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Effects of ibudilast on oxycodone-induced analgesia and subjective effects in opioid-dependent volunteers

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ABSTRACT

Opioid-induced glial activation is hypothesized to contribute to the development of tolerance to opioid-induced analgesia. This inpatient, double-blind, placebo-controlled, within-subject and between-groups pilot study investigated the dose-dependent effects of ibudilast, a glial cell modulator, on oxycodone-induced analgesia. Opioid-dependent volunteers were maintained on morphine (30 mg, PO, QID) for two weeks and received placebo ibudilast (0 mg, PO, BID) during the 1st week (days 1–7). On day 8, participants (N = 10/group) were randomized to receive ibudilast (20 or 40 mg, PO, BID) or placebo for the remainder of the study. On days 4 (week 1) and 11 (week 2), the analgesic, subjective, and physiological effects of oxycodone (0, 25, 50 mg/70 kg, PO) were determined. Analgesia was measured using the cold pressor test; participants immersed their hand in cold water (4 °C) and pain threshold and pain tolerability were recorded. Oxycodone decreased pain threshold and tolerability in all groups during week 1. During week 2, the placebo group exhibited a blunted analgesic response to oxycodone for pain threshold and subjective pain ratings, whereas the 40 mg BID ibudilast group exhibited greater analgesia as measured by subjective pain ratings ($p \leq 0.05$). Oxycodone also increased subjective drug effect ratings associated with abuse liability in all groups during week 1 ($p \leq 0.05$); ibudilast did not consistently affect these ratings. These findings suggest that ibudilast may enhance opioid-induced analgesia. Investigating higher ibudilast doses may establish the utility of pharmacological modulation of glial activity to maximize the clinical use of opioids.

1. Introduction

Opioid agonists are among the most effective tools to manage chronic pain (American Academy of Pain Medicine, 1997). However, in some patients, long-term use of opioids results in complications that can potentially limit their therapeutic utility. These complications include the development of tolerance to opioid-induced analgesia, hyperalgesia, and allodynia, which require escalating doses or increased frequency of opioid administration in order to maintain adequate analgesia (see Angst and Clark, 2006 for a review) and increases the risks of respiratory depression (Dahan et al., 2015). The high abuse potential of opioid analgesics, as evidenced by the sharp increase in non-medical use and abuse of prescription opioids (Center for Behavioral Health Statistics and Quality, 2015), is another concern that limits their therapeutic use. While some studies have demonstrated the immunosuppressive effects of acute and chronic opioid administration (Eisenstein et al., 2006), glial activation and cytokine release following opioid administration has been hypothesized to contribute to tolerance to opioid-induced analgesia, hyperalgesia, and allodynia, and has also been proposed to mediate the rewarding and reinforcing effects of opioids (Cooper et al., 2012). To circumvent these neurobiological effects that significantly limit the therapeutic potential of opioids, the current study was designed to assess the effects of an agent that attenuates opioid-induced glial activation, ibudilast, on oxycodone's analgesic effects and subjective drug effects associated with its abuse liability in opioid-dependent volunteers.

Preclinical studies in laboratory animals have provided evidence for enhanced glial activation following chronic opioid administration (Peterson et al., 1998; Stefano, 1998; Song and Zhao, 2001; Johnston et al., 2004; Takayama and Ueda, 2005; Watkins et al., 2005; Hutchinson et al., 2008), with a temporal association between glial cell activation and the development of opioid tolerance (Raghavendra et al., 2002). Opioid-induced glial activation has also been shown to contribute to the development of opioid-induced hyperalgesia and

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allodynia (Angst and Clark, 2006; Liu et al., 2011; Johnson et al., 2014). Recently, pharmacological modulation of opioid-agonist induced glial activation was shown to be effective in attenuating the development of antinociceptive tolerance, allodynia and hyperalgesia observed as a consequence of repeated opioid exposure in laboratory animals. Specifically, these modulators shift the dose-response curve for opioid-induced analgesia leftward, decreasing the minimum effective analgesic dose. In addition, they delay the development of opioid tolerance, and decrease hyperalgesia and allodynia (Raghavendra et al., 2003, 2004; Dorazil-Dudzik et al., 2004; Ledeboer et al., 2005; Shavit et al., 2005; Mika et al., 2007; Tawfik et al., 2007; Hutchinson et al., 2008, 2009; Johnson et al., 2014; Di Cesare Manneli et al., 2015). Among the agents tested, ibudilast, a phosphodiesterase inhibitor that inhibits glial cell activation and consequent cytokine release, has been shown to increase and prolong opioid-induced analgesia and decrease tolerance after repeated administration (Ledeboer et al., 2006; Hutchinson et al., 2009; Johnson et al., 2014).

These preclinical studies provide a strong rationale for the potential of glial modulators to effectively increase the therapeutic effects of opioids for pain by decreasing the neurobiological sequelae that contribute to the need to escalate opioid dose and frequency of administration in order to achieve adequate analgesia. Furthermore, many of these same inhibitors also decrease the rewarding effects of opioids (Narita et al., 2006; Hutchinson et al., 2007; Hutchinson et al., 2009), an effect hypothesized to be mediated by attenuating opioid-induced dopamine release in the nucleus accumbens (Bland et al., 2009), a neurobiological substrate thought to mediate the rewarding effects of drugs (Koob, 1992). As such, by potentially decreasing the abuse liability of opioids as well as decreasing the negative effects of repeated opioid exposure on analgesia and pain perception, these modulators may serve as promising candidates to increase the therapeutic utility of opioids as analgesics.

