Review Article

Glucocorticoid therapy and the risk of equine laminitis

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Keywords: horse; glucocorticoid; therapy; laminitis; inflammatory

Summary

Although glucocorticoids have been used successfully for the treatment of noninfectious inflammatory diseases of horses for more than 35 years, their use has been attended by a fear of the induction of laminitis. This paper reviews the evidence for this fear and the possible mechanisms whereby glucocorticoids could participate in laminitis induction. Although the association of laminitis with elevated serum cortisol in pituitary *pars intermedia* dysfunction suggests that chronic exposure to glucocorticoids may be part of laminitis pathogenesis, review of published reports and databases suggests that glucocorticoid-induced laminitis is a relatively rare occurrence. However, several of the actions of glucocorticoids are similar to those known to be involved in laminitis pathogenesis. Glucocorticoid administration can induce insulin resistance, lead to vascular dysfunction that potentiates vasoconstriction, and interfere with keratinocyte proliferation and differentiation as well as matrix integrity, all mechanisms that could possibly induce laminitis. Drug formulation, dose and route of administration, and the systemic and hoof disease history of the horse must all be considered when assessing laminitis risk during glucocorticoid treatment. Generally, local glucocorticoid administration presents little risk as does systemic treatment of recurrent airway obstruction without concurrent disease. Caution should be used however in horses that are overweight and/or insulin resistant, or have had a recent bout of acute laminitis of alimentary or endotoxic origin. Overall, however, the risk of laminitis after glucocorticoid treatment, especially local use, is acceptable compared to the many benefits of these drugs.

Introduction

In equine medicine, glucocorticoids are extremely valuable medications for the treatment of noninfectious inflammatory diseases such as recurrent airway obstruction (RAO), arthopathies, dermatological conditions and ocular inflammation. However, since their introduction into equine medicine more than 35 years ago, glucocorticoid use has been accompanied by fear of induction of laminitis, leading veterinarians to use doses that are often inadequate or, even worse, choosing alternative drugs with unproven efficacy. This laminitis fear has found renewed concern after a recent high-profile court case regarding a horse treated with intra-articular triamcinolone-acetonide (TMC) in the UK (Dutton 2007). This case's findings resulted in the recommendation for veterinarians to advise horse owners of the possibility of a small risk of laminitis whenever horses are treated with glucocorticoids. Unfortunately, information regarding glucocorticoid use and the incidence of laminitis development in horses is scarce and often includes cases with confounding factors. For instance, in a handful of older veterinary reports and lay literature that implied an association between laminitis and prior glucocorticoid use, it was unclear if the glucocorticoid was really the cause of the problem. Some of these reports included horses with recurrent airway obstruction (Gerber 1970; Muylle and Oyaert 1973), which are usually older and could have had pituitary *pars intermedia* dysfunction (PPID). Similarly, horses in other reports may have had coexisting gastrointestinal disease (Lose 1980) or what is now known as equine metabolic syndrome (EMS). Pituitary *pars intermedia* dysfunction, EMS and gastrointestinal disease have all been associated *per se* with laminitis. The lack of prospective investigations that include large numbers of horses with and without other diseases likely to induce laminitis makes it difficult to estimate the true laminitis risk accurately in horses treated with glucocorticoids.

Based on retrospective analyses, the risk of developing laminitis does not seem to be very high for most horses. Out of a combined total of 526 horses from 3 studies that looked at multiple risk factors in referred cases of acute or chronic laminitis (Hunt 1993; Slater *et al*. 1995; Cripps and Eustace 1999), only 3 cases were attributed to glucocorticoid use. Reports including the intra-articular use of glucocorticoid in horses suggest a similar clinical picture. A review (Cornelisse and Robinson 2004) of earlier published reports spanning a total of 472 horses (Houdeshell 1969; Swanstrom and Dawson 1974; Vernimb *et al*. 1977; Verschooten *et al*. 1990; Frisbie *et al*. 1997) that were treated intra-articularly or intrabursally with different glucocorticoids, including TMC and followed over a longer period after administration, found no reported cases of laminitis. This is supported by a more recent larger case series of 205 horses (McCluskey 2004) that were treated intra-articularly with TMC (up to 80 mg) and by a recent editorial that included previously unpublished data on intra-articular administration of primarily TMC to 2000 horses (Bathe 2007). Both of these reported only one horse developing laminitis within a week; both horses had had a prior episode of laminitis that probably increased their risk.

