

## Review Article

# A review of equine sarcoid

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## Summary

**Equine sarcoid is the most common tumour of horses and accounts for over half of all equine skin tumours. Six types of sarcoid based on gross appearance and clinical behaviour have been described including occult, verrucous, nodular, fibroblastic, mixed and malevolent. Common locations for sarcoid development include the periocular region, ear pinnae, lips, neck, extremities and ventrum (including groin region). Bovine papillomavirus (BPV) is causally associated with equine sarcoid with genetic haplotype, fly vectors and skin trauma identified as potential risk factors for development of the disease. Histopathology is required for definitive diagnosis of equine sarcoid but incomplete excision is thought to activate latent BPV and stimulate growth. Although there are no uniformly effective treatment options, several modalities have been successful in eliminating or managing equine sarcoid. Surgical excision, intratumoural chemotherapy, cryotherapy, hyperthermia, radiotherapy, immunotherapy and immune modulators are used with degrees of success relative to the accessibility and invasiveness of the tumour. Prevention of equine sarcoid may be facilitated by future development of vaccines against bovine papillomavirus.**

## Introduction

Sarcoids are locally invasive, fibroblastic skin tumours and represent the most common tumour in equids worldwide (Ragland *et al.* 1970; Cotchin 1977; Marti *et al.* 1993), with an incidence ranging from 12.5 to 67% of all neoplasms (Baker and Leyland 1975; Sullins *et al.* 1986). Sarcoids are classified according to their gross appearance and clinical behaviour. There are 6 distinct types of sarcoid based on gross appearance and behaviour including occult, verrucous, nodular, fibroblastic, mixed and malevolent (Knottenbelt *et al.* 1995; Pascoe and Knottenbelt 1999). Occult sarcoids are flat and alopecic with mild scaling. Verrucous sarcoids are wart-like and have a raised, scaly, lichenified appearance with epidermal thickening. Nodular sarcoids are firm, well defined, subcutaneous lesions while fibroblastic sarcoids are fleshy and ulcerated with local infiltration. Mixed sarcoids may include any, or all, of the aforementioned types and often become progressively more aggressive as fibroblastic transformation occurs. Finally, malevolent sarcoids are the most infrequent form and are aggressive, invasive tumours that proliferate rapidly and may spread along fascial planes and vessels. Sarcoids can develop in any location, either as a single tumour or as multiple tumours of different type (Fig 1). The most common locations for sarcoid development include the head (periocular region, ear pinnae and lips) and neck (39%), extremities (35%) and ventrum (26%) (Miller and Campbell 1982;

Sullins *et al.* 1986; Knottenbelt and Kelly 2000). Inactive sarcoids may become aggressive if disrupted by injury, biopsy or inappropriate treatment. Although sarcoid tumours do not metastasise they can significantly impact the function and aesthetics of affected equids based on tumour location, size and frequency. Thus, the value of sarcoid-bearing equids is often dramatically decreased. Sarcoid tumours may cause discomfort and can result in ulceration, infection and occasionally lameness associated with lesion location.

## Aetiology

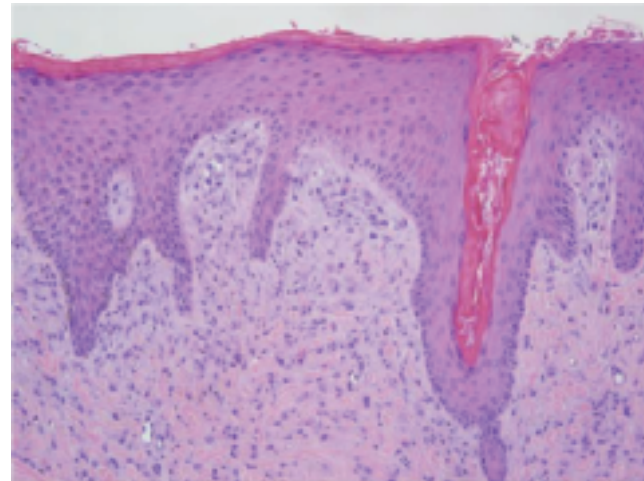
Bovine papillomavirus (BPV) types 1 and 2 are causally associated with the development and pathogenesis of equine sarcoids which represent the only known cross-species papillomavirus infection (Lancaster *et al.* 1979; Gorman 1985; Nasir and Campo 2008). Bovine papillomavirus DNA has been detected in up to 100% of examined sarcoid tumours (Otten *et al.* 1993; Carr *et al.* 2001a,b; Martens *et al.* 2001a,b; Bogaert *et al.* 2007). The majority of these studies report a predominance of BPV-1 DNA compared to BPV-2 DNA which may reflect geographical location (Angelos *et al.* 1991; Otten *et al.* 1993; Martens *et al.* 2001b; Bogaert *et al.* 2007; Wobeser *et al.* 2010). In addition, viral oncogenes and capsid gene transcripts have also been identified in sarcoids, providing evidence for direct involvement of BPV in the pathogenesis of sarcoids (Nasir *et al.* 1999; Carr *et al.* 2001b; Chambers *et al.* 2003). Very recently, intradermal injection of BPV-1 resulted in transient sarcoid-like lesions in foals (Hartl *et al.* 2011). Finally, there is a significant correlation between intratumoural BPV load and disease severity (Haralambus *et al.* 2010).

