of motion of his temporomandibular joint. There were no episodes of oesophageal obstruction during the refeeding period; however, he tired easily after intake of food requiring increased mastication.

Supplementation

Supplementation of vitamin E (Nano E™): 10 iu/kg PO SID and selenium (Selenavite E™): 0.2 g/kg PO SID was implemented in case of nutritional myodegeneration whilst awaiting serum vitamin E and glutathione peroxidase levels. Glutathione peroxidase is a selenium-dependent enzyme which is formed in red blood cells during erythropoiesis and provides an estimation of body selenium status (Valberg, 2018). In this case neither vitamin E nor glutathione peroxidase levels were supportive of nutritional myodegeneration, however, it is possible that the antioxidant activity of supplementation may have been beneficial for the myopathy irrespective of cause.

Physiotherapy

This was initiated 6 days following admission onwards following the guidance of an ACPAT registered physiotherapist. Physiotherapy

was performed 3 times daily initially. The frequency was tapered with improving prehension and mastication.

Initially, massage was performed over the face, focusing on the masseter and temporalis muscles. Following this, the gelding was encouraged to open his mouth, by placement of a gloved finger or dosing syringe in the interdental space. This was repeated 3–5 times on each side. Large quantities of partially masticated food were found in the oral cavity ('food packing') at each exercise for the first 2 weeks and were removed prior to proceeding.

Finally, tongue stretches were performed with gentle tension of his tongue to each side, repeated 3–5 times. The gelding was hand-walked for 20 min 3 times daily. Hand grazing was offered throughout, and a variety of food was offered to encourage prehension and mastication.

Miscellaneous

Omeprazole (4.0 mg/kg bwt PO SID) was administered due to the increased risk of equine gastric ulcer syndrome with persistent anorexia and stress of hospitalisation. Sunflower oil (0.1 ml/kg PO BID) supplemented the daily feeding regime to promote increased calorie intake following normalisation of blood triglyceride levels.

OUTCOME

The gelding was hospitalised for 30 days. Eighteen days following admission, creatinine kinase and triglycerides were both found to be within normal limits (138 U/L and 0.57 mmol/L, respectively). The diffuse swelling of the masseter and temporalis muscles were followed by marked atrophy. Fibrosis following MM has been described but was not clinically identified in this case. The range of jaw opening did not appear to be impaired following gelding's recovery. Gelding's appetite and range of motion gradually increased, and his bodyweight stabilised. On admission, his weight was recorded as 92 kg, reducing to 88.5 kg and then recovering to 95 kg before discharge. Long-term follow-up (>12 months by telephone communication) revealed full recovery from the condition.

DISCUSSION

Masseter myodegeneration is a challenging condition to diagnose and treat. This case report provides a methodical approach to horses presenting with trismus and enlargement of the masticatory muscles.

This is the first reported CT of a horse with MM. The findings were different to those described in dogs, with no significant increase in Ioversol contrast uptake, potentially indicating a different pathogenesis in the horse. The initiating cause in this case was investigated with a series of diagnostic tests, however, further work is required to fully understand the pathophysiology. Repeat CT evaluation to assess areas of fat infiltration/fibrosis following atrophy could be useful but was not employed in this case due to the good clinical progression of the pony and the risks of further anaesthesia.

One cause of MM in the horse is nutritional myodegeneration caused by vitamin E and selenium deficiency. The condition has been reported as a cause of dysphagia in 3 adult individuals, resulting in the euthanasia of 2 of them (Ludvikova et al., 2008). Step et al. (1991) described a similar condition in a single animal that responded to dietary support. Selenium status can be ascertained by blood measurement of glutathione peroxidase, a selenium-containing enzyme. Nutritional myodegeneration is more commonly seen in foals (particularly with selenium deficient dams), characterised by profound muscular weakness, elevation in muscle enzymes, low glutathione peroxidase activities with low or normal serum vitamin E levels and high mortality (Löfstedt, 1997). The pony described in this report had normal vitamin E levels and mildly low glutathione peroxidase (indicative of selenium status). This relative normality of the glutathione peroxidase activity levels indicates that it is unlikely his pathology was nutritional myodegeneration.

Another differential for masseter muscle disease is atypical myopathy, an acute onset toxic rhabdomyolysis associated with ingestion of toxin Hypoglycin A. Hypoglycin A is in seeds or seedlings of Acer tree species (González-Medina et al., 2017). The toxic metabolite of Hypoglycin A is methylenecyclopropylacetic acid (MCPA). Serum analysis for both Hypoglycin A and MCPA-carnitine have been validated previously in horses (González-Medina et al., 2020). In this case, the results did not indicate Hypoglycin A toxin ingestion.

Horses diagnosed with nutritional myodegeneration or atypical myopathy can show signs of myocardial damage (Schefer et al., 2011; Verheyen et al., 2012). Considering this, paired with the sustained tachycardia of the patient over a period of 23 days after admission, serum cardiac troponin I was measured on Day 7 of admission, to determine the likelihood of associated cardiac disease. Cardiac troponin has been found to be a more sensitive marker of myocardial infarction than LD isoenzymes in human patients (Jaffe et al., 1996; Martins et al., 1996). The use of the highly sensitive and specific cardiac troponin I for the detection of cardiac cellular injury has largely superseded that of LD isoenzymes. Cardiac troponin I has been validated for use in equine medicine with a sensitivity of 70% and a specificity of 91% (Phillips et al., 2003; Van Der Vekens et al., 2015). This individual's troponin I level was unrecordably low (<0.02). The gelding's persistent tachycardia could have been as a consequence of pain, stress, tachyarrhythmia or an unrelated cause. No other cardiac anomalies were identified on examination.

Hyperlipaemia has been reported as a secondary complication in a pregnant Falabella mare with suspected MM, therefore, early measurement of triglycerides and implementation of treatment due to this potentially fatal sequela is recommended (Conwell, 2010). Basal insulin testing was performed and did not indicate an underlying endocrinopathy such as equine metabolic syndrome. However, as basal insulin testing has a low sensitivity for EMS, further dynamic insulin testing after glucose administration could have been performed.

Corticosteroid therapy was initiated in this case 24 h following admission due to the presence of marked hypertrophy of the masseter and temporalis muscles and a presumed immune-mediated cause. The

mainstay of treatment of canine masticatory myositis is aggressive immunosuppression (Evans et al., 2004; Mastaglia & Ojeda, 1985). However, this condition is not primarily inflammatory in origin in horses (Pearson et al., 2005). Corticosteroid therapy did not appear to improve this patient's condition and may have been a contributory factor for persistent hyperlipaemia. Following the poor response to initial therapy, corticosteroid therapy was ceased, and flunixin meglumine was commenced with subsequent improvement. Considering this, the use of corticosteroids is not justifiable in equine cases presenting with MM.

Given the delay in response to treatment, partial parenteral nutrition could have been initiated sooner and may have reduced the degree of cachexia suffered. Parenteral nutrition guidelines state that most adult healthy horses can tolerate starvation for up to 72 h without overt systemic side effects; however, it should be considered early in horses with hyperlipaemia, without lipid supplementation (Carr, 2018). Due to the limited size of the gelding nasal passages, any form of naso-gastric tube would not have been of sufficient diameter to allow for meaningful nutritional supplementation.

In summary, the diagnosis of equine MM was aided by the use of CT and histopathology. CT imaging demonstrated diffuse muscle swelling and was useful in excluding differential diagnoses such as trauma or malignancy. In this case, neither trauma nor malignancy was identified, and further investigations ruled out the possibility of atypical myopathy or nutritional myodegeneration. The definitive cause of the myopathy was not identified in this case. Treatment of these cases requires intensive supportive care and nonsteroidal anti-inflammatory drugs. Parenteral nutrition is indicated due to an anticipated prolonged period of anorexia, but as this condition appears to be linked with the development of hyperlipaemia, especially in miniature ponies, this form of nutrition should exclude lipid supplementation. Full recovery from this condition is possible, though this requires commitment from the owner and veterinary team.

AUTHOR CONTRIBUTIONS

All authors were involved with the clinical assessment of the case. A. Wilson prepared the manuscript with assistance from all authors, and all authors have approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest have been declared.

ETHICS STATEMENT

No ethical review required.

ORCID

Amie Wilson https://orcid.org/0000-0002-5987-180X
Fernando Malalana https://orcid.org/0000-0002-5773-9725

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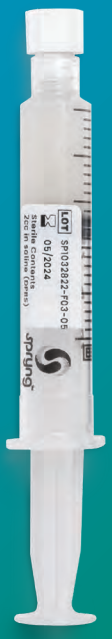

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CLINICAL COMMENTARY

Brief review of masseter muscle disorders

Monica Aleman

Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, California, USA

Correspondence
Monica Aleman
Email: mraleman@ucdavis.edu

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Summary

Regional and systemic disorders of myopathic or neurogenic cause affecting the masticatory muscles have been reported or suspected in horses. The primary masticatory muscles include the masseter, temporalis, lateral and medial pterygoid muscles. The masseter muscle is the largest of the primary masticatory muscles and the most affected based on sporadic reports. This is a brief review of disorders involving the masseter muscle.

KEYWORDS
horse, masseter, masticatory, myodegeneration, myopathy, neuritis

INTRODUCTION

Mastication is the act of chewing food in preparation for deglutition and digestion. Mastication involves proper function of the masticatory muscles and their innervation, temporomandibular joint and oral-dental structures. The temporomandibular joint connects the skull with the mandible (Budras et al., 2008). The primary muscles of mastication include the masseter, temporalis, lateral pterygoid and medial pterygoid muscles (Budras et al., 2008). Other muscles such as the buccinator, suprahyoid (digastric, mylohyoid and geniohyoid) and infrahyoid (sternohyoid, sternothyroid, thyroid and omohyoid) muscle groups also contribute to mastication. The primary muscles of mastication are innervated by motor branches of the mandibular nerve, a branch of the trigeminal nerve, and their main arterial supply is derived from the maxillary artery (Budras et al., 2008).

The masseter is the largest and strongest of the primary muscles of mastication, and its function consists of elevation of the mandible to close the jaw (Budras et al., 2008). The masseter muscle is also responsible for lateral and rotational movements of the jaw during mastication (Budras et al., 2008). These movements are facilitated by the flexibility of the temporomandibular joint (Budras et al., 2008). The temporalis acts in conjunction with the masseter and medial pterygoid muscles to elevate the mandible. The lateral pterygoid muscle lowers the mandible to open the mouth. Contraction of the lateral or medial pterygoid muscle only on one side will result in lateral movements of the mandible (Budras et al., 2008).

In contrast to the embryological origin of trunk, body wall, diaphragm and limb skeletal muscles derived from somites originating from the paraxial mesoderm adjacent to the neural tube; most head muscles derive from somitomeres (segmented mesenchymal structures) originating from the head paraxial mesoderm (Yamane, 2005). This results in specific myofibre-type distribution with contractile protein isoforms adapted for functions such as mastication.

DISORDERS OF MASTICATORY MUSCLES

Disorders of mastication include musculoskeletal and oral-dental disease. This section will discuss only those disorders affecting masticatory muscles and their innervation. In human medicine, disorders involving masticatory muscles are divided into regional (e.g. localised myalgia) and systemic (e.g. myofascial pain and fibromyalgia; De Rossi et al., 2013). The most affected muscle is the masseter, followed by the temporalis, lateral and medial pterygoid muscles. Similarly in horses, the masseter muscle appears to be the most affected based on sporadic reports (Aharonson-Raz et al., 2009; Conwell, 2010; Pearson et al., 2005; Step et al., 1991).

In accordance with human medicine, alterations of the masseter muscle in horses can involve regional and systemic disorders with an underlying myopathic or neuropathic cause (Table 1). Regional disorders are those that affect exclusively the masticatory muscles, which are uncommonly reported in horses (Table 1). Systemic disorders involving these muscles are more common (Table 1).

Masseter myodegeneration due to selenium deficiency and masseter myositis of unknown etiology have been reported or suspected in horses (Pearson et al., 2005; Step et al., 1991). More commonly, nutritional myodegeneration due to selenium or vitamin E and selenium deficiency present as generalised myodegeneration affecting skeletal muscles of the trunk and limbs and in some cases also cardiac muscle (Owen et al., 1977; Pearson et al., 2005; Wilson et al., 1976). In some of these cases, the masseter muscle has also been affected resulting in acute signs of apparent pain, swelling

(unilateral or bilateral), inability to open the mouth, dysphagia and salivation (Figure 1a; Conwell, 2010; Pearson et al., 2005). Exophthalmos and chemosis might be observed during the acute stages of disease. Chronic signs include ongoing dysphagia, masseter atrophy, trismus associated with atrophy and fibrosis, and weight loss (Pearson et al., 2005). Laboratory work reveals increased serum muscle enzymes activities (creatine kinase and aspartate aminotransferase), myoglobinuria, and increases in cardiac troponin I in cases with myocardial involvement. Myodegeneration, myonecrosis, myofibre fragmentation and intramuscular oedema are observed upon histological evaluation. Therapy has consisted of intravenous fluids, nutritional support, antioxidants (vitamin E and selenium) and analgesics. Decompressive fasciotomy might be necessary in cases with severe compressive myopathy/neuropathy due to swelling. Prognosis is guarded, but some cases might recover over a period of months and dependent on the severity of atrophy and fibrosis.

A rare intermittent bilateral or unilateral hypercontraction and fasciculations of the masseter muscle have been observed in adult Quarter Horses with no apparent precipitating events (unpublished data, Monica Aleman, M. A.). Serum muscle enzymes activities, whole blood selenium and plasma vitamin E, are within range. Electromyography reveals spontaneous abnormal activity such as complex repetitive discharges and positive sharp waves. Hypercontracted fibres and rare subsarcolemmal vacuoles have been observed upon histological evaluation. Genetic testing for hyperkalaemic periodic paralysis and malignant hyperthermia has been negative.

Systemic or multifocal disorders can also affect masticatory muscles. Trismus could be observed with hypocalcaemia, tetanus, triggered malignant hyperthermia and myotonic disorders (Figure 1b). However, other signs specific to disease will also be noted. A single case with trismus and dysphagia was reported in a mare and thought to be caused secondary to a focal abscess in the masseter muscle (Aharonson-Raz et al., 2009). Fasciculations can be seen locally or diffusely in cases of hyperkalaemic periodic paralysis and can involve the masseter muscle. Toxicity with ionophores and organophosphates is example of disease with systemic involvement (Aleman, 2011). Organophosphate (OP) toxicity can present as a triphasic event in people, an initial acute cholinergic phase (commonly reported in veterinary medicine), followed by an intermediate syndrome, and lastly a delayed nonlethal polyneuropathy. A herd of miniature horses intoxicated with OP developed acute inability to open the mouth, dysphagia, muscle fasciculations, weakness and lethargy (Myers et al., 2006). Whole blood cholinesterase activity was reduced in these horses, and muscle biopsies revealed severe

TABLE 1 Masticatory muscle disorders.