Even more convincing is the lack of support for a high prevalence of steroid-induced laminitis in published reports of adverse drug reactions. For example, the 1992, 1994 and 1996 reports of the Australian Veterinary Association Adverse Drug Reaction Subcommittee (Maddison 1992, 1994, 1996) did not mention any case of glucocorticoid-induced equine laminitis. Similarly, the FDA-CVM Adverse Drug Experience web pages mentioned only 5 'possibly' drug-related cases of laminitis over

the period 1987–2000. These were associated with a variety of parenterally used glucocorticoids, including dexamethasone (DEX), betamethasone, TMC, and methyl-prednisolone. The lack of information regarding actual numbers of sales for these products and their use for different clinical conditions combined with the likelihood of under-reporting makes it difficult to determine the exact prevalence of glucocorticoid-induced laminitis. However, the inclusion of owner reports in the FDA database does suggest that glucocorticoid-induced laminitis is a relatively rare occurrence.

How might glucocorticoids predispose to the development of laminitis?

Despite the apparently low prevalence of laminitis cases that can definitively be tied to administration of glucocorticoids, there are many actions of these drugs that could be interpreted as increasing laminitis risk. For instance, the association of laminitis with PPID suggests that chronic exposure to glucocorticoids may be part of the laminitis pathogenesis.

Activation of the intracellular glucocorticoid receptor is dependent on the active form of the glucocorticoid molecule, cortisol. Local tissue concentration of cortisol is determined by the net balance of the combined activity of 2 kinetically distinct isoforms of the cell membrane-associated enzyme 11β-hydroxy steroid hydrogenase (11-β HSD). The 11-β HSD-1 isoform primarily converts inactive cortisone into cortisol, whereas 11-β HSD-2 catalyses the reverse reaction (Staab and Maser 2010). Although there is no specific information about the horse laminae, it appears that the net balance between the 11-β HSD isoforms for 9-alpha fluoro-glucocorticoids such as DEX and TMC favours a decreased breakdown of these drugs by 11-β HSD-2 (Best *et al*. 1997; Diederich *et al*. 1998) and hence prolonged glucocorticoid tissue activity. The overexpression of 11-β HSD-1 in adipose tissue of obese mice and human subjects appears to play a major aetiological role in metabolic syndrome, insulin resistance and hyperglycaemia. Furthermore, expression of the 11-β HSD-1 gene HSD11B1 is increased by endotoxin (Ishii *et al*. 2007) and by the proinflammatory cytokines TNF-α and IL-1β, which may explain the increased expression of this gene in inflammatory bowel disease and colitis (see review by Staab and Maser 2010). Similarly, 11-β HSD-1 is increased in laminar tissues of horses with acute experimental laminitis (Johnson *et al*. 2004).

The classic theories on the pathogenesis of laminitis focus on: 1) a primary disturbance of perfusion of the laminae followed by secondary events that lead to laminar injury; 2) a disturbance in the structure and strength of the epidermal and dermal laminae by toxic or metabolic substances; 3) increased matrix metalloproteinease (MMP) activity that can be induced for example, by endotoxins or streptococcal exotoxins; and 4) endocrinopathies primarily relating to PPID, EMD and insulin resistance (Grosenbaugh *et al*. 1991; Weiss 1997; Mungall *et al*. 1998, 2001; Adair *et al*. 2000; Wattle 2001; Treiber *et al*. 2006). Current understanding of the molecular mechanisms of glucocorticoid action can be implicated in most of the above theories.

Vascular effects of glucocorticoids

In certain types of human obesity, increased activity of 11-β HSD-1 (leading to an increased local tissue level of cortisol) is associated with insulin resistance (Masuzaki *et al*. 2001; Paulmyer-Lacroix *et al*. 2002), which in turn is associated with an impaired local production of the vasodilator nitric oxide (NO) by endothelial cells (Masuzaki *et al*. 2001; Paulmyer-Lacroix *et al*. 2002; Steinberg and Baron 2002; Trovati and Anfossi 2002; Bakker *et al*. 2009). In rats, chronic administration of low doses of dexamethasone induces hypertension on the basis of decreased NO production. This hypertension is preceded by a decreased sensitivity to insulin, and both can be blocked by metformin, a drug that increases peripheral insulin sensitivity and cellular glucose uptake (Severino *et al*. 2002). It appears therefore that long-term glucocorticoid therapy or mechanisms that result in increased local tissue active glucocorticoid concentration are associated with insulin resistance and an impaired production of the vasodilator NO. Indeed, hyperinsulinaemia and insulin resistance have now been well documented in horses after systemic administration of TMC and DEX (Cartmill *et al*. 2003; Tiley *et al*. 2007, 2008; Haffner *et al*. 2009) while an impaired production of NO can cause a reduced blood flow to the foot (Baxter 1995; Cogswell *et al*. 1995; Schneider *et al*. 1999). Thus a reduction in the NO production in equine blood vessels would tip the balance toward vasoconstriction from an impaired vasodilator reserve (Baxter 1995; Luft *et al*. 1999). This impaired vasodilator reserve could consequently be at the basis of the reported exaggerated contractile responses of equine skin and digital blood vessels to vasoconstrictors after administration of glucocorticoids (Eyre *et al*. 1979; Cornelisse *et al*. 2006).

