Journal of the American Association for Laboratory Animal Science
Copyright 2008
by the American Association for Laboratory Animal Science

Vol 47, No 6
November 2008
Pages 8–9

Letters to the Editor

Effects of Indomethacin and Buprenorphine Analgesia on the Postoperative Recovery of Mice

Dear Editor,

I was dismayed after reading the article by Blaha and Leon in the July issue[1]. For the past 40+ years I have been an advocate for animal well-being. For the past 20 years I have used Buprenorphine to alleviate postoperative pain in all species of laboratory animals, and for the past 15 years have used Buprenorphine preemptively to improve pain alleviation in rodents. We have routinely documented the rapid recovery of normal behavior, recovery of presurgery weight, and normal weight gain as compared to nontreated controls in mice and rats undergoing a wide range of surgical procedures, including abdominal implants.

I am the attending veterinarian at three AAALAC-accredited institutions. At all of these institutions, we routinely administer Buprenorphine at the recommended dose of 0.05 to 0.1 mg/kg 30 minutes before surgery and every 8-12 hours after surgery until the animal exhibits normal food consumption and normal behavior. In almost all major, invasive procedures including abdominal implants, animals exhibit normal feeding behavior and regain presurgery weight within 48 hours.

The editorial board should be embarrassed about publishing a paper that did not give analgesic at the proper dose rate or at intervals to assure postoperative analgesia (i.e., the authors gave Buprenorphine at an extremely high dose rate and failed to give the analgesic at appropriate intervals to assure analgesia).

I hope you will take steps to assure your reviewers are committed to the ethical principles of animal research. This unethical and scientifically flawed paper will be used by investigators at other institutions to justify withholding opioid analgesics.

Sincerely,
Harold E Farris, DVM
Attending Veterinarian
University of North Carolina at Charlotte

Response to Dr. Farris' Letter to the Editor:

We thank the editors for the opportunity to respond to Dr. Farris' comments on our recent JAALAS article[1]. The fact that Dr. Farris believes that our study was unethical and scientifically flawed, despite rigorous institutional IACUC and JAALAS review and approval, indicates a misunderstanding of the purpose, design, conduct, or conclusions of our study. The purpose of our study was two-fold: (1) to assess the efficacy of buprenorphine and indomethacin on post-surgical recovery rates of mice implanted with radiotelemetry devices and (2) to improve post-surgical dosing strategies by providing oral analgesics and avoiding injections that may be painful.

To ensure effective analgesia, we gave buprenorphine by injection on the day of surgery and provided indomethacin orally 24 h later. Dr. Farris' major contentions were that we provided buprenorphine "at an extremely high dose rate" and neglected to provide the drug "at appropriate intervals to assure analgesia." Rather, Dr. Farris asserts that he uses a buprenorphine dosing regimen (0.5-1.0 mg/kg provided 30 minutes before and every 8-12 hours after surgery) that ensures recovery from major abdominal surgery within 48 h in most of the animals under his care. However, Dr. Farris did not provide details (e.g., the route of administration, types of surgeries, or species for which the efficacy of this regimen has been determined) that would allow us to validate his claims. Although the dose we used (0.3 mg/kg sc) is admittedly a high therapeutic dose, its use in our study design was hardly without precedent. According to Roughan and Flecknell[2], analgesiometric testing by several laboratories found the ED_{50} of subcutaneous buprenorphine in mice to be between 0.25-2.0 mg/kg while Flecknell and Liles[3] showed a dose-dependent increase in the duration of analgesia in rabbits with doses as high as 0.3 mg/kg. Furthermore, Goecke et al. reported that a single subcutaneous dose of buprenorphine at 2.0 mg/kg did not depress food intake in either surgical or non-surgical mice, in contrast to a multiple dosing regimen similar to that suggested by Dr. Farris. Based on these previous studies, our use of a single 0.3 mg/kg sc dose of buprenorphine was not "extreme" and may have afforded a longer duration of pain relief than Dr. Farris' recommended dose.

