Analgesia for canine cesarean section recovery

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Introduction

Safety studies during pregnancy and lactation have not been done or are sparsely published for a variety of drugs including analgesics for both humans and animals. This poses an issue for the use of pain management medications during pregnancy and lactation for the mother, from a safety standpoint for the fetus during gestation, and especially for the neonate during lactation.

Cesarean section and parturition itself can be a risky and painful process in animals, having adverse outcomes on health and welfare, including productivity in livestock species.[1] Postoperative analgesia presents a challenge for the small animal practitioner, especially as the canine dam and neonates are most often sent home soon after surgery and oral or topical medications are the only practical forms appropriate for the owner to administer. The most commonly considered classes of analgesics and available data on safety and efficacy will be addressed, though this is not to be considered an exhaustive review.

Opioids

Tramadol is the most commonly used oral opioid medication dispensed for analgesia in the canine. This drug presents challenges in efficacy for canine analgesia and little is known in terms of safety in suckling canine neonates. Efficacy is controversial as the pharmacokinetics and pharmacodynamics differ significantly between canine and human patients. In humans, two metabolites provide analgesia. One metabolite enhances the inhibitory neurotransmitters (serotonin and norepinephrine), and the other metabolite, O-desmethyltramadol (M1), is a weak opioid with one-onehundredth the mu receptor affinity of morphine. Dogs unfortunately produce very little of the M1 metabolite, and the half-life is very short in the dog, only 1.7 hours.[2-5] Pharmacokinetic studies have also shown that plasma levels are much lower after oral administration in dogs than humans, and that sequential dosing for several days leads to dramatic reductions of these plasma levels.[6,7] Frequent dosing is therefore necessary to maintain acceptable serum levels. However, even with frequent dosing, evidence of any significant analgesic effect using oral tramadol is not convincing.[7,8] There is evidence that parenteral administration of this drug produces a pain modifying effect, but this is not practical for at-home administration.[9-12] The safety to canine neonates suckling from treated dams is unknown, however short term use in human nursing mothers seems to be acceptable and have little effect on the neonate.[13,14] Short term use of tramadol may also be safe in the canine, but the efficacy of oral administration is questionable and in the authors' opinion not advisable, especially as a stand-alone postoperative analgesic.

Fentanyl topical preparations

There is no oral fentanyl preparation available for use in the canine and only one topical fentanyl preparation is approved in the dog (Recuvyra, Elanco, Greenfield, IN). In the past, human fentanyl patches have been used off-label in the dog. Topical preparations are not recommended for use in dams after cesarean section for several reasons, the most compelling of which is neonatal exposure. Nursing canine neonates will attempt to suckle any protruding feature on the dam, including a patch. Covering a patch is difficult and the most effective location for delivery of the patch product is on the caudal abdomen, where neonates will inevitably be exposed.[15] The approved product for dogs is a liquid topical preparation and not normally covered. The product insert warns of exposure risk to humans touching the patient, especially small children, therefore there is great concern for nursing neonates. Efficacy of topical fentanyl preparations is also a consideration. Delivery of the drug using human fentanyl patches (Duragesic, Janssen Pharmaceuticals, Beerse, Belgium) in the canine is extremely variable, affected by location, body temperature, and several other factors.[16] The recommended patch dose is 2 to 4 mcg/kg/hr, but the validity of this recommendation has never been established. Though fentanyl patches have their advocates, there are no scientific data to support their efficacy.[15] Sedation in the dam is also a risk with

these products, affecting attentiveness and care of the neonates. Topical fentanyl preparations therefore are not recommended post-cesarean section in the canine.

Gabapentin

Several studies in humans support the safety and benefit of gabapentin perioperatively for post-surgical pain, but these do not seem to correlate with efficacy in the canine.[17-23] Further studies are indicated to ensure efficacy of gabapentin as a postoperative analgesic in the dog. Safety studies and case reports in humans during breastfeeding are sparse.[24-25] Most reviews indicate the need for further studies in human medicine.[26-27] To the authors' knowledge, there are no studies or reports on milk expression of gabapentin in the canine. Somnolescence is the most common adverse effect in both canine and human patients, so attentiveness to neonates is a concern. Side effects usually spontaneously resolve after a few days of acclimation, though by this time the postoperative treatment course will be finished. The canine dose is based on the human perioperative dose of 10 mg/kg, though no studies support this recommendation.

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are perhaps the most common analgesics used postoperatively in both human and veterinary medicine. There are many studies supporting efficacy, and several drugs in this class are approved specifically for postoperative analgesia in the dog. The availability of oral preparations and ease of administration make these drugs convenient for the owner. The primary concern for any medication used after cesarean section is safety for the nursing neonate. Human studies show low NSAID expression in breast milk.[28,29] However, NSAIDs are contraindicated in breastfeeding mothers of premature infants because the COX-2 enzymes are essential for neonatal renal development.[30] This scenario is likely a more accurate model for the canine species in which kidneys are considered immature at birth. Maturation of the canine kidney does not occur until approximately three weeks after birth, and normal function is not present until approximately six to eight weeks of age.[31] Due to the effect of NSAIDs on nephron maturation, exposure should be avoided until renal development is complete or a safe dose is determined.[32] There are limited data on milk expression of NSAIDS in the dog or on any degree of exposure to the neonate that may be safe. A literature search found milk expression studies in animals for cimicoxib, meloxicam, and carprofen, but no information on firocoxib or deracoxib.