MASTICATORY MUSCLE DISORDERS

Regional *vs* systemic or multifocal*

MYOPATHIC

Non-inflammatory

Altered membrane/channel conduction
- Hyperkalemic periodic paralysis
- Hypocalcemia
- Malignant hyperthermia
- Myotonic disorders

Neoplasia*
- Rhabdomyosarcoma (+/- focal)

Nutritional myodegeneration*
- Selenium deficiency (+/- focal)
- Vit E/Se deficiency

Toxic*
- Ionophores
- Organophosphates
- Pasture myopathies
- Tetanus
- Others

Trauma

TMJ-associated

Inflammatory

Non-infectious (rare)
- Immune mediated*
- Unknown/idiopathic

Infectious* (could be focal)
- **Bacterial**
  - *Clostridium spp.*
  - *Corynebacterium Pseudotuberculosis*
  - Others
- **Parasitic**
  - *Halicephalobus gingivalis*
  - *Haycocknema perplexum*
  - *Sarcocystis fayeri*
  - *Trichinella spiralis*

NEUROPATHIC

Non-inflammatory
- Lead toxicity*
  - Motor
- Neoplasia†
- Pure trigeminal motor neuropathy

Infectious*
- Equine protozoal myeloencephalitis
- *Listeria monocytogenes*
- Others

Inflammatory/granulomatous
- Polyneuritis equi*
  - Sensory/motor
- Trigeminal neuritis
  - Sensory/motor

Note: This table is not an exhaustive list of all possible disorders affecting masticatory muscles. The reader is advised to search for additional information. +/−, could be focal.

*Systemic or multifocal disease.

†Neoplasia specific to mandibular nerve not reported but should be a consideration.

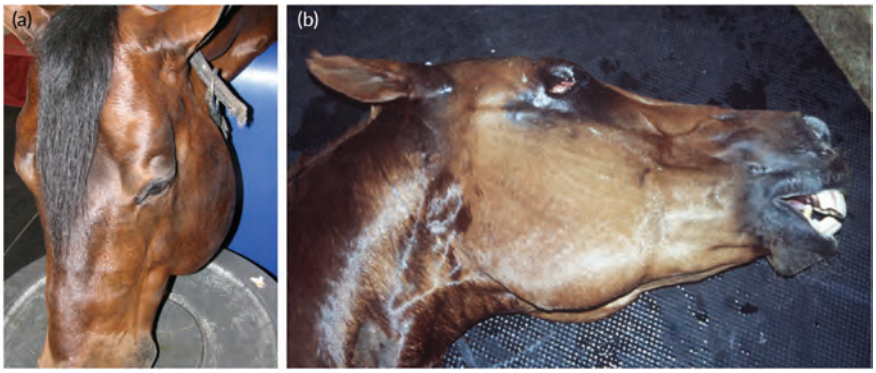

FIGURE 1 Noninflammatory myopathies. (a) Quarter Horse gelding with selenium deficiency. Note swelling of the masseter and temporalis muscles. (b) Triggered malignant hyperthermia in a Quarter Horse gelding. Note diffuse sweating and hypercontraction of multiple muscles causing trismus, masseter contraction, flared nostrils, third eyelid protrusion, sunken eyes due to hypercontraction of retractor bulbi muscle and ears pulled back.

FIGURE 2 Inflammatory myopathies. (a, b) Adult Thoroughbred mare with bilateral masseter myositis of undetermined cause. (c) Six-month-old Appaloosa filly with diffuse immune-mediated myositis involving masticatory muscles. Note bilateral exophthalmos and chemosis.

necrotising myopathy of the masseter muscles with less severity affecting other muscles (tongue, neck, limbs and respiratory; Myers et al., 2006). Other causes were ruled out in this herd of horses (Myers et al., 2006).

Diffuse inflammatory or immune-mediated conditions can also affect masseter muscles (Figure 2a-c). Acute signs include severe masseter swelling, apparent pain, inability or reluctance to open the mouth, salivation and in some cases exophthalmos. Within days, rapid muscle atrophy can develop. Masticatory muscle myositis as described in dogs has not been reported in horses. However, rare bilateral focal immune-mediated disease of undetermined aetiology has been observed by the author (unpublished data, Monica Aleman, M. A.). Bacterial and parasitic infection can be focal (uncommon) or multifocal (more common) involving the masseter muscle (Table 1, Figure 3; Eckert & Ossent, 2006; Pozio et al., 1998). Rhabdomyosarcoma affecting multiple muscles or exclusively the masseter muscle has been reported in horses (Castleman et al., 2011).

Primary neurological disorders can result in secondary masticatory muscle alterations (Table 1, Figure 4). Lead toxicity typically results in motor mononeuropathy or polyneuropathy among other signs and can affect cranial nerves innervating skeletal muscles of the head (Aleman, 2011; Puschner & Aleman, 2010). Neoplasia affecting exclusively the mandibular nerve or nuclei in the brainstem has not been reported in horses. Infectious disease such as equine protozoal myeloencephalitis can affect the brainstem on which the nuclei of cranial nerves are located. *Listeria monocytogenes* commonly affects multiple cranial nerves, particularly the trigeminal nerve resulting in facial sensory and masticatory abnormalities in addition to other signs of disease. Polyneuritis equi, an autoimmune disease of unknown aetiology, affects nerve roots, rootlets and

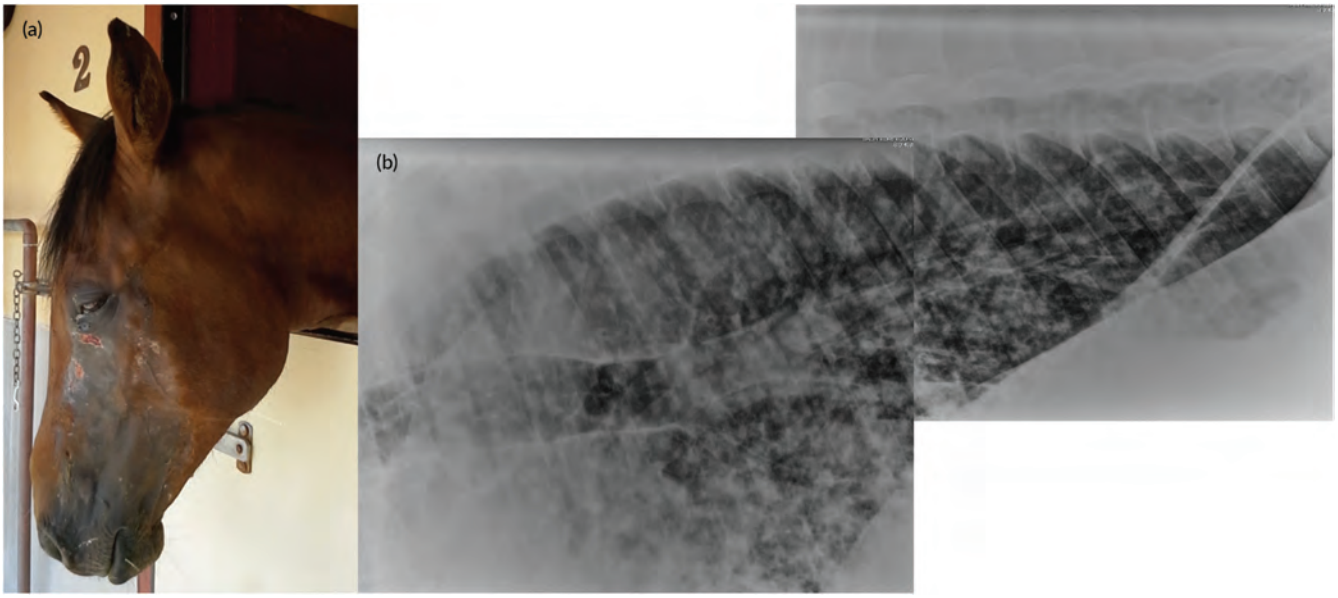

FIGURE 3 Disseminated *Corynebacterium pseudotuberculosis* infection involving masseter muscle. (a) Two-year-old Warmblood gelding with multiple draining abscesses on the face. (b) Pneumonia with multifocal coalescing nodular alveolar infiltrates (abscesses/granulomas).

FIGURE 4 Muscle mass alterations. (a) Adult Quarter Horse gelding with bilateral pure trigeminal motor neuropathy showing severe bilateral atrophy of masticatory muscles. Note severe atrophy of temporalis muscles. (b) By contrast, adult Quarter Horse with hypertrophy of masticatory muscles. Note prominent temporalis muscles.

nerves of the cauda equina and in some cases those of cranial nerves (most common III, V, VII and VIII; Hahn, 2008).

DIAGNOSTIC INVESTIGATION

The following is presenting some diagnostic tests, and it is up to the clinician's criterium to select the most appropriate modalities or perform additional tests not mentioned here as indicated by the specific case(s).

Clinical laboratory is important for the evaluation of the overall health of the horse and should include a complete blood cell count, serum chemistry panel (muscle enzymes activities), cardiac troponin I (if concurrent cardiac disease) and urinalysis (pigmenturia due to myoglobinuria). Determination of whole blood selenium and plasma α-tocopherol (vitamin E) is essential for the investigation of

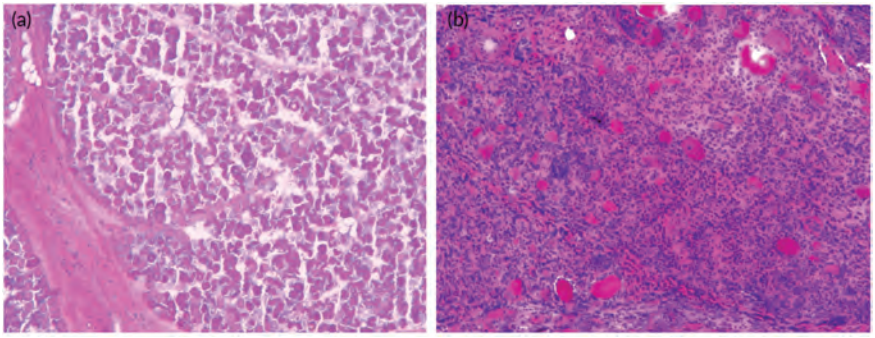

FIGURE 5 Muscle histology. (a) Severe myonecrosis in a miniature horse with organophosphate toxicity. Note no inflammatory cell infiltrates. (b) Severe inflammatory cell infiltration in a horse with masticatory myositis. Both images displayed on haematoxylin-eosin, magnification 4×.

nutritional myodegeneration associated with deficiencies of these compounds (Wilson et al., 1976). In horses supplemented with oral selenium, measurement of selenium-dependent glutathione peroxidase can provide an index of selenium status since it is formed in the erythrocytes during erythropoiesis, and not affected by recent supplementation (Caple et al., 1978).

Imaging such as ultrasonography and computed tomography as shown in the recent case report is useful for the determination of severity and extent of masseter muscle abnormalities (Aharonson-Raz et al., 2009; Wilson et al., 2023). Magnetic resonance imaging aids in the evaluation of masticatory muscles, nerves and adjacent structures. Although not definitive, qualitative or quantitative electromyography can provide useful information in support of a myopathic (e.g. myotonic discharges in support of a myotonic disorder) or neuropathic cause (Aleman, 2011). Biopsies of affected muscles for histological, histochemical or ultrastructural studies are essential in the investigation of possible causes of disease (Aleman, 2011). Cell morphology, evidence of myonecrosis, myodegeneration and regeneration, presence or absence of inflammatory cells and pathogens associated with or causing disease can be evaluated (Figure 5; Aleman, 2011). Furthermore, a muscle biopsy can aid in the distinction of neurogenic versus nonneurogenic or disuse muscle atrophy (Aleman, 2011). Concentrations of vitamin E and selenium can also be determined in muscle tissue. If suspected neurologic disease, additional tests as indicated by the case are needed.

THERAPEUTIC MANAGEMENT

Therapeutic management will depend on the underlying cause of disease and must include supportive therapy while the primary cause is addressed.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest have been declared.

ETHICS STATEMENT

Not applicable.

ORCID

Monica Aleman https://orcid.org/0000-0001-5811-9520

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ORIGINAL ARTICLE

Preliminary observations on the use of ertugliflozin in the management of hyperinsulinaemia and laminitis in 51 horses: A case series

Tania Sundra[1] | Erin Kelty[2] | David Rendle[3]

[1]Avon Ridge Equine Veterinary Services, Brigadoon, Western Australia, Australia

[2]School of Population and Global Health, The University of Western Australia, Crawley, Western Australia, Australia

[3]EMT Consulting, Tiverton, Devon, UK

Correspondence
Tania Sundra
Email: info@avonridgeequine.com.au

Funding information
BOVA

Summary

Background: Hyperinsulinaemia-associated laminitis (HAL) is encountered commonly in equine practice. There are currently no registered medications which specifically target hyperinsulinaemia in horses and ponies. Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have been demonstrated to limit post-prandial insulin responses and prevent the development of diet-induced laminitis.

Objectives: The objective of the study was to evaluate the efficacy of an SGLT2i, ertugliflozin, in the management of hyperinsulinaemia and laminitis.

Study design: Retrospective case series.

Methods: Medical records of 51 horses and ponies that had presented with laminitis and hyperinsulinaemia and had been treated with oral ertugliflozin at 0.05 mg/kg once daily for a minimum of 30 days were reviewed.

Results: After 30 days of treatment with ertugliflozin, there was a reduction in insulin concentrations from a median of >300 μu/ml (IQR: 149, >300) to 43 μu/ml (IQR: 20, 66) ($p < 0.001$). Modified Obel laminitis scores improved, reducing from a median of 10/12 to 1/12 ($p < 0.001$). Median serum triglyceride concentrations increased from 0.6 (IQR: 0.4, 0.9) before treatment to 1.4 (IQR: 0.8, 3.7) mmol/L after 30 days of treatment ($p < 0.001$) before declining, however, none of the horses developed any clinical signs of hyperlipaemia. Ten horses (19%) were reported to have polyuria and polydipsia during treatment, otherwise no adverse clinical effects were identified.

Main limitations: The study was limited by the absence of a control group, the retrospective data collection and the short period of follow-up.

Conclusions: Ertugliflozin may be effective in reducing insulin concentrations in horses and ponies with equine metabolic syndrome and its use may hasten recovery from laminitis associated with hyperinsulinaemia.

KEYWORDS
horse, endocrine, equine metabolic syndrome, insulin, podiatry, SGLT2 inhibitor

INTRODUCTION

Hyperinsulinaemia has been identified to be central to the development of laminitis in horses and ponies (hereafter referred to collectively as horses) with equine metabolic syndrome (EMS) (de Laat & Sillence, 2020; Frank & Tadros, 2014). Laminitis can be induced experimentally following exogenous administration of insulin (Asplin et al., 2007; de Laat et al., 2010), and high serum insulin concentrations are a reliable predictor of future episodes of laminitis (Knowles et al., 2021; Meier et al., 2018a, 2018b; Menzies-Gow et al., 2017). Whilst the exact mechanism by which hyperinsulinaemia causes laminitis is unclear, and other theories are postulated, it has been suggested that insulin may stimulate insulin-like growth factor-1 receptors within the lamellae resulting in cellular proliferation, weakening and subsequent lamellar failure (de Laat et al., 2011, 2013). Reducing serum insulin concentration is therefore considered to be an effective means of preventing hyperinsulinaemia-associated laminitis (HAL) and is advocated in the management of horses with laminitis and equine metabolic syndrome (de Laat & Sillence, 2020).