Although it is widely accepted that BPV infection is necessary for sarcoid development, infection alone is not sufficient for tumour production (Bogaert *et al.* 2005, 2008). Quarter Horses, Arabians and Appaloosas have an increased risk (Angelos *et al.* 1988), suggesting a breed predilection. The increased prevalence of sarcoids in related equids has been previously reported (Ragland *et al.* 1966). Horses with certain equine leucocyte antigen (ELA) haplotypes appear to be at higher risk for development of sarcoids (Lazary *et al.* 1985; Meredith *et al.* 1986; Brostrom *et al.* 1988). Specifically, the frequency of the ELA W13 allele in sarcoid-bearing equids is high and indicates a significant risk, but the overall low incidence of sarcoid tumours in the horse population supports the evidence that other factors are involved. Sites of skin trauma or open wounds are more likely to become affected by a sarcoid (Sundberg *et al.* 1977) but the reason for this is unclear. A proposed mechanism is that flies or other insects may act as vectors of BPV in disease transmission between animals. There is little known about disease transmission in



**Fig 1: a) Verrucous b) fibroblastic and c) mixed sarcoid in a 24-year-old Thoroughbred gelding.**

horses. Early studies showed that transient sarcoid-like tumours can be induced if purified BPV or bovine wart extract is injected intradermally into horses (Olson and Cook 1951; Ragland and Spencer 1969; Lancaster *et al.* 1977). However, BPV-1 variants found in most sarcoids are not present in cattle papillomas (Nasir *et al.* 2007) suggesting that transmission may



**Fig 2: Haematoxylin & eosin stained photomicrograph of equine sarcoid characterised by disorganised neoplastic fibroblasts in the dermis with epidermal proliferation including long rete pegs (200x magnification).**

occur between equids and not between cattle and horses. Recently, BPV-1 DNA was detected in flies trapped in the proximity of sarcoid-bearing equids, suggesting that flies may be able to transmit BPV-1 between horses (Finlay *et al.* 2009). Further research is warranted to elucidate the pathogenesis of this disease.

### Diagnosis

Differential diagnoses for equine sarcoid include granulation tissue, granuloma, papilloma, fibroma/fibrosarcoma, cutaneous lymphoma, squamous cell carcinoma (SCC), habronemiasis, mast cell tumour, melanoma and staphylococcal folliculitis (Sullins *et al.* 1986; Foy *et al.* 2002). A presumptive diagnosis of equine sarcoid is often based on clinical appearance, and the presence of more than one lesion with characteristics of sarcoid is strongly suggestive. A definitive diagnosis of sarcoid requires histopathology but biopsy-induced trauma or irritation may exacerbate the lesion and induce proliferation (Knottenbelt 2003). Therefore, a biopsy is recommended only if the diagnosis is uncertain due to atypical appearance or anatomical site, and only when owners are aware that subsequent treatment will be warranted if a sarcoid is confirmed. Typical histopathological characteristics of equine sarcoid include epidermal acanthosis, hyperkeratosis and hyperplasia with long rete pegs into the dermal fibroblastic tissue which contains immature fibroblasts with mitotic figures in a whorled fibrocellular mass (Fig 2) (Sullins *et al.* 1986; Martens *et al.* 2000; Hewes and Sullins 2009). Histopathologically, equine sarcoid may be confused with fibroma or fibrosarcoma; therefore, an experienced pathologist is often required for an accurate diagnosis.

