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Martinson, Amy M.; Murry, Charles E.; Brabb, Thea L.

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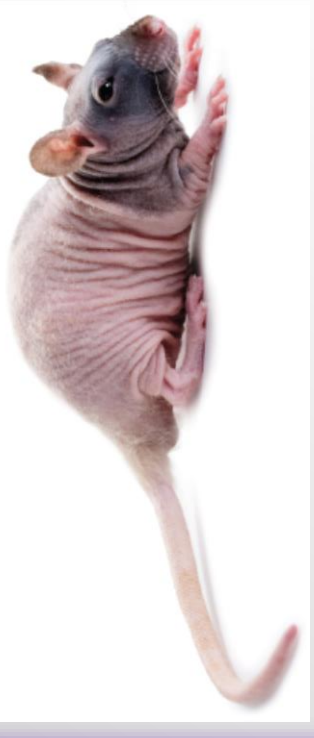
The information contained in this study is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Always seek the advice of a practitioner with any questions you may have regarding a medical condition or the medications used to treat it.

Important Update:

In order to remain compliant with the most current regulatory guidelines, we have updated the labeling on our SR formulations from Buprenorphine and Meloxicam SR to Buprenorphine and Meloxicam ER. **As of July 1, 2022, SR preparations mentioned in the attached study are now labeled as ER**, with no changes to the formulation of the medication(s).



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Neidig, Lauren E.¹; Haenisch, Mike¹; Meeker, Stacey M.¹; Martinson, Amy M.²; Murry, Charles E.²; Brabb, Thea L.¹
 1. Comparative Medicine, University of Washington, Seattle, WA, United States. 2. Pathology, University of Washington, Seattle, WA.

