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Review Article

Review of glucocorticoid therapy in horses. Part 2: Clinical use of systemic glucocorticoids in horses

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Summary

This article is the second in a review series about the use of glucocorticoids to treat medical and musculoskeletal conditions in horses. This segment in the series summarises reported dosages, methods of administration and the efficacy of glucocorticoids for various systemic diseases in equids. The most common use of systemic glucocorticoids reported in the literature for management and treatment of alterations of the respiratory, integumentary, immune and neurological systems are included.

Introduction

Exogenous glucocorticoids have been used to treat a diverse variety of inflammatory conditions in horses due to their potent and rapid effects. The mechanisms of action and the most common glucocorticoids that are used in equine medicine are discussed in a previous review article in this series. The objective of this segment in the series is to summarise reported dosages, methods of administration and the efficacy of glucocorticoids for common systemic inflammatory diseases. The use of glucocorticoids for respiratory, integumentary, immune-mediated and neurological disorders are reviewed.

Respiratory system

Glucocorticoids for recurrent airway obstruction and inflammatory airway disease

Recurrent airway obstruction (RAO), also referred to as heaves and equine asthma, is a chronic inflammatory condition of the lower airways, associated with increased mucus production, contraction of the bronchial smooth muscle and thickening of the airway wall. These changes in the lower airways result in overt increased respiratory effort at rest. The triggering factor for the development of RAO is exposure to organic dust present in the horse's environment (Cornelisse *et al.* 2004). This condition most commonly affects mature horses, and the signs can be reversed with medical therapy and environmental management (Couëtil *et al.* 2007). Inflammatory airway disease (IAD) can affect horses of any age, with subtle clinical signs at rest; however, horses often present with exercise intolerance, poor performance and cough (Couëtil *et al.* 2007). The presence of high eosinophil or mast cell concentrations in the bronchoalveolar lavage fluid (BALF) suggests that aeroallergens might contribute to the development of this condition (Hoffman *et al.* 1998; Couëtil *et al.* 2007).

Recurrent airway obstruction and inflammatory airway disease are the most common airway conditions in horses in which glucocorticoids are used for therapy (Ivester and Couëtil 2014). The use of glucocorticoids for their anti-inflammatory effects, together with bronchodilators and environmental changes, have shown to improve chronic lower airway inflammation in many cases (Léguillette 2003; Couëtil *et al.* 2007; Ivester and Couëtil 2014). In some horses, respiratory conditions such as RAO and IAD can be managed successfully with strict environmental changes in order to minimise allergen exposure, but in cases with significant clinical signs, pharmacological therapy is often necessary to accelerate recovery (Couëtil *et al.* 2007; Ivester and Couëtil 2014). Since inflammation contributes to the pathogenesis of RAO and IAD, it should be considered the main target of therapeutic intervention (Léguillette 2003; Laan *et al.* 2006).

Medications containing glucocorticoids are commonly delivered by either the parenteral, oral or inhalation routes in horses, and the severity of the condition often determines the route of treatment; horses with severe inflammation may require parenteral administration to achieve adequate results. The severity and possible cause of airway obstruction and inflammation can be primarily assessed by analysis of BALF, but cytological analysis of fluid collected by transtracheal wash (TTW) is also useful. Microscopic evaluation of these samples will show the type and amount of inflammatory cells involved in the process and the presence of microorganisms (Léguillette 2003; Hewson and Arroyo 2015). Findings from these diagnostic tests in combination with the clinical examination can determine the treatment of choice. Ideally, before glucocorticoid therapy is utilised, the clinician should determine through physical examination findings, cytological examination of BALF or TTW fluid, possibly culture of a TTW sample, and complete blood count, whether or not an infectious respiratory problem is present (Couëtil *et al.* 2007; Hewson and Arroyo 2015). Glucocorticoids may not be recommended if bacterial infection is present or, at minimum, concurrent antimicrobial therapy may be needed.

Parenteral and enteral use

Enteral or parenteral routes for glucocorticoid administration are usually more economical than inhalation therapy, and no specialised equipment is required. Parenteral use of glucocorticoids, especially i.v., is recommended for acute and severe airway obstruction in cases of RAO until the clinical signs are controlled enough to be able to change to enteral or inhaled therapy (Léguillette 2003). Systemic administration of dexamethasone rapidly improved clinical signs, lung function and percentage of neutrophils in BALF

within 24 h in horses with RAO (Robinson *et al.* 2002). Intravenous use of dexamethasone caused significant improvement in lung function of RAO affected horses within 2 h with a peak effect at 4–6 h (Cornelisse *et al.* 2004). In RAO challenged horses, the use of dexamethasone at 0.1 mg/kg bwt i.v. once daily, when compared to i.m. use of dexamethasone-21-isonicotinate and prednisone orally, was the only treatment that improved the lung function and decreased the percentage of neutrophils in the BALF (Robinson *et al.* 2002).

Dexamethasone is one of the most common glucocorticoids used for treatment of RAO (Cornelisse *et al.* 2004; Couëtil *et al.* 2006). As was mentioned previously, the parenteral route is more efficacious for critical cases, but once the condition is stable, the enteral route is widely used due to the ease of administration (Robinson *et al.* 2002; Grady *et al.* 2010). The injectable formulation approved for i.v. and i.m. use, is commonly prescribed by veterinarians for extralabel use orally, as it is inexpensive and readily available when compared to the dexamethasone powder labelled for oral use (Grady *et al.* 2010). In a pharmacokinetic study, the injectable form of dexamethasone showed to have variable bioavailability, ranging from 28 to 88% (Grady *et al.* 2010), being greater in fasted animals (Cornelisse *et al.* 2004). It should be acknowledged that, according to the Animal Medicinal Drug Use Clarification Act (1994), due to the fact that oral formulations of dexamethasone are available in the market, the extralabel use of the drug is not allowed, unless it has been established by a veterinarian that there is no local availability of the oral form.

Based on efficacy for treatment of human asthma, oral prednisone has been used in the past to treat recurrent airway obstruction in horses; however, Peroni *et al.* (2002) demonstrated that prednisone is poorly absorbed, and its active metabolite prednisolone is rarely produced, with almost no plasma levels detected, therefore its therapeutic use is not recommended in horses. Since prednisone was not detected in serum after oral administration, it is thought that the lack of effectiveness is due to poor intestinal absorption; however, failure of the liver to convert prednisone to prednisolone, and the low affinity of prednisone to plasma proteins such as transcortin warrant further research (Alvinerie *et al.* 1988; Peroni *et al.* 2002). Prednisolone by contrast can be used to treat inflammatory conditions involving the lower airways, and is commonly used to manage RAO in horses. Even though prednisolone is less potent than dexamethasone, it has been shown to improve pulmonary function of affected horses at a 2 mg/kg bwt dose orally once daily after 7 days. However, dexamethasone given orally at a dose of 0.05 mg/kg bwt showed a greater improvement in the pulmonary function after 3 and 7 days of treatment, when compared to prednisolone, even under continuous antigen exposure (Leclere *et al.* 2010).