The regulation of digital blood flow is, however, not simply under the control of one mediator but is due to a complex interplay between vasoconstrictors such as endothelin (ET) and vasodilators such as NO (Cardillo *et al*. 1999; Miller *et al*. 2002). Glucocorticoids increase secretion of insulin in a rat model (Sood and Ismail-Beigi 2010) and hyperinsulinaemia has, besides the reduction in endothelial NO production, also been associated with elevated concentrations of the potent vasoconstrictor ET-1 (Juan *et al*. 1999; Strawbridge *et al*. 2006; Tousoulis *et al*. 2008). In addition, hyperinsulinaemia in both a rat model as well as in diabetic patients can lead to excess arteriovenous blood shunting as a consequence of altered vasomotor tone (Stevens *et al*. 1991; Kihara *et al*. 1994). Interestingly, redistribution of digital blood flow away from laminae through arteriovenous anastomoses was the explanation proposed to reconcile the conflicting observations of decreased laminar perfusion coupled with increased total digital blood flow and heat in the foot of laminitis ponies (Coffman *et al*. 1970; Robinson *et al*. 1976; Hood *et al*. 1978; Robinson 1990).

Thus it appears that glucocorticoids, via mechanisms of insulin resistance and/or hyperinsulinaemia, could induce a bias towards vasoconstriction due to alterations in the vasomotor activity. Glucocorticoid associated laminitis could therefore be consistent with disturbance of perfusion of the laminae followed by secondary events that lead to laminar injury. Support for this mechanism exists in the high prevalence of peripheral vascular disease in human patients with obesity and diabetes (Miller *et al*. 2002) and recent studies that have shown that prolonged administration of insulin can induce laminitis in healthy ponies (Asplin *et al*. 2007a; Nourian *et al*. 2009) and horses (de Laat *et al*. 2010). This mechanism could also help explain why horses suffering from certain diseases that are already associated with an altered vasomotor status such as endotoxaemia (Baxter

1995) or with elevated ET-1 concentrations such as in chronic laminitis (Katwa *et al*. 1999; Eades *et al*. 2007), or that are accompanied by insulin resistance (e.g. from endotoxaemia, a lush pasture or a fructan-rich diet) are perceived to be at greater risk for laminitis after glucocorticoid treatments (Menzies-Gow *et al*. 2004; Bailey *et al*. 2007; Toth *et al*. 2008; Geor 2009).

