

Safety of Epidural Morphine with Preservative in Domestic Goats (*CAPRA HIRCUS*)

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ABSTRACT

The purpose of this study was to determine if epidurally (L6-S1) administered morphine (0.1 mg/kg; 15 mg/ml) preserved with phenol (2.5 mg/ml) and formaldehyde (3 mg/ml) (MWP) and diluted with normal saline to 0.05 ml/kg produces clinical or spinal cord changes that were different from those seen with epidurally administered preservative free morphine (PFM; 0.1 mg/kg), epidurally administered normal saline (SAL; 0.05 ml/kg), or no epidural. One hundred crossbred goats of both sexes (52 intact or neutered males; 48 females) weighing 21.4 ± 3.14 kg were determined to be in good health by physical exam and were randomly assigned to a treatment group. Animals were fasted overnight prior to intravenous sedation (xylazine 0.11 mg/kg) for the epidural drug administration. Goats were

randomized into seven groups given no epidural or epidural morphine (0.1 mg/kg) with or without preservatives and equal volume saline with different times to necropsy (2 to 4 week sampling time). Clinical status after the epidural was also evaluated. Histology was performed on the spinal cords removed from the lumbar region to the cauda equina at necropsy. All slides were examined by a veterinary pathologist blinded to treatment groups for neurotoxicity, determined by the presence of gliosis, central chromatolysis of neurons, white blood cell infiltrates, thickening of dura mater, and fibrosis. Clinical or histologic signs of neurotoxicity were not found in any treatment group. In conclusion, a single dose (0.1 mg/kg) of MWP administered epidurally in goats does not cause clinical or histologic evidence of neurotoxicity and may be considered acceptable for epidural use in goats.

INTRODUCTION

Pain management is a widely discussed topic in veterinary medicine. Multimodal methods of analgesia and anesthesia are popular due to synergistic effects of multiple drugs allowing one to minimize dosages of each drug used. However, these analgesics must be administered pre-emptively, as they are not as effective after a painful stimulus is already applied (Galatos 2011). Opioids are frequently given to control postoperative pain, but it has been shown that parenteral administration in ruminants can inhibit rumenoreticular contractions for up to 20 minutes (Carroll et al. 2007). In humans, the administration of epidural opioids decreased postoperative ileus compared to when given systemically (Masuo et al. 1993). For this reason, alternate routes of administration such as epidurally, are often sought out.

Opioid epidurals are given to patients receiving abdominal or limb surgery to provide prolonged analgesia post-operatively, in addition to reducing the intra-operative requirement for inhalant anesthetics that have negative cardiopulmonary effects (Pablo 1993; Torske & Dyson 2000; Galatos 2011). Furthermore, lower anesthetic concentrations can reduce the time it takes for an animal to recover and resume a standing position, which is ideal in ruminants to prevent myopathy and bloat (Pablo 1993).

One of the most commonly used epidural opioids for preemptive perioperative multimodal analgesia is morphine (Gari-mella & Cellini 2013). Morphine has a slow onset and long duration of action. The low lipid solubility allows morphine to migrate cranially so it is useful for forelimb and thoracic procedures. Once morphine reaches the cerebral spinal fluid (CSF), it persists and has a long duration of analgesic action on the dorsal horn of the spinal cord (Hendrickson et al. 1996; Torske & Dyson 2000).

There are two prevalent formulations of morphine—morphine with preservatives (MWP; typically formaldehyde and phenol), and preservative-free morphine (PFM). The preservative formaldehyde has the ability to cross through the blood brain barrier and

cause axonal swelling, and has been shown to cause neurotoxicity (Songur et al. 2010). Phenol does not readily pass through the dura, but is known to cause spinal nerve root damage. The resulting analgesia was once a sought out “adverse effect” in the treatment of severe pain or spasticity in humans (McGuinness & Cantees 1990; Katz et al. 1995).

