



Short communication

Ibudilast attenuates subjective effects of methamphetamine in a placebo-controlled inpatient study



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ABSTRACT

Background: Despite numerous clinical trials no efficacious medications for methamphetamine (MA) have been identified. Neuroinflammation, which has a role in MA-related reward and neurodegeneration, is a novel MA pharmacotherapy target. Ibudilast inhibits activation of microglia and pro-inflammatory cytokines and has reduced MA self-administration in preclinical research. This study examined whether ibudilast would reduce subjective effects of MA in humans.

Methods: Adult, non-treatment seeking, MA-dependent volunteers ($N = 11$) received oral placebo, moderate ibudilast (40 mg), and high-dose ibudilast (100 mg) via twice-daily dosing for 7 days each in an inpatient setting. Following infusions of saline, MA 15 mg, and MA 30 mg participants rated 12 subjective drug effects on a visual analog scale (VAS).

Results: As demonstrated by statistically-significant ibudilast \times MA condition interactions ($p < .05$), ibudilast reduced several MA-related subjective effects including High, Effect (i.e., any drug effect), Good, Stimulated and Like. The ibudilast-related reductions were most pronounced in the MA 30 mg infusions, with ibudilast 100 mg significantly reducing Effect (97.5% CI $[-12.54, -2.27]$), High (97.5% CI $[-12.01, -1.65]$), and Good (97.5% CI $[-11.20, -0.21]$), compared to placebo.

Conclusions: Ibudilast appeared to reduce reward-related subjective effects of MA in this early-stage study, possibly due to altering the processes of neuroinflammation involved in MA reward. Given this novel mechanism of action and the absence of an efficacious medication for MA dependence, ibudilast warrants further study to evaluate its clinical efficacy.

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1. Introduction

Methamphetamine (MA) dependence remains an international public health problem with significant medical and psychological consequences (Darke et al., 2008; Dean et al., 2013; Freeman et al., 2011; Ostrow et al., 2009). An efficacious pharmacotherapy could reduce this negative public health impact, but no medications have strong empirical support. Thus, identification of an efficacious pharmacotherapy remains a high priority (Brensilver et al., 2013; Ling et al., 2006; Vocci and Appel, 2007).

Previously tested medications for MA dependence primarily targeted dopamine or other neurotransmitter systems (Brensilver et al., 2013). The neuroimmune system is involved in MA dependence, and may provide a novel target for pharmacological

treatment (Coller and Hutchinson, 2012; Hutchinson and Watkins, 2014). In preclinical studies MA increased activation of microglia and astrocytes, and blockade of glial activation attenuated MA-related reward and neurodegeneration (Narita et al., 2006, 2008; Thomas and Kuhn, 2005). Microglia activation temporally precedes striatal dopaminergic neurotoxicity, suggesting a causal role of neuroinflammation in MA-induced neurodegeneration (LaVoie et al., 2004). In humans, abstinent MA users had greater microglia activation than controls (Sekine et al., 2008), and MA users' peripheral inflammation was strongly correlated with severity of cognitive impairment (Loftis et al., 2011). Altogether these findings support neuroinflammation as a potential target for MA pharmacotherapy.

Ibudilast is a non-selective phosphodiesterase inhibitor that inhibits glial cell activation and production of macrophage migration inhibitory factor and increases expression of neurotrophic factors (Cho et al., 2010; Gibson et al., 2006; Suzumura et al., 1999). Ibudilast has reduced microglia activation and pro-inflammatory cytokine signaling *in vitro* (Mizuno et al., 2004), and has also reduced MA self-administration and reinstatement of MA use in

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rodents (Beardsley et al., 2010; Snider et al., 2013). These findings support ibudilast as a potential MA pharmacotherapy in humans. In a sample of MA-dependent adults, we examined whether ibudilast would produce lower subjective ratings of MA than placebo.

2. Methods

2.1. Subjects

From 110 participants who initiated screening, 15 were randomized but four withdrew prior to completing the study, leaving 11 participants who completed the study and comprise the current sample. Inclusion criteria included age 18–55, current MA dependence verified via clinical interview (Spitzer et al., 1995), not seeking treatment for MA dependence, urine-verified recent methamphetamine use, and stable cardiovascular health. Exclusion criteria included current dependence on alcohol or other drugs, seizure disorder, history of head trauma, current use of psychotropic medication, recent suicide attempt, or serious medical/psychiatric illness. UCLA Westwood and Harbor institutional review boards approved the study.

2.2. Study design

2.2.1. Randomization and medication. Participants were randomized under a double-blind, within-subjects crossover design (see Fig. 1). Placebo, ibudilast 40 mg, and ibudilast 100 mg were administered orally in 7-day blocks with twice-daily dosing, with medication sequence randomized between-subjects as placebo–40 mg–100 mg ($n = 5$) or 40–100 mg–placebo ($n = 6$). After the 21-day medication phase and a three-day washout, participants were discharged and completed a two-week follow-up safety check. No serious adverse events occurred and adverse events were limited to common side effects of ibudilast or MA infusions such as insomnia, upset stomach, headaches, or pain at the infusion site (DeYoung et al., under review).

