Presumed generalised seizure following caudal epidural administration of morphine and detomidine in a pony

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Keywords: horse | epidural | morphine | seizure | analgesia

Summary

A 9-year-old Show Pony mare became acutely lame following removal of a bone sequestrum of the distal phalanx of the right thoracic limb. The mare also suffered from ongoing right dorsal colitis secondary to previous long-term non-steroidal anti-inflammatory drug (NSAID) use. To avoid further NSAID use, a protocol for caudal epidural administration of morphine and detomidine in an increased volume was used to provide analgesia to the thoracic limbs. A total volume of 50 ml (0.2 ml/kg) was administered over approximately 90 seconds. Immediately following the injection, the pony collapsed into lateral recumbency, and experienced an apparent generalised seizure characterised by loss of consciousness and frantic paddling of all four limbs. The pony recovered rapidly without intervention and no residual neurological deficits were noted. The epidural analgesia resulted in a marked improvement in comfort levels. The speed of injection is thought to have caused a change in epidural and intracranial pressures resulting in a generalised seizure and highlights the importance of administering large volumes slowly.

Introduction

The use of caudal epidural analgesia in horses has increased in recent years. It provides a technically relatively easy, cheap and effective way to manage musculoskeletal pain, particularly in the pelvic limbs. Morphine and detomidine have been shown to produce profound, long lasting, pelvic limb analgesia when administered via the epidural route in horses (Goodrich et al., 2002; Sysel et al., 1996; Valverde et al., 1990; van Loon et al., 2012). Injection of larger volumes can facilitate cranial diffusion and has been shown to effectively control thoracic limb pain (Freitas et al., 2011). High volume epidural analgesia has also been recommended for use in

horses with laminitis (Hopster and van Eps, 2019). The following case report describes a generalised seizure in a pony following the administration of a large volume caudal epidural injection containing morphine and detomidine. To the authors' knowledge, this is the first report detailing this complication secondary to caudal epidural injection of morphine and detomidine in a horse and emphasises the importance of administering large volumes slowly.

Case history

A 9-year-old, 250 kg Show Pony mare had been admitted to the Royal Veterinary College Equine Referral Hospital eight days previously for further investigation and treatment of mild colic signs. The pony had been stabled for two weeks prior to admission due to suspected laminitis and had been treated with flunixin meglumine (Finadyne oral paste, 1.1 mg/kg bwt p.o. q. 24h)[1] and phenylbutazone (Equipalazone, 2.2-4.4 mg/kg bwt p.o. q. 12-24h)[2] concurrently during this period. Transrectal palpation at the time of admission identified a large colon impaction, which resolved following enteral fluid therapy. Serum biochemistry identified moderate hypoalbuminaemia (23 g/L, rr: 28-36 g/L) and abdominal ultrasonography identified thickening of the right dorsal colon wall, consistent with right dorsal colitis. In addition, severe multifocal, depressed, haemorrhagic lesions at the pylorus were noted during gastroscopy. Both findings were thought to be secondary to previous administration of non-steroidal anti-inflammatory drugs (NSAIDs). Treatment with NSAIDs was discontinued and misoprostol (Cytotec, 5 µg/kg bwt p.o. q. 12h)[3] and sucralfate (12 mg/kg bwt p.o. q. 12hr)[4] were administered to support mucosal repair. An acute right thoracic lameness was noted during hospitalisation and radiographs of the foot identified a bone sequestrum in the distal phalanx. This was debrided under general

anaesthesia seven days after admission. Peri- and post-operative analgesia consisted of transdermal fentanyl (Victanyl 75 µg/hr)[5], acetaminophen (Paracetamol 500 mg tablets BP, 20 mg/kg bwt p.o. q. 12hr)[6] and morphine sulphate (Morphine Sulphate 30 mg/ml BP 0.1 mg/kg bwt i.m.)[7].