Currently, no registered medications are available for the treatment of hyperinsulinaemia in horses, although both metformin and levothyroxine have been used to manage horses with equine metabolic syndrome (Durham et al., 2019). Whilst metformin has been demonstrated to limit insulin responses to orally administered dextrose (Rendle et al., 2013) the oral bioavailability of metformin in horses is poor and studies showing its effectiveness at improving insulin sensitivity have yielded inconsistent results (Durham et al., 2008, 2019; Hustace et al., 2009, Tinworth et al., 2012). Levothyroxine administration is associated with a reduction in insulin concentrations and a doubling of insulin sensitivity (Frank et al., 2008; Sommardahl et al., 2005). Compounds such as glucagon like peptide-1 inhibitors, pioglitazone and sweet taste inhibitors have also been identified as having potential for reducing hyperinsulinaemia but are not used in clinical practice currently (de Laat & Sillence, 2020; Durham et al., 2019).

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have recently been developed for the treatment of diabetes in humans (Kalra et al., 2016; Nauck, 2014) and may have the potential to reduce insulin concentrations in horses through promotion of urinary glucose excretion (Kalra et al., 2016; Nauck 2014). The SGLT2i velagliflozin has been demonstrated to reduce hyperinsulinaemia and prevent the development of HAL in experimental models in which ponies were fed diets high in nonstructural carbohydrates (Meier et al., 2018a, 2018b, 2019). Canagliflozin, another SGLT2i, has also been reported to be effective in decreasing the insulin response to an oral sugar test in horses when used in combination with octreotide (Frank, 2018). To date, there are no SGLT2i registered for the treatment of hyperinsulinaemia in horses. Velagliflozin is unavailable currently, and canagliflozin is unavailable in a number of countries. Ertugliflozin (Steglatro: Merck Sharp & Dohme) is more widely available and is relatively inexpensive. This study reports the short-term clinical outcomes associated with the administration of ertugliflozin in the treatment HAL.

MATERIALS AND METHODS

Horses

A convenience sample of clinical records of horses treated at Avon Ridge Equine Veterinary Services between January 2021 and February 2022 were reviewed to identify horses in which ertugliflozin had been administered for the treatment of HAL. According to the practice protocol, ertugliflozin had only been administered where lameness and insulin concentrations had failed to improve after diet and management changes had been implemented for a minimum of 6 weeks. All horses had been treated with ertugliflozin at 0.05 mg/kg once daily per os. Only horses where complete clinical and clinical chemical assessments had been performed at 0 and 30 days were included in the study (Figure 1). Horses were not included if follow-up was not available, other treatments that might affect insulin concentrations (for example metformin or levothyroxine) had been administered or if diet was altered during or within 6 weeks prior to the administration of ertugliflozin to avoid these potentially confounding effects on insulin concentrations. Clinical data retrieved included modified Obel lameness scores (Meier et al., 2021) and measures of adiposity including the estimated weight assessed with a validated weigh tape (Virbac) and measurements of neck circumference (Martinson et al., 2014), heart girth (Martinson et al., 2014) and abdominal girth (Jones et al., 1989). In accordance with practice protocols, blood samples had been collected consistently 90 min after the provision of forage for the assessment of insulin concentration. All horses treated with ertugliflozin had an insulin concentration above the reference limit for the laboratory (40 u/L) prior to commencing treatment. Clinical chemical assessments included measurement of serum concentrations of triglycerides, gamma-glutamyl transferase (GGT) and creatinine in addition to insulin. In a subset of horses, further clinical and clinical chemical assessments were performed at Days 60, 90, 120, 150, 180, 210 and 240, as part of routine monitoring.

Laboratory investigations

Clinical chemistry had been performed at a commercial laboratory (Vetpath Laboratory Services) with insulin concentration measured using an Immulite 2000 (Siemens) with an upper limit of the validation of 300 μu/ml. Creatinine, gamma glutamyl transferase (GGT) and triglyceride concentrations had been measured using a Cobas Pro (Roche Products Pty Limited).

Following commencement of ertugliflozin, owners had been asked to obtain a free-catch urine sample and measure urinary glucose concentration via a Covetrus Vet 10-Way Urine Test Strip. Timing for urine collections had not been standardised.

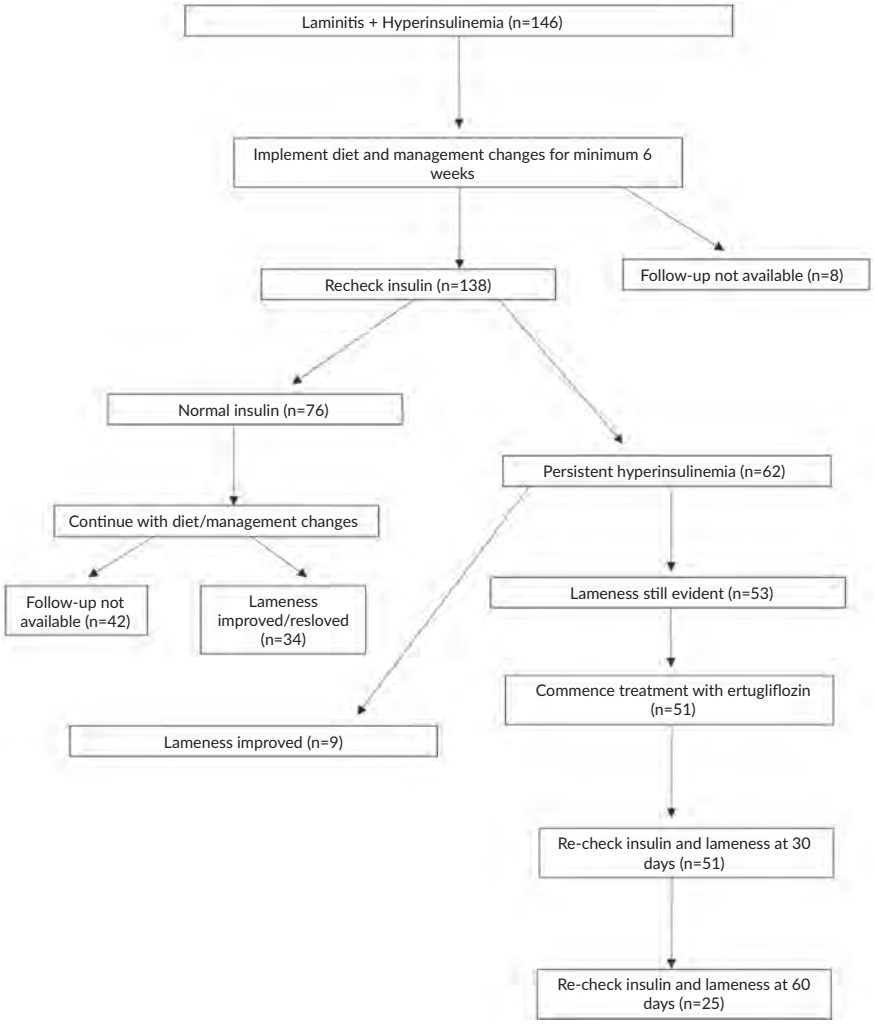

FIGURE 1 Flow chart detailing the treatment of horses with laminitis and hyperinsulinaemia

Medication

All horses were administered ertugliflozin at 0.05 mg/kg bwt by mouth once daily in the horse's first morning feed. Fifteen horses received Steglatro (Merck Sharpe & Dohme [Australia] Pty Limited) as 5 mg or 15 mg tablets and 36 horses received a compounded ertugliflozin paste at 5 mg/ml (BOVA Aus). The decision on which formulation was administered was made in consultation with the owners following discussions of the advantages and disadvantages of registered versus unregistered medicines and tablets versus paste. All owners provided informed written consent for the use of medications not registered for use in horses. Owners were advised of potential side effects including inappetence, colic, polyuria/polydipsia, hyperlipidaemia, lethargy or altered demeanour and were instructed to report any abnormal signs or events immediately.

Data analysis

The study made use of a convenience sample (retrospective cohort); thus, no formal sample size calculation was performed. Signalment and clinical data were transposed from case records to Microsoft Excel for subsequent analysis. Comparisons between continuous measures taken at baseline and 30 days were made using Wilcoxon matched pairs signed rank tests. A nonparametric test was selected to account for the lack of normally distributed data and for the upper limit of detection for insulin (>300 μu/ml). Analysis was carried in out in StataMP version 17 (StataCorp).

RESULTS

Horses

A total of 146 horses were presented for the treatment of HAL during the study period. Clinical records from 51 horses that fulfilled the inclusion criteria were identified (Figure 1). A range of breeds were represented. Pony breeds were dominant, including 17 Welsh/Welsh cross ponies (33%), nine Shetland/Shetland cross ponies (18%) and eight miniature ponies (16%). Other breeds included Quarter horses (8%), Arabian/Arabian crosses (6%) and Warmbloods (4%). Of the 51 horses, 23 were mares (45%) and 28 were geldings

(55%). The median age was 17 years (range 4–28 years). All horses had lameness as a result of laminitis which had been present for a median of 41 weeks (range 6–304).

All horses were already being managed for equine metabolic syndrome and laminitis and had previously been changed to a low sugar hay fed at 1%–1.5% bodyweight, for a minimum of 6 weeks prior to treatment with ertugliflozin (Figure 1). A range of forage types were fed including meadow hay (47%), lucerne hay (16%), rhodes grass hay (12%), rhodes/lucerne hay mix (14%) and meadow/lucerne mix (12%). Water-soluble carbohydrate values of forage (obtained from a local hay supplier, Western Hay) ranged from 6.5% to 10%. All horses were regularly attended by a farrier and were unshod. For each horse, the diet had remained consistent throughout the period of treatment and was thus the same at pre- and post-treatment testing. Similarly, the timing of testing in relation to feeding had been consistent in each horse. Two horses had received access to grazing in addition to being fed hay at 1% bodyweight, and in these horses, measurements had been taken at the same time of day, following the same period of turn-out. No changes in diet or management had been made at the onset of treatment with ertugliflozin or whilst horses were receiving it. Twelve horses had concurrent pituitary pars intermedia dysfunction (PPID). Previously measured ACTH concentrations demonstrated the PPID was well-managed, and the horses had received pergolide (Prascend, Boehringer Ingelheim) at 2mcg/kg whilst they were on treatment with ertugliflozin. Thirty-three out of fifty-one horses were receiving phenylbutazone paste (Ranvet) at 1–2.2 mg/kg for lameness associated with laminitis when they commenced treatment with ertugliflozin.

Following the commencement of ertugliflozin, the owners of 10 of the horses (19%) had reported polyuria and polydipsia, no other changes or adverse effects had been reported by owners or identified on clinical examination. All owners reported that they had complied with treatment recommendations except for one owner who missed a single dose of ertugliflozin on Day 13 of treatment.

Follow-up information was obtained for a median of 60 days (range 30–240 days). When records were reviewed, 33 horses remained on treatment either because insulin concentration remained increased, or it had increased when treatment was withdrawn. All horses that remained on treatment were all sound and had returned to their previous (prior to laminitis) level of exercise without the need for nonsteroidal anti-inflammatories or other analgesic medications. Of the 18 horses that were no longer recorded as being on treatment, 10 had had treatment discontinued as laminitis and insulin concentrations had improved and were being controlled with diet and management alone. Further records were not found for the remaining 8 horses, 5 had changed ownership, and 3 owners declined further follow-up due to financial constraints.

Insulin and triglyceride concentrations

Prior to treatment, 27 horses (53%) had post-prandial insulin concentrations exceeding 300μu/ml (Table 1) with the lowest concentration being 46 μu/ml. Following 30 days of treatment with ertugliflozin the highest insulin concentration was 233 μu/ml. Median insulin concentration reduced from >300 μu/ml (IQR: 149, >300) at Day 0 to 43 μu/ml (IQR: 20, 66) at Day 30 ($p < 0.001$). There was no significant difference in serum insulin concentration between horses treated with the ertugliflozin tablets versus paste. For the subset of horses with follow-up data beyond 30 days, insulin concentrations remained below baseline values (Figure 2), with a median concentration of 32 μu/ml (IQR: 17, 77) for the samples taken between Days 60 and 240.

Before treatment, 30 horses (59%) had triglyceride concentrations above the laboratory reference interval of 0–0.6 mmol/L, with results ranging from 0.1 to 2.6 mmol/L (median 0.62 mmol/L). Treatment was associated with an increase in triglycerides ($p < 0.001$), with 45 horses (88%) having triglyceride concentrations above the reference interval at Day 30, with results ranging from 0.2 to 16.1 mmol/L (median 1.4 mmol/L). In a subset of 21 horses

TABLE 1 Clinical and clinical chemical data for 51 horses with hyperinsulinaemia and laminitis treated with ertugliflozin for 30 days

	Laboratory ref intervals	Day 0	Day 0 ranges	Day 30	Day 30 ranges	*p*-Value
Insulin[a] (μu/ml), median (IQR)	10–30	>300 (149, >300)	46 - >300	43 (20, 66)	1–233	**<0.001**
Insulin >300 μu/ml, *n* (%)	-	27 (53%)	-	0 (0.0%)	-	-
Triglycerides (mmol/L), median (IQR)	0.0–0.6	0.6 (0.4, 0.9)	0.1–2.6	1.4 (0.8, 3.7)	0.2–16.1	**<0.001**
Modified Obel laminitis score, median (IQR)	-	10 (4, 12)	2–12	1 (0, 2)	0–8	**<0.001**
Bodyweight (kg), median (IQR)	-	272 (182, 492)	-	251 (173, 470)	-	**<0.001**
Heart girth (cm), median (IQR)	-	151 (130, 183)	-	145 (130, 179)	-	**<0.001**
Neck girth (cm), median (IQR)	-	81 (73, 97)	-	76 (70, 93)	-	**<0.001**
Belly girth (cm), median (IQR)	-	167 (148, 202)	-	160 (145, 196)	-	**<0.001**
GGT (u/L), median (IQR)	10–50	29 (23, 37)	9–150	31 (21, 48)	8–161	>0.9
Creatinine (u/L), median (IQR)	60–168	79 (65, 87)	41–134	76 (62, 90)	47–162	>0.5

[a]300 μu/ml was the upper limit of quantification for measures of insulin.

with triglyceride concentrations measured at Day 60, 13 (62%) were above the normal range, with a range of values from 0.2 to 5.3 mmol/L (median 1.0 mmol/L). Beyond Day 60 concentrations ranged from 0.2 to 3.9 mmol/L (Figure 3).

Laminitis

Prior to treatment, the modified Obel laminitis score ranged from 2 to the maximum score of 12 with a median of 10 (IQR: 4, 12). Following 30 days of treatment, there was a reduction in laminitis score ($p < 0.001$) (Video S1–S3), with a maximum score of 8 and a median of 1 (IQR: 0, 2) (Table 1). Scores were also available for a subset of horses up to 240 days following the commencement of treatment. Median laminitis scores remained below two from Day 30 onwards (Figure 4). Between Days 7 and 14 of ertugliflozin treatment, 28 horses that were receiving phenylbutazone had sufficient improvement in lameness such that phenylbutazone was discontinued without any regression in laminitis score.

Estimated bodyweight and morphometric measurements

A significant reduction in estimated bodyweight and morphometric measurements were observed after 30 days of ertugliflozin treatment ($p < 0.001$) (Table 1). Reductions in estimated bodyweight were observed in 48 horses (94%) with reductions ranging from 2 to 71 kg (median 16 kg) or 0.6% to 19% bodyweight (median 6%).