In the authors' clinical experience, and based on scientific data previously described, for significant exacerbations of inflammatory lower respiratory conditions such as RAO, a positive response has been observed when using dexamethasone i.m. at an initial dose of 0.1 mg/kg bwt once daily for 3–7 days and tapering for a total of 3–4 weeks of therapy (**Table 1**) in conjunction with environmental management. Once the acute phase of the condition has passed (beginning at Week 2–3), treatment is continued with orally administered dexamethasone. A shorter course of dexamethasone (0.1 mg/kg bwt i.m. once daily for 7 days) with no taper may also be effective if comprehensive environmental changes are instituted concurrently (Ivester and Couëtil 2014).

TABLE 1: Recommended dosing schedule with parenteral use of dexamethasone for treatment of recurrent airway obstruction. Duration and dosages may vary depending on the patient's progression

Dose (mg/kg bwt)	Route	Frequency	Duration
0.1*,†	i.m.	Once daily	3 days
0.075	i.m.	Once daily	3 days
0.05‡	i.m.	Once daily	7 days
0.025	i.m. or *per os*	Once daily	7 days
0.025	i.m. or *per os*	Every other day	7 days

*Ivester and Couëtil (2014). †Robinson *et al.* (2009). ‡Leclere *et al.* (2010).

Similar to RAO, successful response to treatment of horses with IAD is better when a combination of both environmental management and medical therapy is utilised. Both systemic and aerosolised glucocorticoids can be used to control the neutrophilic airway inflammation in cases of IAD (Couëtil *et al.* 2007). Positive results have been observed with the use of oral prednisolone at a starting dose of 2.2 mg/kg bwt orally once daily for 7–10 days, then tapering to 1.0 mg/kg bwt once daily for 7–10 days, and then 1.0 mg/kg bwt every other day for 7–10 days; and in general, 2–4 weeks of glucocorticoid therapy is often prescribed for horses with IAD (Couëtil *et al.* 2007; Ainsworth and Cheetham 2010a). In racehorses, oral dexamethasone used at a dosage of 10 mg daily every other day for a total of five doses has showed a positive effect (Berthold and Robinson 2009).

Inhalation therapy

Inhalation therapy for the treatment of lower respiratory tract inflammation in horses such as RAO and IAD is becoming a more common method of treatment. Inhaled glucocorticoids result in less adverse effects for the horse because the therapeutic dose is usually lower, and the drug acts locally within the respiratory system (Lavoie 2001; Rush 2002, 2004). The response to treatment is usually positive within a short period, with significant changes observed after 72 h after initiation of therapy with fluticasone propionate; if combined with bronchodilators, the response can be even faster (Lavoie 2001; Léguillette 2003; Robinson *et al.* 2009; Ivester and Couëtil 2014). Treatment of RAO and IAD with inhaled glucocorticoids is usually accompanied by the use of bronchodilators such as albuterol, salmeterol, fenoterol or pirbuterol.

To administer an aerosolised medication, a special delivery device should be used. The purpose of these devices is to optimise and maximise drug delivery into the lung (Rush 2002; Robinson *et al.* 2009). Some devices consist of a nose piece that adapts over a nostril (**Fig 1a**), while others are a face mask that fits the horse's muzzle (**Fig 1b**).

The efficacy of inhaled drugs depends on the dose and distribution of aerosol deposited locally as well as the potency of the drug. Distribution of an aerosol is determined by particle size, and shape, as well as by patency of the airways and breathing pattern (Rush 2002). Aerosolised

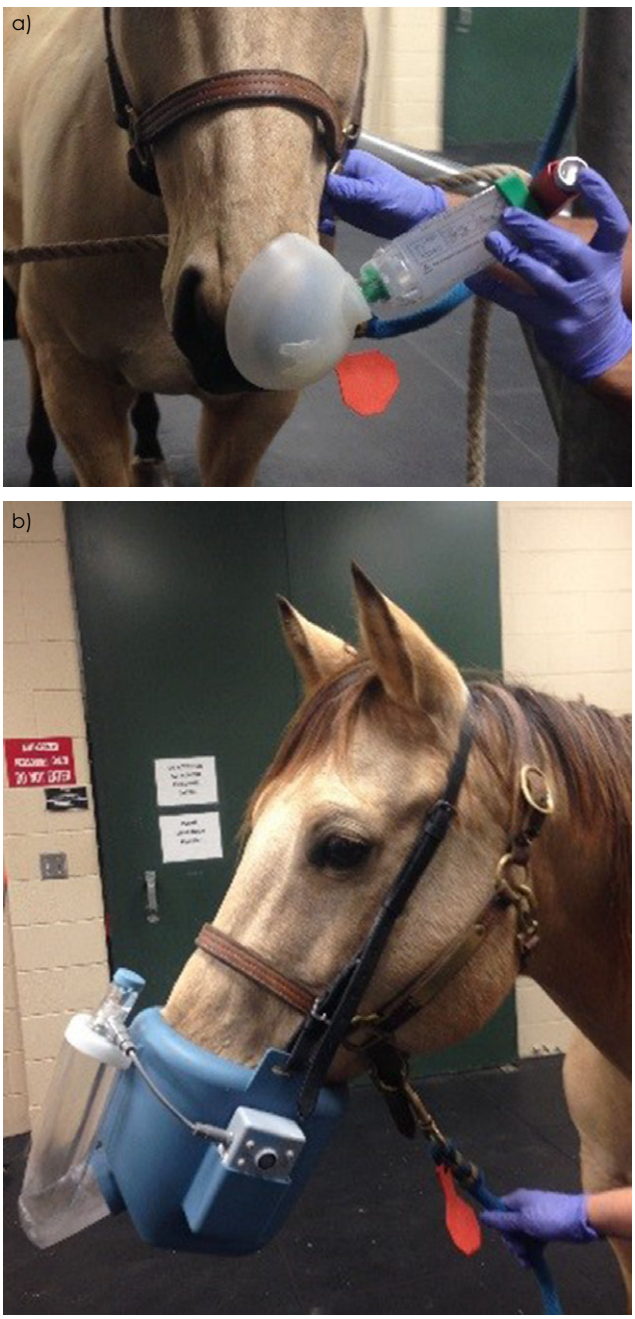

Fig 1: Delivery devices for the administration of inhaled glucocorticoids. a) AeroHippus™ hand-held device, and b) Flexineb™ nebulizer.

particles >10 μm will usually stay in the upper airways, whereas submicron-sized droplets are not deposited but exhaled. This diameter will vary depending on the type of inhalation delivery system and the formulation of the drug (Lavoie 2001). Both Equine Haler and AeroHippus consist of hand-held chambers connected to a nose mask that is placed over one nostril and should be held on the nostril for three respiratory cycles to ensure complete inhalation of the dose (Bertin *et al.* 2011). In contrast, Flexineb equine nebuliser, is a mask type inhaler designed to be used with metered-dose inhalers or wet nebulisation.