Clinical findings

Twenty-four hours post-operatively, a marked deterioration in the pony's comfort level was observed. Consistent weight shifting between the thoracic limbs was noted and the pony was reluctant to ambulate in the stable. Physical examination identified a heart rate of 68 beats/min, a respiratory rate of 16 breaths/min and a temperature of 38.3^{o}C. Digital pulses were hyperkinetic in all limbs. Appetite and faecal output were reduced. Orthopaedic examination identified marked lameness of the right thoracic limb at walk (grade 5/5, AAEP scale). The composite pain score (CPS) was 10 (Bussières *et al.,* 2008). Due to the ongoing right dorsal colitis, administration of further NSAIDs was not desirable. It was therefore planned to use caudal epidural analgesia, with a combination of morphine and detomidine administered in a larger volume (0.2 ml/kg bwt) to facilitate cranial diffusion and provide analgesia to the thoracic limbs (Hopster and van Eps, 2019).

Treatment

The pony was sedated in the stable with detomidine hydrochloride (Domidine, 0.01 mg/kg bwt i.v.)[2] and butorphanol tartrate (Dolorex, 0.01 mg/kg bwt i.v.)[1]. The sacrococcygeal space was identified by raising and lowering the tail while palpating the intervertebral space, and the overlying skin was clipped and aseptically prepared. Following desensitisation of the skin with 2 ml mepivacaine (Intra-Epicaine 20 mg/ml)[2],

an 18 gauge 1.5-inch hypodermic needle was inserted through the skin at approximately 60_0 to the horizontal plane until it was felt to penetrate the interarcuate ligament. Placement in the epidural space was confirmed by the hanging-drop technique and a lack of resistance to injection (a 10mL syringe containing sterile saline and an air bubble was attached to the needle and no compression of the air bubble was appreciated during saline injection). Using aseptic technique, 60 mg morphine sulphate (Morphine Sulphate BP, 0.2 mg/kg bwt)[7] and 1 mg detomidine hydrochloride (Domidine, 0.004 mg/kg bwt)[2] diluted in 0.9% sterile saline (Vetivex 1)[2] to a total volume of 50 ml was injected over approximately 90 seconds. No increase in resistance was encountered during injection. Five seconds following completion of the injection, the pony became increasingly sedated with rigid extension of the limbs and collapsed into lateral recumbency. Extensor rigidity of all limbs was observed, and the pony appeared unresponsive to external stimuli. After 12 seconds, rapid paddling of all four limbs began and persisted for 35 seconds. The pony regained consciousness after approximately 45 seconds and remained in sternal recumbency for several minutes. She was responsive but appeared mildly sedated. No cranial nerve deficits were identified but recurrent chewing and lip smacking were noted. The pony stood up without difficulty. Abbreviated gait assessment within the stable three hours after the episode did not identify any evidence of ataxia or paresis.

Outcome

The epidural injection resulted in a marked improvement in comfort levels. Physical examination three hours after the injection identified a heart rate of 44 beats/min, and the pony was no longer weight shifting between the thoracic limbs. The CPS was not measured at this time but had decreased to 4 (Bussières et al., 2008) 24 hours after

the procedure. Normal mentation and behaviour were observed throughout the remainder of hospitalisation. Epidural injection was not repeated. Additional analgesia was provided by a lidocaine infusion (1.3 mg/kg bwt i.v. bolus, then 0.05 mg/kg bwt/min i.v.)[8] and firocoxib (Previcox, 0.3 mg/kg bwt p.o. once then 0.1 mg/kg bwt p.o. q. 24h)[9]. The pony was discharged from the hospital eight days later. No further seizures or abnormal neurological behaviour have been reported.

Discussion

Adverse effects secondary to NSAID use such as right dorsal colitis appear to be more commonly recognised in horses, possibly due to an increased awareness. Therefore, it is not infrequent that equine clinicians search for alternatives to provide effective analgesia. Caudal epidural administration of a mixture of opioids and α_2-agonists is now routinely used to provide analgesia to the pelvic limbs. More recently, the use of larger volumes to extend the analgesic effect to the thoracic limbs has also been advocated (Hopster and van Eps, 2019). Morphine binds to the μ receptor in the central nervous system (CNS) and exerts its effects via inhibition of substance P from Aδ and C fibres in the spinal cord (Valverde et al., 1990). Analgesia might result from the direct interaction with opioid receptors located at the dorsal horn of the spinal cord or from systemic absorption through blood vessels in the epidural space (Natalini, 2010). Behavioural side effects of morphine in the horse include a dose-dependent increase in locomotor activity (Clutton, 2010) and muscle fasciculations, nostril flaring, and ataxia were observed in horses receiving high doses (0.5 mg/kg bwt) of morphine intravenously (Knych et al., 2014). Generalised seizures have been reported in people following high doses of intravenous morphine (Gregory et al., 1992). Generalised seizures have also been documented after epidural administration of morphine in