Hepatic and renal markers

Serum GGT activity was outside the laboratory reference interval in eight horses (16%) at Day 0, and in 11 horses (22%) at Day 30. Overall, there was no difference in GGT concentrations between Day 0 and Day 30 ($p > 0.9$) (Table 1). All the horses with increased GGT activity at 30 days subsequently had normal activity at later follow-up periods despite remaining on treatment with ertugliflozin. No horses had creatinine values that exceeded normal reference intervals and there was no difference in median creatinine concentration from Day 0 to Day 30 ($p > 0.7$).

Urinary glucose

Urinary glucose measurement was available in nine horses with a median concentration of 27.8 mmol/L (range 2.8–55.5).

DISCUSSION

The use of ertugliflozin was associated with a marked reduction in insulin concentrations and lameness associated with laminitis at 30 days. Whilst these results need to be interpreted with caution given the limited case numbers and the absence of a control group, ertugliflozin clearly merits further investigation for the treatment and prevention of HAL. Many of the horses in the study had shown limited or no response to previous treatments and management interventions. The 0.05 mg/kg dose of ertugliflozin reflects the dose that is being used in equine practice based on publications from other species and

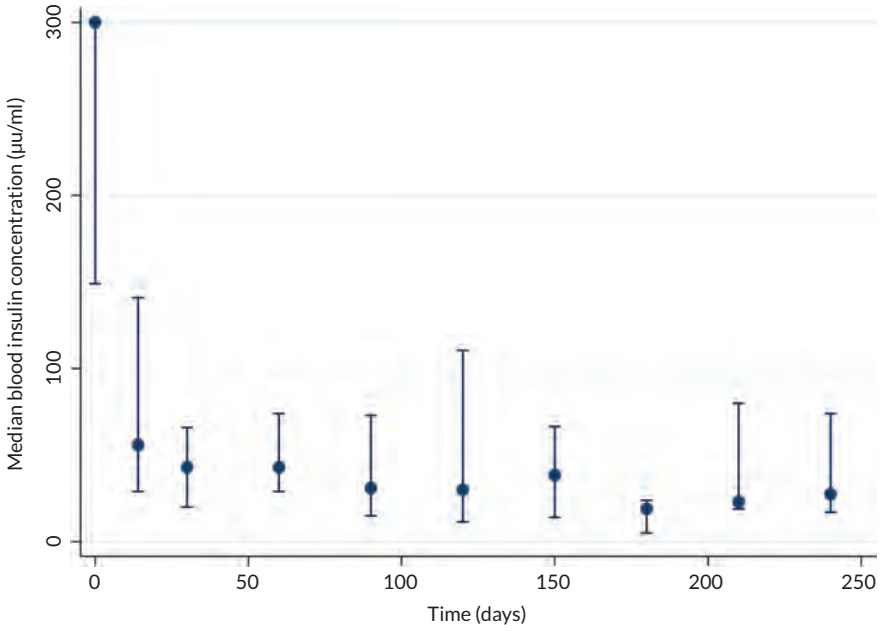

FIGURE 2 Median blood insulin concentration (µu/ml) and interquartile range following the commencement of treatment with ertugliflozin. Day 0: $n = 51$, Day 14: $n = 27$, Day 30: $n = 51$, Day 60: $n = 25$, Day 90: $n = 19$, Day 120: $n = 8$, Day 150: $n = 8$, Day 180: $n = 5$, Day 210: $n = 6$, Day 240: $n = 6$

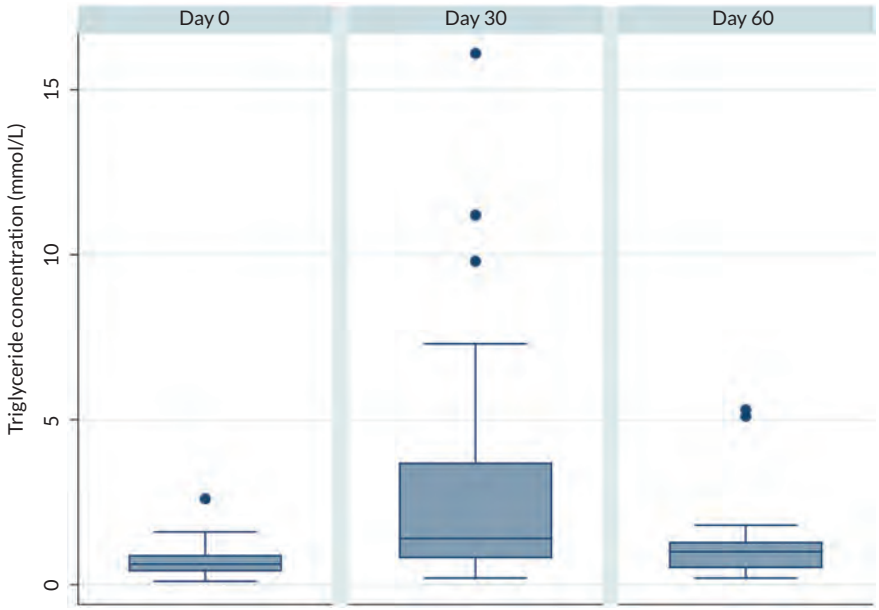

FIGURE 3 Box plot showing triglyceride concentrations (mmol/L) in horses treated with ertugliflozin for the management of hyperinsulinaemia and laminitis, at baseline ($n = 51$), Day 30 ($n = 51$) and Day 60 ($n = 21$)

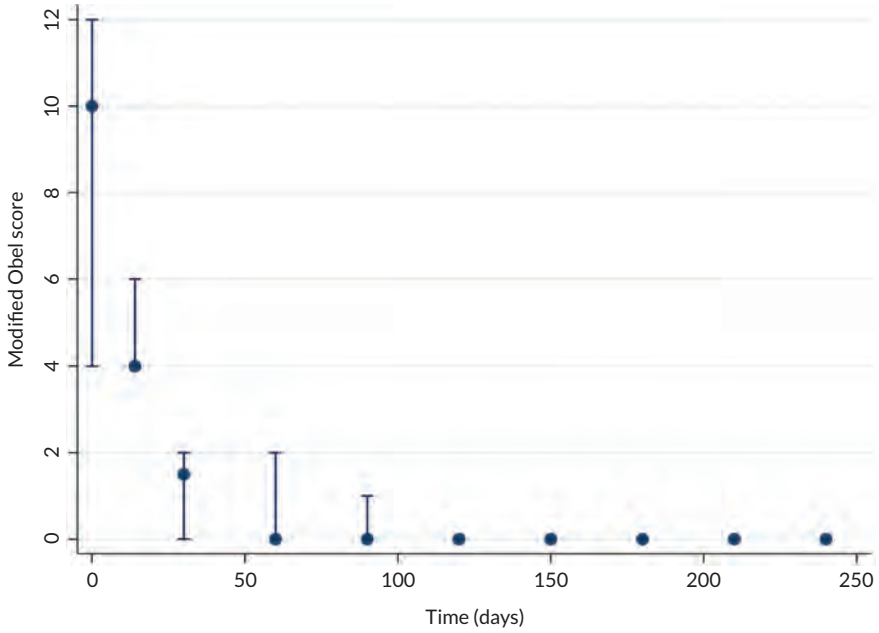

FIGURE 4 Median and interquartile range of modified Obel score assessing lameness, following the commencement of treatment with ertugliflozin. Day 0: $n = 50$, Day 14: $n = 5$, Day 30: $n = 50$, Day 60: $n = 16$, Day 90: $n = 16$, Day 120: $n = 8$, Day 150: $n = 5$, Day 180: $n = 3$, Day 210: $n = 7$, Day 240: $n = 6$

anecdotal experience, it does not have an evidential basis in the horse. Pharmacokinetic and pharmacodynamic studies are warranted to establish the most appropriate dosing regimen for this drug in horses.

Sodium-glucose cotransporter 2 inhibitors reduce insulin concentrations through promotion of urinary glucose excretion (Kalra et al., 2016; Nauck, 2014). Under normal circumstances, almost all glucose is reabsorbed from the proximal convoluted tubule of the human kidney leaving minimal amounts excreted in urine (Gerich, 2010). The regulation of glucose reabsorption from glomerular filtrate in humans is mediated by both SGLT1 and SGLT2 receptors (Gerich, 2010) with SGLT2 being responsible for reabsorption of more than 90% of filtered glucose in the human kidney and SGLT1 the remaining 10%. SGLT2i therefore decrease renal glucose resorption resulting in a lowering of blood glucose concentrations (Bays, 2013; Kalra, 2014; Sha et al., 2011) and subsequent reduction in secretion of insulin from the pancreas. SGLT2i have been demonstrated to

reduce insulin concentrations in humans, rodents, dogs and horses (Frank, 2018; List & Whaley, 2011; Meier et al., 2018a, 2018b, 2019; Neumiller, 2014, Paskiewicz et al., 2018). Whilst there is no pharmacokinetic data for ertugliflozin in horses, studies performed in other species demonstrate that ertugliflozin is rapidly absorbed, reaching peak plasma concentrations 1 h following a single oral dose with a bioavailability of 69% in rats and 94% in dogs (Fediuk et al., 2020). Given the clinical responses observed, the dosage used in this study appears to be effective and well tolerated but investigation of the pharmacokinetics and pharmacodynamics of ertugliflozin in horses are warranted to optimise dosing regimens.

Insulin concentrations reduced in all horses in association with 30 days of ertugliflozin treatment and in most horses remained low through subsequent follow-up tests (Figure 1). However, in eight horses an increase in insulin was identified beyond 30 days of treatment, and we speculate that this may have been due to upregulation of SGLT1 receptors. Studies in humans and rodents have demonstrated that despite SGLT2 accounting for 90% of glucose reabsorption, during SGLT2 inhibition, glucose reabsorption is only reduced to 40–50% which is hypothesised to be the result of a compensatory role of SGLT1 (Rieg et al., 2014). Whilst this potential mechanism has not been proven in human medicine, inter-patient variability and up-regulation of SGLT1 in response to SGLT2 inhibition may account for the increase in insulin concentration in a subset of horses in this study. SGLT2i vary in their selectivity for SGLT2 over SGLT1, and ertugliflozin is highly selective for SGLT2 (Fediuk et al., 2020). Alternatively, some owners may have failed to adhere to long-term diet and management recommendations resulting in increased dietary sugar intake and subsequent increase in serum insulin concentration.

The improvement in laminitis in association with a reduction in insulin concentration following ertugliflozin treatment is consistent with recent research that has demonstrated a link between hyperinsulinaemia and laminitis (de Laat & Sillence, 2020). Insulin concentrations have been shown to be associated with future risk of laminitis (Knowles et al., 2021; Menzies-Gow et al., 2017), and reduction in insulin concentration is therefore assumed to reduce the risk of clinical laminitis developing (de Laat & Sillence, 2020). The speed and magnitude of improvement in lameness was unexpected, given that these were chronic cases; to the authors' knowledge, this is the first study to report a rapid improvement in clinical laminitis following the use of drugs that reduce insulin concentrations. All owners reported rapid improvement in lameness and general demeanour within 7–21 days and where veterinary examination was performed at 14 days, a marked clinical improvement was observed. The use of phenylbutazone may have contributed to an improvement in lameness, however, the addition of ertugliflozin resulted in a further improvement in lameness grade. Without a control group the possibility of a temporal association, rather than a treatment effect, cannot be ruled out. Further investigations are warranted but if the findings of the current study translate to larger populations, then ertugliflozin and other similar drugs might have the potential to improve the speed of recovery from laminitis and alleviate considerable suffering. New episodes of laminitis did not develop during treatment with ertugliflozin. As these were clinical cases with financial constraints, radiography was not performed consistently. However, some cases were radiographed and marked reduction in lameness was evident even when there was radiographic evidence of rotation and displacement of 3rd phalanx. If the administration of ertugliflozin was relevant to the improvement in lameness, the mechanism is unknown. Reduction in insulin concentrations might have prevented further laminar damage but would not be expected to ameliorate the pain associated with chronic pathology. Acute laminar pathology associated with hyperinsulinaemia may be a significant source of pain and may be a greater factor relative to chronic mechanical changes than assumed previously. In humans, insulin resistance reproduces several aspects of neuropathic pain through cerebral hypoperfusion and modulation of ion channels in afferent neurons with administration of insulin-sensitising drugs being associated with a reduction in pain (Pappolla et al., 2021).

Although most horses lost weight (based on estimates obtained via a validated weigh tape) whilst they were on treatment with ertugliflozin, rates of weight reduction were variable. In humans, weight loss is reported with the use of SGLT2i and appears to be biphasic; there is initial weight reduction thought to be a result of caloric loss due to glucose excretion, loss of body water due to osmotic diuresis and reduction in fat mass (Janež & Fioretto, 2021; Kalra, 2014; Rosenstock et al., 2013), which is then followed by a slower rate of weight loss. Fat loss associated with SGLT2i is likely the result of a shift to fatty acid utilisation and lipolysis (Ferrannini et al., 2014, 2016) due to increased glucagon secretion from pancreatic alpha islet cells in response to reduced blood glucose and insulin concentrations (Janež & Fioretto, 2021; Sargent, 2015). The horses which lost the most weight were subjectively the horses that were the most obese which is consistent with findings in humans where the greatest reduction in bodyweight is seen in patients with a higher pretreatment weight (Kalra, 2014). Ertugliflozin merits further investigation to determine whether it offers a means of promoting reduction in adiposity beyond what can be achieved with dietary restriction alone.

Ertugliflozin was well tolerated by all horses. All but four of the horses exhibited hypertriglyceridemia following 30 days of treatment yet clinical signs of hyperlipaemia were not observed. In the absence of other clinical or clinicopathological abnormalities that might have indicated hyperlipaemia or hepatic lipidoses, it was considered appropriate to continue ertugliflozin with further careful monitoring. Hypertriglyceridemia secondary to endocrine dysfunction, without any evidence of clinical abnormalities, has been reported previously (Dunkel et al., 2014). Given the potential for life-threatening complications and the predisposition of horses with EMS to hypertriglyceridemia (Durham et al., 2019; Morgan et al., 2014), it is important that horses on treatment with ertugliflozin are monitored closely for signs of hyperlipaemia and hepatic lipidosis and owners are counselled on the potential risk associated with the use of SGLT2i. Interestingly, a reduction in triglyceride concentrations are reported in humans treated with SGLT2i (Heymsfield

et al., 2020; Pradhan et al., 2019); however, circulating ketone concentrations are increased, presumably due to a decrease in blood glucose concentrations (Ferrannini et al., 2017; Qiu et al., 2017). Given that ketogenic pathways are relatively unimportant in horses (Rose & Sampson, 1982), the authors' hypothesise that triglycerides are increased in response to lowered blood glucose and insulin concentrations, increased glucagon secretion and subsequent lipolysis (Janež & Fioretto, 2021; Sargent, 2015; Zhu et al., 2021).