Beclomethasone dipropionate is one of the most widely used inhaled glucocorticoids for treatment of human asthma. In horses, beclomethasone use results in marked improvement in respiratory function in horses affected with RAO by decreasing transpulmonary pressure and total pulmonary resistance, and increasing the partial pressure of oxygen (Ammann *et al.* 1998). In a study by Couëtil *et al.* (2006), RAO challenged horses weighing between 341 and 521 kg, were treated with either low dose beclomethasone dipropionate (500 μg every 12 h) for 10 days or one single injection of dexamethasone isonicotinate (0.06 mg/kg bwt i.m.). After 10 days, the horses treated with the inhaler showed significant improvement in respiratory function, when compared with the horses treated with dexamethasone i.m. No changes in BALF cytology or expression of the proinflammatory transcription factors nuclear factor-κB and activator protein-1 were identified in the horses treated with either dexamethasone i.m. or inhaled beclomethasone dipropionate (Couëtil *et al.* 2006). Even though pulmonary function testing responses and clinical signs of airway obstruction improve by administration of beclomethasone, the magnitude of response is less marked than the response of i.m. use of dexamethasone when given by daily injections, comparing at Days 7, 10, 14 and 21 of treatment (Rush *et al.* 1998).

Studies have shown that in horses exposed to a dusty environment, after discontinuation of inhalation therapy with beclomethasone, clinical signs of RAO return within 7 days if the environmental allergen exposure is not minimised (Rush *et al.* 1998; Rush 2004). Unlike human patients, horses are more sensitive to the adrenosuppressive effects of aerosolised beclomethasone. Low dose (500 μg) beclomethasone administration caused similar improvement in pulmonary function, compared with high-dose beclomethasone (1000 and 1500 μg), and caused less suppression of endogenous cortisol production (Rush *et al.* 2000). Adrenal suppression, determined by a decrease in circulating cortisol, is a sensitive indicator of systemic absorption of aerosolised glucocorticoids, and even though the adverse effects of systemic glucocorticoids have not been reported with the use of beclomethasone or fluticasone, these drugs should be used judiciously at the lowest effective dose (Rush *et al.* 2000; Díaz *et al.* 2014; Munoz *et al.* 2015).

Fluticasone propionate is the most potent, most lipophilic, and has the least potential for adrenal suppression of the available aerosolised glucocorticoids (Dauvillier *et al.* 2011). Reported dosages for fluticasone propionate range between 2–4 μg/kg bwt every 12 h (Ainsworth and Cheetham 2010b), which is about 2000 μg for horses weighing between 410 and 535 kg (Lavoie 2001; Dauvillier *et al.* 2011). Dosages of fluticasone propionate can vary from 2000 μg up to 6000 μg every 12 h, depending on the severity of the condition and the horse's bodyweight (Wilson and Robinson 2015). Fluticasone has shown to be effective in prevention and maintenance of RAO; however, for the treatment of acute exacerbations, systemic use of dexamethasone provides a faster and more significant positive effect in pulmonary function (Robinson *et al.* 2009).

Aerosolised glucocorticoids have been shown to induce a dose dependent suppression of endogenous cortisol in horses suggesting that systemic effects may occur (Rush *et al.* 1999). Aged horses with a bodyweight between 419 and 550 kg treated with 2000 μg every 12 h of fluticasone for 6 months

showed a decrease in cortisol concentration; however, concentrations returned to a level similar to baseline values when the dose was given once a day (Díaz *et al.* 2014). This suggests that long-term therapeutic use of aerosolised fluticasone suppresses endogenous cortisol through its action over the hypothalamic–pituitary–adrenal axis. For long-term treatment, the lowest effective dose of fluticasone should be utilised and it should be combined with environmental management (Díaz *et al.* 2014).

Systemic absorption of inhaled glucocorticoids occurs via the respiratory or gastrointestinal tract, and is reflected by the observed adrenal suppression in different studies (Rush *et al.* 1999, 2000; Díaz *et al.* 2014). It has been documented that about 23% of the beclomethasone administered via the metered-dose inhaler is deposited and metabolised in the lower respiratory tract; meaning that the remaining may be absorbed from the lungs to systemic circulation, or swallowed from the nasopharynx (Rush *et al.* 1999). This brings some concerns about possible systemic side effects of circulating glucocorticoids after inhalation therapy; however, no studies have been performed in horses to determine the likelihood of adverse effects after the use of inhaled glucocorticoids.

In man, fluticasone propionate was observed to have poor oral absorption and low systemic bioavailability after intranasal administration, concluding that systemic side effects were unlikely (Daley-Yates and Baker 2001); however, this conclusion must be taken with caution in horses, since they have shown to be more sensitive to adrenal suppression than humans (Barnes 1995). It is important to mention that hygiene must be considered when administering inhaled glucocorticoids, since contaminated delivering devices could be a source for pathogens in the respiratory tract (Duvivier *et al.* 1997; Lavoie 2001). In man, there is a risk of oropharyngeal candidiasis with the long-term use of inhalation therapy, especially in elderly or immunosuppressed human patients (Barnes 1995; Battaglia *et al.* 2015); however, this is not reported in horses. To analyse better the possible side effects due to inhalation therapy with glucocorticoids in horses, studies comparing side effects in different body systems between inhalation and systemic administration need to be performed in horses. Extrapolating from human studies, complications in at-risk-populations of respiratory infections, ocular damage, or bony changes could arise; however, when compared with the use of systemic glucocorticoids, these side effects were less pronounced (Battaglia *et al.* 2015).