Although MWP is specifically labelled “not for epidural or intrathecal use,” a literature search did not reveal any evidence documenting neurotoxicity with a single dose. The drug shortage crisis in the United States continues to worsen (Ventola 2011) and in 2016, the U.S. Food and Drug Administration (FDA^a) and the American Society of Health-System Pharmacists (ASHP^b) recognized a shortage of PFM, which is the standard formulation for epidural or intrathecal use. Due to unavailability of PFM, many livestock veterinarians have recently been influenced to instead use MWP in epidurals to provide analgesia. Thus, it is necessary to investigate whether the practice of MWP epidurals is safe. It was hypothesized that a single dose of MWP administered epidurally to goats would not cause histologic or clinical signs of neurotoxicity.

MATERIALS AND METHODS

This study protocol was approved by the Texas A&M University Institutional Animal Care and Use Committee. This study was designed as an equivalency study to show that PFM and MWP treatments are equal. It was assumed that PFM animals would have no pathology while 5% of MWP animals may have pathology, and we would consider +/- 10% difference to be equivalent. Assuming a significance level of 5% and power of 80%, group sizes of 13 animals were determined. Group sizes were rounded to fifteen to account for any attrition due to unexpected illness or mortalities.

One hundred random source mixed breed goats (52 intact or neutered males; 48 females) that were part of a terminal third year veterinary surgical teaching laboratory were used for this study. Animals were approximately 6 – 8 months old and weighed a

mean \pm SD (range) of 21.4 ± 3.14 kg (12-30 kg). Animals were kept in large groups in outdoor concrete pens with shelter from the elements, and fed coastal Bermuda grass hay, a commercial pelleted ration for goats, and water ad libitum. One to three days prior to the teaching laboratory, goats were moved to indoor housing, and housed in groups of four to five.

Animals were fasted at least 12 hours before sedation to minimize the risk of bloat. They were assigned using a random number generator to one of seven groups based on control (no epidural), sterile normal saline (SAL), or drug (MWP or PFM), and time until necropsy (2 to 4 weeks). Group 1: no epidural, 2 weeks (n=15); Group 2: SAL, 2 weeks (n=15); Group 3: SAL, 3 weeks (n=11); Group 4: PFM, 2 weeks (n=15); Group 5: PFM, 4 weeks (n=14); Group 6: MWP, 2 weeks (n=15); Group 7: MWP, 4 weeks (n=15). Because of different concentrations between MWP (15 mg/ml, West-Ward Pharmaceutical Corp, Eatontown, NJ, USA) and PFM (2 mg/ml, Hospira Inc, Lake Forest, IL, USA), the volume of injection was set at 0.05 ml/kg. Both PFM and MWP were given at a dose of 0.1 mg/kg. Thus, a 20 kg animal would receive 1 ml of PFM, 0.13 ml MWP diluted in 0.87 ml of saline, or 1 ml of saline depending on treatment group.

Sedation was achieved with xylazine 0.11 mg/kg intravenously (AnaSed, 20 mg/ml, Lloyd Laboratories, Shenandoah, IA, USA). Once sedated, animals were positioned in sternal recumbency with pelvic limbs extended cranially to open the lumbosacral space. The lumbosacral region was clipped and aseptically prepped. A 20g x 1 1/2" spinal needle was advanced into the lumbosacral space at L6-S1 until a "pop" through the ligamentum flavum was felt. Correct placement in the epidural space was determined by lack of blood or CSF outflow, and lack of resistance to the injection. Animals remained in sternal recumbency through recovery. All animals recovered from sedation uneventfully, and were able to walk back to their home pen within an hour.

Animals in Group 1 were not sedated. All animals were evaluated daily for clinical and neurological status.

Following the terminal teaching laboratory, lumbosacral spinal cords were removed from euthanized animals with a bone saw and any gross abnormalities noted. Suture was used to tag the spinal cord at the approximate location of the epidural (L6-S1). Spinal cords were fixed in 10% formalin and trimmed into an average of five cassettes per animal. Transverse sections (2-3 mm in width) were taken every centimeter from 5 cm cranial to the site of the injection, to 5cm caudally into the cauda equina. Longitudinal sections were taken from areas between transverse sections; only the dorsal half was included in the cassette. Each animal had an average of 21 sections of spinal cord trimmed into cassettes. Cassettes were then transferred to 70% alcohol, and processed and embedded into paraffin blocks. Two slides were made from each block, one of which was stained with hematoxylin and eosin (H&E) and the other with Masson's trichrome.