### Treatment

Currently, there is no uniformly effective therapy for equine sarcoid. Surgical management (including conventional excision and carbon dioxide [CO<sub>2</sub>] laser excision), cryotherapy, hyperthermia, radiotherapy, chemotherapy, immunotherapy, topical immune modulation and antiviral agents are used with variable degrees of success.

### Conventional excision

Tumours that are easily accessible and in a location such that skin closure is possible are often treated with conventional surgical excision. It is critical that wide margins (2–3 cm) be removed to prevent recurrence due to inadequate removal of all extensions of the sarcoid into surrounding tissue (Carstanjen *et al.* 1997; McCauley *et al.* 2002). Because this is often difficult to achieve, conventional surgical excision alone has yielded success rates of 30–50%, with most tumours recurring within 6 months (Genetzky *et al.* 1983; McConaghy *et al.* 1994; Knottenbelt and Kelly 2000). Recurrent tumours are often aggressive and regrow more rapidly than the initial tumour (Tarwid *et al.* 1985; McConaghy *et al.* 1994). This effect may be due to latent BPV present in normal skin that is disrupted and activated by surgical trauma (Carr *et al.* 2001a; Bogaert *et al.* 2008). It is recommended that focal recurrences at the suture line be addressed while they are still very small (Hewes and Sullins 2009).

### Laser removal

A CO<sub>2</sub> laser is a surgical instrument that cuts and vaporises soft tissue with minimal intraoperative haemorrhage and less post operative oedema and pain compared to scalpel blades (Palmer 1989, 1996). A success rate of 60–80% has been reported when the laser is used to cut and vaporise sarcoid tumours (Vingerhoets *et al.* 1988; Carstanjen *et al.* 1997; Martens *et al.* 2001c; McCauley *et al.* 2002). This relatively high success rate is likely due to careful selection of horses for treatment, the wide margin of normal skin that was resected and limited disruption of quiescent tumour cells compared to scalpel excision. Regardless of surgical method, the difficulty in completely resecting sarcoid tumours, especially those in the periorbital region, often necessitates other treatment options for primary or adjunctive therapy.

### Cryotherapy

Cryotherapy involves application of liquid nitrogen at -196°C, either by spray or probe, to destroy tumour cells through the formation of intracellular ice and subsequent rupture of cell membranes. Thermocouples should always be used to monitor the temperature and depth of the freeze. Typically, 3 freeze-thaw cycles that decrease the tissue temperature to -20° to -30°C should be applied to each tumour (Hewes and Sullins 2009). It is also recommended that normal appearing tissue within 0.5–1 cm of the tumour be treated to decrease the chance for recurrence. Sloughing of tissue will occur 2–4 weeks after cryotherapy and tissue depigmentation may remain for 6 or more months. Repeated treatments may be required for large or recurrent lesions and post treatment complications may include damage to nearby tissue and extreme scar contraction. Overall, a success rate of approximately 70–80% has been previously reported for cryotherapy following surgical debulking of sarcoids (Lane 1977; Fretz and Barber 1980; Martens *et al.* 2001c). Tumour recurrence is more likely for periorbital sarcoids (Knottenbelt and Kelly 2000) because achieving full freezing in this area may be more difficult.

### Hyperthermia

Hyperthermia has been reported to induce regression for at least 7 months in 3 cases of equine sarcoid (Hoffman *et al.* 1983). For treatment of equine cutaneous neoplasia, a

radiofrequency hyperthermia device is held against the tumour tissue and heated to 50°C for 30 s. Tumour cells are preferentially destroyed as neoplastic cells with a disorganised and compact vascular structure have difficulty dissipating heat. Hyperthermia may therefore cause tumour cells to undergo apoptosis in direct response to applied heat, while healthy cells can more easily maintain a normal temperature. However, only tumours <1.0 cm in diameter can be treated at one time and heat penetration is limited. Because of the limited reports of hyperthermia for the treatment of sarcoid tumours, it is difficult to make recommendations regarding its use.