Inhalation therapy could be adequate for many horses with IAD, where, unlike horses with RAO, a rapid effect is not needed to control severe bronchospasm in an acute crisis. Fluticasone propionate alone can be used to manage cases of IAD, and a suggested dose for an average sized mature horse is to start at a dose of 2000 μg every 12 h for one week, then 2000 μg once daily for one week, then 1500 μg once daily for another week, followed by 1500 μg every other day until discontinuation; and this treatment is reported up to 3 months in duration (Mazan 2009). In general, the same drugs used for the treatment of RAO are beneficial in cases of IAD; however, a positive effect is observed with lower dosages for shorter treatment durations in horses with IAD. Two to 4 weeks of glucocorticoid therapy is often prescribed (Rush 2002; Couëtil *et al.* 2007).

There is sufficient scientific evidence for the use of glucocorticoids in the management of both RAO and IAD in horses, either by the enteral, parenteral or inhalation route. Dosages have been established based on clinical studies; however, the practitioner will encounter a diverse response depending on the case and management practices, leading to the use of different dosing regimens.

Glucocorticoids for the treatment of interstitial pneumonia

Interstitial pneumonia is a cause of acute or chronic lower respiratory tract disease in horses. Even though infectious organisms or toxins have been implicated in the pathogenesis of the disease, it is often referred to as idiopathic due to the difficulty in identifying a causative agent (Wilkins *et al.* 2015). The inflammation in the lung parenchyma will cause structural changes in the lung, reducing the number of functional alveoli and therefore affecting ventilation. This reduction in lung compliance is associated with the loss of distensible alveoli, the presence of pulmonary oedema and fibrosis (Wilkins and Lascola 2015). Glucocorticoids are thought to work in decreasing the inflammation that precedes the development of fibrous tissue and early and aggressive use may lead to a better long-term outcome for cases of interstitial pneumonia (Spelta *et al.* 2013). The course of therapy is usually prolonged, ranging from 6 to 12 weeks, and is often accompanied by treatment with antimicrobial medications. Treatments described include dexamethasone i.m. or i.v. at 0.02–0.04 mg/kg bwt every 12–24 h, and prednisolone *per os* at 1 mg/kg bwt every 12–24 h (Wilkins and Lascola 2015). Equine multinodular pulmonary fibrosis is a chronic and progressive type of interstitial pneumonia associated with the presence of equine herpesvirus type 5 (Spelta *et al.* 2013; Kessell *et al.* 2014). Since an infectious organism is often the cause of multinodular pulmonary fibrosis in horses, glucocorticoid therapy is sometimes avoided due to its immunosuppressive effects; however, inhibition of the inflammatory response is a key factor to avoid irreversible damage to the lung (Niedermaier *et al.* 2010). Long-term therapy with systemic glucocorticoids in cases of interstitial pneumonia may put the animals at risk for developing gastric ulceration, or delay in healing of already existing ulcers, therefore gastric acid suppression may be indicated for the duration of the treatment (Boothe and Mealey 2012).

Gastrointestinal system

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is characterised by inflammatory cell infiltration of the bowel wall (**Fig 2**). Depending on the inflammatory cells involved, they are classified as granulomatous enteritis (GE), multisystemic eosinophilic epitheliotropic disease (MEED), eosinophilic enterocolitis, lymphocytic–plasmacytic enteritis (LPE) and basophilic enterocolitis (Davis 2009). Infiltration occurs in the mucosa and submucosa, and the cause may be associated with parasitic, infectious or neoplastic processes (Schumacher 2009). Horses will typically present with progressive weight loss and intermittent abdominal discomfort. Diarrhoea may or may not be present, and hypoproteinaemia is common due to intestinal protein loss. The clinical signs are similar regardless of the type of cellular infiltrate (Davis 2009; Schumacher 2009). Definitive diagnosis is based on results of histological examination of an intestinal biopsy specimen (Schumacher *et al.* 2000).

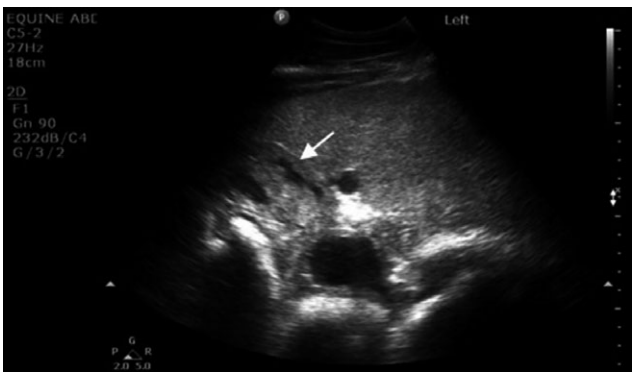

Fig 2: Thickening of the small intestinal wall (arrow) in a case of lymphocytic-plasmacytic enteritis.

Management of mature horses with inflammatory bowel disease is typically unsuccessful long term (Barr 2006). Glucocorticoids are the drugs used most commonly to treat IBD because they reduce intestinal inflammation (Schumacher 2009). Since a prolonged and high dose course of therapy is often required, horses must be monitored for any adverse clinical signs, such as immunosuppression, gastric ulceration or increased susceptibility to infections (Barr 2006). Anecdotally, long-term use of systemic glucocorticoids has been related to the development of laminitis; however, there is no scientific evidence to support this. No relationship was found in a previous retrospective study of horses on long-term therapy with prednisolone and the occurrence of laminitis (Jordan *et al.* 2015).

Even though prognosis for horses with IBD is poor, there are case reports describing that long-term survival and parenteral use of dexamethasone appeared to produce better results (Duryea *et al.* 1997; McCue *et al.* 2003; Carmalt 2004). There are no large studies assessing the efficacy of glucocorticoids in the treatment of IBD using different protocols for each specific type of cellular infiltrate, therefore the presented dosing regimens are based on case reports, with a degree of variability among them.

A prolonged, tapering course of glucocorticoids is recommended, and parenteral administration is initially necessary because absorption of orally administered medication may be poor (Barr 2006; Schumacher 2009). A suggested initial dose for dexamethasone is 0.05–0.1 mg/kg bwt i.m. for 2–4 weeks (Kemper *et al.* 2000; Schumacher 2009); however, most reported cases of IBD in horses have been fatal despite aggressive treatment with glucocorticoids (Schumacher 2009). For some cases, high doses of dexamethasone, up to 0.2 mg/kg bwt once daily, are recommended (Davis 2009). The dosing schedule should be adjusted to meet each horse's needs, tapering or increasing it based on response to the treatment; as well as decreasing or even discontinuing the therapy if there is concern of adverse effects such as laminitis or secondary infections (Kalck 2009). A dosing schedule is described in **Table 2**. The suggested protocol can be adjusted based on clinical response; it is important to evaluate the clinical condition prior to decreasing the medication. Since the protocol for these cases is long and with high doses, owners should be aware of possible adverse effects such as delayed wound healing, gastric ulceration or immunosuppression, as well as the likelihood of relapses, in which case the dosage should be reviewed. In horses in which clinical improvement is noted, maintenance with low doses of dexamethasone from 0.02 to 0.05 mg/kg bwt orally once daily can be attempted; however, signs may re-appear (McCue *et al.* 2003; Barr 2006).

