ABSTRACT	TITLE	AUTHOR(S)	INSTITUTION	
#23	Pharmacokinetics and Analgesic Efficacy of a Novel Extended-Release Buprenorphine Formulation in Rats	Stephanie Yang (1) Christopher Fry (2) Laura Durham (3) Daniel Myers (4) Patrick Lester (5)	University of Michigan	Abstract

ASR-26-23

Pharmacokinetics and Analgesic Efficacy of a Novel Extended-Release Buprenorphine Formulation in Rats

Stephanie Yang, University of Michigan
Christopher Fry, University of Michigan
Daniel Myers, University of Michigan
Laura Durham, University of Michigan
Patrick Lester, University of Michigan

Introduction

The laboratory rat is a commonly used animal research model. Rats often are a part of experimental and surgical models that may infer pain and discomfort. The inclusion of analgesia in the care for these animals is an ethical and regulatory obligation for both their welfare and well-being. Therefore, the selection for the safest and most effective pharmacologic intervention for postoperative pain management is critical.

Buprenorphine has a unique profile making it a useful analgesic for post-operative pain management in rats and other species. However, users of the standard buprenorphine formulation (Bup-HCl) are required to repeat dosing every 6-8 hours to maintain analgesic efficacy in rats. Moreover, recent pharmacokinetic studies have shown that Bup-HCl plasma concentrations tend to fall below the purported minimum therapeutic level (0.5 - 1 ng/ml) between 4 and 6 hours after an injection.

For rats, there are several long-acting parenteral buprenorphine products available on the market. Each product is formulated to gradually release buprenorphine over time using slow-release drug delivery technology. Recently, a third formulation of injectable long-acting buprenorphine has been introduced for use in research mice and rats: Bup ER, is an extended-release buprenorphine formulation based on a biodegradable water insoluble matrix depot incorporated in an organic solvent (Epicur Pharma-Stokes Pharmacy, Mt. Laurel, NJ) with a medium to low viscosity similar to a light oil or syrup. Bup ER is manufactured in a cGMP compliant FDA registered facility qualifying as pharmaceutical grade as cGMP safeguards and ensures the quality, strength, and purity standards as established by U.S. Pharmacopeia (USP). Bup ER demonstrated plasma concentrations exceeding 1 ng/ml up to 120 hours in mice and up to 72 hours of analgesia based upon tail flick and hypersensitivity testing.

The goal of this study is to evaluate the pharmacokinetics of a new extended-release buprenorphine (Bup ER) in rats over a 168-hour period and its analgesia effectiveness using thermal tail flick nociception evaluation and a plantar incision hypersensitivity model. The study includes 4 objectives: 1) to evaluate the pharmacokinetics of Bup ER in male and female SD rats for up to 168 hours following a single administration; 2) to determine whether a single dose of Bup ER would attenuate tail flick thermal nociception compared to saline control; 3) to determine whether a single dose of Bup ER would attenuate mechanical (Von Frey) and thermal hypersensitivity (Hargreaves) over time and 4) to report any gross adverse effects. We hypothesized that a single dose of Bup ER would do the following:

maintain clinically significant plasma levels > 1 ng/ml in rats for 72 + hours, attenuate mechanical and thermal hypersensitivity and demonstrate minimal adverse effects.

Methods

One-hundred and twelve combined healthy male and female rats were included in this study. The animals were obtained from Charles River Laboratories (Wilmington, MA). Exclusion criteria included previous analgesic administration and tail abnormalities.

Experimental procedures included three separate studies. Rats were utilized in a pharmacokinetic study to establish optimal dosing for analgesic efficacy evaluation (0.5, 2, 4, 8, 24, 48, 72, 96, 120, and 168 hours post-injection). Thermal tail flick nociception testing was performed at set timepoints (0.5, 1, 2, 4, 8, 24, 48, 72, and 96 hours) post-treatment. Mechanical and thermal hypersensitivity studies were performed together on same groups to assess presence or absence of hypersensitivity and attenuation at 1, 4, 8, 24, 48, 72, and 96 hours, following undergoing a plantar incisional surgery.

Results

PK Analysis

Bup ER sustained plasma buprenorphine levels above 1 ng/mL for 72 hours in female and male rats at 2 mg/kg and had continued sustained plasma buprenorphine levels above 0.5 ng/mL at 96 hours, yet plasma concentrations > 1 ng/ml demonstrated variability up to 96 hours. Plasma buprenorphine concentrations were measured in male rats receiving Bup ER 3 mg/kg SC (n=3 males) at 0.5, 2, 4, 8, 24, 48, 72, 96, 120, and 168 hours and found to exceed 1 ng/ml at all time points.

Tail Flick Nociception

Male and female rats demonstrated significant differences in %MPE values compared to saline controls from 2 hours (females, $p=0.019$) and 4 hours (males, $p=0.003$) up to 48 hours in female rats ($p=0.042$) and 72 hours in male rats ($p=0.029$). There were no significant differences between male and female SD rats in Bup ER or saline groups at all time points. There were no significant differences between male saline (mean 3.07 +/- 0.62) and male Bup ER (mean 2.98 +/- 0.51) baseline latency (seconds). There were no significant differences between female saline (3.53+/-0.49) and Bup ER (3.42 +/- 0.57) baseline latency (seconds).

Mechanical and Thermal Hypersensitivity

Mechanical hypersensitivity was not observed in male Bup ER treated rats up to 96 hours and only at the 1h time point versus baseline in female Bup ER rats. Thermal hypersensitivity was not observed in male Bup ER rats yet was observed in female Bup ER rats at 1 and 96 hours. Significant differences were noted between mechanical and thermal testing saline and Bup ER groups from 1 to 72 hours male rats and 1 to 96 hours female rats.

Conclusions

This study demonstrates that Bup ER is a highly effective long-acting analgesic for use in rats. Pharmacokinetic data revealed that a single dose of 2 mg/kg SC Bup ER achieved therapeutic levels of 1 ng/ml within 30 minutes that were maintained between 0.5 - 1 ng/ml up to 96 hours with female rats demonstrating higher plasma concentrations over time. Male and female SD rats demonstrated slight variances in PK profiles, yet plasma concentrations and pharmacokinetic parameters observed in this study support early onset and long-term analgesic efficacy.

Additionally, mechanical hypersensitivity was not displayed for up to 96 hours in both male and female SD rats while thermal hypersensitivity was attenuated up to 48 hours in a plantar incisional hypersensitivity assay demonstrating long-acting analgesia. The absence and reduction of mechanical or thermal hypersensitivity up to 48-96 h provides assurance that Bup ER should be effective for treatment of acute pain, yet additional studies are needed to fully elucidate acute efficacy in more invasive surgical models. The higher and prolonged plasma concentrations make Bup ER more favorable for invasive or painful procedures (e.g., orthopedic, or neuropathic) where potential analgesic therapy up to 120 hours may be warranted.

Bup ER offers a positive refinement and welfare advantage for postoperative pain management in rats via reductions in stress and adverse clinical effects due to reduced handling and fewer injections. Withdrawing Bup ER from vial using medium sized needles such as 23-gauge needles and then switching to a smaller needle (28-30 gauge) is preferred. Regardless of choice of needle size, accurate injection into the subcutaneous space without inadvertent administration of Bup ER into dermal skin layers is paramount. Future studies should continue to evaluate the clinical safety and efficacy of Bup ER in other rat stocks, immune status, surgical procedures, and in combination with other analgesics for a multimodal approach.