Dermal and epidermal effects of glucocorticoids

The wall of the hoof is attached to the distal phalanx via interdigitations between sensitive and insensitive laminae. Epidermal keratinocytes cover the surface of the sensitive laminae and, depending on their anatomic location, either produce keratin or anchor and remodel it in order to allow growth of the hoof wall. The anchoring filaments of the hemidesmosomes attach epidermal keratinocytes to the basement membrane, which is connected to the dermal connective tissues and the periosteum of the distal phalanx (Bowker 2003; Pollitt *et al*. 2003). Hoof formation is akin to production of skin and it is therefore logical to consider glucocorticoid effects on skin when considering the risk of laminitis. Glucocorticoids can alter proliferation and differentiation properties of both keratinocytes and fibroblasts, resulting in thinning of the epidermis and decreased collagen synthesis. This process results in a weakened structural supporting matrix leading to skin atrophy and impaired wound healing (Schoepe *et al*. 2006). Keratinocyte effects of glucocorticoids include decreases in cell size and rate of proliferation, and increases in maturation rate so that keratinocytes have a shorter lifespan. These effects are highly dependent on corticosteroid potency with effect increasing from prednisolone through DEX and TMC, to potent topical agents such as betamethasone dipropionate (Hengge *et al*. 2006; Schoepe *et al*. 2006). Clinically significant thinning of the skin can be found after 1–2 weeks of daily topical fluorinated glucocorticoids (Korting *et al*. 2002). In the case of fibroblasts, as little as 3 days of topical glucocorticoid treatment results in down regulation of the collagen synthesis in human skin (Haapasaari *et al*. 1998; Oikarinen *et al*. 1998). Because the epidermal anchorage to the basement membrane and the latter to the distal phalanx support the weight of the horse, any changes in the structural integrity and mechanical properties of collagen and epidermal structures are likely to lead to dermo-epidermal separation, tearing of laminae, inflammation and rotation of the distal phalanx within the hoof capsule. Exposure of laminae to elevated concentrations of glucocorticoids resulting in weakened dermal and epidermal attachments to the distal phalanx could therefore be one of the mechanisms for laminitis in PPID and EMD and also a consequence of glucocorticoid administration. Furthermore, because loss of keratinocytes by apoptosis (Faleiros *et al*. 2004; Mobasheri *et al*. 2004) and delayed regeneration of anchoring filaments between keratinocytes and basement membrane (Kuwano *et al*. 2005) are features of acute and chronic laminitis, respectively, and because regenerations of hemidesmosomes and anchoring filaments must occur during healing, it is possible that glucocorticoids could further contribute to the severity of laminitis or delay remodelling of the hoof during recovery.

Glucocorticoids, insulin and insulin resistance

The following evidence indicates that elevated insulin concentrations and insulin resistance (deceased insulin sensitivity) are associated with some forms of laminitis: 1) laminitis can be induced by insulin infusion in ponies and horses (Asplin *et al*. 2007a; Nourian *et al*. 2009; de Laat *et al*. 2010); 2) elevated insulin concentration predicts laminitis episodes in ponies (Carter *et al*. 2009); 3) laminitis-prone ponies are relatively insulin resistant (Bailey *et al*. 2008) and, at pasture, have higher blood insulin concentrations than control ponies (Bailey *et al*. 2007); and 4) insulin resistance is associated with factors known to be associated with laminitis, such as intake of dietary fructans (Bailey *et al*. 2007), endotoxaemia (Toth *et al*. 2008) and EMS (Geor and Frank 2009).

Lamellar cells have a high demand for glucose (Pass *et al*. 1998). Reduction of glucose supply will cause dermo-epidermal separation in hoof explants (French and Pollitt 2004); thus insulin resistance would seem to increase the laminitis risk by denying glucose. The latter may be unlikely, however, because lamellar explants may be able to take up glucose independent of insulin (Asplin *et al*. 2007b). It is therefore more likely that insulin's promotion of laminitis may be because of its vascular (see above and review by Imrie *et al*. 2010) and pro-inflammatory actions that include activation of MMPs and generation of reactive oxygen species (see reviews by Avogaro *et al*. 2010; Geor and Frank 2009). During insulin resistance (a term defining insulin's effects on glucose), insulin's pro-inflammatory actions apparently are not diminished (Avogaro *et al*. 2010).

In stressful situations, release of endogenous glucocorticoids results in high concentrations of insulin accompanied by insulin resistance and increased turnover of stored energy so that free energy (glucose and fatty acids) is available to fuel body metabolism. Similar effects of synthetic glucocorticoids have been clearly demonstrated in horses. In healthy horses, long-term (21 day) administration of DEX (0.08 mg/kg bwt i.v. q. 48 h) causes marked insulin resistance (Tiley *et al*. 2007) and a single i.m. dose of TMC (0.05 mg/kg bwt) has a similar effect that persists for 3–4 days (French *et al*. 2000). Even a single dose of DEX (0.04 mg/kg bwt i.v.), such as would be used in the DEX suppression test for equine Cushing's disease, results in decreased insulin responsiveness that peaks at 24 h but is over by 72 h. The insulin increase in response to DEX is further magnified in laminitis-prone ponies (Bailey *et al*. 2007). The information that is critically lacking is if and how this glucocorticoid-induced insulin resistance increases the laminitis risk.

Glucocorticoids and matrix metalloproteinase activity

There is strong evidence that excessive activation of MMPs is responsible for the dermo-epidermal separation that occurs in carbohydrate overload-induced laminitis and that this activation could be due to absorption of *Streptococcus bovis* exotoxin from the horse's hind gut (Moore *et al*. 2004). Glucocorticoids could potentially facilitate dermo-epidermal separation via an increased insulin concentration-induced MMP over-expression and activity (Fischoeder *et al*. 2007; Boden *et al*. 2008). However, dermo-epidermal separation was not a feature of the laminitis induced by insulin infusion in ponies (Nourian *et al*. 2009), and the direct effect of glucocorticoids is actually downregulation of MMP gene expression and activity in skin and elsewhere (Schroen and Brinckerhoff 1996; Garvican *et al*. 2010; Schoepe *et al*. 2010), making this an unlikely mechanism for glucocorticoid-induced laminitis.