TABLE 2: Treatment for the management of inflammatory bowel disease in horses using dexamethasone

Dose (mg/kg bwt)	Route	Frequency	Duration
0.1	i.m.	Once daily	14–21 days
0.075	i.m.	Once daily	21 days
0.05	i.m.	Once daily	21 days
0.025	i.m. or *per os*	Once daily	21 days
0.025	i.m. or *per os*	Every other day	Maintenance

Adjusted from Kalck (2009).

Prednisolone administered orally from 0.5 to 2.0 mg/kg bwt once daily was proven to be ineffective in the treatment of equine granulomatous enteritis (Woods *et al.* 1993). Even though there is a lack of literature reporting success after treatment of IBD with orally administered prednisolone, the reported dose of this drug ranges from 0.2 to 4.4 mg/kg bwt orally every 12–24 h (Barr 2006; Kaikkonen *et al.* 2014).

Clinical cases of horses with GE and LPE have been reported to respond favourably to treatment with dexamethasone (Duryea *et al.* 1997; Kemper *et al.* 2000). However, in most of the published reports of horses with LPE, affected animals were subjected to euthanasia because of poor condition or lack of response to treatment (Kemper *et al.* 2000; Schumacher 2009). In a case report of LPE in an Arabian gelding, dexamethasone was administered daily starting at 0.1 mg/kg bwt i.v.; the dose was tapered by 10 mg weekly until a dose of 10 mg was reached. During the treatment, clinical signs improved for short periods and then returned, so the horse was ultimately subjected to euthanasia (Barr 2006). Another report of treatment of GE was reported to respond to long-term treatment with dexamethasone administered i.m., starting at 40 mg and tapering over a 16-week period. Five months after discontinuation of therapy, the horse was brighter and back to normal activity (Duryea *et al.* 1997).

There are several reports of horses with MEED being successfully treated with glucocorticoids. In one report, there was a positive response to treatment, initially with dexamethasone administered i.v., followed by subsequent oral administration; the horse was reported to remain clinically normal after discontinuation of treatment (Carmalt 2004). Another horse was treated with low doses of dexamethasone starting at 0.1 mg/kg bwt i.v. once daily and tapered to 0.018 mg/kg bwt once daily until treatment was stopped at Day 52. The horse was followed for 17 months and dexamethasone was adjusted intermittently based on appearance of eosinophilia (Carmalt 2004). In a case report of MEED in which the horse showed clinical improvement for at least 18 months, it was determined that the minimum effective dose of dexamethasone was 0.03 mg/kg bwt i.v. every 24 h for 14 days, after which it was gradually decreased (McCue *et al.* 2003).

Since the type of cellular infiltrate varies among cases of IBD, it may be inappropriate to compare the response to treatment among them (Kalck 2009). It is therefore important to mention that even though some dosing regimens are

provided, due to the complexity of this condition, and the high variability in responses, dosing frequency and duration often have to be adjusted.

Integumentary system

Insect bite hypersensitivity

Insect bite hypersensitivity (IBH) is the most common cause of pruritus in horses, and reaction to bites by various *Culicoides* spp. gnats is the most well documented cause (Petersen 2009; Stepnik *et al.* 2012). IgE-mediated, type I hypersensitivity with release of histamine and other inflammatory mediators are often involved in IBH. However, in some horses, cell-mediated, type IV hypersensitivity may also contribute to the pathogenesis (Jonsdottir *et al.* 2015). Common signs include pruritus and papules, usually observed along the dorsum, mane, rump and tail base. Histologically, the lesions are characterised by mixed perivascular to diffuse cellular infiltrates consisting of mononuclear cells and eosinophils in acute lesions (Schaffartzik *et al.* 2012). Intradermal testing (IDT) has been used in horses as a diagnostic tool for conditions such as IBH, urticaria, or RAO. It is known that horses with clinical signs of *Culicoides* hypersensitivity have stronger IDT reactions than healthy horses do, which is an advantage when immunotherapy is considered to prevent flare-ups of the condition (Jose-Cunilleras *et al.* 2001).

Decreasing exposure to insects is the most important management practice; however, severely affected horses, particularly those with marked pruritus, may need anti-inflammatory treatment with systemic glucocorticoids (Rees 2005; Petersen 2009; Schaffartzik *et al.* 2012). Prednisolone at 1 mg/kg bwt orally every 24 h or dexamethasone at 0.05–0.1 mg/kg bwt orally once daily can be used until pruritus and self-trauma are controlled, at which point the dose is tapered to the lowest dosage that controls pruritus (Pilsworth and Knottenbelt 2004; Petersen 2009). In severe cases, prednisolone can be administered at 2 mg/kg bwt orally once daily for 3–10 days until the pruritus is controlled, followed by tapering to 0.5 mg/kg bwt every other day (Marsella 2013). Glucocorticoid therapy should be discontinued as soon as the biting season has passed (Pilsworth and Knottenbelt 2004). It is important to mention that despite medical therapy or environmental management, equine insect hypersensitivity is a seasonal and recurrent condition, with no long-term cure. Based on results of IDT, hyposensitisation injections are useful in preventing this condition or any other atopic dermatitis. Injections are usually recommended for at least one year, and continue thereafter based on the clinical response of the patient (White 2015). The aim of the therapy is to control and prevent acute exacerbations (Pilsworth and Knottenbelt 2004; Ferroglio *et al.* 2006).

Atopic dermatitis

Atopic dermatitis is an IgE mediated type I hypersensitivity response to environmental allergens. The condition may be seasonal or nonseasonal, depending on the allergens involved (White 2015). Clinical signs of atopic dermatitis in horses may include urticaria and/or pruritus; usually affecting the face, distal legs or trunk (White 2005). The most effective way to prevent and control this condition is by identifying the triggering allergens and reducing exposure.

In clinical cases, the response to glucocorticoids is usually prompt and administration of dexamethasone at a dose of 0.05 mg/kg bwt may result in complete resolution (White 2015). For cases requiring ongoing therapy, once daily administration of 1 mg/kg bwt of prednisolone orally, followed by gradual reduction of the dose, proved to be effective with a low likelihood for adverse effects (Littlewood 2011). Resolution of the pruritus or urticaria has been achieved by the use of prednisolone at 200–400 mg/500 kg administered orally once daily, or dexamethasone at 0.05–0.1 mg/kg bwt, either by the enteral or parenteral route, once daily (White 2005).