All slides were examined by a veterinary pathologist blinded to treatment groups for lesions associated with neurotoxicity, including: gliosis, central chromatolysis of neurons, white blood cell infiltrates, thickening of dura mater, and fibrosis.

RESULTS

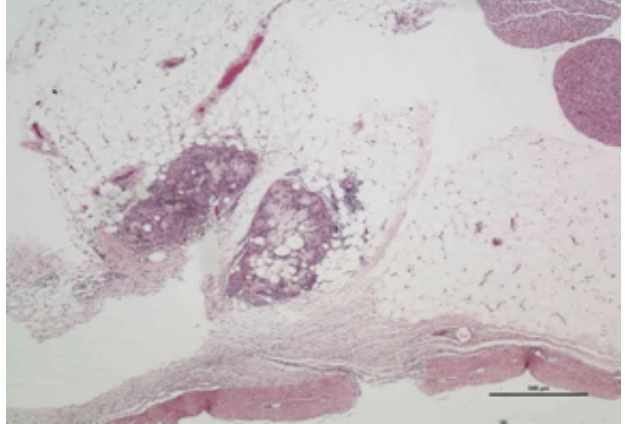
Initially, there were one hundred and five animals enrolled in the study. A saline epidural group was to be carried out to 4 weeks, but due to scheduling difficulties with the surgical teaching laboratories, 11 animals had to be euthanized at 3 weeks, and only four animals remained at 4 weeks. Thus, group 3 (SAL, 3 wk) was formed with eleven animals, and the remaining four animals were removed from the study as it was determined to be no longer statistically valid. One animal in group 5 (PFM, 4 wk) was misidentified and given the wrong treatment, so was also removed from the study, leaving 14 goats in the group. Of the five animals removed from the study, four

were female, and one was male. Histopathologic examination was still performed for these five animals, and but no neurotoxicity was found.

No animals presented with neurological signs following epidural administration, or for the duration of the study. Gross and histopathological lesions were documented for each spinal cord obtained. The highest incidence of gross lesions was in group 6 (MWP, 2wk), with two animals having mild hemorrhage on the ventral aspect of the spinal cord. However, no histologic lesions were seen in these animals. One animal each from groups 4 (PFM, 2 wk), 5 (PFM, 4 wk), and 7 (MWP, 4 wk) had an accumulation of fluid (edema) in the subdural space. Similarly, no histologic lesions were seen in these animals. The groups receiving no epidural or SAL epidurals had no gross lesions noted.

Two animals had mild focal inflammation present in only one of the cord sections that were examined for each animal. One animal in group 5 (PFM, 4wk) had macrophages and multi-nucleated giant cells in the fat surrounding the dura at the epidural site (Figure 1). One animal in group 7 (MWP, 4

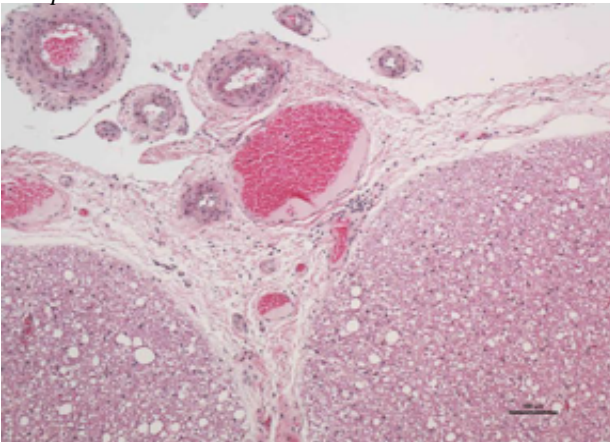
Figure 1. Animal from group 5 (PFM, 4 wk); macrophages and multi-nucleated giant cells in fat surrounding the dura at the epidural site.



wk) had mild focal perivascular lymphocytic cuffing, found intradurally at the epidural site (Figure 2). Animals from remaining groups had no histologic lesions noted on H&E. No fibrosis or thickening of the dura were found on Masson's trichrome slides across all groups.

