Pharmacokinetic Profiles of a Buprenorphine Sustained-Release Formulation in Mice

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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 in Polymer. **As of April 1, 2024, SR preparations mentioned in the attached study are now labeled as in Polymer**, with no changes to the formulation of the medication(s).

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Linda Nguyen[1], Termeh Feinberg[2], Meghan Villers[2,3], Caitlin Montgomery[2,3*], Elizabeth Engler-Chiurazzi[4], Jeffrey Wimsatt[2,3]

1-Department of Basic Pharmaceutical Sciences, School of Pharmacy; 2-Department of Epidemiology, School of Public Health; 3-Department of Medicine, School of Medicine. 4-Department of Physiology and Pharmacology, School of Medicine.

Introduction

Laboratory animal research is crucial to the rational development of new therapeutic strategies in human pre-clinical and veterinary clinical settings. Animal experiments can involve potentially painful or invasive procedures such as surgery. Hence, adequate pain control is essential for the validity of the experimental results and to assure adequate animal welfare. Buprenorphine is one of the most widely used analgesics for research involving rodents, but in practice only lasts 3-5 hours in mice (Gades et al., 2000). This requires frequent re-dosing to be optimally effective. A reformulated biopolymer-based sustained-release formulation of buprenorphine (Bup-SR), was recently developed with the goal of deriving a reliable three-day analgesic effect following a single subcutaneous dose. Blood plasma levels ≥1 ng/ml generally correspond to adequate pain relief in humans (Guarnieri et al., 2012). Additional studies have shown similar results for mice (Healy et al., 2014), so levels ≥1 ng/ml were used as the study endpoint. Our goal was to offer a stable and reliable pain management plan, while decreasing labor costs and handling-associated stress. All procedures were approved by WVU IACUC.

Materials and Methods

Materials

- Buprenorphine HCl (Buprenex®).
- Buprenorphine-Sustained Release (WildPharm Inc. Windsor, CO).
- Bup-SR Polymer Vehicle (WildPharm Inc. Windsor, CO).
- EDTA powered plasma collection tubes (B-D Company Franklin Lakes, NJ).

Methods

- Acclimated male 7 w Swiss-Webster mice.
- Doses studied: 1.0, 1.5 & 2.0 mg/kg.
- 9 time points per study: 0.5, 2, 4,8, 12, 24, 48, 72, 96 hours (3 replicates each); randomized by dose and time.
- Subcutaneous dosing in the neck dorsum with a 25 ga. needle & luer-lock 1 cc syringe.
- Blood samples: 0.5 - 1 ml intracardiac under isoflurane general anesthesia into powdered EDTA tubes.
- Plasma submitted for LC-MS analysis (Protea Inc., Morgantown WV).

Hot plate Testing

- Hot plate temperature: 55 °C.
- Nocioceptive behavior included hindpaw licking or jumping
- Total nocioceptive behaviors recorded
- 30 sec. trial to assess pain sensitivity