Vasculitis

Vasculitis is a histopathological term that implies the presence of inflammatory changes in the walls of blood vessels, and it is associated with a broad spectrum of disorders. In horses, vasculitis is most often seen as a feature of drug reactions, urticaria, photosensitisation or purpura haemorrhagica (White *et al.* 2009).

Glucocorticoids have been recommended in the treatment of equine cutaneous vasculitis due to both their anti-inflammatory and immune-suppressive effects (White 2014). The use of prednisolone at 1 mg/kg bwt given orally twice daily or dexamethasone at 0.08–0.2 mg/kg bwt once daily have been described in a retrospective study (White 2009). The previously mentioned glucocorticoid treatment was administered for 2 weeks, and then tapered over the next 4–6 weeks. In this study, the clinical response was variable, and recurrence of the condition was observed in approximately 25% of the cases (White 2009).

Purpura haemorrhagica is characterised by leucocytoclastic vasculitis leading to extensive oedema and haemorrhage of the mucosa and subcutaneous tissue (**Fig 3**). The disease has been recognised as a sequela to infection or exposure to *Streptococcus equi* ssp. *equi*, *Streptococcus zooepidemicus*, *Rhodococcus equi* and *Corynebacterium pseudotuberculosis* (Knottenbelt 2002). Immune complexes primarily composed of IgM or IgA and streptococcal M protein may be present in capillaries, leading to a type III hypersensitivity reaction. Prolonged treatment with glucocorticoids (2–4 weeks) has resulted in a favourable outcome and low relapse rate (Kaese *et al.* 2005). Depending on the severity of clinical signs, the proposed dosage is 0.04–0.2 mg/kg bwt of dexamethasone once or twice daily or 0.5–1.0 mg/kg bwt of prednisolone orally once or twice daily, with a gradual reduction of the dosage (Aleman and Watson 2015a). Doses of prednisolone as high as 2 mg/kg bwt twice daily have been used for prolonged periods (Kaese *et al.* 2005).

Pemphigus foliaceus

Pemphigus foliaceus is an autoimmune disorder characterised by the production of autoantibodies and histologically by intraepidermal acantholysis. The clinical lesions recognised in horses are primarily scaling and crusting (Vandenabeele *et al.* 2004). The recommended treatment is glucocorticoids, such as prednisolone at 1 mg/kg bwt orally every 12–24 h or dexamethasone at 0.08–0.1 mg/kg bwt orally once daily, then tapering (White 2009). In a retrospective study, horses with pemphigus foliaceus were reported to have been in remission for 1–3 years, some of them receiving medications for up to 12 months (prednisolone 0.5–1 mg/kg bwt orally every other day)

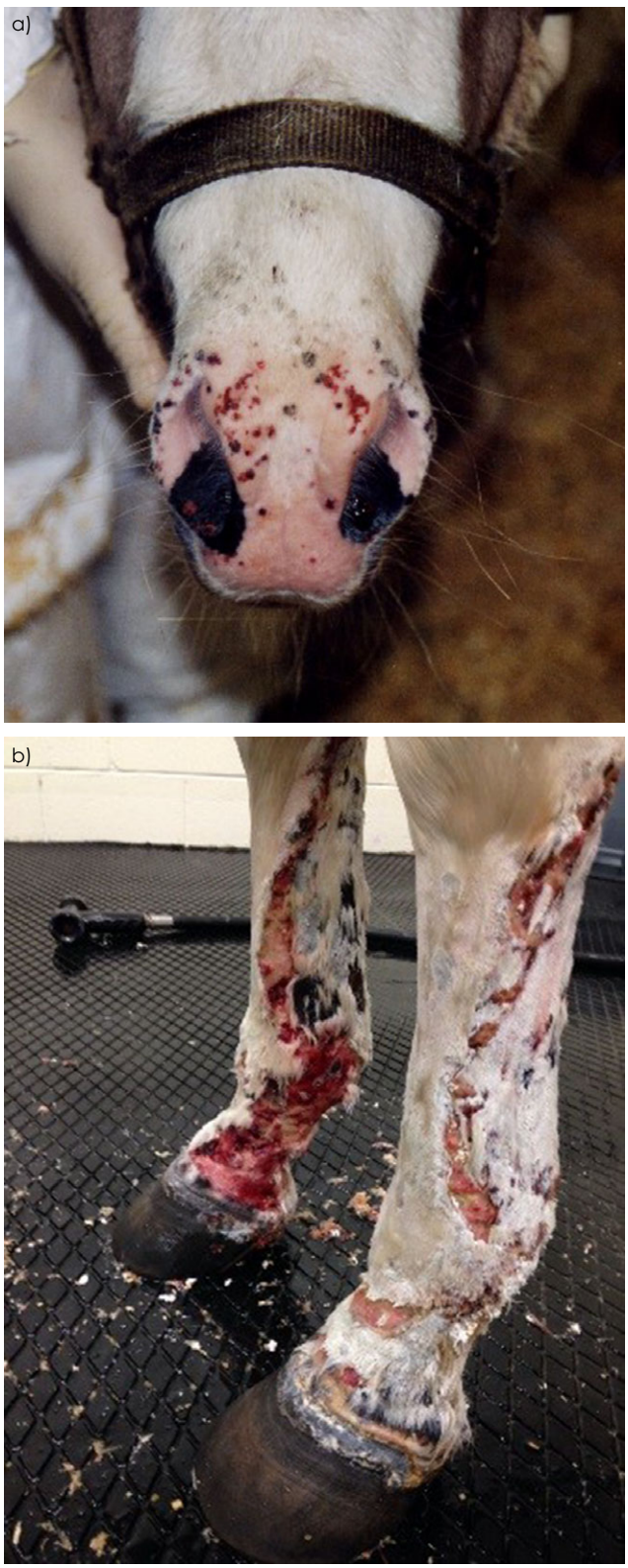

Fig 3: Lesions characteristic of purpura hemorrhagica in horses, showing haemorrhage in the muzzle region (a), and lesions on the limbs with vasculitis, necrosis and exudate (b, photography courtesy Dr Sarah Ujvari).

(Vandenabeele *et al.* 2004). The prognosis following treatment for pemphigus foliaceus in horses is guarded, and the response varies (White 2009). Many horses require lifelong administration of medication to control the clinical signs, others may be gradually weaned from medication without further relapse (White 2009).

Nervous system

The use of glucocorticoids for conditions involving the central nervous system is controversial. There is a lack of evidence for benefits of glucocorticoid use in large animals, and recommendations have been extrapolated from humans and small animals. The use of these drugs is based on the fact that they are thought to stabilise microvasculature permeability, reduce oedema formation, reduce intracranial pressure and decrease oxygen-derived free radicals (Dowling 2004).