Ten horses exhibited polyuria and polydipsia. Studies in humans have demonstrated that urinary excretion of glucose with SGLT2i leads to a chronic osmotic diuresis (List & Whaley, 2011) with volume depletion being a potential consequence (Neal et al., 2017). Whilst there were no clinical signs of dehydration or hypovolaemia in horses in this study, clinicians should be aware of the potential for volume depletion and should ensure free access to ample quantities of water in horses treated with ertugliflozin. SGLT2i have the potential to cause urinary tract infections (UTI) due to glucosuria (Washburn & Poucher, 2013). No signs of UTI were observed in horses in this study and in humans treated with dapagliflozin, the incidence of UTI did not increase despite increasing urinary glucose concentrations (Johnsson et al., 2013). A recent meta-analysis of human studies demonstrated that the use of SGLT2i was not associated with an increased risk of UTI (Wilding, 2019). Urinalysis performed in the current study confirms that glucosuria develops in association with the use of SGLT2i in horses.

The study was limited by small sample size, heterogeneity in treated horses, absence of blinding and the retrospective nature of data collection. In accordance with practice protocols, measures were taken to ensure consistency of the conditions around pre- and post-treatment sampling; however, this was not an experimental study in which all factors were under the investigators control. The administration of pergolide and phenylbutazone to some horses had the potential to confound assessments of insulin concentration and lameness. All horses were exhibiting clinical signs of laminitis prior to treatment and the presence of pain and stress may have the potential to falsely elevate insulin concentrations (Durham et al., 2019; Frank & Tadros, 2014). Given the absence of a prospective study design with a control group, it could be argued that some horses may have improved by 30 days irrespective of treatment; however, most of the horses presented in this study exhibited chronic laminitis which had not improved for several months. Whilst some follow-up data were available, data were less frequent at subsequent time points. Thus, more extensive studies would be needed to assess the long-term efficacy and potential side effects in animals treated with ertugliflozin. Significant findings in small populations do not always translate when larger, more robust clinical trials are performed (Button et al., 2013). This is a common challenge in veterinary research, and the findings of this study should prompt further work as the potential impact on animal welfare of an effective treatment for HAL is huge.

In conclusion, this study suggests that ertugliflozin may have potential as an effective pharmacological aid for the treatment of hyperinsulinaemia and the management of HAL in horses and ponies who have not responded to dietary management. Larger, blinded, randomised clinical trials, long-term safety data and investigations of the pharmacokinetics and pharmacodynamics of ertugliflozin and potentially other SGLT2i are warranted.

AUTHOR CONTRIBUTIONS

The study was conceived by D. Rendle and T. Sundra. Data were collated by D. Rendle and T. Sundra and analysed by E. Kelty. All authors contributed to the preparation and final approval of the manuscript.

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BOVA subsidised some laboratory testing for the study.

CONFLICT OF INTEREST STATEMENT

D. Rendle provides consultancy services to BOVA who produce an extemporaneous ertugliflozin paste specifically for horses. T. Sundra has received subsidised travel expenses to CPD events organised by BOVA. Written client consent was obtained prior to the use of medications and consent provided for the use of patient clinical data.

ETHICS STATEMENT

The study was reviewed and approved by the Animal Ethics Office of The University of Western Australia under reference F78787.

ORCID

Tania Sundra https://orcid.org/0000-0003-0556-4406
Erin Kelty https://orcid.org/0000-0002-0841-2216
David Rendle https://orcid.org/0000-0001-6943-6425

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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ORIGINAL ARTICLE

Relationships between the shape of the hoof capsule and orientation of the distal phalanx in long toe underrun heels in donkeys

Ahmed El-Marakby | Ahmed Abdelgalil | Mohamed Mostafa | Ahmed Soliman

Department of Veterinary Surgery, Anesthesiology and Radiology, Faculty of Veterinary Medicine, Cairo University, Giza, Egypt

Correspondence
Mohamed Mostafa
Email: mostafa1955ug@yahoo.com

Summary

Background: There is limited information on the morphology, radiography and orientation of the distal phalanx in the hoof capsule in long toe underrun heels in donkeys.

Objectives: This study aimed to determine the relationships between the hoof capsule shape and distal phalanx radiographic parameters.

Study design: Post-mortem collected feet.

Methods: A total of 68 cadaver front hooves with long toe underrun heels were used in the study. Lateral photographic and lateromedial radiographic parameters of the feet were obtained.

Results: The mean hoof wall angle (HWA) was strongly significantly correlated with heel angle (HA), dorsal HWA, HA measured through radiography and distal phalanx to toe distance and was modestly correlated with distal phalanx angle, solar border of the distal phalanx angle, coronet angle and distal phalanx to frog distance. The linear hoof wall length (HWL) and heel length showed a strong and modest significant correlation with distal phalanx to bottom, dorsal HWL and distal phalanx to toe distance.

Main limitations: The feet included in the study were obtained from many yards and different body sizes.

Conclusions: This study supports an association between radiographic and morphologic parameters in long toe underrun heels. The strong and modest correlations between measured photographic and radiographic parameters may indicate the relationships between the hoof capsule shape and distal phalanx orientation.

KEYWORDS
distal phalanx, donkey, hoof capsule, long toe underrun heel, measurements

INTRODUCTION

A long toe underrun heel is one of the most common foot abnormalities in the horse industry (O'Grady, 2020). Long toe or low heel conformation showed smaller dorsal hoof angle and weakened, underrun or collapsed heels (O'Grady & Poupard, 2003). Long toe underrun heels in donkeys had a marked increase in the toe and heel lengths (HLs), and the toe curled proximally out of the weight-bearing surfaces. The dorsal hoof wall was concave or convex. The hoof capsule was oblong, the heels moved forward, and the apex of the frog extended. The solar surface had asymmetrical and elongation in the shape, and the heel width was reduced (Mostafa et al., 2018). The toe and heel angles (HAs) in long toe underrun heels were significantly decreased ($p < 0.01$) compared with the clinically healthy donkey (Mostafa et al., 2020). Long toe underrun heel was noted in 52% of sound performance horses (Turner & Stork, 1988), 77% of lame horses (Turner, 1986), 10% of unilateral lame horses (Dyson et al., 2011a) and 24.6% of donkeys (Mostafa et al., 2018). Recently,

hoof diseases and lameness are highly prevalent in donkeys, and hoof care depends on close collaboration between veterinarian, farrier and owner (Thiemann & Poore, 2019). The most common diagnosed hoof conditions in donkeys were overlong or neglected hooves (18.6%), foot abscess (10.7%) and white line disease (26%) (Thiemann & Rickards, 2013).

The lateromedial digital radiographic image was used in the assessment of foot imbalance and position of the distal phalanx (White et al., 2008). The radiological relationship between the hoof capsule conformation and measurement of the distal phalanx has been described in horses (Eliashar et al., 2004; Kalka et al., 2021; Kummer et al., 2006). Currently, farriers and veterinarians used radiography as a guideline for corrective shoeing and treatment in daily practice (Kummer et al., 2004).

Long toe underrun heel was attributed to alterations in the deep digital flexor tendon (DDFT) and navicular bone and distal interphalangeal joint pathology in horses (O'Grady & Poupard, 2003). Toe angle has a direct effect on tissue strain within the hoof, distal limb lameness, angulations of the joint and external features of foot balance (Dyson et al., 2011a). The orientation of the distal phalanx in hindlimbs was correlated with the external characteristics of the hoof capsule in the horse (Kalka et al., 2021).

To the best of our knowledge, there are no data about the relationship of the orientation of the distal phalanx within the hoof capsule in long toe underrun heels in donkeys with the shape of the hoof capsule. Therefore, this study aimed to describe (1) the shape of the hoof capsule and orientation of the distal phalanx within the hoof capsule in long toe underrun heels and (2) the correlations of the hoof wall angle (HWA), HA, hoof wall length (HWL) and HL with the hoof capsule shape and distal phalanx orientation. These data can be used by veterinarians and farriers as a guideline for hoof trimming and shoeing.

MATERIALS AND METHODS

This study was conducted on 68 front hooves of 34 male donkeys' cadavers affected with long toe, collapsed heel and atrophied and degenerated frog. The age ranged from 3 to 14 years, and bodyweight ranged from 193 to 365 kg. The hoof capsule was evaluated from the dorsal, lateral and palmar aspects and the solar surface (Mostafa et al., 2020). Lateral photographic images of the foot were acquired according to the guidelines by White et al. (2008) using a digital camera (Kodak AF 3× Optical Aspheric Lens, 8.2 megapixels). The camera was placed at a standardised distance (50 cm) from the limbs.

Standardised radiographs were obtained according to the guidelines by Kummer et al. (2004). In lateromedial projection, the horizontal x-ray beam was centred 2 cm below the coronary band, at the midpoint between the bulbs of the heel and the proximodorsal aspect of the hoof wall (Kummer et al., 2006). The radiographic setting factors ranged from 50 to 55 KV, 10 mAs and 90 cm focal spot film distance. The dorsal and palmar aspect of the hoof wall was marked by two metal wire markers. Moreover, a small metal ball is placed just dorsal to the apex of the frog. Both photographic and radiographic measurement parameters were evaluated using the analysis software AutoCAD 2019 programme.

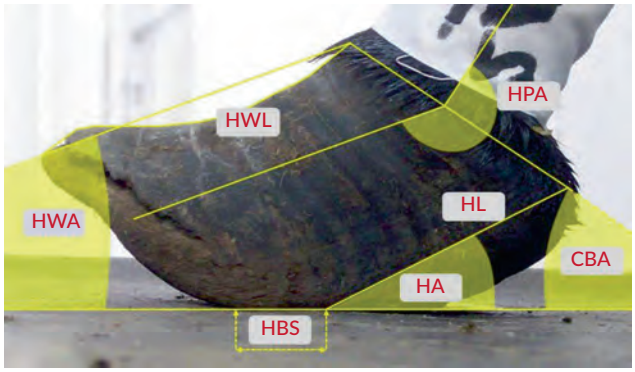

FIGURE 1 Photograph of the foot of a donkey with a long toe underrun heel showing the hoof wall length (HWL), heel length (HL), hoof wall angle (HWA), heel angle (HA), coronary band angle (CBA), hoof pastern axis (HPA) and hoof base of support (HBS).

The shape of the hoof capsule and radiographic parameters of the distal phalanx was determined according to the described methods by Dyson et al. (2011a) and Kalka et al. (2021). The photographic parameters of the shape of the hoof capsule (Figure 1) were obtained from the lateral view and included HWL, HWA, HA, HL, coronary band angle (CBA), hoof base of support (HBS) and hoof pastern axis (HPA).

The distal phalanx radiographic measurements parameters (Figures 2 and 3) included dorsal HWA (DHWA), solar border of the distal phalanx angle (P3BA), HA, distal phalanx angle (P3A), coronet angle (CA), distal phalanx to bottom distance (P3B), dorsal HWL (DHWL), distal phalanx to toe distance (P3T) and distal phalanx to frog distance (P3F). Repeatability for each angle and length measurement was assessed using 10 repeated measurements for each angle and length for 10 limbs. To determine repeatability, both photographic and radiographic evaluation of five donkeys' front hooves with long toe underrun heel had been performed four times. All these parameters were performed by one person (AIM).

Statistical analysis

All statistical analyses were performed using SPSS (IBM SPSS version 24) software. Kolmogorov–Smirnov test was used for normality, and significance was considered at a p-value >0.05. Descriptive statistics included the calculation of the mean, standard error of the mean (SE) and minimum and maximum values. Spearman's correlation coefficient (r_s) was used to assess the correlation between HWA, HWL, HA and HL measured photography and all other parameters. Significance was considered at a p-value <0.05.

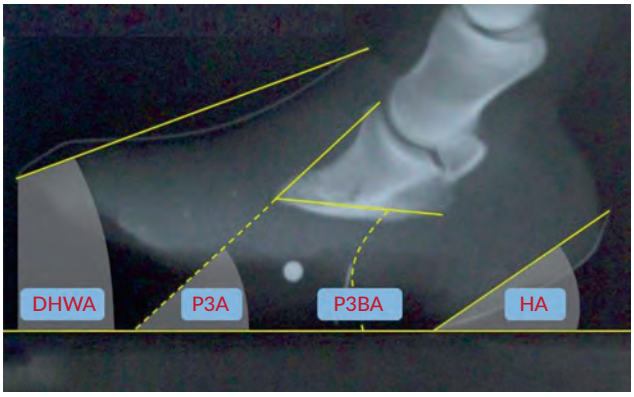

FIGURE 2 Lateromedial distal phalanx radiograph of the foot of a donkey with a long toe underrun heel, showing the dorsal hoof wall angle (DHWA), distal phalanx angle (P3A), distal phalanx solar border angle (P3BA) and heel angle (HA).

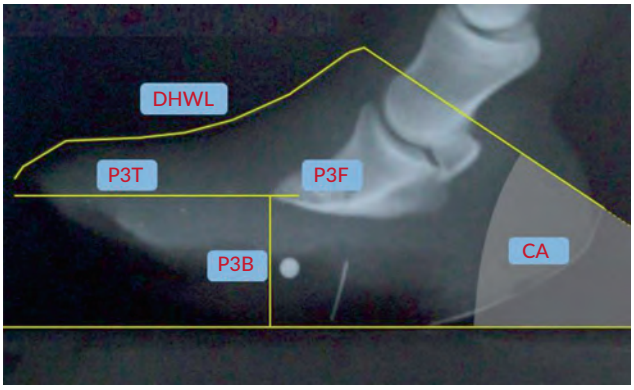

FIGURE 3 Lateromedial distal phalanx radiograph of the foot of a donkey with a long toe underrun heel showing the dorsal hoof wall length (DHWL), distal phalanx to toe distance (P3T), distal phalanx to bottom distance (P3B), distal phalanx to frog distance (P3F) and coronet angle (CA)

RESULTS

Long toe underrun heels presented as a concave dorsal hoof wall, displacement of the coronary band, elongation of the frog and collapsed heels. The hoof capsule appeared oblong, and the heels moved forward.

All parameters are presented as mean ± SE (Table 1). The DHWL determined through radiography was 3.4 mm larger than the HWL determined through photography. The HWA and DHWA measured from the radiographs and photographs were similar at 49.51° ± 1.14°. The mean difference between the HA and HWA was 3.7° in radiography and 7.5° in photography. The HA measured through radiography (45.55° ± 1.08°) was higher than the HA measured through photography (41.83° ± 0.92°). The CBAs were the same in radiography and photography (21.53° ± 0.87°).

The correlation coefficients (r_s) between the HWA and HA measured through photography and variable measurement parameters were recorded (Table 1). The HA was strongly positively correlated with HWA ($r_s = +0.69$, $p < 0.0001$), DHWA ($r_s = +0.65$, $p < 0.0001$), HA measured through radiography ($r_s = +0.69$, $p < 0.0001$), P3A ($r_s = +0.71$, $p < 0.0001$) and P3BA ($r_s = +0.66$, $p < 0.0001$) but strongly negatively correlated with CA ($r_s = -0.65$, $p < 0.0001$). The CBA ($r_s = -0.46$, $p = 0.001$), HPA ($r_s = -0.47$, $p = 0.001$), CA ($r_s = -0.46$, $p = 0.001$) and P3B ($r_s = -0.37$, $p = 0.008$) were moderately negatively correlated with HWA. The HBS ($r_s = +0.49$, $p < 0.0001$), P3A ($r_s = +0.53$, $p < 0.0001$), P3BA ($r_s = +0.47$, $p = 0.001$) and P3F ($r_s = +0.59$, $p < 0.0001$) were moderately positively correlated with HWA. The HA was moderately negatively correlated with P3B and P3T. The HWL and HL were negatively correlated with HWA. The HPA and HWA-HA difference was weakly negatively correlated with HA.