Dosing in Rats

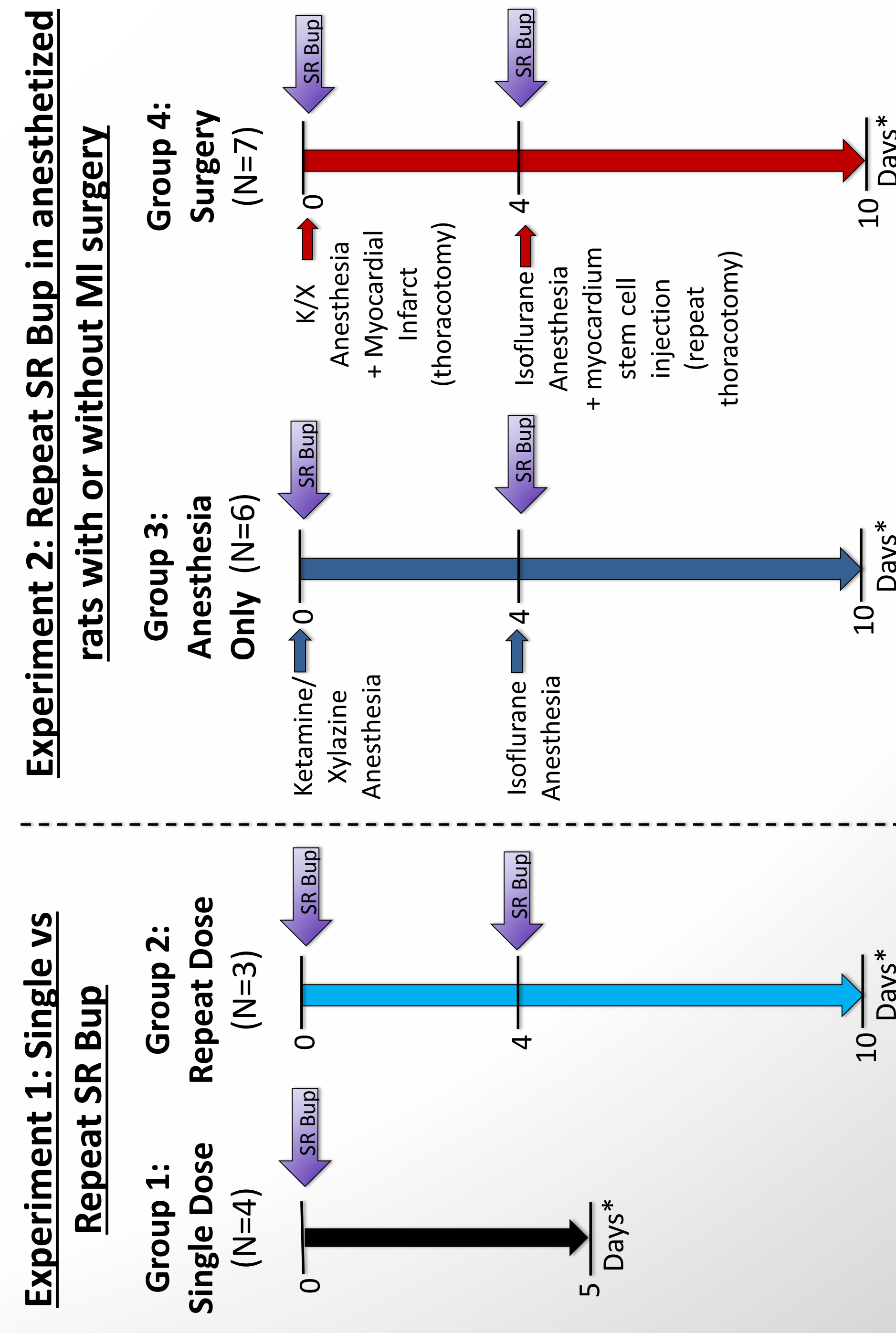


Introduction & Abstract

Sustained release formulation of buprenorphine (SR Bup) has become widely utilized in laboratory animal medicine, particularly in rodents, where reduced handling likely decreases stress while providing extended analgesic coverage. Current literature has documented blood plasma levels at or above 1 ng/ml (therapeutic level) for 72 hours following a single subcutaneous (SQ) dose in rats; however, there is a lack of published data on repeated dosing for animals undergoing multiple survival surgeries. Side effects associated with higher levels of buprenorphine in rats such as rebound hyperalgesia, respiratory depression, gastrointestinal distress and pica, highlight the need for SR Bup to be administered at appropriate dosages and time intervals. In this study, the pharmacokinetics of SR Bup were examined when a second dose was administered four days after the initial dose. Adult athymic nude male rats (Hsd:RH-Foxn1^{tmw}) received a dose of SR Bup, 1mg/kg SQ, on day 0 and again 90 hours later. Half of the animals (n=3) underwent ischemia reperfusion cardiac injury (MI) via thoracotomy (ketamine/xylazine anesthesia) followed by a repeat thoracotomy (isoflurane anesthesia) for stem cell therapy four days later. The control group (n=3) underwent the same anesthetic protocol, but no surgery. Serum buprenorphine levels were determined at 12-14 time points (0 to 8-10 days) after the first dose. Serum chemistry screens, before the first procedure and preceding the second dose of SR Bup, indicated no underlying renal or hepatic impairment. Rats in the control group had serum buprenorphine levels consistently above 1 ng/ml (1.12 ± 0.07 ng/ml) >100 hours (>4 days) following the repeat dose, and above 0.5ng/ml (0.78 ± 0.13) for 150 hours (>6 days) after the second dose. In rats that received surgery, serum buprenorphine levels remained above 0.5 ng/ml for 100 hours (> 4 days) following the second dose of SR Bup. Area under the curve analysis revealed elevated serum buprenorphine levels in the three days following the second dose compared to the three days after the first dose in the control group (p= 0.001). These results suggest that protocols with multiple survival surgeries within close time proximity may need to consider altering the dose and timing of repeat SR Bup administration.

Two new groups were later added to the experimental design (see study design below) including additional rats added to group 3 and 4. These data sets were collected at different dates but treated the same and samples were analyzed collectively.

Study Design:



Methods Overview:

- Buprenorphine SR™ Lab (ZooPharm) dosed at 1mg/kg, to athymic nude rats and serum levels measured via mass spectrometry
- Group 1 received a single dose of SR Bup and serum levels were obtained for 5 days post-dosing
- In group 2, rats received a second dose of SR Bup on day 4 (initially dosed at day 0) and serum levels tracked for 10 days total
- Rats in group 3 and 4 underwent ketamine/xylazine and isoflurane anesthesia. Group 4 had thoracotomy for myocardial infarct (MI) on day 0 with SR Bup, and repeat thoracotomy on day 4 for stem cell injection with SR Bup. Serum levels were monitored for 10 days