Cimicoxib

Cimicoxib is approved in the European Union for perioperative and osteoarthritic pain in the canine.[34,35] Limited data are available on cimicoxib. One study documented non-inferiority compared to carprofen for postoperative pain; however there is a lack of overall peer reviewed published data for osteoarthritic pain.[35] Another study has shown that oral cimicoxib given at a dose of 2 mg/kg to lactating bitches had a high transfer rate into the milk, with milk to plasma ratio of 1.7 to 1.9, as the drug is very lipophilic. Twenty-eight day old neonates suckling from these dams were sampled 8.5 and 24 hours after administering a single dose of cimicoxib to the dams. All puppies had cimicoxib concentrations near or below the limit of quantification (0.01 mcg/ml). The conclusion of this study was that after administration of cimicoxib to whelping bitches, suckling puppies should be minimally exposed to the drug through the dam's milk and no serious adverse effect should occur.[36] It should be noted, however, that use in pregnant or lactating dams is labeled as a contraindication with this drug, and efficacy as a standalone analgesic in a single postoperative dose is questionable.

Meloxicam

The efficacy of meloxicam for postoperative analgesia in the canine is well documented. Reproductive studies with meloxicam have been done in the bovine, ovine, and swine species; however, a literature search found no reproductive studies in the canine. Varying effects may prevent findings in one species from being extrapolated to another species. For example, one study concluded meloxicam is safe for use in pregnant cows, but another study showed NSAID inhibition of COX-2 in term sheep caused

prolonged gestation.[37,38] Unfortunately, no studies have been done in the postpartum canine demonstrating safety in neonates exposed to milk from treated dams. Further study is indicated to determine the safety of meloxicam in the canine as a postoperative analgesic for canine caesarian section.

Carprofen

The efficacy of carprofen for postoperative analgesia in the canine is also well documented. There are multiple reproductive studies investigating carprofen use in the lactating cow. Most notably, one study showed minimal milk expression of carprofen in mastitic and normal control cows.[39] This prompted a pilot study (previously unpublished) done by the author in six Labrador retrievers with similar findings. Carprofen was administered to bitches at 2 mg/kg every 12 hours following cesarean section for four days. Validated milk assays were performed on samples collected three hours after the morning dose, when peak levels were expected, daily for five days. Milk assays were performed on three bitches 24 hours prior to caesarian section as controls. One bitch had detectable carprofen levels in five of six samples, peaking at 21 ng/ml. All other milk samples showed no detectable carprofen concentration (lower limit of assay 1 ng/ml). Matching serum samples from one bitch revealed concentrations ranging from 547 ng/ml on day two to 21,564 ng/ml on day five of administration, indicating effective absorption and serum levels. The conclusion of this pilot study was that carprofen is minimally expressed in canine milk. A larger study with paired milk and serum samples on all test subjects is indicated to confirm initial findings.

Despite the minimal likelihood of carprofen expression in canine milk, the more significant concern is determination of a safe level of carprofen exposure for nursing neonates. A study involving serum assays in neonates would prove difficult due to the low levels expressed in milk and the limits of assay sensitivity. The lower level of expected neonatal absorption may be difficult if not impossible to quantify. There are also logistical and ethical concerns with blood sampling in neonatal puppies. An alternative study (previously unpublished) evaluating offspring from dams treated with carprofen at the pilot study doses was considered and is ongoing. To date, 55 dogs have been studied from 46 litters. Blood urea nitrogen (BUN) and creatinine alone were evaluated in 15 of the 55 dogs, and complete blood counts and serum chemistries were evaluated in the remaining 40 dogs. Thirty-seven litters were represented by one dog each and nine litters by multiple dogs each. Twenty-four breeds were represented. The average age of dogs was 39.5 months (range 5 to 106 months) and average body weight was 29.0 kg (range 4.3 to 82.6 kg). Average BUN was 18.0 mg/dL (range 10 to 44 mg/dL, reference range 6 to 31 mg/dL) and average creatinine was 1.0 mg/dL (range 0.5 to 1.6 mg/dL, reference range 0.5 to 1.6 mg/dL). Two individual dogs from the same litter had BUN values outside the reference range (32 & 44 mg/dL). However, both dogs had normal creatinine (1.6 & 1.1 mg/dL, respectively) and were clinically normal. When the study population was limited to dogs over five years of age (n=11), the average BUN was 15.55 mg/dL and average creatinine was 1.0 mg/dL. In total, 394 cesarean sections have been performed at the authors' clinic from 2000 to 2015, and approximately 320 of those bitches were treated with carprofen for postoperative analgesia. There are no known cases of acquired renal abnormalities in any of those litters based on verbal follow-up with the breeders. One case of suspected renal dysplasia occurred in a puppy that was clinically abnormal at birth and was significantly smaller than its normal littermates. This puppy developed clinical signs of renal disease around nine weeks of age and was euthanized due to progressive renal failure at seven months of age. The preliminary evidence from this study is promising for the safety of neonates exposed to milk from dams treated with carprofen. Continued evaluations will be done to confirm these findings.

Conclusion

Pregnancy and lactation are pharmacologically challenging periods because administering a drug to one patient, the dam, has the potential to affect the offspring as well. While some bitches may behave stoically after cesarean section, this is unquestionably a painful procedure and providing appropriate postoperative analgesia should be the standard of care. The sparse data on drug use during lactation in the dog make decisions about drug choice difficult. The efficacy of oral opioids, such as tramadol, is

questionable, as is the safety of topical preparations like fentanyl. Efficacy and safety data are lacking for gabapentin. Nonsteroidal anti-inflammatory drugs are the most promising category of analgesics for further study. In the meantime, clinicians should consider the welfare of all affected animals, dam and offspring, when making decisions regarding postoperative analgesia.

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