COMPANION OR PET ANIMALS

Myoclonus and hyperalgesia following intended epidural morphine administration in a dog

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SUMMARY
A West Highland White Terrier was presented after development of hindlimb myoclonus and hyperalgesia following intended epidural administration of morphine at a referring veterinary practice. MRI was unremarkable, except for the spinal cord extending to the caudal half of the L7 vertebrae. Treatment with systemic analgesia of methadone and sedation/analgesia with medetomidine resolved the clinical signs within 24 hours. The mechanism by which morphine causes adverse neurological side effects has yet to be fully determined; the morphine-3-glucuronide (M-3-G) metabolite is suspected to be responsible for the adverse effects seen. Hypotheses include action of morphine or the M-3-G metabolite on non-opioid inhibitory (glycine) or excitatory (N-methyl D-aspartate) receptors. However, more work is needed to determine the exact pathogenesis. Neuroexcitatory side effects are rarely reported following administration of morphine in dogs and this case demonstrates successful treatment with the use of an alternative opioid, methadone.

BACKGROUND
Performing epidurals in patients undergoing hindlimb, tail or perineal surgery is an effective means of providing analgesia both intraoperatively and postoperatively. A variety of drugs can be administered into the epidural space, but most often combinations of local anaesthetics and opioids are used. Side effects following epidural administration are fortunately uncommon; this case highlights a rare but significant side effect of intended epidural morphine administration in a dog and outlines a successful treatment protocol.

CASE PRESENTATION
An 8.2 kg six-year-old neutered female West Highland White Terrier was presented to the University of Liverpool Small Animal Teaching Hospital following right hindlimb wedge sucolastomy and tibial tuberosity transposition performed by the referring veterinary surgeons. Preanaesthetic medication at the referring practice was 0.03 mg/kg acepromazine (Calmvet 5 mg/ml, Vetquinnol France) and 0.02 mg/kg buprenorphine (Vetergesic, Alstoe Animal Health) intramuscularly. At the same time, Meloxicam (Metacam 5 mg/ml solution for injection, Boehringer Ingelheim) at 0.2 mg/kg and potentiated amoxicillin at 8.75 mg/kg (Synulox RTU injection, Pfizer Animal Health) were given subcutaneously. A 22-gauge catheter was placed in the right cephalic vein. Anaesthesia was induced with propofol (PropoFlo, Abbott Animal Health) to effect. The trachea was intubated with a 7.0 mm endotracheal tube and anaesthesia was maintained with isoflurane vaporised in oxygen via a non-rebreathing system.

Prior to the start of surgery, the dog was placed in sternal recumbency and a lumbosacral epidural was performed with a total of 2.5 mg (0.3 mg/kg) of undiluted morphine (Morphine sulfate 10 mg/ml, Wockhardt UK) with sodium metabisulphite as preservative. For up to 10 minutes after the epidural, mild focal repeated contractions of the tail were noted, which then resolved spontaneously. Surgery was performed without complications. After surgery, as consciousness was regained, the dog began vocalising violently (described as screaming), repeated rapid muscle contractions between one to two seconds duration and hypertoncity of both hindlimbs and tail were noted. Vocalisation was observed to increase when the hindlimbs or tail were gently touched. The dog was re-anaesthetised with intravenous propofol to effect and the trachea was re-intubated. The dog was transported under total intravenous anaesthesia with propofol to the University for investigation and treatment.

