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Buprenorphine-sustained release alters hemodynamic parameters in a rat burn model

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ABSTRACT

Background: It has been previously shown that anesthesia and analgesia can affect outcomes in the rat burn model and that buprenorphine alleviated pain without drastically altering the outcomes of interest. Recently, the use of a sustained release (SR) formulation of buprenorphine has been promoted over conventional buprenorphine. In this study, we assessed whether buprenorphine-SR altered hemodynamic parameters in our rat model of severe burn injury.

Materials and methods: Adult male Sprague-Dawley rats were randomized to receive either conventional buprenorphine (0.05 mg/kg) or buprenorphine-SR (1 mg/kg). Buprenorphine-SR was administered 24 h before the experiment. Buprenorphine was administered on the day of experiment. These groups were further randomized to control or scald burn (60% of total body surface area). Systolic and diastolic blood pressure (SBP, DBP) and heart rate (HR) were measured using a noninvasive blood pressure system before receiving analgesia and after 72 h.

Results: As expected, HR was significantly higher after burn injury regardless of analgesic ($P < 0.0001$). Both SBP and DBP were significantly decreased in burned animals receiving conventional buprenorphine ($P < 0.0001$), but neither was altered in the buprenorphine-SR –treated burned animals. However, SBP, DBP, and HR were significantly increased after 72 h in control animals receiving buprenorphine-SR ($P < 0.0001$).

Conclusions: These data indicate that buprenorphine-SR alters the hemodynamic response to injury and may not be an appropriate choice for a model of severe burn injury. If this analgesic is used, investigators must cautiously form conclusions, especially in experimental conditions that would be expected to alter cardiac hemodynamics.

Introduction

Animal models of disease are used to determine underlying mechanisms, identify novel therapeutic targets, and test the efficacy and safety of therapeutics. For these models to provide reliable translatable information, the model must mimic the human disease conditions as well as control for any variables that may confound results. Our institution has

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investigated the clinical implications of severe burn injury as well as used both small and large animal models to investigate the mechanisms of burn-induced organ dysfunction.[1-3] One such model is a rodent scald burn model where 60% of the total body surface area is injured. This model exhibits many of the key characteristics of human burn injury including elevated levels of cytokines, increased heart rate (HR), and weight loss.[3] Investigators at our institution previously showed that the choice of anesthesia, analgesia, and euthanasia method can profoundly affect outcomes in this model. From this study, it was determined that buprenorphine was the optimal analgesic choice as it alleviated pain without drastically altering the cytokine profile.[4]

Buprenorphine acts as a partial agonist of μ-opioid receptors, whereas it antagonizes δ-and κ-opioid receptors.[5,6] Buprenorphine is highly effective for reducing pain in rodents and has been shown to be more effective than other common analgesics including carprofen and tramadol.[7-9] Thus, for many years, it has been the standard of care in many laboratory animal species. However, buprenorphine can depress cardiac function, cause unwanted sedation, and increase pica behavior.[10-12]

Recently, the use of buprenorphine-sustained release (SR), a polymer system that releases buprenorphine for 72 h, has been promoted over conventional buprenorphine, which is generally administered every 8-12 h.[7,13] The longer duration of action reduces stress to the animal as a result of handling and repeated injections. Buprenorphine-SR has been shown to equivalently reduce pain in various rodent models of pain without the side effects often reported with conventional buprenorphine.[14,15] However, there are no reports to date of whether buprenorphine-SR alleviates pain in animal models of severe burn injury. Thus, the aim of this study was to determine whether buprenorphine-SR altered outcomes in our rodent model of severe burn injury.

Materials and methods

Animal model of burn injury

The protocol for this study was approved by the University of Texas Medical Branch—Galveston Institutional Animal Care and Use Committee. Animals were cared for and handled according to the *Guide for the Care and Use of Laboratory Animals*. As previously described, a full-thickness 60% total body surface area scald burn was applied to male Sprague-Dawley rats.[3,4] Animals were allocated to either burn or control. General anesthesia was accomplished using isoflurane (1%-3% in air). Toe pinch was used to ascertain the level of anesthesia. After the burn, lactated Ringer's solution (40 mL/kg) was administered for resuscitation. Analgesia was given as described in the following. Control animals were treated similarly to the burn animals with the exception of the burn procedure and resuscitation. All animals were allowed to recover from anesthesia under high-flow oxygen and then housed individually in wire bottom cages throughout the experiment.

Experimental design

Experiment A

Adult male Sprague-Dawley rats ($n = 16$, Charles River Laboratories, Inc, Wilmington, MA) received buprenorphine-SR (1 mg/kg subcutaneous [SC]) 24 h before the beginning of the experiment. Animals were then randomized to control or burn. The experiment was terminated 72 h after the burn, as per veterinarian recommendation, with euthanasia via CO_2.

Experiment B

Adult male Sprague-Dawley rats ($n = 20$, 5/group) were randomized to receive either buprenorphine-SR or conventional buprenorphine. Buprenorphine-SR was administered at 1 mg/kg SC 24 h before the experiment. Conventional buprenorphine was administered at 0.05 mg/kg SC on the day of the experiment. Animals were then further randomized to control or burn. Animals were euthanized via decapitation without anesthesia 72 h after the burn. Plasma was collected for measurement of cytokines.

Hemodynamic measurements

Rodent blood pressure measurements were recorded using the Kent Scientific CODA Non-Invasive Blood Pressure System (Kent Scientific, Torrington, CT). Data were collected according to manufacturer specifications. Briefly, rats were put in weight-appropriate animal holders and placed on a warming platform. Size-appropriate occlusion and volume pressure recording cuffs were placed on the tail of each animal, which was then allowed to acclimatize for at least 5 min. Animals were considered ready for analysis once their tail measured at least 32°C. Volume pressure recording sensor cuff readings were collected over 20 cycles consisting of occlusion cuff inflation (up to 250 mm Hg) followed by 20 s of deflation while the blood pressure was measured. Measurements were determined valid if not rejected by the CODA NIBP software, and these values were included in the final analysis.

Cytokine analysis

Serum concentrations of proinflammatory cytokines were determined using readily available kits. Enzyme-linked immunosorbent assays used to analyze interleukin 1β (IL-1β), interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), and cytokine-induced neutrophil chemoattractant-1 (CINC-1) and -2 were purchased from R&D Systems Inc (Minneapolis, MN). Monocyte chemotactic protein-1 was purchased from BioSource International Inc (Camarillo, CA). All assays were performed according to the manufacturer's instructions.

Statistical analysis

Hemodynamic parameters were modeled by mixed analysis of variance with relation to all combinations of treatment group and time point, blocking on animal to control for repeated measures. Differences among treatments and times were assessed by Tukey-adjusted contrasts.

Cytokine expression data were analyzed with one-way analysis of variance followed by Tukey-Kramer's *post hoc*