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Premedication with meloxicam exacerbates intracranial hemorrhage in an immature swine model of non-impact inertial head injury

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Abstract

Meloxicam is a cyclo-oxgenase-2 preferential non-steroid anti-inflammatory drug with very effective analgesic and anti-inflammatory effects in swine. Previous reports in piglets have demonstrated that meloxicam also inhibits cyclo-oxgenase-1 and reduces production of thromboxane significantly. We use pre-injury analgesia in our immature swine (3–5 day old piglets) model of brain injury using rapid head rotations without impact. In 23 consecutive subjects we found that premedication with meloxicam (N=6) produced a significantly higher mortality rate (5/6 or 83%) than buprenorphine (N =17, 1/17 or 6%, $p < 0.02$). On gross neuropathologic examination of the meloxicam-treated swine, we observed massive subdural and subarachnoid bleeding which were not present in buprenorphine-premedicated animals. To our knowledge there are no previous reports in swine of increased bleeding or platelet inhibition associated with meloxicam administration and further research is needed to define mechanisms of action in piglets. We caution the use of meloxicam in swine when inhibition of platelet aggregation might adversely affect refinement of experimental research protocols, such as in stroke, trauma, and cardiac arrest models.

Keywords

swine; refinement; meloxicam; bleeding; brain injury

Swine have become a popular laboratory animal model for biomedical research. Swine have several advantages over small animal models for modeling human disease, including physiology and organ structure and maturation. Moreover, large animals offer the opportunity to use instrumentation designed for humans. Adequate anesthesia and analgesia during and after procedures which may produce pain or discomfort must be provided. Analgesic drugs have various pharmacodynamic effects which may vary by species and age, and can affect study outcome measures.

Two common classes of medications to provide analgesia to swine are opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Opioid analgesics can cause central nervous system depression and decreased respiratory drive, which may be undesirable side effects in physiologic studies. NSAIDs have the advantage of providing analgesia without these unwanted physiologic side effects. NSAIDs provide analgesia by inhibiting the activity of

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cyclo-oxygenase (COX). COX is an enzyme that catalyzes the conversion of arachidonic acid into prostaglandin-like molecules. There are two important isoforms: COX-1 and COX-2. COX-1 inhibition by non-preferential NSAIDs disrupts normal gastrointestinal and platelet physiology. COX-1 within platelets is responsible for the production of prostaglandin H_2 which in turn is converted into thromboxane A_2 (TxA_2). TxA_2 plays a major role in platelet aggregation and clotting. To avoid the COX-1 dependent adverse effects, COX-2 preferential inhibitors have been developed. Meloxicam (Metacam, Boehringer Ingelheim Vetmedica, Inc) is a COX-2 preferential NSAID which is marketed for use in humans as well as several domestic species including swine. Previous studies of meloxicam administration in swine have reported COX-1 inhibition, but adverse bleeding side effects have not been observed.(1–3) We hypothesize that meloxicam in swine may result in increased intracranial bleeding and mortality rates in our model of traumatic brain injury and adversely affect refinement of experimental research protocols. We have developed an immature swine model of non-impact inertial head injury which produces detectable neurobehavioral deficits and in this communication we report our experience using two different analgesia plans; a opioid based (buprenorphine) compared to an COX-2 preferential NSAID (meloxicam). (4) Of note, all protocols were approved by the Institute of Animal Care and Use Committee of the University of Pennsylvania. Under general anesthesia (isoflurane 2–4%), 3–5 day old farm piglets' heads (N =23) were secured to a padded bite plate. Then using the HYGE pneumatic actuator, piglets experienced head rotation rotations in the axial direction (160–200 rad/s)(5, 6). Rotational velocity was measured by an angular rate sensor (ATA, Inc.) attached to the linkage of the sidearm. After the head rotation, animals were monitored for return of pinch reflex and extubated and survived for several days for neurobehavioral outcome studies. Return of pinch reflex usually occured on average 6–7 minutes after the head rotation, and animals were able to appropriately ambulate, vocalize and feed within 2 hours of injury before being returned to general husbandry care.(4, 7) Neurobehvarioal deficits in visual based problem solving and open field behavior are observed in injured animals compared to sham animals on post injury day 1 and 4 but resolve by post injury day 11.(4) On neuropathologic examination, we typically observe diffuse axonal injury (β-amyloid precursor protein immunohistochemistry), as well as scattered amounts of subarachnoid and subdural hemorrhage.