Infectious conditions

The use of glucocorticoids to treat cases of equine encephalitis (eastern, western, Venezuelan, equine herpesvirus 1 and West Nile virus) and equine protozoal myeloencephalitis (EPM) remains controversial, since all of these conditions are caused by infectious organisms (Long 2014). In immunosuppressed horses, there is a concern about recrudescence of infection and clinical relapse with the use of glucocorticoids in these conditions (Dirikolu *et al.* 2013; MacKay 2015). However, in addition to the supportive care, treatment of inflammation associated with these diseases is described using dexamethasone at a suggested doses of 0.05–0.1 mg/kg bwt administered i.v. or i.m. once or twice daily for 1–3 days (MacKay 2015). For cases of EPM, the available literature recommends that use of glucocorticoids should be reserved for horses that exhibit signs of brain involvement or recumbency; and dexamethasone at a dose of 0.1 mg/kg bwt i.v., once or twice daily for the first several days has been described (Howe *et al.* 2014; Reed *et al.* 2016). It has been also suggested to restrict the use of glucocorticoids to 1–3 days of treatment with dexamethasone at 0.05 mg/kg bwt every 12 h only in horses severely affected by EPM (Dirikolu *et al.* 2013). However, there is no scientific evidence demonstrating any positive effect after the use of systemic glucocorticoids for treatment of EPM. Long-term glucocorticoid treatment should be avoided due to the effects upon immune clearance of the causative agent (Dubey *et al.* 2015).

The use of glucocorticoids in horses with bacterial meningitis is controversial, with diverse results among studies in species other than horses. One human study showed that there is a benefit in survival rate in adults affected with bacterial meningitis with the use of dexamethasone in the acute phase of the disease (Fritz *et al.* 2012). However, a clinical trial in 2029 human patients with bacterial meningitis showed no significant reduction in death or neurological disability between dexamethasone and placebo treated groups (van de Beek *et al.* 2010). In a retrospective study of 28 horses with meningitis and meningoencephalomyelitis, treatment with a single dose of dexamethasone (dose not recorded) was reported for five of the horses. No significant difference in outcome was found with this therapy; however, the small sample size was a limitation in the study (Toth *et al.* 2012).

A positive outcome was reported in a case report of presumed parasitic encephalitis, in which recovery was observed after treatment with dexamethasone at 0.1 mg/kg bwt i.v. once daily for 5 days, along with anthelmintic and antimicrobial medications (Wilford *et al.* 2013).

Head trauma

The use of glucocorticoids in horses with head trauma remains controversial, and effects such as reduction of cerebral oedema, improvement in brain perfusion and membrane stabilisation, are the main suggested purposes of their use (Nout 2010; Hurcombe 2015). The effect of treatment with glucocorticoids in cases of head trauma remains unclear, and it is no longer recommended in human patients, based on clinical trials showing an increase in short- and long-term mortality in adults treated with steroids after traumatic head trauma (Czekajlo and Milbrandt 2005; Edwards *et al.* 2005). There is no evidence that glucocorticoids improve the outcome or reduce human intracranial pressure (Bullock and Povlishock 2007). In horses, the use of dexamethasone, prednisolone, and methylprednisolone is reported in cases of head trauma, and a retrospective study showed that dexamethasone was the most commonly used at a dose ranging from 0.03 to 0.08 mg/kg bwt administered i.v. (Feary *et al.* 2007). In this study, there was lack of evidence to support the use of this treatment in horses, where associations between treatments and nonsurvival were not performed (Feary *et al.* 2007). Another source suggests the use of dexamethasone at a dose of 0.1–0.2 mg/kg bwt i.v. every 6 to 8 h for the first 24 h after the head trauma, and then once daily for 2–3 days; however, the value of this treatment protocol is uncertain in horses with a noninflammatory cerebral injury (Divers 2008).

Spinal cord injury

The use of glucocorticoids is controversial in cases of acute, severe human spinal cord injury; only small neurological improvements have been demonstrated with methylprednisolone used shortly after the acute onset of clinical signs (Bracken *et al.* 1992). Methylation increases the lipophilic characteristics of methylprednisolone, enhancing cell penetration. It has been observed in man that plasma concentrations are linear and proportional to the dose, and not determined by plasma protein binding as it occurs with prednisolone; even though the chemistry of both drugs is the same, these characteristics give methylprednisolone increased efficacy in the face of plasma protein variations (Rohatagi *et al.* 1997). Similarly in horses, the use of glucocorticoids for spinal trauma remains controversial, and if they have any benefit, it is likely in the acute stage and should be given early (Hurcombe 2010). The use of methylprednisolone sodium succinate, 10–30 mg/kg bwt i.v. within 1 hour from trauma, has been described; however, its use is rare and there are no reports describing the efficacy (Divers 2008). Another source described the use of methylprednisolone sodium succinate as a bolus of 25 mg/kg bwt i.v. shortly after the spinal cord trauma, followed by a constant rate infusion at 5–8 mg/kg bwt/h i.v. for 23 h (Hurcombe 2015). Reported dosages of dexamethasone for spinal cord trauma range from 0.1 to 0.3 mg/kg bwt i.v. every 6–24 h for 2–4 days (Divers 2008; Nout 2010). The main purpose of the therapy with dexamethasone is to reduce inflammation, thereby decreasing cytokine release and free radicals (Nout 2010).

Based on a pharmacokinetics study comparing dexamethasone and prednisolone after i.v. and i.m. administration in horses, it was determined that dexamethasone has a higher volume of distribution and longer half-life, which are desired characteristics when trying to reach therapeutic drug concentrations in tissues (Toutain *et al.* 1984). It is then inferred that dexamethasone will be the drug of choice if glucocorticoid administration is elected to treat head or spinal cord trauma, followed by methylprednisolone.

For cases of cervical vertebral stenotic myelopathy (CVSM), glucocorticoids may reduce the oedema associated with spinal cord compression, and provide transient improvement of the clinical signs; however, full recovery, if feasible, will not be achieved without dietary or surgical intervention (Rush 2009). In one retrospective study, there was a report of horses treated with flunixin meglumine at 1 mg/kg bwt orally every other day alternated with dexamethasone at 0.02 mg/kg bwt orally every other day for 30 days; and when compared to other types of treatments such as vitamin E supplementation, dimethyl sulfoxide, dietary changes, osteoarthritis medications, and exercise restriction, there was no significant effect on prognosis (Hoffman and Clark 2013). Another retrospective study showed clinical improvement in 3 out of 5 horses with CVSM treated with glucocorticoids by referring veterinarians; a total of 22 cases of CVSM were analysed, but neither the name of the medication, dosages nor duration of therapy was provided (Levine *et al.* 2007).