INVESTIGATIONS
On arrival at the hospital, the dog was connected to a non-rebreathing system, and isoflurane vapourised in oxygen was delivered at 4 l/minute to maintain anaesthesia. Heart rate on admission was 60 bpm, respiratory rate was 16 breaths per minute, rectal temperature was 34.8°C, palpebral reflex was absent and eyes were rotated ventromedially. Muscle tone was flaccid in all four limbs, but anal tone was present. A forced warm air blanket (Bair Hugger, Arizant healthcare) was placed to increase body temperature. Lactated ringer’s solution (Hartmann’s solution) was administered intravenously at 32 ml/hour. Continuous monitoring included heart rate, respiratory rate, end-tidal carbon dioxide, measured via a sidestream gas analyser and percentage haemoglobin saturation, estimated via a pulse oximeter probe placed on the tongue using a multiparameter monitor (Datex ohmeda, GE healthcare). Indirect oesophageal blood pressure was measured at five-minute intervals with a cuff placed on the left forelimb over the palpable metacarpal artery (Cardell veterinary monitor 9401, Paragon medical). Body temperature was measured with a rectal thermometer. All measured parameters, which the exception of rectal temperature, were within normal limits throughout.
After 20 minutes, isoflurane was discontinued, and oxygen was continued at 4 l/minute. Palpebral reflex returned after 10 minutes, swallowing reflex was absent, five minutes later repeated rapid contractions and of the tail and hindlimb and hypertoncity of the hindlimb muscles were present, and normal tone was present in the forelimbs. Withdrawal reflex was normal in the forelimbs but delayed in the hindlimbs. Isoflurane vaporised in oxygen was restarted until palpebral reflex was absent and muscle contraction ceased. The dog was taken for MRI of the lumbar sacral spine. An MRI (Magnetom Harmony 1Tesla scanner, Siemens) was performed with T1 and T2 weighted images, which showed the spinal cord extending to the caudal half of L7 with the dural sac extending into the sacrum. There was also moderate dorsal protrusion of the annulus of L7-S1 intervertebral disc, but no significant compression of spinal cord. Mild foraminal stenosis with no significant compression was noted. No other abnormalities were identified. Immediately after removal from the MRI room, heart rate was 58 bpm, respiratory rate was 16 breaths per minute and rectal temperature had reduced to 33.5°C. Due to lack of clinically significant findings on MRI, it was suspected the hyperalgesia and neurological abnormalities of the hindlimbs and tail were due to morphine administration.

TREATMENT

Whilst still anaesthetised, the dog was taken to the intensive care unit; 0.3 mg/kg of methadone (Comfortan, Eurovet animal health) and 0.002 mg/kg medetomidine (Sedotor, Dechra veterinary products) were given intravenously to provide analgesia and sedation for recovery. As it was most likely that morphine administration into either the epidural or intrathecal space had caused the hyperalgesia and hindlimb and tail contractions seen, alternative analgesia with methadone was given and medetomidine was used to provide additional analgesia and muscle relaxation. A forced warm air blanket and electric heating pad (HotDog, Augustine Temperature Management) were used to increase patient temperature. Isoflurane was discontinued and oxygen was continued at 4 l/minute for a further 20 minutes. The trachea was extubated 75 minutes after discontinuation of isoflurane once palpebral reflexes and swallowing reflex had returned. Rectal temperature at this time had increased to 35.5°C. Mild to moderate muscle twitching of both hindlimbs were present at the time of extubation, and withdrawal was present in all four limbs. As consciousness was regained, no vocalisation was noted, the dog appeared calm and not distressed. Once rectal temperature was 37.0°C and the dog was able to maintain sternal recumbency without assistance, she was returned to a kennel. A pain score of 3/20 was recorded using a short form of the Glasgow composite pain score (Reid and others 2007).

Methadone was continued at 0.3 mg/kg intravenously every 4 hours for 12 hours, and hindlimb muscle twitching reduced in frequency overnight. Pain score 12 hours after extubation was 2/24; at this time, there were no neurological abnormalities of the hindlimbs present and no response to palpation of the hindlimbs and tail was noted. The dog was 9/10 lame on the right hindlimb, which was expected following the orthopaedic procedure performed. Methadone was continued at 0.3 mg/kg for a further 12 hours and then stopped, and meloxicam (Metacam oral suspension for dogs, Boehringer Ingelheim) was given per os once daily starting 24 hours after initial injection. After discontinuation of methadone, buprenorphine (Vetgesic 0.3 mg/ml, Alstoe animal health) at 0.02 mg/kg was administered intravenously every 4 hours for 24 hours, after which point it was stopped.

OUTCOME AND FOLLOW-UP

The dog was discharged from the hospital 48 hours after presentation and showed no further neurological abnormalities when examined 10 days postsurgery.