Experiment 1: Buprenorphine levels after single vs repeat dosing

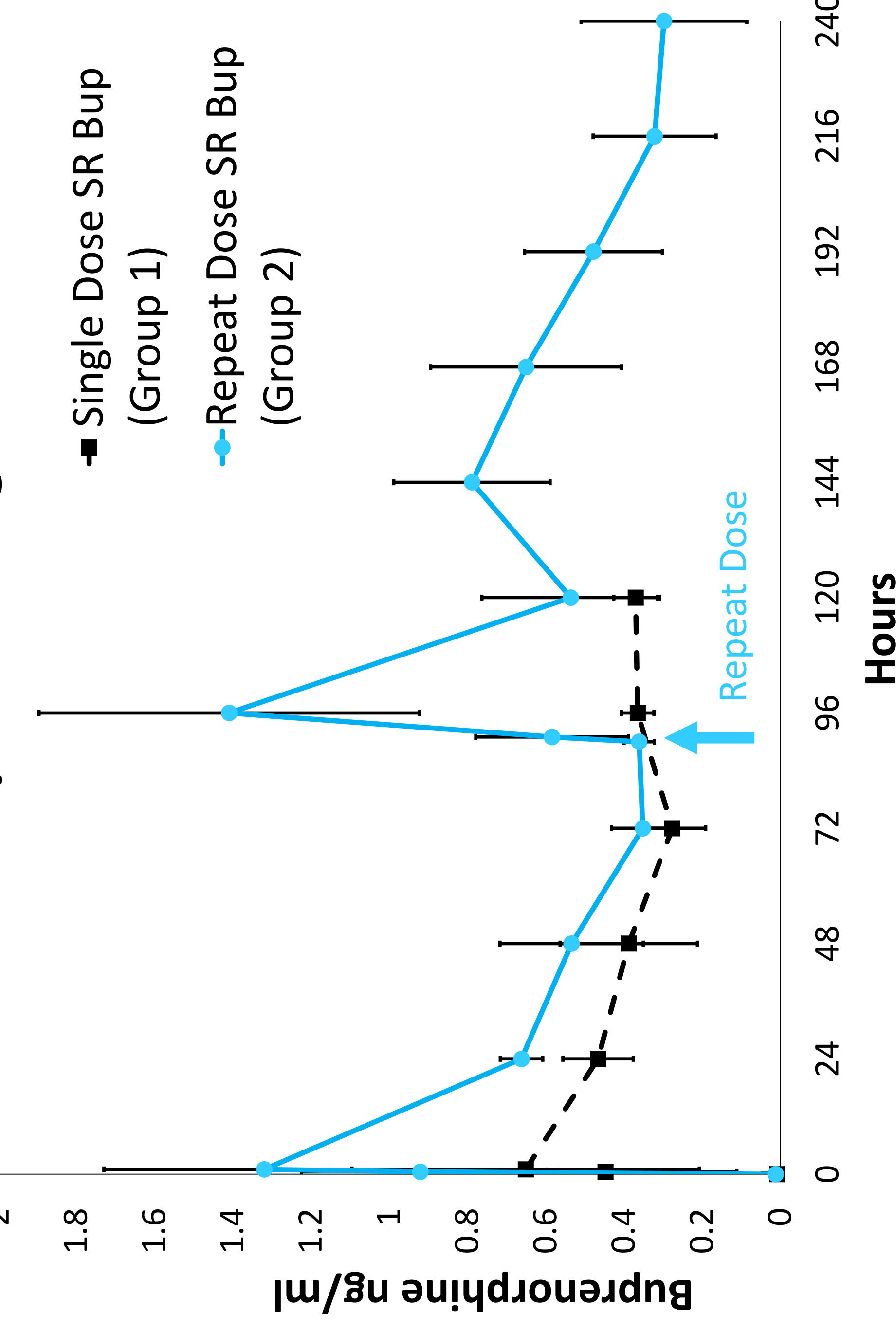


Figure 1. Mean buprenorphine serum levels in un-manipulated rats after a single (n=4) or repeat dose (n=3) of SR Bup. Error bars=standard deviation (SD)

Results:

- Peak serum levels were reached within the first 24 hours of the initial SR Bup dose and averaged 0.98 ng/ml (group 1 & 2)
- 72 hrs after the first dose, serum levels averaged 0.31ng/ml, significantly lower than currently described (groups 1 & 2)
- Peak serum levels were reached within 12 hours of the repeat SR Bup dose and averaged 1.4ng/ml (group 2)
- Serum buprenorphine remained at measurable doses over 6 days after a repeat dose of SR Bup (group 2)