What is the risk of laminitis following glucocorticoid administration?

When considering the risk of laminitis during glucocorticoid treatment, it is vital to consider both the drug, including its formulation, dose and route of administration, and the horse, especially its hoof and systemic disease history.

Drug formulation

The effects of a synthetic glucocorticoid depend on: 1) the drug formulation, dose, and route and frequency of administration; 2) the concentration of the active form in the tissue, which is determined by factors such as the local activation/inactivation kinetics by 11-β HSD-1 and 11-β HSD-2; and 3) the glucocorticoid receptor affinity and intrinsic genomic effects of the agent.

Acid esters (e.g. acetate or propionate) have slower systemic absorption and longer presence in the body compared to the alcohol or sodium phosphate/ succinate analogues (Schimmer and Parker 1995). Current formulations of TMC in use in veterinary medicine are those of the long-acting acetonide esters.

Different glucocorticoids can have different transcriptional potencies in different tissues, which results in tissue differences in magnitude of effect that can bypass the classical order of glucocorticoid potencies (Jaffuel *et al*. 2000, 2001). For example, in the classical order, TMC would be regarded as 5 times less potent than DEX, but it is equipotent with DEX in its diabetogenic effect because it induces similar increases in the activity of the gluconeogenic enzyme tyrosine aminotransferase (Jaffuel *et al*. 2001). In addition, the earlier described relative refractoriness of fluoro-glucocorticoids such as TMC and DEX to 11-β HSD-2 inactivation could therefore mean that, even during alternate day glucocorticoid therapy, the vasculature of the hoof, fibroblasts and keratinocytes are exposed for long periods to the activated form of drug. Furthermore, although the reported plasma half-life of i.v. TMC in the horse is shorter (1.39–1.58 h) (French *et al*. 2000) than that of DEX (2.63 h) (Cunningham *et al*. 1966), TMC appears to have a longer gluocorticolid-receptor-binding half-life (Rohdewald *et al*. 1986) and also produces long-lasting insulin resistance (French *et al*. 2000).

Route of administration

Intravenous or i.m. administration produces the highest plasma concentrations of drug while plasma concentrations after oral administration depend on oral bioavailability. For example, oral and i.v. DEX are equally efficacious for treatment of RAO when the oral dose is adjusted for its bioavailability (Cornelisse *et al*. 2004). Prednisone is a pro-drug that must be absorbed from the gut and then converted into active prednisolone in the liver. Apparently one or both of these steps is deficient in horses, as prednisolone concentration increases in the blood are minimal after oral administration of prednisone tablets (Peroni *et al*. 2002).

When compared to systemic administration, the local application of glucocorticoids for treatment of skin, eye, musculoskeletal and lung diseases is likely to result in much lower systemic concentrations and less likelihood of complications such as laminitis. Most investigations have been conducted in joints, tendon sheaths and bursae, where glucocorticoid therapy is associated with low, short duration, systemic concentrations, and thus poses a relative smaller risk for additional side effects. Triamcinolone (18 or 30 mg intra-articularly) results in detectable serum concentrations for <48 and 102 h with peaks between 4 and 12 h, respectively. The lower dose suppresses cortisol for <120 h (Chen *et al*. 1992; Koupai-Abyazani *et al*. 1995), compared to 336 h (Slone *et al*. 1983) after a similar i.m. dose. Diabetogenic effects after intra-articular application in horses have not been studied, but in diabetic and nondiabetic human subjects the intra-articular administration of methylprednisolone acetate or TMC is associated with relatively short-term (i.e. days) modest increases in blood glucose (Habib *et al*. 2008; Uboldi *et al*. 2009).