DISCUSSION

The spinal cord in dogs normally terminates between L6 and L7, but occasionally extends to the caudal half of L7 in small breed dogs, as was observed on the MRI in this patient, with the dural sac extending into the sacrum (Dyce and others 2002). Epidurals are usually performed at the lumbar sacral space in dogs as this provides the largest area for access to the epidural space (Valverde 2008). Lumbar sacral intrathecal injections can be performed but it is recommended to reduce the dose of drug given to a quarter to a half of that normally given epidurally (Wetmore and Glowaski 2000). It is possible in this case the injection may have been intrathecal rather than epidural, and the caudal position of the spinal cord meant that accidental penetration into the subarachnoid space would have been possible. The referring veterinary surgeon did not report the presence of cerebrospinal fluid or blood in the hub of the needle when performing the procedure, and correct placement of the needle in the epidural space was reported to be confirmed by lack of resistance to injection; however, aspiration from the needle prior to injection of morphine was not performed. It has previously been shown that accidental intrathecal injection can occur in dogs positioned in sternal recumbency, even when cerebrospinal fluid is not detected in the hub of the needle before injection (Bosmans and others 2011) and aspiration from the needle is advised prior to injection. The dose given to this patient was 2.5 mg (0.3 mg/kg), although the recommended epidural dose for morphine is no more than 0.1 mg/kg; at higher doses than this, side effects are more likely to be seen, with no improvement in analgesia (Valverde 2008). In the absense of other findings on the MRI scan to explain the clinical signs, it was presumed the neurological abnormalities in this case were due to administration of morphine into the epidural or subarachnoid space. To the authors’ knowledge, there are no reports of similar clinical signs in dogs following epidural, rather than intrathecal, administration of morphine.

Hyperalgesia is defined as an increased sensitivity to pain and allodynia is a painful response to normally non-noxious stimuli (Hardy and others 1950), and it can be difficult to distinguish between the two in canine patients. The presence of hyperalgesia and/or allodynia in this case was suspected due to increased vocalisation on palpation of the hindlimbs and tail. It could be predicted that pain would be present following orthopaedic surgery of the right hindlimb, but response to touching the left hindlimb and tail would not be expected. The response was also thought to be excessive for the type of surgery performed. Vocalisation, such as persistent howling or squealing, has been reported in dogs recovering from anaesthesia with isoflurane (Love and others 2007, Laing and others 2009) that had not undergone painful procedures, making interpretation of these clinical signs somewhat difficult. It was the clinical opinion of the veterinary surgeon in this case that the described vocalisation was due to pain rather than emergence excitement following anaesthesia.

Cases of opioid induced hyperalgesia are well documented in the literature (Angst and Clark 2006, Koppert 2007) and can be seen following systemic or spinal administration. It is more commonly seen following chronic exposure, but has been reported in humans and animals following single high doses (Angst and Clark 2006). Myoclonus, brief, shock-like contractions of a
Muscle or group of muscles, is less common but has been reported following intrathecal administration of preservative-free morphine in dogs at normal doses (Kona-Boun and others 2003, Iff and others 2012) and following inadvertent overdose (Da Cunha and others 2007). Myoclonus with hyperalgesia has been reported in humans receiving chronic pain management with repeated large doses of intrathecal morphine (Krames and others 1985, De Conno and others 1991). Stiffness of the arms and legs has also been documented after an accidental large dose of epidural morphine (Atanassoff and Alon 1988) and myoclonus described following combined epidural and systemic morphine (Radbruch and others 1997) in human patients.

It is unknown by what exact mechanism these neuroexcitatory effects occur; however, there are a number of hypotheses. It is thought that morphine or a metabolite of morphine, morphine-3-glucuronide (M-3-G), may be responsible (Smith 2000). One proposed mechanism by which morphine or M-3-G causes neuroexcitation is via antagonism of glycine receptors within the spinal cord. In a study by Yaksh and others (1986), rats given high doses of intrathecal morphine, M-3-G or strychnine, a glycine receptor antagonist, displayed similar signs of hyperalgesia and allodynia. Glycine has an inhibitory effect on dorsal horn neurons by promoting chloride ion conductance, leading to membrane hyperpolarisation (Yoshimura and Nishi 1995). Removing this inhibition may lead to neuroexcitation, which could manifest as myoclonus and hyperalgesia. However, in vitro studies (Bartlet and others 1994) have failed to demonstrate binding of morphine or M-3-G to glycine receptors, throwing doubt on this theory. Another hypothesis is that morphine or M-3-G indirectly activates N-methyl D-aspartate (NMDA) receptors thereby causing excitation. Hempstead and others (2003) demonstrated in vitro activation of NMDA receptors by M-3-G on rat hippocampal neurons.