Other systemic uses of glucocorticoids

Immune-mediated haemolytic anaemia

Immune-mediated haemolytic anaemia is associated with the production of autologous antibodies directed against the animal's own red blood cells. It can occur as a primary idiopathic disorder, but it is more often associated with another primary disease process. Secondary autoimmune haemolytic anaemia in horses has been associated with conditions such as purpura haemorrhagica, lymphoma, chronic bacterial infections and medications, especially procaine penicillin (Weiss and Moritz 2003; Carlson 2009; Cottle and Hughes 2010; Johns *et al.* 2011).

Glucocorticoids are often used to disrupt the immune response, and a suggested therapy is the use of dexamethasone at an initial dose of 0.05–0.1 mg/kg bwt every 24 h for a 450 kg horse, given parenterally. This dose can be continued for 3–5 days, then decreased gradually over 7–14 days (Carlson 2009). If there has been no response in 5–7 days, the diagnosis should be reviewed. Once the haemolytic process is under control, treatment can be transitioned to orally administered prednisolone at a dosage of 0.8–1 mg/kg bwt once daily (Carlson 2009). Dexamethasone at 0.04–0.06 mg/kg bwt i.v. given once daily has been reported to be effective in cases of immune-mediated haemolytic anaemia secondary to *Rhodococcus equi* pneumonia in foals, together with antimicrobial treatment and supportive care; and once the clinical condition improved, the dexamethasone was tapered over a 25 day period (Johns *et al.* 2011). It is important to determine if the cause of the immune-mediated process is the use of a medication that needs to be discontinued, or an infectious

process, in which case the therapy should be directed at the primary agent and glucocorticoids might be contraindicated (Carlson 2009; Cottle and Hughes 2010). Response to glucocorticoid therapy is usually positive (Carlson 2009; Johns *et al.* 2011); however, in a report of a case of immune-mediated anaemia and thrombocytopenia, there was no response to doses as high as 0.2 mg/kg bwt i.v. once daily of dexamethasone, and the animal was subjected to euthanasia (McGovern *et al.* 2011; Väänänen *et al.* 2013).

Neoplasia

Lymphoma is one of the most common malignant neoplasms in the horse and originates from the lymphoid system (Taintor 2015). Neoplastic lymphocytes may arise from reactive B-cell clones producing antibodies responsible for gammopathies and immune-mediated processes. Lymphomas of B-cell, T-cell, and mixed B- and T-cell origin have been reported (Rendle *et al.* 2012). Equine lymphoma is classified as multicentric or generalised, alimentary, mediastinal, cutaneous, and solitary tumours of extranodal sites. Clinical signs may vary depending on the organs involved, however, horses more commonly present with weight loss, anorexia, or lethargy (Taintor 2015).

Glucocorticoids for treatment of lymphoma have been used alone or in conjunction of chemotherapeutic agents. In a case report of a horse diagnosed with a T-cell rich, B-cell lymphoma, cyclophosphamide and vincristine were used with dexamethasone at 0.04 mg/kg bwt orally on Day 1, and then decreased to 0.02 mg/kg bwt orally once daily from Day 2 to 30; this protocol was followed by the use of acyclovir, due to the horse testing positive for equine herpesvirus-5. The outcome was positive and one year after initiation of therapy the horse was reported to be in remission and had returned to its normal activities (Vander Werf and Davis 2013). Another protocol used prednisolone at 1.1–2.2 mg/kg bwt orally every 24 h, with the concomitant use of cyclophosphamide and cytosine arabinoside (Taintor and Schleis 2011). The duration of the glucocorticoid therapy is usually the same as the duration of the chemotherapy. Most of the chemotherapeutic protocols range from 2 to 3 months, then followed by a maintenance protocol consistent of gradual decreases of prednisolone (Aleman and Watson 2015b). Recurrence of the clinical signs are often observed once the therapy is discontinued (Taintor and Schleis 2011; Aleman and Watson 2015b). Therapy may be also attempted with glucocorticoids alone; using dexamethasone at 0.2 mg/kg bwt orally or i.v. once daily for 5 days, followed by prednisolone 1–2 mg/kg bwt orally once daily; however, the clinical response in affected horses after the use of this protocol was not described (Aleman and Watson 2015b). Treatment of a horse diagnosed with an angiotrophic T-cell lymphoma using one dose of dexamethasone at 0.1 mg/kg bwt i.v., followed by 10 days of prednisolone at 1 mg/kg bwt orally once daily, failed to respond to therapy and had a fatal outcome (Raidal *et al.* 2006).

Although some periods of remission have been reported, the long-term prognosis for this condition has been poor, and glucocorticoid treatment in cases of lymphoma rarely ameliorate the clinical condition, even with the concomitant use of chemotherapeutic drugs (Raidal *et al.* 2006). Due to the low number of reported cases treated with chemotherapy, there is limited information available, and dosages are extrapolated from other species. Pharmacokinetic studies in horses are needed to incorporate proper usage of these drugs. It is also difficult to assess the effect of the glucocorticoids in cases of remission, since chemotherapy was used concomitantly; therefore, studies using glucocorticoids alone are necessary to make conclusions.

Conclusion

Glucocorticoids are known to be drugs with a potent and rapid effect to decrease inflammation and are successfully used to treat many systemic inflammatory conditions in horses. Adverse effects such as delayed wound healing, immunosuppression, laminitis, gastric ulceration or adrenal suppression have been linked to the treatment with glucocorticoids, especially with higher doses or long duration of therapy (Flaminio *et al.* 2009; Bailey 2010; Ivester and Couëtil 2014). There is little scientific evidence to support some of the attributed adverse effects of glucocorticoids in horses, such as the development of laminitis, which is based on anecdotal case reports (Bailey 2010). A study showed no correlation between treatment with glucocorticoids and the occurrence of gastric ulcers in racehorses (Murray *et al.* 1996); however, glucocorticoid therapy increases the risk of gastric ulceration in human patients and small animals (Boothe and Mealey 2012; Filaretova *et al.* 2014). More studies to identify the risk for the development of gastric ulcers in horses after high doses or prolonged therapies with glucocorticoids are warranted. Depending on the condition to be treated and the severity, there is a wide variation of dosages among the literature reviewed, and the decision whether or not to use steroidal anti-inflammatory medications should be supported by historical and physical examination findings, and laboratory data and followed by close monitoring (Ivester and Couëtil 2014).

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