The current exploratory study was designed to investigate the effects of ibudilast on oxycodone-induced analgesia and subjective ratings related to abuse liability in opioid-dependent volunteers. Ibudilast has been used to treat asthma and post-stroke dizziness for over 20 years in Japan (Gibson et al., 2006), and is currently being explored as a potential treatment for neuropathic pain (Rolan et al., 2008) and neurodegenerative indications including progressive multiple sclerosis (Barkhof et al., 2010; Johnson et al., 2014). Ibudilast was recently reported to be safe and well tolerated in opioid-dependent volunteers, and effectively decreased some withdrawal symptoms during detoxification (Cooper et al., 2016). Thus, the two primary goals of this study were to assess the effects of ibudilast on both the analgesic and abuse liability-associated subjective effects of the mu-opioid agonist, oxycodone. This between-groups, within-subjects study assessed the effects of cumulative doses of oxycodone (0, 25, and 50 mg/70 kg) in three groups of participants before receiving ibudilast, then again during daily ibudilast administration. Participants were randomized to receive placebo (0 mg, BID), a low dose (20 mg, BID) or a high dose (40 mg BID) of ibudilast during the second study week.

Based on the preclinical findings, it was hypothesized that ibudilast would decrease tolerance and increase oxycodone's analgesic effects during the 2nd study week in the ibudilast-treated groups relative to the placebo- treated group. A secondary hypothesis was that the positive subjective effects associated with oxycodone's abuse liability would be attenuated in the ibudilast-treated groups during the 2nd study week, and that ibudilast would decrease heroin craving.

2. Methods

2.1. Participants

Healthy heroin users ages 21–45 years were recruited through local newspaper advertisements. Those who met inclusion/exclusion criteria after an initial telephone screen were invited to the laboratory for further screening. Prior to enrollment, participants gave written informed consent, received a psychiatric and medical evaluation, and provided detailed drug use and medical histories. Participants were accepted into the study if they were healthy, as determined by a physical examination (including electrocardiogram, and urine and blood chemistries), heroin dependent, as determined by a naloxone challenge, and not dependent on any other substances aside from nicotine or caffeine. Volunteers seeking treatment for their heroin use, and women who were pregnant or nursing were excluded from study participation. Participants were admitted into the study only after written informed consent to participate was given and eligibility criteria were verified. All study procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute and were in accord with the Declaration of Helsinki.

2.2. Design and procedures

This inpatient study consisted of 3, 1-week phases. Study week 1 consisted of a morphine stabilization period during which time all participants received morphine (30 mg, PO) 4 times per day (0800, 1400, 1900, and 2300 h) and placebo ibudilast (0 mg, PO) 2 times a day at 0830 and 2030 h. This week served to stabilize participants and standardize the level of opioid dependence before the detoxification phase that occurred during the 3rd study week when morphine administration was terminated. The effects of ibudilast on withdrawal during the 3rd study week and degree and type of adverse effects associated with ibudilast are described in an earlier publication, which reports that ibudilast was well tolerated (Cooper et al., 2016). During study week 2, participants were randomly assigned to receive placebo, 20, or 40 mg ibudilast (PO) twice per day at 0830 and 2030 h. On the 4th days of study weeks 1 and 2, volunteers participated in laboratory sessions designed to investigate the effects of ibudilast on the analgesic, subjective, and physiological effects of oxycodone (cumulative doses of 0, 25, and 50 mg/70 kg PO). On these days, blood samples (15 cc each) were drawn to determine ibudilast plasma levels; methods and results are discussed in an earlier publication (Cooper et al., 2016).

2.2.1. Laboratory sessions

Laboratory sessions were performed on the mornings of the 4th day of study weeks 1 and 2 (inpatient days 4 and 11). A standardized breakfast was provided prior to the session. Physiological monitoring (blood pressure, heart rate, oxygen saturation, measurement of pupil diameter) began prior to drug administration, and continued throughout the session. Baseline pain responsivity and subjective effects were assessed before and at specified time points after dosing.

2.2.2. Analgesic effects

The cold pressor test (CPT) was used to assess analgesic responses. The cold pressor apparatus consisted of two water coolers, fitted with metal frameworks. One cooler was filled with warm water (37 °C) and the other was filled with cold water (4 °C). An aquarium pump constantly circulated the water in each cooler. The coolers were equipped with a wire cradle upon which the participant was instructed to rest his/her hand during the test. Participants were instructed to remove all jewelry and to spread the fingers of the hand during the test.

The CPT began with an immersion of the hand into the warm-water bath for three minutes. During this time, blood pressure and heart rate were measured. Immediately after removal of the hand from the warm water, skin temperature of the thumb pad was recorded and the experimenter read a standardized script to the participant describing the procedures of the test. Immediately after measurement of skin temperature following warm water immersion, participants immersed the hand into the cold-water bath. Participants were instructed to report the first painful sensation after immersion. They were asked to tolerate the stimulus as long as possible, but were permitted to withdraw their hand from the cold water if the stimulus was too uncomfortable.