The increase in the HWL measured from photographs (Table 2) showed a strong positive correlation with DHWL ($r_s = +0.92$, $p < 0.0001$), P3B ($r_s = +0.77$, $p < 0.0001$) and P3T ($r_s = +0.63$, $p < 0.0001$). Conversely, P3F had a significantly weak negative correlation with HWL. The HL measured through photography was moderately positively correlated with HWL ($r_s = +0.46$, $p = 0.001$), DHWL ($r_s = +0.49$, $p < 0.0001$), P3T ($r_s = +0.58$, $p < 0.0001$) and P3B ($r_s = +0.55$, $p < 0.0001$).

DISCUSSION

The relationship between distal phalanx orientation and hoof capsule conformation was described by photographic and radiographic parameters in donkeys. All photographic and radiographic parameters in this study showed smaller values than that reported in normal donkeys (Collins et al., 2011; El-Shafaey et al., 2017; Mostafa et al., 2020; Nocera, Aliboni, Ben David, et al., 2020; Nocera, Aliboni, Puccinelli, et al., 2020). These differences might be attributed to the anatomical variation of the *Equus asinus* in different regions in Egypt and European donkeys. Long toe underrun heels had a significantly strong positive ($p < 0.0001$) correlation with the mean HWA (49.52°) and HA (41.83°). However, the normal HWA and HA in healthy donkeys were 58.2° and 54.1°, respectively, and the HA was 3° lower than HWA (Mostafa et al., 2020). However, in the present study, HA was 7.53° ± 0.78° lower than HWA and was moderately positively correlated with HWA. Furthermore, in the present study, the angular difference between the DHWA and P3A was 5.16°. Meanwhile, the angle difference in normal donkeys was 2.5°, and that in donkeys with laminitis was 12.5° with a marked capsular deviation in European donkeys (Collins et al., 2011). Similar findings have been reported in Amiata donkeys (Nocera, Aliboni, Ben David, et al., 2020). Compared with normal donkeys, donkeys with long toe underrun heels showed significantly decreased DHWA, HA and P3A with marked hoof capsular deviation.

Previously, the decrease in HWA has been linked to musculoskeletal injuries (Kane et al., 1998), increase in the stress within the hoof at the laminar junction (Thomason et al., 2005) and change in the angulations of the distal interphalangeal joints (Chateau et al., 2006). The observed significant moderate negative ($p < 0.0001$) correlation

TABLE 1 Descriptive statistical analysis for hoof shape and radiographic distal phalanx parameters and Spearman's correlation coefficient (r_s) between HWA and HA and all measured parameters

				HWA		HA	
Parameters	**Mean ± SE**	**Min. value**	**Max. value**	**Correlation coefficient (r_s)**	***p*-Value**	**Correlation coefficient (r_s)**	***p*-Value**
Hoof shape parameters							
HWA	49.52 ± 1.18	21	56.5	1.000	–	+0.69**	<0.0001
HA	41.83 ± 0.92	27	54	+0.69**	<0.0001	1.000	–
CBA	21.16 ± 0.83	12	37	−0.46**	0.001	−0.65**	<0.0001
HPA	190.73 ± 2.1	153	225	−0.47**	0.001	−0.17	0.23
HWA-HA	7.53 ± 0.78	−7	19	+0.45**	0.001	−0.16	0.26
HWL (mm)	64.83 ± 1.29	37.16	96	−0.22	0.11	−0.24	0.08
HL (mm)	48.82 ± 1.06	36.95	66.56	−0.26	0.06	−0.28*	0.04
HBS (mm)	49.9 ± 2.63	19.65	92.43	+0.49**	<0.0001	+0.56**	<0.0001
Radiographic distal phalanx parameters							
DHWA	49.51 ± 1.14	20	61	+0.78**	<0.0001	+0.65**	<0.0001
HA	45.55 ± 1.08	31	62	+0.62**	<0.0001	+0.69**	<0.0001
P3A	54.67 ± 1.02	39	75	+0.53**	<0.0001	+0.71**	<0.0001
P3BA	4.55 ± 1.09	−17	23	+0.47**	0.001	+0.66**	<0.0001
CA	21.53 ± 0.87	10	41	−0.46**	0.001	−0.65**	<0.0001
P3B (mm)	20.27 ± 0.81	8.32	35.83	−0.37**	0.008	−0.43*	0.002
DHWL (mm)	67.2 ± 1.33	42.23	95.13	−0.30*	0.031	−0.29*	0.038
P3F (mm)	10.03 ± 1.26	−21.06	23.07	+0.59**	<0.0001	+0.44*	0.001
P3T (mm)	32.01 ± 0.998	20.08	50.32	−0.66**	<0.0001	−0.45*	0.001

Abbreviations: CA, coronet angle; CBA, coronary band angle; DHWA, dorsal hoof wall angle; DHWL, dorsal hoof wall length; HA, heel angle; HBS, hoof base of support; HL, heel length; HPA, hoof pastern axis; HWA, hoof wall angle; HWL, hoof wall length; P3A, distal phalanx angle; P3B, distal phalanx to bottom distance; P3BA, distal phalanx solar border angle; P3F, distal phalanx to frog distance; P3T, distal phalanx to toe distance.
*Significant at ($p < 0.05$). **Significant at ($p < 0.001$).

TABLE 2 Correlation coefficient (r_s) between hoof wall length and heel length and the hoof shape and radiographic distal phalanx parameters in long toe underrun heels in donkeys

	HWL (mm)		HL (mm)	
Parameters	**Correlation coefficient(r_s)**	***p*-Value**	**Correlation coefficient(r_s)**	***p*-Value**
Hoof shape parameters				
HWL	1	–	+0.46**	0.001
HL	+0.46**	0.001	1	–
HBS	+0.26	0.065	−0.36*	0.011
Radiographic distal phalanx parameters				
P3B	+0.77**	<0.0001	+0.55**	<0.0001
DHWL	+0.92**	<0.0001	+0.49**	<0.0001
P3F	−0.35*	0.013	−0.32*	0.022
P3T	+0.63**	<0.0001	+0.58**	<0.0001

Abbreviations: DHWL, dorsal hoof wall length; HBS, hoof base of support; HL, heel length; HWL, hoof wall length; P3B, distal phalanx to bottom distance; P3F, distal phalanx to frog distance; P3T, distal phalanx to toe distance.
*Significant at ($p < 0.05$). **Significant at ($p < 0.001$).

with the CA ($r_s = -0.46$) and HPA ($r_s = -0.47$) in the present study led to an increase in the load on the palmar aspect of the foot during weight-bearing (Parks & Mair, 2009), producing an extension of the distal interphalangeal joint and increase in the strain of DDFT (O'Grady, 2020). Therefore, the decrease in HWA was associated with a decrease in HA and increase in CBA and HPA in the present study.

Dorsal hoof wall angle measured through radiography and HWA measured through photography were similar and had strong positive correlation ($r_s = +0.78$) in the current study. In contrast, DHWA determined radiographically in lame horse was smaller than DHWA measured photographically, and there was no perfect correlation (Dyson et al., 2011b). The concave or convex dorsal hoof wall, abnormal hoof growth and trimming methods were attributed to these differences (Dyson et al., 2011a).

The angles and lengths of the hoof capsule might have a significant influence on the position and anatomy of the distal phalanx in the horse (Kummer et al., 2009). In the current study, the P3A was larger than the HWA measured photographically and had a strong positive correlation with HA and moderate correlation with HWA. Contrary to these findings, there was a strong correlation between HWA and P3A than between HA and P3A in the lame horse (Dyson et al., 2011a). Therefore, the shape of the hoof capsule in long toe underrun heels has a significant influence in predicting the orientation of the distal phalanx within the hoof capsule.

In a previous study, the reduction in HWA and P3BA increased the strain in the DDFT and compressive force on the navicular bone (Eliashar et al., 2004). Recently, a positive correlation between the P3BA and DHWA and HA in the hind feet of Thoroughbred racehorses has been documented (Kalka et al., 2021). Furthermore, there was a significant positive correlation between the P3BA and HA in the horse (Dyson et al., 2011a). Similarly, in the present study, the P3BA was positively correlated with HWA and HA. Moreover, the mean P3BA value in long toe underrun heels in the present study was smaller (4.55° ± 1.09°) compared with normal and laminitic European donkeys (Collins et al., 2011) and Amiata donkeys (Nocera, Aliboni, Ben David, et al., 2020; Nocera, Aliboni, Puccinelli, et al., 2020). These findings were consistent with the recently reported results in the hind feet in a group of horses (Kalka et al., 2021), and the previous suggestion that the palmar processes of the distal phalanx were closer to the ground in long toe–low heel conformation in the horse (Butler et al., 2008). Moreover, the orientation of the distal phalanx palmar border has been changed and moved closer to the ground (Eliashar et al., 2004). Furthermore, the moderate positive correlation of HWA with P3A and P3BA might indicate the relationship between the hoof shape capsule and distal phalanx orientation in the present study.

Accordingly, the finding in the present study showed that the HWA and HA measured through photography exhibited a strong positive correlation with DHWA ($r_s = +0.78$, $p < 0.0001$) and a moderate positive correlation with P3A ($r_s = +0.53$, $p < 0.0001$), HA ($r_s = +0.62$, $p < 0.0001$) and P3BA ($r_s = +0.47$, $p = 0.001$). There was a strong to moderate correlation ($p < 0.0001$) between the photographic measured parameters and radiographic distal phalanx parameters in long toe underrun heels. Therefore, the shape of the hoof capsule in long toe underrun heels correlated with the orientation of the distal phalanx within the hoof capsule in the donkey. Similarly, the orientation of the distal phalanx in hindlimbs was correlated with the external characteristics of the hoof capsule in the horse (Kalka et al., 2021).

The P3A in the present study was larger than the HWA and had a moderate positive correlation with HWA and strong positive correlation with HA. The same has been reported in laminitic donkeys with distal phalanx deviation (Collins et al., 2011). In contrast, the P3A in lame horses was smaller (Clements et al., 2020; Dyson et al., 2011b). In a previous study, the decrease in P3A was associated with an increase in CBA. The decrease in P3A by 1° increased the CBA by 1° in the horse (Eliashar et al., 2004). Similar observations have been found in the current study. Therefore, the moderate positive correlation between HWA and P3A and the moderate negative correlation of HWA with CA and HPA might reflect the close relationship of the orientation of distal phalanx and hoof capsule in donkeys.

The correlations of the photographic linear measurements of hoof wall and HLs with P3B, DHWL and P3T measured through radiography were strongly positively correlated with HWL and moderately positively correlated with HL. The P3F was significantly positively correlated with HWA and HA. The position of the frog apex in a horse depends on trimming and hoof condition; flat hooves with low heels tend to elongate the frog apex (Parks, 2003). This is consistent with the finding in the present study that, as HWA decreased, the P3F decreased with elongation of the frog in long toe underrun heels. The P3T distance was strongly negatively correlated ($r_s = -0.66$, $p < 0.0001$) with HWA and moderately correlated with HA ($r_s = -0.45$, $p = 0.001$). A significant decrease in the HWA before trimming was associated with increase in P3B, decrease in P3F and increase in P3T in horses (Kummer et al., 2006). Previous radiographic studies have proved the migration of the distal phalanx toward the dorsal aspect of the hoof wall in long toe underrun heels (O'Grady, 2013).

Consequently, this coincided with the obtained findings in the present study as HWA decreased the P3B increased, P3F decreased and P3T distance increased. In recent studies in flat racing Thoroughbreds, a relationship was observed between the orientation of the distal phalanx and shape of the hoof capsule in the hindlimbs. Moreover, the P3BA was positively correlated with the HWA and photographic HA (Clements et al., 2020; Kalka et al., 2021).

In conclusion, the strong and moderate correlation measured through photography and radiography between HWA, HA, HWL and HL and P3A, P3BA, CBA, HPA, P3F, P3B and P3T might predict the relationships between the shape of the hoof capsule and orientation of the distal phalanx in long toe underrun heels in donkeys. The present study provides a database for farriers and veterinarians for the corrective trimming of long toe underrun heels in donkeys based on the obtained results.

AUTHOR CONTRIBUTIONS

A. El-Marakby contributed to the study design and study execution. A. Abdelgalil contributed to data collection, radiographic preparation and data analysis. M. Mostafa contributed to data analysis interpretation and preparation of the manuscript. A. Soliman contributed to the design, interpretation and analysis of data. All authors gave their final approval of the manuscript.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest have been declared.

ETHICS STATEMENT

The study has been approved by the Ethical Committee of Cairo University (CU II F 32 20).

ORCID

Mohamed Mostafa https://orcid.org/0000-0002-5096-580X

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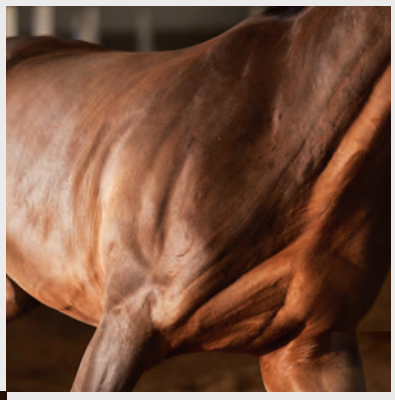

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REVIEW ARTICLE

Review of glucocorticoid therapy in horses: Intra-articular corticosteroids

Sophie Boorman[1] | Mattie A. McMaster[2] | Erin Groover[1] | Fred Caldwell[1]

[1]College of Veterinary Medicine, Auburn University, Auburn, Alabama, USA

[2]College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK

Correspondence
Fred Caldwell, College of Veterinary Medicine, Auburn University, Auburn, Alabama, USA.
Email: caldwfj@auburn.edu

Summary

This is the third article in a review series on the use of glucocorticoids to treat medical and musculoskeletal conditions in horses. This article in the series reviews the use of corticosteroids in the treatment of osteoarthritis and includes an appraisal of the most commonly used corticosteroids in equine practice. The regulatory rules concerning the use of corticosteroids are discussed, along with incidence, diagnosis and treatment of possible complications relating to intra-articular therapy.

KEYWORDS
horse, corticosteroids, osteoarthritis, synovial joint

INTRODUCTION

Osteoarthritis (OA) is a painful, progressive, irreversible disease of the joint that limits the career of the equine athlete and compromises the welfare of the horse (USDA, 2011). Although the exact pathogenesis of OA is incompletely understood, what is established is that the biomechanical properties of cartilage are altered and ultimately fail as the articular tissue is degraded by biochemical and molecular events within the joint (Pearle et al., 2005). A key component of equine OA is inflammation of the articular tissues, particularly within the synovium (Menarim et al., 2020; Sohn et al., 2012). Intra-articular (IA) administration of corticosteroids aims to decrease inflammation thereby slowing the progression of OA through the suppression of proinflammatory genes and inhibition of the arachidonic acid cascade (DiBattista et al., 1991; Frisbie & Johnson, 2018). However, corticosteroids demonstrate dose-dependent cytotoxicity that has the potential to have a negative impact on articular tissues, and their use is associated with several potential complications (Byron et al., 2008; Fubini et al., 2001). A thorough understanding of the rationale for IA corticosteroids, along with the appropriate choice and dosage of the medications available, are prerequisites for successful therapy.