Historically, we had previously premedicated animals with burprenorphine 0.02mg/kg intramusculary (IM) prior to injury with a low mortality rate (5–10%), but with the concerns of possible central nervous depression and alteration in physiology and respiratory drive, a switch was made to the NSAID, meloxicam. Six animals were premedicated with meloxicam 0.2 mg/kg IM, and we observed a mortality rate of 83% within 24 hours following head rotation (Table 1). Meloxicam premedication was then discontinued in favor of buprenorphine for the next 17 consecutive subjects with a return to our expected mortality rate (1/17, 6%), despite no reduction in angular velocity of the head (Table 1). Gross neuropathologic evaluation of the meloxicam-treated animals revealed massive subdural and subarachnoid bleeding with mass effect, whereas buprenorphine-treated animals had thin subdual and subarachnoid hemorrhage accumulations in the sulci. Due to the high early mortality rate of the meloxicam treated group, we were unable to perfusion fix the brains and compare axonal injury assessed by immunohistochemistry between the 2 groups. Meloxicam is marketed as a preferential COX-2 inhibitor. Human studies have demonstrated that meloxicam does inhibit TxA_2 formation but not to significant levels that alter in vivo platelet function or clotting times.(8) However, NSAID selectivity of COX isoform inhibition can be species dependent.(9) Fosse et al performed pharmacokinetic and pharmacodynamic studies of meloxicam in 2–3 week old farm piglets.(3) A carrageenan-sponge model of acute inflammation was used to evaluate the effects of meloxicam. Animals received meloxicam 0.4 mg/kg intravenously or saline vehicle. Exudate levels of prostaglandin E_2 were measured as an indirect indicator of COX-2 activity and serum levels of thromboxane B_2 (TxB_2) as an indicator of COX-1 activity. Profound inhibition of TxB_2 was observed for at least 8 hours after administration of meloxicam, indicating strong inhibition of COX-1 in piglets.(3) In another study, 2 month old swine were challenged with endotoxin and randomized to treatment with meloxicam or placebo. TxB_2 levels were found to be markedly reduced in meloxicam treated animals compared to placebo.(10) Unfortunately, no coagulation profile or platelet aggregation studies were performed in either study to determine if decreased TxB_2 levels resulted in alterations in bleeding times or platelet aggregation. Our swine model may be more sensitive to smaller changes in platelet aggregation associated with COX-1 inhibtion, due to the known clinical association of traumatic brain injury with coagulopathy.(11)

Our experience with meloxicam in our head injury model would corroborate the strong COX-1 inhibition by meloxicam in immature swine previously reported. (3, 10) Unlike the buprenorphine-premedicated animals,most of the meloxicam-treated piglets developed lethal massive intracranial hemorrhage after experiencing non-impact head rotation. We speculate that the unexpected lethal intracranial hemorrhage was the result of meloxicam inhibition of COX-1, resulting in decreased TxA_2 levels, and reduction in platelet aggregation. Although meloxicam appears to have higher selectivity for COX-2 inhibition, its COX-1 selectivity is not trivial(3). We caution the use of meloxicam in swine when inhibition of platelet aggregation might adversely affect refinement of experimental research protocols, such as in stroke, trauma, and cardiac arrest models. Further research is needed to define meloxicam's effects in swine on bleeding and platelet aggregation.

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Table 1

Mortality and angular velocity of meloxicam and buprenorphine-treated piglets

	Meloxicam	**Buprenorphine**
Mortality (%)	5/6 (83%)	1/17 (6%)*
Angular Velocity (rad/s)	187.2 ± 6.7	194.3 ± 6.9^

* $p < 0.02$ by Chi-square test,

^ $p = 0.06$ by student t-test