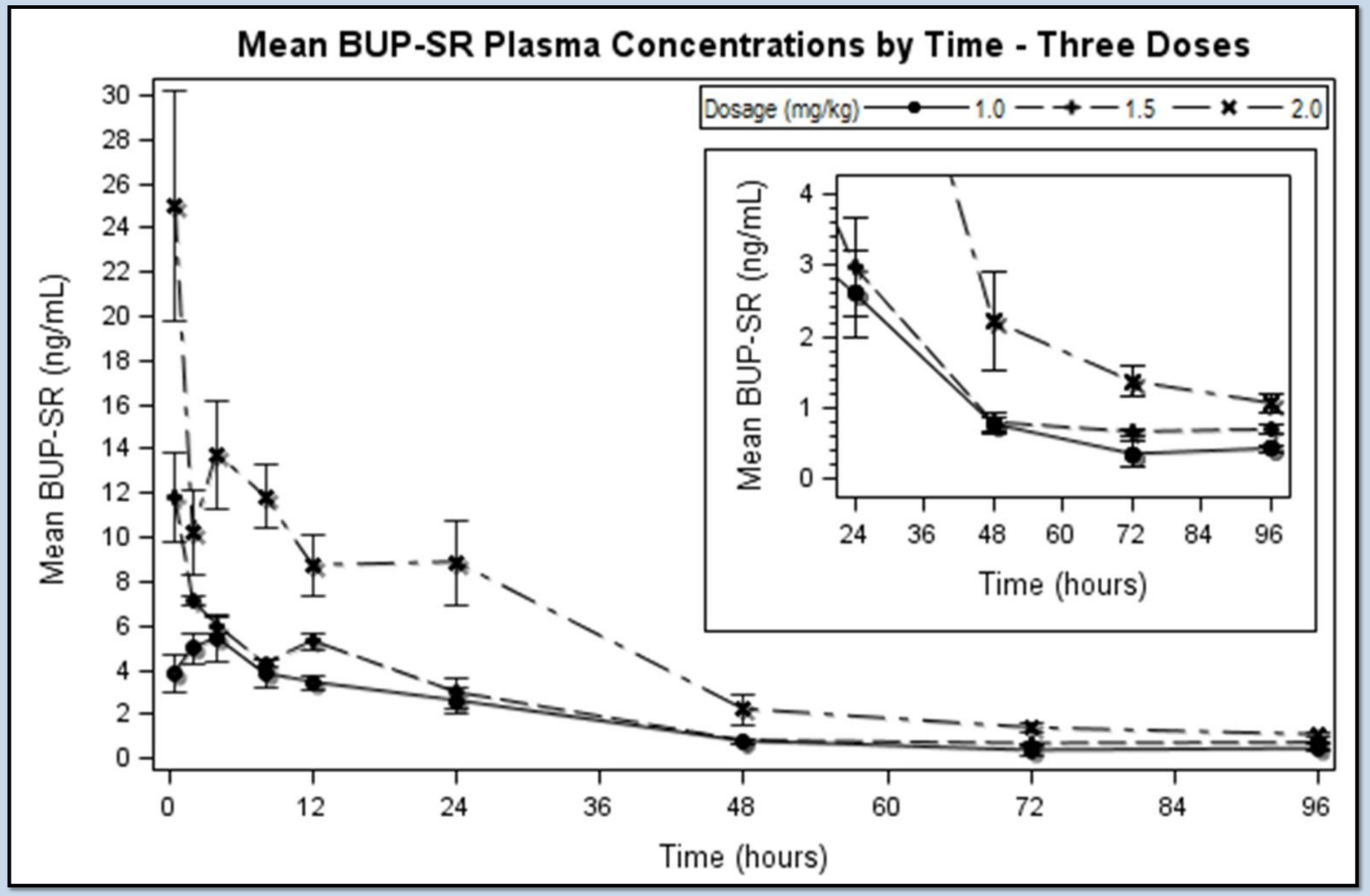

Figure 1: Time courses of plasma concentration of Bup-SR after subcutaneous administration (1.0, 1.5, and 2.0 mg/kg) to mice. Each value represents mean ± SE.
***Inset*:** Represents only the data from 24-96 hours.

Parameter	Bup-SR Dose (mg/kg)		
	1.0	1.5	2.0
Mean (SD)	2.85 (2.05)	4.40 (3.69)	9.23 (7.93)
C_{max}	5.44	11.79	25
T_{max}	4	0.5	0.5
AUC_{last}	149.23	195.25	453.26
$t_{1/2}$	22.30	4.27	1.49

Table 1: Nonparametric analysis following subcutaneous administration of Bup-SR (1.0, 1.5, or 2.0 mg/kg) to mice.

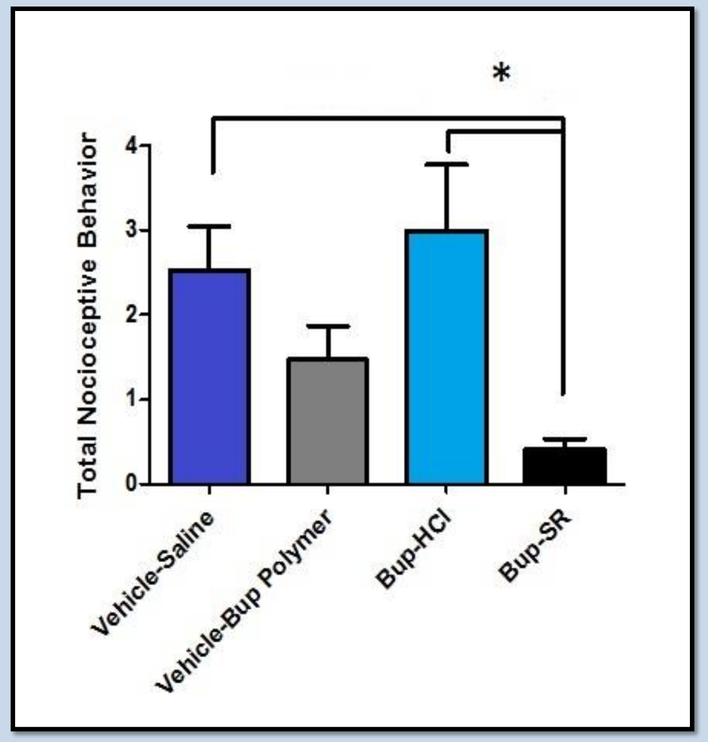

Figure 2: Hot Plate. Nocioceptive behavior on hot plate test after 72 hours for the four groups (VehBup-HCl 2.0 mg/kg, Bup-SR 2.0 mg/kg).

Results

Figure 1: Plasma decay curves over time show that 2 mg/kg Bup-SR provides at least 3 days of Bup levels above 1 ng/ml, whereas the lower doses retained this blood concentration for at least 24 hours.
Table 1: Higher doses led to higher peak concentrations (C_{max}), a shorter half-life ($t_{1/2}$), a larger Area Under the Curve (AUC), and trended toward a shorter analgesic induction time (T_{max}).
Figure 2: A 1-way ANOVA with treatment as the independent variable and using post hoc testing with Bonferroni correction for multiple comparisons indicated a significant difference of Bup-SR compared to Bup HCL and Saline but not Vehicle Polymer (* $p < 0.05$). Using this criterion, Bup-SR (2.0mg/kg) was analgesic for at least 72 hours.

Discussion

- Use of 2.0 mg/kg Bup-SR subcutaneously in the neck dorsum has the potential to sustain pain relief for 3 days in mice.
- No antagonist effects were evident.
- Lesser doses by the same method may be useful for shorter periods of analgesia delivery.
- Bup-SR may have somewhat variable induction times possibly related to dose and technique that should be taken into consideration when using this analgesic formulation preemptively.
- When used at the highest dose, Bup-SR has the potential to avoid lapses in analgesic delivery for 3 days. This should reduce labor costs and lapses in analgesic coverage.

Selected References

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