### Radiotherapy

Radiotherapy uses ionising radiation to kill neoplastic cells by damaging DNA and protein. There are 2 forms of radiotherapy available: teletherapy and brachytherapy. Teletherapy is high energy x-ray or  $\gamma$ -ray radiation applied 80–100 cm from the tumour by a linear accelerator or cobalt-60 unit and thus requires multiple treatments under general anaesthesia. The limited availability of delivery systems and relative expense of teletherapy may preclude its use. The second form of radiotherapy is brachytherapy in which small, sealed, radioactive sources are implanted within, or placed on, tumours to allow high doses of radiation to be delivered for a given radiation dose. Examples include iridium-192 and iodine-125 (interstitial brachytherapy) and strontium-90. Iridium-192 is the most commonly used implant and is available in grains (seeds) or wires. These implants are often placed into the tissue after surgical debulking during anaesthesia and remain in the tissue for approximately 3 weeks. Of 16 sarcoid-bearing horses treated with iridium-192 brachytherapy, 15 (94%) were tumour-free one year post treatment (Turrel *et al.* 1985). In a separate study, iridium-192 brachytherapy for equine periocular sarcoids resulted in 86.6 and 74% success rates at one and 5 years post treatment, respectively. Similarly, a one year success rate of 87% and a 2 year success rate of 81% have also been reported following iridium-192 implantation for sarcoid tumours (Walker *et al.* 1991). Finally, iridium-192 alone or following surgical debulking resulted in an 89% success rate for 4–91 months (Byam-Cook *et al.* 2006). These studies show that brachytherapy yields relatively high success rates but sarcoid tumour relapses can occur several months to years after treatment.

### Chemotherapy

Intratumoural chemotherapy is commonly used to treat equine sarcoid. Cisplatin (cis-diammine dichloroplatinum) is a heavy metal compound that inhibits DNA synthesis by directly binding to DNA and is commonly used in equine medicine. Two approaches are available for controlled-release administration: percutaneous injection of a viscous fluid and implantation of biodegradable beads. The first method involves reconstitution of crystalline cisplatin powder with sterile water at a concentration of 10 mg/ml, followed by mixing with sesame seed oil (60%) and sorbitan monooleate (7%) by use of the pumping method (Theon 1997). The resulting solution is 3.3 mg cisplatin/ml and the dosage is 1 mg cisplatin per cubic centimetre of tissue. The treatment recommendation includes 4 intratumoural injections given at 2 week intervals (Theon *et al.* 2007) and should be initiated immediately following surgery (Theon *et al.* 1993, 1999, 2007).



Biodegradable cisplatin beads are typically implanted through stab incisions at 1.5 cm intervals in the tumour bed and surrounding skin. It is recommended that large tumours (>1.5 cm) be debulked immediately prior to implantation while smaller tumours can be treated with bead implantation alone (Hewes and Sullins 2006). In general, 2 applications of cisplatin beads at one month intervals are recommended for treatment of sarcoids. A retrospective analysis of long-term outcome after cisplatin injections revealed that overall tumour resolution at 4 years was 96.3% for sarcoids (Theon *et al.* 2007). Similarly, sarcoids were controlled after cisplatin injections in 85–90% of affected horses in 2 additional studies (Theon *et al.* 1993, 1999). An earlier retrospective analysis found only a 33% success rate using injectable cisplatin but the authors reported extreme difficulty in their ability to ensure adequate drug delivery at each treatment interval (Knottenbelt and Kelly 2000). Intratumoural cisplatin beads have also been effective in treating sarcoids with a cure rate of 91% for all spindle cell tumours (sarcoids, fibroma/fibrosarcoma) (Hewes and Sullins 2006). Advantages of the cisplatin beads over the injections are the ease of handling and less frequent treatment.

Cisplatin electrochemotherapy (ECT) is a novel therapy for equine sarcoid that utilises electrical field pulses to increase cell membrane permeability and thus increase cisplatin delivery to the tumour. A retrospective analysis of 48 sarcoid-bearing equids treated with cisplatin ECT alone, or in combination with surgical excision, yielded a 4 year nonrecurrence rate of 98% (Tamzali *et al.* 2012). However, ECT requires general anaesthesia with the number of treatment sessions dependent on tumour size, location and depth of infiltration.

Five-fluorouracil (5-FU)<sup>1</sup> is a topical chemotherapeutic drug that exerts its effects by inhibiting DNA synthesis and is commonly used for treatment of small mucocutaneous SCC in horses (Pucket and Gilmour 2011). Intratumoural injection of 5-FU every 2 weeks for up to 7 treatments resulted in complete resolution of sarcoids in 61% of horses for up to 3 years (Stewart *et al.* 2006). Smaller sarcoids were significantly more likely to resolve with this treatment than larger sarcoids.