patients with a history of epilepsy (Borgeat et al., 1988; Shih et al., 2005) and epidural morphine administration has been used to induce myoclonic activity in a rodent model (Shohami et al., 1986). Morphine-3-glucuronide (M3G), one of the main metabolites of morphine has been associated with neuroexcitation in rats (Hemstapat et al., 2009) and it has been suggested that high concentrations of M3G may be responsible for the CNS excitation associated with high-dose administration of morphine in horses (Knych et al., 2014). Detomidine is frequently used to provide a synergistic effect by increasing the onset of action of morphine and providing additional analgesia (Doherty and Valverde, 2006). Side effects associated with epidural administration include ataxia and recumbency, particularly with large doses (Wittern et al., 1998). The use of detomidine in a large volume epidural has not been previously reported in the horse. It is possible that diffusion of detomidine into the CNS or the presence of preservative in the solution contributed to the adverse reaction seen. However, the dose of detomidine used in this case was extremely low (0.004mg/kg bwt), making this unlikely.

To our knowledge, there are no published reports of seizure following epidural injection in the horse. In the described case, a high dose of morphine was injected in a large volume over approximately 90 seconds. Possible causes for the observed seizure activity include a rapid change in intracranial pressure, a direct effect of morphine on the brain, or neurotoxicity from the preservatives in the morphine. The use of large volume epidural injections has been previously described for thoracic limb analgesia in horses. In one study (Freitas et al., 2011) volumes of 0.15 ml/kg were administered at a rate of 1 ml/10 seconds without any adverse effects. Volumes of 0.2 ml/kg bwt are recommended for treatment of laminitis, but a suitable speed of injection is not

specified (Hopster and van Eps, 2019). Beagles receiving increasing volumes of epidural lidocaine via a catheter placed at the level of T7 showed stupor, depression and ataxia with volumes above 0.1 ml/kg bwt. (Son et al., 2015). Increased severity and frequency of these side effects were observed when 0.2 ml/kg bwt were administered, although this may be due to the effect of lidocaine rather than the volume alone. Little is known about the optimum of speed of epidural injection in either people or animals. Rapid injection of large volumes may cause compression of the nerve endings in the epidural space, resulting in collapse (Natalini and Robinson, 2000). Smaller volumes of up to 10 ml have been injected over 5-10 seconds in adult horses (Bird et al., 2019). Studies where larger volumes were injected used a significantly slower rate of injection (1 ml/10 seconds) (Freitas et al., 2011; Natalini and Robinson, 2000). Rates as slow as 1 ml/minute have been described in dogs (Son et al., 2015). In people, peak epidural pressure is associated with the speed of the injection but not with the volume, while the residual epidural pressure correlates directly with the volume of injection, but not with the speed (Cardoso and Carvalho, 1998). Speed of injection is also linked to epidural pressure in dogs (Son et al., 2014). Compression of the dural sac may push cerebrospinal fluid (CSF) cranially, resulting in an increased intracranial pressure (ICP). Epidural injection of 10 ml caused increases in ICP of 11-63 mmHg in human patients (Hilt and Gramm 1986) but the relationship between raised ICP and seizure activity remains unclear in people (McNamara et al., 2003).