Experiment 2: Buprenorphine levels are elevated in animals post-MI

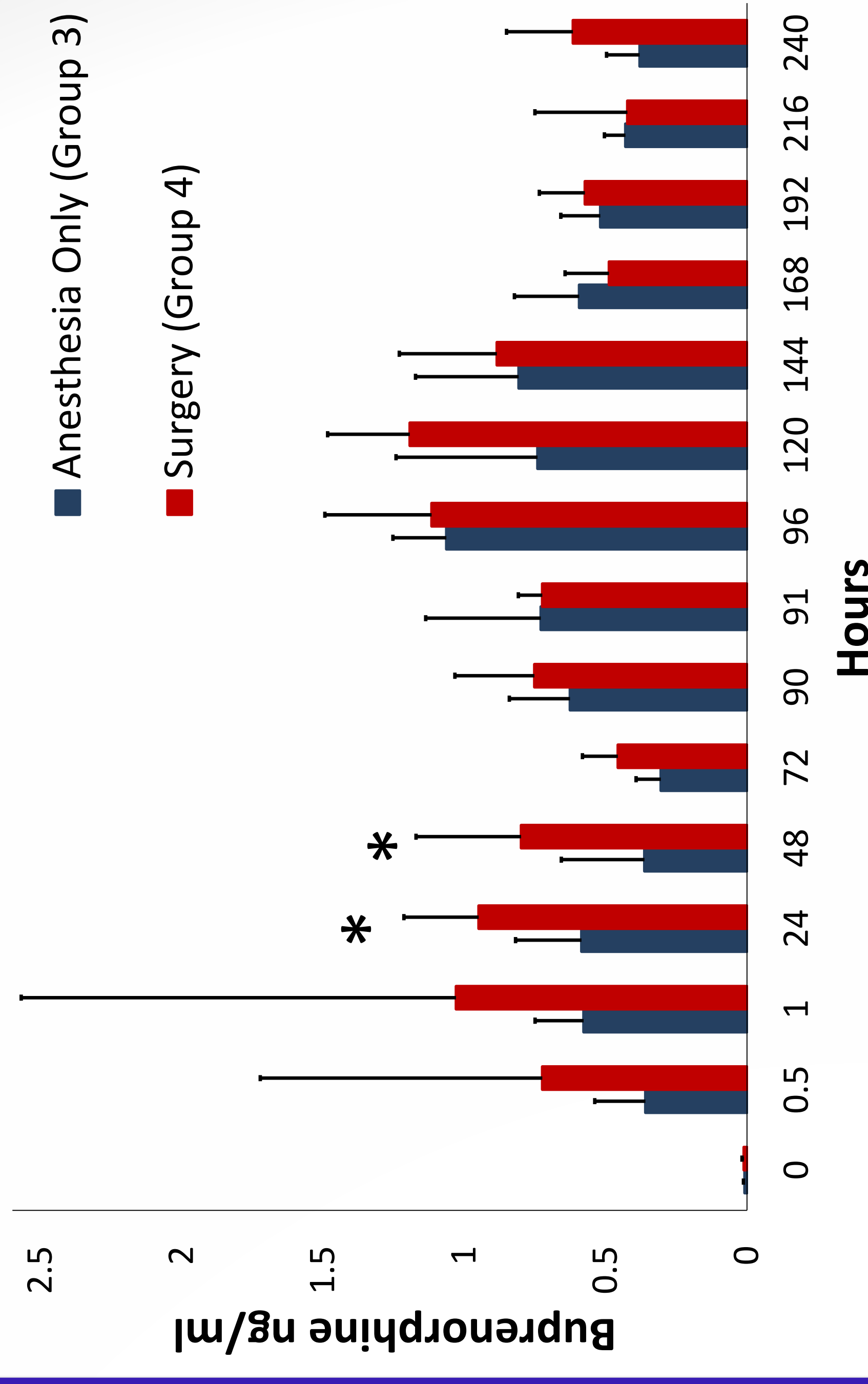


Figure 2. Comparison of mean serum buprenorphine levels in rats that underwent anesthesia only (n=6) vs surgical group (n=7). SR Bup was administered on day 0 and day 4. Error bars = SD. *p < 0.05.

Results:

- Serum buprenorphine levels are significantly elevated at 24 and 48 hours after a single dose of SR Bup in rats that underwent MI surgery compared to rats that only received anesthesia
- Buprenorphine levels remained over 0.5 ng/ml for over 100 hours after the repeat SR Bup dose in rats in group 3 & 4
- At day 10, rats in group 3 had average buprenorphine serum levels of 0.38ng/ml (n=6) while group 4 averaged 0.62ng/ml (n=4)
- Comparing rats that underwent anesthesia to those that did not (group 2 vs group 3), did not reveal significant changes in serum buprenorphine levels

Discussion :

- The results of this study indicate that buprenorphine may be present in the circulation at notable levels past 72 hours after a single dose of SR Bup.
- These residual levels should be taken into consideration if animals need to receive subsequent doses of SR Bup.
- Additionally, animals with compromised cardiovascular systems (myocardial infarct in this study) had higher serum buprenorphine levels than control and decreased dosing may be indicated
- Considerable variation was noted between animals within groups potentially indicating the need for larger sample sizes