The horse

Despite the previously described extensive evidence supporting the hypothesis that corticosteroids predispose horses to laminitis, there are multiple clinical and research reports of systemic glucocorticoid administration for shorter or longer periods, and often at high doses, without mention of laminitis as a complication. For example, a single i.m. dose of dexamethasone (10 mg/horse) administered in many horses with PPID, of which a large percentage also had prior episodes of laminitis, did not induce or exacerbate the laminitis (Dybdal *et al*. 1994). Similarly, laminitis was not reported as a complication during or after treatment with either systemic administration of TMC (0.09–0.2 mg/kg bwt) (Lapointe *et al*. 1993; Lepage *et al*. 1993; French *et al*. 2000) or DEX at clinical (0.1 mg/kg bwt for up to 10 days) (Rush *et al*. 1998; Robinson *et al*. 2002, 2009; Cornelisse *et al*. 2004) or even higher doses (1 mg/kg bwt for 9 days) (Tumas *et al*. 1994). To the contrary, multiple simultaneous intra-articular doses that result in a high total dose (a total of 80 mg TMC plus 20 mg DEX i.m.) (Dutton 2007) and long-term repeated i.m. doses of TMC (20 mg for 10 days) (Ryu *et al*. 2004) have been associated with the induction of laminitis in individual animals within a relatively short period after administration. This is presumably due to a high total dose and long exposure to the glucocorticoid, respectively. For these reasons it is always necessary to consider the disease history of the horse before glucocorticoid administration.

Horses with PPID and EMS are likely to have been exposed to increased concentrations of endogenous cortisol and to be insulin resistant. They may also be in a proinflammatory condition, to have weakening of the dermo-epidermal junction, and perhaps even have had clinical laminitis. These animals are most likely to progress toward clinical laminitis after systemic glucocorticoid administration. A similar risk applies to the laminitis-prone pony, especially when it is at pasture.

Horses that have had a recent bout of acute laminitis of alimentary or endotoxic origin also should be treated cautiously. In our opinion, the longer the time since the previous laminitis bout, the less would seem to be the risk.

Using systemic DEX to treat horses with RAO generally carries a low risk of laminitis as long as the animal does not concurrently have PPID and is not excessively overweight. Doses up to 0.1 mg/kg bwt for 3 days can generally be safely administered to gain control of the disease. The dose can be gradually reduced until a maintenance dose is determined. Administration of fluticasone propionate by aerosol would seem to reduce laminitis risk but the risk of insulin resistance has not been determined.

Intra-articular injection, topical skin treatment and intraocular therapy pose the least laminitis risk as long as the cumulative dose and duration of treatment are not excessive. Although at present a recommendation for a total cumulative intra-articular dose of TMC is not available, a cumulative (total) dose up to 18 mg/horse appears safe. It is clear from the case in UK, however, that dramatically exceeding this dose can have dire consequences. At the time of writing, the American Association of Equine Practitioners is considering raising the cumulative TMC intra-articular dose for racehorses. However, such a dose should not be applied uniformly to all horse groups. A dose that can be safely administered to a young slender racing Thoroughbred may not be as safe when given either to an older, well-fleshed, Warmblood performing in dressage or to other horses likely to be insulin resistant.

Predicting the likelihood of laminitis after glucocorticoid therapy

It would be useful to be able to quantify the laminitis risk before corticosteroid use. Algorithms that include items such as horse age and disease history, drug, dose and route of administration would be one approach, but the database necessary for such an algorithm would require extensive epidemiological investigation. Measurement of plasma insulin concentration might be another approach: the higher the insulin possibly the greater the risk. Finally, a measure of skin sensitivity to corticosteroids could be developed and this might include the change in skin temperature following a small local injection of the therapeutic agent. A similar skin-blanching test is used in man (Wiedersberg *et al*. 2009). All of this will require investment, which is unlikely to occur because, presently, the cost of the occasional case of laminitis does not threaten the equine market for glucocorticoids.

Conclusion

Current research is getting closer to unravelling the mechanisms of action of glucocorticoids and it appears that the newer glucocorticoids and their formulations have long activity at the tissue level. Their genomic effects are tissue dependent and do not necessarily follow the classical ordering of glucocorticoids. Their effects can be associated with vascular dysfunction and interfere with keratinocyte proliferation/differentiation as well as matrix integrity, all mechanisms that possibly could initiate laminitis. Thus selection of clinical cases, choice of drug, dose, route and frequency of treatment should be carefully considered before the start of treatment. However, overall, based on review of clinical reports, comments and use in research settings, it appears that the risk of laminitis after glucocorticoid treatment, especially local use, is acceptable compared to its many benefits.

Acknowledgements

The authors thank Drs Ray Geor and Frank Nickels (Department of Large Animal Clinical Sciences, Michigan State University) for their reviews of this paper.

Authors' declaration of interests

No conflicts of interest have been declared.

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