AW3/4-LUDES<sup>2</sup> are compounded topical chemotherapy creams that contain 5% fluorouracil, heavy metals and thiouracil. They are caustic agents that are dispensed at varying concentrations and cause inflammation and necrosis of sarcoid tissue without harming normal skin (Knottenbelt and Walker 1994; Newton 2000). Application of the cream daily or every other day is recommended for 3–5 treatments with necrosis of the sarcoid expected 5–10 weeks after the final treatment (Newton 2000). One study reported a success rate of 80% in horses with sarcoids after a single treatment of AW3-LUDES (Knottenbelt and Walker 1994) while 2 treatments were required to cause tumour regression in a separate single case reported by Newton (2000). AW4-LUDES was used as a primary treatment modality in 146 horses with 159 small periorbital sarcoids and yielded only a 35% success rate (Knottenbelt and Kelly 2000).

### Immunotherapy

Immunotherapy is a treatment modality for equine sarcoid that relies on local immune stimulation to attack and kill tumour cells. The most common immunomodulator used is Bacillus Calmette and Guerin (BCG), an attenuated strain of *Mycobacterium*

*bovis*. These agents are thought to stimulate a local cell-mediated immune response when injected intratumourally and thus induce cytotoxic T cell and natural killer cell activity against tumour cells (Davies 1982; Misdorp *et al.* 1985). Histopathology of treated sarcoids showed that only tumour cells became necrotic, suggesting a tumour-specific mechanism (Vanselow *et al.* 1988). Success rates from 83 to 100% have been observed for periorbital sarcoids (Wyman *et al.* 1977; Murphy *et al.* 1979; Schwartzman *et al.* 1984; Lavach *et al.* 1985; Owen and Jagger 1987; McConaghy *et al.* 1994; Knottenbelt and Kelly 2000; Newton 2000) but for sarcoids found elsewhere on the body, success rates have only been approximately 50% (Owen and Jagger 1987; Vanselow *et al.* 1988; McConaghy *et al.* 1994; Goodrich *et al.* 1998). In one study, there was an overall success rate of 69% for immunotherapy of fibroblastic sarcoids but treatment of other forms of sarcoid gave poorer results (Knottenbelt and Kelly 2000). It is recommended that intratumoural injections be repeated every 2–4 weeks until regression occurs; an average of 12 ml per treatment and 3.2 treatments were required to achieve regression of periorbital sarcoids in one study (Lavach *et al.* 1985). Severe complications, including death, have been reported with the use of BCG. Fatal (Vanselow *et al.* 1988) and nonfatal anaphylaxis (Landsheft and Anderson 1984) have occurred as well as severe local inflammatory reactions (Klein *et al.* 1986) and septic arthritis (Owen and Jagger 1987). These complications may be reduced by administration of dexamethasone (0.05 mg/kg bwt i.v.)<sup>3</sup> or flunixin meglumine (1.1 mg/kg bwt i.v.)<sup>4</sup> prior to BCG injection. Because of the risk of local inflammation following treatment, it is contraindicated to treat penile tumours with BCG. Furthermore, tumour regression may require several months of weekly therapy (Lavach *et al.* 1985; Klein *et al.* 1986; Vanselow *et al.* 1988). Other immunomodulators used to treat equine sarcoid include mycobacterial cell wall extracts and systemic propionibacterial cell wall extracts but controlled studies are lacking.

Topical immune modulators have also been used to treat equine sarcoid. XXTERRA<sup>5</sup> and Sarc-off<sup>6</sup> are herbal, compounded creams that contain bloodroot and zinc chloride and are meant to stimulate the local immune response to activate killing of tumour cells. They have been anecdotally reported to successfully treat sarcoids after topical application but no controlled studies are available. In a small pilot study of previously untreated sarcoids, 60% of tumours completely regressed after treatment with the immunomodulator imiquimod 5% cream<sup>7</sup> (Nogueira *et al.* 2006). In addition, 80% of tumours showed more than a 75% reduction in size. Imiquimod was applied to the tumours 3 times weekly until resolution or 32 weeks. Complications included alopecia, erythema, erosions and depigmentation of the tumour and periphery (Nogueira *et al.* 2006). More studies are required to corroborate these findings.