In this case, injecting over several minutes would have been challenging as a large syringe was attached directly to the needle hub and the pony was intermittently shifting weight between the pelvic limbs. Slow epidural injection of 20 ml has been associated

196 with discomfort (Natalini and Robinson, 2000) and small movements of the patient
197 may result in displacement of the needle. Attachment of a narrow bore extension
198 should be considered to minimise needle movement when a large syringe is attached
199 to facilitate slower injection and maintain the correct needle position. Alternatively, a
200 short-term epidural catheter could be placed to facilitating much slower administration
201 of drugs without an indwelling needle.
202
203 Morphine may be absorbed into the systemic circulation by epidural vessels, resulting
204 in an excitatory episode (Doherty and Valverde, 2006). However, administration of
205 morphine at this dose and higher doses intravenously has not been associated with
206 such dramatic side effects (Knych et al., 2014) and it is less likely that this caused the
207 observed signs. Hydrophilic drugs such as fentanyl have a rapid onset of action but
208 quickly undergo extensive systemic absorption, to the extent that there is little benefit
209 in epidural administration (Natalini, 2010). Morphine is hydrophilic and epidural
210 administration results in a slower onset of action, but concentrations remain high in
211 the CSF for longer. The rapidity of the seizure in this case makes systemic absorption
212 less likely. However, diffusion of morphine via CSF by absorption into the
213 subarachnoid space across the dura mater from the epidural space is a possibility.
214 This mechanism has been suggested in Beagles receiving large volume thoracic
215 epidurals (Son et al., 2015). Subarachnoid morphine would be more likely to result in
216 neuroexcitation (Natalini, 2010). Direct subdural administration is extremely unlikely
217 due to the use of the sacrococcygeal space, where there is no risk for CSF puncture
218 due to the anatomy of this area. Cranial spread to the brain along the epidural space
219 is also considered less likely; when volumes of 0.2 ml/kg bwt were injected in foals,
220 dye diffused only to the 6th and 7th thoracic vertebrae (Lansdowne et al., 2005).

However, further work is needed in adult horses to determine the extent of cranial diffusion of large volume epidural injections.

The morphine used in this case was not preservative-free due to supply issues and neurotoxicity may have resulted from the sodium metabilosulphite preservative. However, a large volume (48 ml) of preservative-free saline was used for dilution as recommended (Doherty and Valverde, 2006). In addition, solutions containing metabilosulphite have been used in rodent models and clinically in dogs without any reported side effects (Sibanda et al., 2006; Taniguchi et al., 2004).

Acetaminophen was used with the aim of providing additional analgesia while avoiding the use of additional NSAIDs in light of the right dorsal colitis. The mechanism of action of acetaminophen is still not fully understood. In people, evidence for its analgesic properties is limited, although meta-analyses have demonstrated superior analgesia compared to a placebo for osteoarthritis (Towheed et al., 2006) and post-operative pain (De Oliveira et al., 2015; Lee et al., 2019; Liang et al., 2017). Reports of use in horses are extremely sparse (West et al., 2011, Foreman et al 2016). Anecdotally, use of acetaminophen as an analgesic in horses is increasing (Bowen et al., 2020) and the authors have used it as part of a multimodal approach in other cases with perceived positive effects. Acetaminophen has been shown to be safe in horses at the dose used in this report (Mercer et al., 2020).

Conclusion

This report documents the occurrence of a presumed generalised seizure in a pony receiving epidural morphine. Although the exact pathogenesis remains unclear, a

change in intracranial pressure resulting from rapid injection or diffusion of morphine into the CSF are thought to be most likely. Further work is needed to determine the optimum volume and speed of intra-thecal injection in horses but in the meantime, it appears prudent to administer large volumes over a period of several minutes, using a flexible extension set or an epidural catheter to facilitate this. Generalised seizures in an adult horse may pose a serious risk to people and safety should be taken into consideration, particularly if the procedure is performed in a confined area.

Manufacturers' addresses

1. MSD Animal Health, Milton Keynes, Buckinghamshire, UK
2. Dechra Veterinary Products, Northwich, Cheshire, UK
3. Pfizer Ltd., Sandwich, Kent, UK
4. BOVA Specials UK Ltd, London, UK
5. Accord-UK Ltd., Barnstaple, Devon, UK
6. M&A Pharmachem Ltd., Bolton, Lancashire, UK
7. Wockhardt UK Ltd, Wrexham, UK
8. Fresenius Kabi AG, Bad Homburg, Germany
9. Boehringer Ingelheim Animal Health UK Ltd., Bracknell, Berkshire, UK

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