It was reported that similar adverse effects were not seen when alternative opioids, such as methadone and sufentanil, are administered (Yaksh and others 1986). These do not undergo significant glucuronidation, adding weight to the theory that M-3-G is responsible for the adverse neurological effects seen. Methadone has been used as an alternative to morphine when myoclonus or hyperalgesia has been observed in human patients, resulting in resolution of the adverse effects (Sjogren and others 1994). It has NMDA antagonist properties, and so in theory should attenuate neuroexcitatory effects, if they are mediated by NMDA receptor activity. Recently, however, methadone has been reported to cause myoclonus at high doses (Ito and Liao 2008) in humans, which was speculated to be due to its activity at delta receptors. Stimulation of delta receptors has been shown to induce myoclonic contractions in rats when injected directly into the ventricles (Dzoljic and Poel-Heisterkamp 1982). Methadone’s effects on delta receptors were hypothesized to predominate over NMDA antagonist effects when given in high doses leading to myoclonus (Ito and Liao 2008). Interestingly, in the same study by Dzoljic and Poel-Heisterkamp (1982), morphine injected intraventricularly failed to produce myoclonic contractions in rats. These conflicting findings highlight that more work is still needed to determine the exact pathogenesis by which opioids can produce neuroexcitation.

Morphine used in this case contained sodium metabisulphite as preservative. It is generally recommended to use preservative-free solutions in epidurals to eliminate the risk of toxic effects of preservatives on the spinal cord, if inadvertent intrathecal injection is performed (Valverde 2008). However, morphine with sodium metabisulphite has not been shown to produce any adverse clinical signs or neuropathology when given to dogs as a single epidural dose (King and others 1984) or when chronically administered intrathecally to people (Sjøberg and others 1992). Therefore, it was not felt that the use of this preservative contributed to the clinical signs in this case.

An important difference when compared with two similar reported cases in dogs by Kona-Boun and others (2003) and Da Cunha and others (2007) is that, in this patient, myoclonus resolved under inhalational anaesthesia with isoflurane. Treatment in this case consisted of intravenous methadone, which has been successful in resolving cases of opioid induced hyperalgesia and myoclonus in human patients (Sjøgren and others 1994). This is thought to be due to either its lack of active metabolites or NMDA receptor antagonist actions. Medetomidine, an alpha 2 adrenoceptor agonist, was also given, and it may have contributed to resolution of myoclonus due to its centrally acting muscle relaxation as another alpha 2 agonist, tizanide, has been found to resolve muscle spasticity in humans (Nance and others 1994).

Other possible treatments include benzodiazepines that have been used successfully to treat myoclonus following perioperative spinal opioid administration in humans (Bamgbade and others 2009) and dogs (Iff and others 2012). When used in a case of intrathecal morphine overdose in a dog (Da Cuhna and others 2007), effects quickly diminished with repeated doses until no effect was seen. Ketamine, an NMDA receptor antagonist, has also been reported to resolve hyperalgesia and myoclonus following chronic intrathecal opioid administration in a person when given as a low dose infusion (Forero and others 2011). Experimentally, a systemic bolus of ketamine resolved morphine induced hindlimb myoclonus in mice (Kolesnikov and others 1997). However, it was unsuccessful in resolving neuroexcitation in a dog following a perioperative dose of intrathecal morphine (Iff and others 2012). Both of these could have been used as additional medication in this patient if clinical signs persisted. Naloxone has been shown to be ineffective in a number of cases (Werz and MacDonald 1982, Da Cuhna and others 2007), which is possibly because the neuroexcitatory effects of morphine are not opioid receptor mediated (Werz and MacDonald 1982). A number of other medications have been used in existing case reports involving dogs and include intravenous phenobarbitone, pentobarbitone, atracurium, acepromazine and butorphanol with varying degrees of success (Kona-Boun and others 2003, Da Cuhna and others 2007, Iff and others 2012).

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