Acyclovir, an antiviral drug that has been used successfully to treat herpesvirus-induced skin lesions in humans (Beutner *et al.* 1995) was found to induce tumour regression in 68% of small, occult sarcoids in one study (Stadler *et al.* 2011). In this study, 5% acyclovir cream was applied to the sarcoid once daily for 2 months. Treatment failure was associated with deeper lesions, suggesting limited drug penetration. Although recurrence rates were not rigorously assessed in this study, the absence of side effects and low expense may warrant treatment of small, occult sarcoids.

### Vaccination

Recently, therapeutic vaccines composed of chimeric virus-like particles have resulted in tumour regression in approximately half of treated equids (Ashrafi *et al.* 2008; Mattil-Fritz *et al.* 2008). Further research is needed in this field and attempts to circumvent virus-mediated immunosuppression are ongoing.

### Conclusion

Equine sarcoids persist as a therapeutic challenge. The variable definitions of success and lengths of follow-up make it difficult to compare studies and limits our ability to draw conclusions from the reported findings. However, novel and emerging treatment modalities have improved the outcome in affected animals and future research in these fields is promising. Client education remains critical since early recognition of tumours and subsequent intervention are likely to decrease complications associated with equine sarcoids.

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### Manufacturers' addresses

<sup>1</sup>Efudex, Valeant Pharmaceuticals International, Mississauga, Ontario, Canada.

<sup>2</sup>D.C. Knottenbelt, University of Liverpool, Neston, South Wirral, UK.

<sup>3</sup>AgriLabs, St. Joseph, Missouri, USA.

<sup>4</sup>Banamine, Schering Plough/Merck, Whitehouse Station, New Jersey, USA.

<sup>5</sup>Larson Labs Inc., Vetline Equine, Fort Collins, Colorado, USA.

<sup>6</sup>Forum Products Ltd., Forum Animal Health, Redhill, Surrey, UK.

<sup>7</sup>Aldara, 3M Pharmaceuticals, St. Paul, Minnesota, USA.

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for greater doses. Safety is further increased if a remote technique is used (Clutton 1997). Drug combinations which the clinician has previously used successfully to control excited, aggressive or violent horses, including feral equidae, should be used in the first instance because he or she then has at least some experience against which adverse responses may be identified.

In the absence of such experience, detomidine (80 µg/kg bwt) morphine (0.3 mg/kg bwt) and acepromazine (0.1 mg/kg bwt) mixed together in the same syringe and injected i.m. can be recommended. Butorphanol (0.05 mg/kg bwt) should be used if morphine is unavailable. In the unlikely event that the animal has been weighed, drug dosing should be based on an over-estimate of the animal's body mass, to ensure modest over-dosage, rather than potentially ineffective under-dosing results. The full effect of such injections may take up to 20 min to occur, so as soon as conditions allow, pads and blankets should be arranged so as to protect the animal's legs and eyes. The external jugular vein should be cannulated as soon as possible because i.v. injection will allow the most rapid control of any persisting neurological phenomena. There is a paucity of literature on the acute pharmacological management of severe neurological conditions in horses and that which does exist will probably be of limited value; the equine practitioner facing manic animals under farm conditions is unlikely to carry the required medication (and in sufficient quantities) that would be stocked in referral centres. Under these conditions, the practitioner must resort to those drugs available. Xylazine (0.5 mg/kg bwt i.v. repeated at 2 min

intervals) is probably the most appropriate drug for the control of excitatory phenomena because it is short-acting and so its effects are more easily titrated than the longer acting  $\alpha_2$  agonists detomidine and romifidine.

Whilst diazepam is an appropriate 'first-response' drug for seizing animals, the ambulatory practitioner may have insufficient quantities to achieve adequate control and so suitable formulations of pentobarbital may be necessary. The role of acepromazine in promoting epileptiform reactions in small animals has never been convincingly substantiated and small doses (10-25 mg/kg bwt i.v.) - particularly in conjunction with  $\alpha_2$  agonists - may prove useful in 'manic' large animals encountered under suboptimal conditions. When these measures fail, the penultimate option is to induce general anaesthesia. Any familiar technique used for field anaesthesia would be appropriate for the reasons given previously, although signs of anaesthesia and the duration and quality of recovery may well differ from those experienced in the 'normal' anaesthetised horse.

#### **Authors' declaration of interests**

No conflicts of interest have been declared.

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