However, in light of our observed inhibitory effects of buprenorphine on food intake, we suggested (Discussion, p. 15) that a lower therapeutic dose (0.05-0.1 mg/kg) may be beneficial. In reference to his suggestion to use more frequent dosing, Dr. Farris fails to recognize that our experimental design required an oral route of administration. Oral administration is not feasible with buprenorphine because its rate of high first-pass elimination by the liver significantly reduces its efficacy after oral administration. Thus, providing multiple oral doses of oral buprenorphine in this study would have been scientifically and ethically inappropriate, as pain relief would not have been assured. To overcome this limitation and ensure more adequate pain relief, we provided oral indomethacin and acknowledged (Discussion, p. 16) that our 24 h dosing interval was likely insufficient to ensure effective analgesic relief for the entire time period, and should likely be shortened to ≤12 h intervals.

Finally, for Dr. Farris to suggest that our "paper will be used by investigators at other institutions to justify withholding opioid analgesics" is neither credible nor justified from our study conclusions. We specifically emphasize that our study results, which were specific to male C57BL/6J mice intraperitoneally implanted with a radiotelemetry device, may not be the same for other mouse strains or genetic knockouts. Our data suggest that substituting an oral NSAID for a parenterally injected opioid

Letters to the Editor

Letters discuss material published in *JAALAS* in the previous 3 issues. They can be submitted through email (journals@aalas.org) or by regular mail (9190 Crestwyn Hills Dr, Memphis, TN 38125). Letters are not acknowledged upon receipt nor are the authors generally consulted before publication. Whether published in full or part, letters are subject to editing for clarity and space. The authors of the cited article will be given an opportunity to respond in the same issue in which the letter is published.

may promote surgical recovery of mice, but this in no way provides a rationale for withholding any type of analgesic. According to the Scientists Center for Animal Welfare (SCAW) newsletter "the mainstay of oral analgesic therapy in rodents" is NSAID drugs, which are also recommended for long-term parenteral applications[5]. We agree that NSAID analgesia offers significant advantages that make them worth considering in any animal research program, but as scientists ultimately concerned with long-term pain relief and advancements in animal care and well-being, we suggest that further work is necessary in this area to determine the optimal analgesic and dosing regimen for pain relief in all species.

Collectively, we have over 20 years of experience with intraperitoneal implantation of radiotelemetry devices and are intimately familiar with the impact of these devices on post-surgical recovery rates in mice and rats. Despite extensive experience with this technique, our laboratory remains committed to ensuring improvements in post-surgical analgesia and will continue to explore new methods to ensure optimal pain relief for the animals under our care.

Sincerely,

Michael D. Blaha, MS
Lisa R. Leon, PhD
Thermal and Mountain Medicine Division
US Army Research Institute of Environmental Medicine
Natick, MA 01760

References

1. **Blaha MD, Leon LR.** 2008. Effects of indomethacin and buprenorphine analgesia on the postoperative recovery of mice. J Am Assoc Lab Anim Sci **47:**8-19.
2. **Roughan JV, Flecknell PA**. 2002. Buprenorphine: a reappraisal of its antinociceptive effects and therapeutic use in alleviating post-operative pain in animals. Lab Anim **36:**322–343.
3. **Flecknell PA, Liles JH.** 1990. Assessment of the analgesic action of opioid agonist-antagonists in the rabbit. J Assoc Vet Anaesth **17:**24-29.
4. **Goecke JC, Awad H, Lawson JC, Boivin GP.** 2005. Evaluating postoperative analgesics in mice using telemetry. Comp Med **55:**37-44.
5. **Wixson SK.** 2008. Rabbits and rodents: anesthesia and analgesia. SCAW **30:**7-12.

Erratum

In the September issue of *JAALAS*, National Meeting abstract P94, entitled "Wild-caught Virginia Opossums (*Didelphis virginiana*) Thriving in a Research Environment," was mistakenly printed with the wrong genus and species name. AALAS regrets this error and apologizes to the authors.