EQUINE OSTEOARTHRITIS

Synovial joints consist of opposing bony articular surfaces covered by articular cartilage, a joint capsule lined with synovium, periarticular ligaments and synovial fluid (Palmer & Bertone, 1994). In order for a synovial joint to function optimally, the articular cartilage must be able to fulfil its role in maintaining frictionless movement and conducting load to the underlying subchondral bone (Brittberg & Winalski, 2003; Knudson & Knudson, 2001; Pearle et al., 2005). This role is achieved through the unique properties of the cartilage extracellular matrix (ECM); a collagen fibril network in a concentrated solution of proteoglycans, water, inorganic salts, glycoproteins and lipids (Becerra et al., 2010; Frisbie & Johnson, 2018). Proteoglycans, predominantly aggrecan, contain negatively charged glycosaminoglycans (GAGs), which cause the inward movement of water molecules (Frisbie & Johnson, 2018; Goodrich & Nixon, 2006). This movement of water into the ECM creates resistance to compressive forces, while the collagen network counteracts tensile stresses at the articular surface. The cartilage ECM health is maintained by chondrocytes and synoviocytes, the cells of the cartilage and synovium, respectively (Iwanaga et al., 2000). Importantly, cartilage does not have a vascular, nervous or lymphatic supply and nutrients are supplied by the synovial fluid, which is produced and maintained by the synovial membrane (Palmer & Bertone, 1994). Oxygen is limited and therefore chondrocytes primarily rely on anaerobic metabolic pathways for energy.

Osteoarthritis (OA) has long been established as a significant disease that compromises the welfare and contributes to the loss of use of the horse. OA is not only a disease of cartilage but rather a group of differing pathologies that may affect any of the periarticular tissues. There is progressive disruption of the articular cartilage, subchondral bone sclerosis (increased volume but decreased

mineralisation), osteophyte formation and synovitis (McIlwraith et al., 2012). Some horses may have static OA, often compatible with ongoing athleticism, but in cases where the disease progresses, chronic lameness results. A common scenario in the progression of equine OA is the development of a catabolic state. In this state, there are increased levels of cytokines, including interleukin 1 (Il-1β) and tumour necrosis factor (TNFα), that stimulate the production of matrix metalloproteinases (MMPs) by chondrocytes and synoviocytes (Miller et al., 2014). These enzymes and others dismantle the components of the ECM and stimulate leukotriene production. These are important neuropeptides that stimulate periarticular nerve endings, resulting in pain and inflammation (Sutton et al., 2009). Complete erosion of the cartilage exposes the subchondral bone, which is richly innervated and highly responsive to pathological processes within the synovial environment (Stewart & Kawcak, 2018). Clinically, the horse typically has synovitis, with synovial fluid that has decreased viscosity due to decreased hyaluronan concentration (Tulamo et al., 1996). Chronic inflammation of the synovium results in fibrosis and reduced compliance of the joint capsule, resulting in a decreased range of motion and chronic lameness.

CORTICOSTEROIDS

Corticosteroids are steroid hormones produced in the adrenal cortex or made synthetically. Corticosteroids are grouped as mineralocorticoids, involved in water and salt balance, glucocorticoids, involved in cellular metabolism and androgenic steroids, involved in sexual characteristics (Harkins et al., 1993). In veterinary medicine, glucocorticoids have the most widespread applications.

All therapeutic corticosteroids consist of a 21-carbon, 4-ring steroid skeleton. Slight variations in their chemical structure result in differences in potency, duration of action, affinity for their respective receptors and degree of protein binding (Cuming et al., 2018). Corticosteroids have two main mechanisms of action: genomic and nongenomic. The genomic mechanism occurs as a result of cellular glucocorticoid receptor drug interactions; steroids are low molecular weight molecules that are lipophilic and freely cross the phospholipid cell membrane to bind to cytosolic receptors (cGCR, cytosolic glucocorticoid receptor) (Strehl et al., 2011). The glucocorticoid-cGCR complex moves to the nucleus and increases the expression of anti-inflammatory proteins (transactivation) or decreases the production of proinflammatory proteins (transpression) (Stahn & Buttgereit, 2008). The nongenomic mechanisms include nonspecific effects caused by interactions with cellular membranes, specific effects caused by interactions with membrane-bound receptors and by nongenomic effects caused by interactions with the cGCR (Panettieri et al., 2019).

Corticosteroid action in cells depends on the local concentration of the corticosteroid, the receptor expression and the local corticosteroid metabolism within the target tissue. At a tissue level, exogenous glucocorticoids and endogenous glucocorticoids are both interconverted between inactive and active forms by the 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes (Cooper & Stewart, 2009). 11β-HSD1, in particular, is responsible for increasing local levels of active glucocorticoids, whereas 11β-HSD2 is the primary inactivation pathway (Coutinho et al., 2012). Expression of 11β-HSD1 varies between cell types and increases with age and in response to Il-1β and TNFα (Hardy et al., 2006). This indicates that synovial tissue metabolises glucocorticoids (mostly activation) and this metabolism increases with inflammation.

RATIONALE FOR IA CORTICOSTEROID THERAPY

Corticosteroids modulate pain by reducing inflammation, primarily by suppressing the expression of proinflammatory genes and inhibiting the arachidonic acid cascade (DiBattista et al., 1991). They induce the expression of lipocortin-1, which inhibits phospholipase and thereby the arachidonic acid cascade, decreasing inflammation (Caron, 2005). Intra-articular (IA) administration is hypothesised to provide a maximal decrease in inflammation, while limiting the considerable systemic effects of corticosteroids (Caron, 2005). The gene-altering effect of corticosteroids may continue beyond the limit of detection of the drug in serum or urine (Knych et al., 2017, 2018). This is important for both the regulatory control of these drugs (see *Regulation of IA corticosteroid therapy in horses*) and for optimal clinical use. There is evidence to suggest that corticosteroids have the potential to slow the catabolism of the articular cartilage ECM. Part of the regulatory process triggered by corticosteroids within the cell is the decreased release of Il-1β and TNFα (Barton et al., 2021; Caron et al., 2013). Therefore, corticosteroids directly inhibit the collagenolysis that results from cytokine-driven production of MMPs and aggrecanse by articular cells.

IA CORTICOSTEROIDS IN CLINICAL PRACTICE

Intra-articular corticosteroid therapy has been employed in the treatment of OA since the 1950s and is widely utilised in both human and equine practice (Centeno & Moore, 1994; Leveaux & Quin, 1956; Wheat, 1955). Corticosteroids currently approved for use in the United States by the FDA for IA use in horses include methylprednisolone acetate (MPA), triamcinolone acetonide (TA), betamethasone acetate and betamethasone sodium phosphate (BAP), isoflupredone acetate, flumethasone and prednisolone acetate (animaldrugsatfda.fda.gov) (Table 1). Of these, the three most common corticosteroid preparations utilised are MPA, TA and BAP (Ferris et al., 2011). In the UK, only MPA is licensed for IA administration (vmd.defra.gov.uk); however, TA and BAP are commonly utilised off-label for IA use.

Despite the long history of corticosteroid use as IA therapy, the choice of corticosteroid, dose and frequency of administration remains largely based on clinical experience (Caron, 2005; Ferris et al., 2011). Common dose regimens of corticosteroids approved

TABLE 1 Corticosteroids approved by the FDA for intrasynovial use in horses (animaldrugsatfda.fda.gov)

Corticosteroid	Trade name	Concentration (mg/ml)	Dose (mg)	Potency relative to hydrocortisone	Relative duration of action
Methylprednisolone acetate	Depo-medrol[a]	40	40–120	5	Long
Triamcinolone acetonide	Vetalog[b]	6	6–18	5	Medium
Betamethasone acetate and betamethasone sodium phosphate	Betavet[c]	6	3–18	30	Medium-long
Isoflupredone acetate	Predef 2X[a]	2	5–20	50	Short-medium
Flumethasone	Flucort[a]	0.5	1.25–2.5	120	Short-medium
Prednisolone acetate	Metricortelone (discontinued)[d]	25	50–100	4	Short

[a]Zoetis Inc.
[b]Boehringer Ingelheim Animal Health USA Inc.
[c]American Regent Inc.
[d]Intervet Inc.

for IA use are listed in Table 1. In a 2011 survey of members of the American Association of Equine Practitioners (AAEP), it was found that 77% of the respondents to the survey use TA in high-motion joints and 73% of respondents use MPA in low-motion joints (Ferris et al., 2011). Recently, this study was repeated and the results were similar (Zanotto & Frisbie, 2021). Another survey of AAEP members found that IA corticosteroids remain the treatment of choice for horses with joint pathology, above newer therapies such as autologous conditioned serum or platelet-rich plasma (Velloso Alvarez et al., 2020). As interest in nonsteroidal intra-articular therapies increases, it will be interesting to see whether in vivo research can demonstrate any advantage of these therapies over traditional corticosteroid therapy, particularly with regards to cartilage metabolism and longevity.

In vitro and in vivo models of equine OA

The widespread impact of OA in both humans and in horses has led to an intense academic interest in understanding the pathogenesis of this disease and the development of potential therapeutics. A wide range of models, both in vitro and in vivo, have been developed with the aim to replicate the arthritic scenario (Makarczyk et al., 2021). In vitro models include 2D culture (monolayer or co-culture), 3D culture (scaffold-free or scaffold-based), ex vivo/explant-based culture and the less common dynamic culture, 3D biofabrication and organotypic models (Johnson et al., 2016). These models are generally limited to one cell type, require specialist equipment and cannot capture the effect of mechanical force or physiology but are important for pre-animal trial hypothesis testing. It is important to note that many of the discussed in vitro studies in this review are underpowered or examine one cell type and consequently do not capture the complexities of cell cross-talk. Additionally, OA is often induced with cytokine stimulation of tissues, usually with 10 μg/ml IL-1β and/or 10 μg/ml TNFα. These concentrations are much higher than in naturally occurring OA in order to facilitate the rapid progression of the in vitro model: One study that assayed the synovial fluid of human patients with OA for IL-1β and TNFα found average concentrations of 21 and 80 pg/ml, respectively (Kahle et al., 1992). Therefore applying the results of these studies directly to the clinical patient may not be appropriate.

The horse has been utilised as an animal model for in vivo research. Horses are easy to acquire, their size means biological fluids such as blood or synovial fluid are more readily available than smaller animals, their cartilage thickness and histological distribution of collagen and chondrocytes are comparable to that of humans (Frisbie et al., 2006; Malda et al., 2012). Probably, the most commonly utilised model is the carpal osteochondral fragment exercise model, in which an 8 mm osteochondral fragment is created arthroscopically in the distal dorsal aspect of one of the radial carpal bones, followed by a controlled exercise program over 70 days. This typically results in changes in increased synovial fluid total protein concentrations, synovial membrane hyperplasia and fibrosis and articular cartilage erosions, similar to those seen in post-traumatic OA, without causing severe lameness (Frisbie et al., 1997, 2008). But, this model is not without disadvantages. It is expensive, requires specialist facilities and personnel and only utilises one joint per horse. Other models have been developed, but a full discussion of these is outside the scope of this review. No one model provides a perfect replication of OA.

Equine in vitro and in vivo IA corticosteroid research

Despite the widespread popularity of IA corticosteroids for equine OA, in vitro research indicates time and concentration-dependent detriment to articular tissues. Methylprednisolone acetate (MPA) decreases proteoglycan production by equine chondrocytes, depresses collagen production and prevents chondrocyte differentiation (Byron et al., 2008; Fubini et al., 2001). The reduction in the

viability of chondrocytes and synoviocytes following treatment with 40 mg MPA suggests that it is somewhat cytotoxic to synovial cells (Sherman et al., 2015). Similar findings were observed in deep digital flexor tendon and navicular bone fibrocartilage explants treated with MPA (0.5 mg and 5 mg/ml, 6- and 12-h exposure time), suggesting that use in synovial structures other than joints may also be questionable (Sullivan et al., 2021).

The relative detriment to articular tissue caused by MPA treatment has been shown by in vivo research. Normal horses treated with 60 mg MPA at 2-week intervals for a total of 3 doses had suppression of procollagen II synthesis and increased degradation products of aggrecan present in synovial fluid as determined by gel chromatography (Robion et al., 2001). In an osteochondral fragment model of OA, horses treated with 100 mg MPA once a week for 4 treatments had inferior healing of cartilage defects when compared to saline-treated controls (Shoemaker et al., 1992). A second osteochondral fragment experiment found that joints treated with 100 mg MPA on postsurgical days 14 and 28 had lower PGE_2 concentrations in sampled synovial fluid and less intimal layer hyperplasia and vascularity than control joints (Frisbie et al., 1998). However, increased cartilage erosion and other morphologic lesions present in MPA-treated joints led the authors to conclude that the net effect of MPA on the synovial joint was negative. Furthermore, no clinical improvement in lameness or joint effusion was noted, which challenges MPA's status as a symptom-relieving drug. It is important to note that the doses and treatment intervals used in these studies exceed those usually recommended for clinical patients. The negative effect of MPA on cartilage has led to its use is being generally restricted to 'low-motion' joints, for example, the tarsometatarsal and distal intertarsal joints, where preservation of cartilage health and joint function is not paramount to the horse's movement (Ferris et al., 2011).

In contrast to MPA, some of the in vitro research concerning TA suggests a positive treatment effect on synovial tissues. Treatment of IL-1β stimulated chondrocytes with 0.06 mg/ml or 0.6 mg/ml TA mitigated the catabolic effect of IL-1β on GAG metabolism (Schaefer et al., 2009). In a synovium and cartilage co-culture model, 10^{-10} M TA inhibited the production of catabolic cytokines and MMP activity (Beekhuizen et al., 2011). Administration of 10^{-10} M TA decreased PGE_2 production by inflamed articular tissues (Trahan et al., 2018). Importantly, treatment with 40 mg TA did not negatively affect chondrocyte or synoviocyte viability, suggesting that, in contrast to MPA, TA is not cytotoxic at physiologic doses (Sherman et al., 2015).

These positive results have also translated to in vivo research. In an LPS-synovitis model, horses treated with 9 mg TA had reduced lameness, oedema and synovial fluid total protein compared with controls (Kay et al., 2008). In an osteochondral fragment model, horses treated with 12 mg TA on days 13 and 27 post-surgery were significantly less lame than saline-treated controls (Frisbie et al., 1997). Triamcinolone-treated horses had less synovial membrane hyperplasia and fibrosis, improved cartilage histomorphological parameters and higher synovial fluid GAG concentrations (Frisbie et al., 1997). In a second osteochondral fragment model with the same doses, treatment with TA improved lameness without altering bone remodelling or fragility (Kawcak et al., 1998). However, not all results have been positive. Gene expression in synovial fluid of exercised, TA-treated horses revealed an increase in anti-inflammatory gene expression and downregulation of proinflammatory cytokines; however, collagen gene expression was also suppressed after a single 9 mg dose (Knych et al., 2017). Recently, an LPS model of synovitis compared a single 12 mg TA treatment with saline control and found higher synovial fluid GAG and PGE_2 levels in the TA group (Kearney et al., 2020). This suggests that in the presence of inflammation, TA may potentiate matrix destruction and endogenous joint inflammation. A study that examined treatment with TA (12 mg every 2 weeks for 3 doses) in an osteochondral fragment model determined that TA resulted in increased collagen degradation and aggrecan turnover (Céleste et al., 2005). Typically TA is thought of as a more 'joint friendly' corticosteroid and therefore is utilised in more 'high-motion' joints such as the stifle or metacarpal/metatarsal-phalangeal joint (Ferris et al., 2011; Zanotto & Frisbie, 2021). The somewhat conflicting evidence from the scientific literature merits careful consideration, and further in vivo trials are required to fully elucidate the beneficial versus deleterious action of TA.