2.2.2. Saline and MA infusions. Intravenous (IV) MA infusions allowed optimal control of drug delivery and were delivered over 2 min using an automatic pump. Both 15 mg and 30 mg MA infusions were tested in fixed, ascending order (see Fig. 1) to allow optimal testing of safety and dose-dependent drug interactions. Heart rate and blood pressure were monitored continuously during infusion sessions and are reported elsewhere (DeYoung et al., under review). Each 7-day medication block involved two infusions on Day 4 (morning saline, afternoon MA 15 mg) and on Day 6 (morning saline, afternoon MA 30 mg), with active MA always administered 4 h after saline.

2.3. Drugs

Blinded 10 mg capsules of delayed release ibudilast and placebo were provided by MediciNova, Incorporated. Blister packages for each condition contained the entire course of study medication. Medications were administered twice-daily in five capsules, with 10 mg ibudilast or placebo distributed according to study condition.

2.4. Measures

2.4.1. Sample characteristics. Demographic and clinical covariates from the Addiction Severity Index-Lite (Cacciola et al., 2007) included age, sex, race, route of MA use, recent (past-month) frequency of MA use, and recent use of other substances, including alcohol and marijuana, assessed via self-report and urine drug screens.

2.4.2. Subjective drug effects. Participants rated the subjective intensity of 12 drug effects (Morean et al., 2013) on a visual analog scale (VAS) ranging from 0 (Not at all) to 100 (Extremely). At 15 min pre-infusion and eight times post-infusion, participants rated “Effect” (Any drug effect?), “High” (How high are you?), “Good” (Any good effects?), “Like” (How much do you like the drug?), “Stimulated” (How stimulated do you feel?), “Want” (How much do you want the drug?), “Use” (How likely would you use the drug?), “Bad” (Any bad effects?), “Nervous” (How nervous do you feel?), “Sad” (How sad do you feel?), “Crave” (How much do you crave the drug?), and “Refuse” (How easily could you refuse the drug?).

2.5. Data analysis

Sequence conditions were compared on baseline covariates using chi-square tests and analysis of variance (ANOVA). Multilevel models were used to analyze all post-infusion VAS ratings controlling for the pre-infusion VAS rating, which is superior to change score models when testing experimental conditions (Vickers and Altman, 2001). Random person-level and day-level intercepts accounted for clustered observations. Models used restricted maximum likelihood estimation which is robust to small sample sizes (Hoyle and Gottfredson, 2014). Covariates included demographics, route of MA use, recent use of MA and other substances, ibudilast sequence, study day, and post-infusion time. Subjective effect models first examined MA condition main effects and potential interactions with time and ibudilast sequence, which were retained if statistically significant ($p < .05$). Primary models then tested ibudilast \times MA condition interactions, with statistically-significant interactions ($p < .05$) probed by testing the simple ibudilast effect within each MA condition. Planned contrasts compared each ibudilast condition to placebo, using an alpha (.025) and confidence interval (97.5% CI) adjusted for multiple comparisons. Analyses were conducted in Stata 13.0 (StataCorp, 2013).

3. Results

3.1. Demographics and clinical characteristics

The sample ($N = 11$) was 82% male and 64% white, with mean age of 42.7 years ($SD = 7.2$). Most of the sample were MA smokers ($n = 8$, 73%), with a few intravenous MA users ($n = 3$, 27%). The mean past-month drug use was 17.4 days ($SD = 9.6$) for methamphetamine, 10.2 ($SD = 8.8$) for alcohol, and 5.2 days ($SD = 7.4$) for marijuana. The ibudilast sequence conditions did not differ significantly on sex, $X^2(1) = 0.92$, $p = .34$, ethnicity, $X^2(1) = 2.21$, $p = .14$, route of MA use, $X^2(1) = 1.40$, $p = .50$, alcohol use, $F(1, 9) = 1.25$, $p = .29$, or marijuana use, $F(1, 9) = .01$, $p = .95$. Participants in the placebo–40–100 condition were significantly younger, $F(1, 9) = 15.09$, $p < .01$, and had greater recent MA use, $F(1, 9) = 8.83$, $p < .05$, so subsequent models covaried for age and MA use.

3.2. Effects of MA condition, time, and ibudilast sequence on subjective drug effects

Compared to saline infusions, active MA produced prototypical changes in all subjective drug effects, with significantly greater ratings of Effect, High, Good, Like, Stimulated, Want, Bad, Nervous, Sad, and Crave and significantly lower ratings of “Refuse.” Significant MA condition \times time interactions for Effect, High, Good, Like, Stimulated, Want and Use indicated MA infusions (as compared to saline infusions) produced greater in-session peaks and greater time-related reductions during the infusion session. For other subjective effects, the time-related changes in VAS ratings were similar following MA and saline infusions, with significant decreases

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