Since animals exhibited no clinical signs and did not meet any of the histopathological criteria of neurotoxicity, statistical analysis was unable to be performed within or across treatment groups. An analysis of variance (ANOVA) confirmed there was no difference ($p > 0.05$) in body weight among goats in the treatment groups.

Figure 2. Animal from group 7 (MWP; 4 wk); mild focal perivascular lymphocytic cuffing, found intradurally at the epidural site.



DISCUSSION

Though not seen with animals on this study, reported adverse clinical signs following epidural morphine include pruritus and muscle spasms in the rear legs and tail. Due to the intensity of the pruritus, some animals have been reported to chew on and self-traumatize their rear legs and tail as a response (Wetmore & Glowaski 2000). In a study administering MWP in the subarachnoid space of ewes, one animal was noted to be licking and chewing incessantly at her flank and hindquarters during

recovery (Wagner et al. 1996).

There is report of a man presenting with confusion and disorientation following 10 days of MWP use through a lumbar epidural catheter. He reported a burning sensation during administration, but had no sensory or motor loss. His clinical signs resolved with cessation of MWP and administration of PFM (Du Pen et al. 1987). Other reports in the human literature describe sterile meningitis, pachymeningitis, arachnoiditis, epidural fibrosis, spinal cord damage, and nerve root injury as a result of preservative-containing medications administered into the central nervous system (Masuo et al. 1993).

Lesions that were found grossly or histologically in this study were largely non-specific. Gross lesions were attributed to normal perimortem changes associated with collection of the cord. The lesions found in the group 5 (PFM, 4 wk) animal with macrophages and multinucleated giant cells in the fat surrounding the dura is consistent with a foreign body reaction. However, this could not be confirmed, as foreign material nor bacteria could be found on section. The focal perivascular lymphocytic cuffing found in the group 7 animal (MWP, 4wk) is a non-specific inflammatory response. Possible reasons for lack of neurotoxic lesions may be due to individual variation in the extent of dural transfer and uptake of opioids, which can vary based on adipose tissue mass and epidural venous drainage (Torske & Dyson 2000).

Another possibility for the lack of histologic lesions is that neurotoxic lesions might be only inducible with chronic use. Animals in this study received a single dose of drug, whereas other studies that had reported neurotoxicity were after chronic administration of drugs in the epidural space. In a study by Larsen et al. in 1986, goats were given repeated installations of PFM and saline via an epidural catheter over 8 days. Histologic lesions for the saline group were minimal while animals receiving PFM had severe changes, including a diffuse cellular inflammatory reaction in the epidural space,

fat cell necrosis, occasional focal exudative inflammation, and a chronic inflammatory reaction by the fibrous membrane around the catheter. They concluded the histologic lesions were consistent with an irritant effect, since the degree of irritation following repeated saline was far less. In a similar study in sheep, an epidural catheter was used to deliver PFM or SAL over 9 or 30 days. They found a trend of more inflammation in the epidural space and dural thickening in the PFM group compared to the SAL control at 9 days. At 30 days, spinal cord parenchymal damage and partial local spinal cord necrosis was observed (Coombs et al. 1994).

CONCLUSION

In conclusion, a single dose of MWP administered epidurally in goats may be considered a safe practice, as it did not cause histologic or clinical signs of neurotoxicity in this study. Safety of chronic administration of morphine containing preservatives was not assessed. Thus, clinicians needing to administer multiple doses of MWP into the epidural space over time should use caution and carefully monitor animals post injection for adverse clinical signs.

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FOOTNOTES

- a. http://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm
- b. <http://www.ashp.org/drugshortages/current/>

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