While MPA is classically considered 'joint unfriendly' and TA is 'joint friendly', consensus regarding the status of BAP is lacking. One study found that treatment with 6 mg/mL BAP resulted in no significant chondrocyte death after 7 days of treatment (Davis et al., 2010). Another reported complete loss of chondrocyte and synoviocyte viability after 1 and 7 days of co-culture, after treatment with 5 mg BAP (Sherman et al., 2015). At higher concentrations (0.1–100 μg/mL), BAP suppressed proteoglycan synthesis by articular tissues and had no significant effect at lower concentrations (0.001–0.05 μg/mL) (Frean et al., 2002). These conflicting results have been reflected in in vivo research. Treatment of normal joints with 3 doses of 24 mg BAP resulted in increased levels of synovial fluid hyaluronate and proteoglycan, suggesting increased cartilage ECM turnover (Ronéus et al., 1993). In an osteochondral fragment model, no clinical benefit nor any histological detriment of 16 mg BAP treatment performed on days 14 and 35 post-surgery was found (Foland et al., 1994).

EQUINE CLINICAL IA CORTICOSTEROID RESEARCH

Unfortunately, in comparison to the numerous preclinical research trials concerning IA corticosteroids, there are few clinical studies. A retrospective study of 51 horses compared the clinical response to IA MPA (median dose per joint was 55 mg) and IA TA (median 9.8 mg per joint) in the tarsometatarsal and/or distal intertarsal joints (Labens et al., 2007). This study found no difference between MPA and TA treatment. Of the 34 horses that had to follow-up information, only 13/34 had a positive outcome as defined as being able to return to work without oral nonsteroidal anti-inflammatory drugs. Horses were enrolled in the study based on a positive response to IA analgesia and diagnostic imaging findings. The small number of

TABLE 2 Detection times of commonly utilised intra-articular corticosteroids, based on recommendations by the Racing Medication and Testing Consortium (RMTC)

Corticosteroid	Detection threshold	Experimental administration dosage	Time to LOQ/LOD	Detection time	References
Methylprednisolone acetate	100 pg/ml of plasma or serum	Total of 100 mg in one joint, 200 mg in two joints	240 h to LOQ (plasma) 21 days to LOQ (urine) 77 days above LOD (synovial fluid)	14 days (100 mg dose) 28 days (200 mg dose)	Lillich et al. 1996, Soma et al. 2006
Triamcinolone acetonide	100 pg/ml of plasma or serum	Total of 9 mg in one joint	144 h to LOQ, 168 h to blow LOD (plasma) 240 h to below LOD (urine)	7 days	Soma et al. 2011, Knych et al. 2013
Betamethasone	10 pg/ml of plasma or serum	Total of 9 mg in one joint	72 h to LOQ (plasma) 96 h to below LOD (plasma) 7 days to below LOD (urine)	7 days	Luo et al. 2005, Knych et al., 2017
Isoflupredone acetate	100 pg/ml of plasma or serum	Total of 20 mg in one joint	144 h to LOQ, 168 h to below LOD (plasma)	7 days	Lillich et al. 1996, Knych et al. 2016

Note: The RMTC currently recommends a mandatory 14-day stand-down period for all intra-articular medications. Intramuscular injection of corticosteroids will result in serum or plasma concentrations that remain above LOD for weeks or even months.

Abbreviations: LOD, limit of defection; LOQ, limit of quantification.

cases and the nonstandardised treatment protocol limited the value of the results.

A large-scale clinical trial examined outcomes for horses with 'high-motion' joint lameness treated with 12 mg TA and 12 mg TA with 20 mg high molecular weight hyaluronan (HA) administered IA (de Grauw et al., 2016). Treated joints included distal interphalangeal, metacarpo/metatarsophalangeal, middle carpal and radiocarpal joints. The rationale for treatment with HA was that exogenously administered HA supplements re-establishes the depleted HA in the arthritic joint, thereby restoring the viscosity of the synovial fluid and lubrication of articular tissues (Balazs, 2004). Hyaluronan is antioxidative, anti-inflammatory and analgesic (Gupta et al., 2019). Concurrent administration with a corticosteroid was aimed at offsetting the harmful effects of the corticosteroid on chondrocytes while preserving the anti-inflammatory effect of the corticosteroid. The result of the study was that concurrent TA-HA treatment resulted in poorer success rates compared with TA alone. Only half of all treated horses returned to their previous level of activity. Although most in vitro work indicates that TA is chondroprotective, this does not appear to consistently translate to benefitting the clinical case in the long term.

REGULATION OF IA CORTICOSTEROID THERAPY IN HORSES

The rationale for the prohibition of corticosteroids in competition horses is that they may provide an unfair advantage to the horse by enhancing performance. A horse may be able to perform at a level that otherwise it would not have the ability to, this is potentially dangerous as the horse will not be properly physiologically adapted to such a level and injury may result. This increased performance does not just pertain to decreased lameness. For example, the pulmonary function has been shown to be improved by intra-articular administration of corticosteroids (Bessonnat et al., 2020). Additionally, the potent pain-relieving effect of corticosteroids may increase the potential for injury by suppressing the effects of minor or major pathologies that may ultimately worsen if the horse does perform (see *Complications: Musculoskeletal injury*). Subsequently, horses that test positive for these drugs can be disqualified from the competition. However, regulatory bodies, such as the Racing Medication and Testing Consortium (RMTC) and Fédération Équestre Internationale (FEI) among others, recognise that the use of these medications between competitions is justified because they pertain to the treatment of the horse. In order to help veterinarians and owners ensure that the treated horse does not test positive, these regulatory bodies have released various guidelines to help guide the timing of treatment (McIlwraith, 2013). Most define 'detection time' as the interval between the administration of the drug and the last moment when a testing method can demonstrate evidence of the drug or its metabolite in samples from the horse (Toutain, 2010). The detection time is therefore the absolute minimum amount of time that must pass between administration and competition. Multiple pharmacokinetic

studies examining common IA corticosteroids have facilitated the publication of detection times for each medication, based upon detection in plasma, urine and synovial fluid (Table 2). The 'withdrawal time' is based upon the known detection time, which is determined by rigorous scientific study, plus an estimated 'safety factor' added to allow for physiological variations between individuals that may affect individual drug metabolism (age, sex, disease status, etc.). The withdrawal time is therefore determined by the clinician familiar with the horse, the client and their particular circumstances. The rules pertaining to IA corticosteroid use in competition horses are continuously updated, and judicious double-checking of the current regulations prior to use is recommended. At the time of writing, the RMTC recommends a mandatory 14-day stand-down period for all IA medications, which is irrespective of drug detection times.

COMPLICATIONS OF ADMINISTRATION OF IA CORTICOSTEROIDS

Complications associated with the administration of IA corticosteroids can be considered broadly as complications inherent to the act of performing an IA administration (i.e. septic arthritis, acute aseptic inflammation/joint flare and periarticular cellulitis) and complications specific to the effects of corticosteroids (i.e. musculoskeletal injury, osseous metaplasia and laminitis). It is well-established that corticosteroids administered into a synovial cavity will be dispersed systemically, therefore there is potential for any of the known side effects of corticosteroid administration to occur (Cuming et al., 2018).

Septic arthritis

The incidence of septic arthritis following administration of IA medications is low, reports range from 2.1 to 7.8 septic joints per 10,000 joint injections (Gillespie et al., 2016; Smith et al., 2019; Steel et al., 2013). Sepsis results from inoculation of the skin microflora into the synovial environment by the needle, usually Staphylococcus species (Schneider et al., 1992). Diagnosis is made via a combination of the recent history of IA medication, sudden onset of lameness, presence of heat or sensitivity of the afflicted joint and synovial fluid analysis. A positive synovial fluid culture is the gold standard of diagnosis but is obtained in less than 50% of confirmed cases (Taylor et al., 2010). Differentiation between septic and nonseptic inflammatory arthritis is somewhat confused by the overlap between clinicopathological values; however, the presence of synovial fluid leucocytosis (>30 $\times 10^9$ nucleated cells/L), neutrophilia (>80–90% neutrophils), hyperproteinaemia (>30 g/L), cytological evidence of sepsis such as neutrophil degeneration, presence of intracellular bacteria and increased serum amyloid A concentration all provide convincing evidence for diagnosis (Haralambus et al., 2021; Ludwig et al., 2016; Sinovich et al., 2020). Treatment strategies include arthroscopic evaluation, through-and-through needle lavage, arthrotomy and systemic and local antibiotic administration (Crosby et al., 2019). With appropriate therapy, the prognosis for survival and return to use is good (Crosby et al., 2019).

The significant emotional, financial and clinical consequences to the horse, client and veterinarian following the development of synovial sepsis after IA injection have resulted in justified interest in prevention strategies (Pezzanite et al., 2022). Concurrent prophylactic administration of an antibiotic theoretically reduces the risk of synovial sepsis by eliminating any iatrogenically inoculated bacteria through locally established MIC. However, prophylactic antibiotic use does not appear to decrease the incidence of sepsis and may be detrimental to the synovial tissue (Bohlin et al., 2014; Pezzanite et al., 2020; Steel et al., 2013). Risk factors for synovial sepsis following intra-articular injection that have been identified include breaches in aseptic technique, the experience of the clinician with injections, use of multi-dose vials, clipping hair from injection sites, larger needle gauge, needle angle of insertion, reusing a needle and not using a stylet in a spinal needle (Adams et al., 2010; Gillespie et al., 2016; Steel et al., 2013). Despite a lack of clear scientific evidence for prophylactic antibiotic use with IA injection, concurrent treatment remains common in clinical practice (Zanotto & Frisbie, 2021).

Acute aseptic inflammation (joint flare)

A usually self-limiting, aseptic inflammatory response following IA medication administration is referred to as a 'joint flare', with a frequency of occurrence around 2% (Caron, 2005). This response can be seen following administration of any IA medication and may be more common following treatment with certain nonsteroidal IA therapies (Velloso Alvarez et al., 2020). In the case of corticosteroid treatment, the inflammatory response is thought to be secondary to the microcrystalline suspension of the corticosteroid ester (McCarty & Hogan, 1964). The horse is typically lame, with pain, swelling and heat in the affected joint. Crucially, the synovial clinicopathological parameters do not indicate sepsis (Harkins et al., 1993). As differentiation between a joint flare and septic arthritis can be difficult, and successful treatment of septic synovial structures is time-dependent, treatment for either condition is usually similar.

Periarticular cellulitis

Cellulitis is infection and/or inflammation of the subcutaneous tissues: In cases of periarticular cellulitis, an inoculation of skin microflora into the subcutaneous space overlying the joint occurs during medication delivery (Adam & Southwood, 2006). While the exact incidence is unknown, it is thought to be relatively uncommon (Caron, 2005). In two retrospective reports of limb cellulitis, a history of recent IA medication administration was identified as the cause of cellulitis in 0%–7% cases (Adam & Southwood, 2007; Fjordbakk et al., 2008). Both of these studies found Staphylococcus and Streptococcus species to be the most commonly identified. Diagnosis is made based on the history of recent IA medication administration, sudden occurrence

of lameness, periarticular swelling and heat and the presence of pitting oedema (Adam & Southwood, 2006). Treatment strategies include regional and systemic antimicrobial administration, cold hydrotherapy, hand-walking and compressive bandaging (Fjordbakk et al., 2008). Attempts at locally medicating the joint are actively discouraged because in vitro models have shown that needle insertion through tissues affected by cellulitis can inoculate the synovial environment and potentially result in septic arthritis (Smyth et al., 2015).

Musculoskeletal injury

Corticosteroid use in foals has been associated with pathologic changes in developing bone (Glade & Krook, 1982). This early research raised concerns about the risk of musculoskeletal injury following corticosteroid injection due to osteonecrosis or disruption of the bone's ability to adapt to cyclic loading. Subsequent work found that IA TA and MPA had no effect on subchondral bone (Kawcak et al., 1998; Murray et al., 2002). One epidemiological study demonstrated an increased risk of catastrophic injury over a defined period following IA corticosteroid injection (Whitton et al., 2014) while another showed this therapy was not associated with increased risk, although the power of the second study was low (Hitchens et al., 2018). It is postulated that IA corticosteroid injection provides analgesia, which has a masking effect. So in horses where there are mild clinical signs of impending fracture, these are masked and the horse may be pushed closer to injury when instead rest would be beneficial. A recent clinical study of 1488 racing Thoroughbreds treated with intrasynovial medications determined that 3 or more treatments were associated with a greatly increased risk of fracture (Smith et al., 2018). This study did not have a control group of unmedicated horses so the validity of this finding is questionable. While no direct link between medications and catastrophic injury has been definitively established, the possibility for increased risk of injury should be considered when IA medication is being administered prior to intensive exercise.

Osseous metaplasia

Metaplastic bone formation can result following inadvertent deposition of corticosteroids (MPA) into the periarticular tissues. The mechanism and incidence of this condition are unknown, and few scientific reports are available for reference. Potential clinical implications include the progressive limitation of joint movement and resultant lameness. Diagnosis is by physical examination and diagnostic imaging, no treatments are currently described.

Laminitis

Currently, there is no scientific proof that corticosteroids cause laminitis; however, there is a perception that some formulations, particularly TA, may contribute to a laminitic event (Ferris et al., 2011). This is despite several retrospective studies finding no causative link between TA use and laminitis (Haseler et al., 2020; McCluskey & Kavenagh, 2004). One hypothesis is that corticosteroids cause a rapid increase in plasma insulin and glucose; systemic hyperinsulinaemia results in the upregulation of lamellar inflammatory pathways and subsequent clinical disease (Watts et al., 2019). While no study has been able to demonstrate a causative link between corticosteroid administration and laminitis, it may be prudent to limit the dosage and frequency of treatment in horses that appear to be at risk for equine metabolic syndrome-associated laminitis (Potter et al., 2019). Diagnosis is by the presence of typical clinical signs such as 'leaning back' shifting lameness, presence of bounding digital pulses and radiographic changes. Attempts at treatment are based upon the severity of clinical signs and include continuous cold therapy, corrective podiatry, analgesia and supportive care.

CONCLUSION AND TAKE-HOME MESSAGES

Intra-articular corticosteroid therapy remains a popular choice for equine joint disease, despite several important drawbacks to therapy. A growing body of evidence suggests that they may negatively affect synovial tissue metabolism, though clear scientific evidence linking corticosteroid therapy to progressive joint disease is lacking. We recommend using the lowest feasible dosing interval and avoiding 'maintenance' injections of sound horses. Additionally, using the more 'joint friendly' preparations in high-motion joints should be considered. As more information regarding the use of orthobiologic therapies is available, it may be prudent to alternate corticosteroid therapy with one of these medications or even replace IA corticosteroid therapy altogether. The incidence of reported complications of IA corticosteroid therapy is low, but using an appropriate total body dose and strict aseptic technique is important to avoid them.

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ORCID

Sophie Boorman https://orcid.org/0000-0003-2082-7702
Erin Groover https://orcid.org/0000-0001-7143-1666

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