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Assessment of human abuse potential of dasotraline compared to methylphenidate and placebo in recreational stimulant users

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ABSTRACT

Aims: The aim of this study was to evaluate the abuse potential of dasotraline, a novel dopamine and norepinephrine reuptake inhibitor with slow absorption (t_{max}, 10–12 h) and elimination ($t_{1/2}$ = 47–77 h) that is in development for the treatment of attention deficit hyperactivity disorder (ADHD).
Methods: Recreational stimulant users (N = 48) who had specific experience with cocaine, and who were able to distinguish methylphenidate (60 mg) versus placebo in a qualification session, were randomized, in a 6-period, double-blind, crossover design, to receive single doses of dasotraline 8 mg, 16 mg, and 36 mg, methylphenidate (MPH) 40 mg and 80 mg, and placebo. The primary endpoint was the Drug Liking Visual Analog Scale (VAS) score at the time of peak effect (E_{max}).
Results: There were no significant differences between the 3 doses of dasotraline and placebo on the drug liking VAS at E_{max}, and on most secondary endpoints. Both doses of MPH had significantly higher VAS-drug liking scores at E_{max} relative to both placebo (P < 0.001 for all comparisons) and dasotraline 8 mg (P < 0.001), 16 mg (P < 0.001) and 36 mg (P < 0.01). The increase in heart rate for MPH and dasotraline 36 mg showed a time-course that closely matched subject-rated measures such as Any Effects VAS.
Conclusions: In this study, dasotraline was found to have low potential for abuse, which may be, in part, related to its established pharmacokinetics (PK) profile, which is characterized by slow absorption and gradual elimination.

1. Introduction

Drugs that increase dopamine levels may be associated with stimulant effects and abuse (e.g., cocaine and amphetamine), whereas drugs that increase 5-HT and/or NE levels are not generally associated with recreational abuse (e.g., selective serotonin reuptake inhibitors, atomoxetine). Several of the most widely prescribed treatments for ADHD (e.g., methylphenidate, amphetamine preparations) increase dopamine levels, and are typically associated with stimulant effects, increased risk of abuse (Wilens et al., 2008), and enhanced vulnerability to abuse of other drugs (Mannuzza et al., 2008; Dalsgaard et al., 2014).

Dasotraline [(1R,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-amine] is a potent inhibitor of human DA transporters (DAT; dopamine uptake IC_{50} 3 nM) and NE transporters (NET; norepinephrine uptake IC_{50} 4 nM), and a weaker inhibitor of human serotonin transporters (SERT; serotonin uptake IC_{50} 15 nM; Sunovion, data-on-file, 2014). In humans, dasotraline has a time to maximum plasma concentration (t_{max}) of 10–12 h, a terminal elimination half-life ($t_{1/2}$) of 47–77 h, and achieves steady state plasma concentration after 2 weeks of daily dosing (Koblan et al., 2015; Hopkins et al., 2015). Among drugs with effects on dopamine neurotransmission, drugs with a slow onset of effect typically have reduced abuse potential (Busto and Sellers, 1986; Farré and Camí, 1991; Volkow et al., 1995; Volkow and Swanson, 2003; Swanson and Volkow, 2003). In addition, there is evidence that an increased half-life reduces the rewarding effects and lowers abuse liability due to sustained elevations in drug concentrations resulting in sustained inhibition of DA transporters (Swanson and Volkow, 2003; Schoedel et al., 2010). Dasotraline is being developed to evaluate its use in treating the symptoms of attention-deficit/hyperactivity disorder (ADHD; American Psychiatric Association, 2013). A 4-week, fixed-dose, placebo-controlled trial supported dasotraline as an efficacious treatment option for adults with ADHD (Koblan et al., 2015). Thus, the pharmacokinetic and pharmacodynamic characteristics of

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dasotraline suggest that its therapeutic effects in the treatment of ADHD, with sustained inhibition of DA and NE reuptake, may be associated with lower abuse potential than methylphenidate.

The primary aim of the current study was to evaluate the abuse potential of dasotraline compared to placebo and methylphenidate in recreational stimulant users. Peak Drug Liking VAS ("at this moment") was selected as the primary endpoint since it is the standard measure of abuse in human abuse liability studies. (Food and Drug Administration, 2010, 2013).

2. Methods

2.1. Design and subjects

This was a randomized, double-blind, double-dummy, 6-way crossover study in healthy recreational stimulant users in which the abuse potential of single doses of dasotraline (8 mg, 16 mg, and 36 mg) were compared to placebo and methylphenidate (40 mg and 80 mg; positive controls).

The study was conducted at a single clinical research unit located in Toronto, Ontario, Canada (INC Research Toronto, Inc.), was approved by the local IRB, and was conducted in accordance with ICH GCP guidelines and with the Declaration of Helsinki. All subjects reviewed and signed an informed consent document explaining study procedures and potential risks. Subjects were compensated for their participation in the study according to local guidelines.

Healthy recreational CNS stimulant users, age 18–55 inclusive, were eligible for enrollment if they reported a history of ≥10 lifetime experiences with CNS stimulants (e.g., amphetamines, cocaine, methylphenidate), and use of a CNS stimulant within 12 weeks prior to Screening, and use of cocaine within 12 months prior to Screening. Reasons for exclusion included: an active medical condition, including clinically significant neurological illness, or psychiatric illness (as assessed by the Symptom Checklist-90-Revised [SCL-90-R]); any clinically significant abnormality on physical examination, laboratory testing, or ECG; subjects currently with pending legal charges or on probation; subjects meeting DSM-IV-TR criteria (American Psychiatric Association, 2000) for drug or alcohol dependence (excluding nicotine and caffeine) or who had ever been in a substance rehabilitation program.

2.2. Study drug

Three doses of dasotraline were tested (8 mg, 16 mg, 36 mg) to allow examination of the dose-response curve ranging from a high therapeutic dose (8 mg) to a supra-therapeutic dose (36 mg) consistent with standard guidelines for abuse liability studies (Balster and Bigelow, 2003; Food Drug Administration, 2013; Griffiths et al., 2003; McColl and Sellers, 2006). The 40 mg and 80 mg doses of methylphenidate were selected based on previous studies (Kollins et al., 2001; Parasrampuria et al., 2007a,b) identifying these as doses that produced significant positive psychostimulant effects while minimizing potentially aversive effects, such as dizziness or nausea, that are associated with doses >80 mg that can increase ratings of negative effects and potentially confound the assessment of rewarding effects such as ratings of Drug Liking.

To ensure double-dummy, double-blind administration, the capsules received at each treatment visit were identical. Each dose consisted of 20 capsules: 18 capsules of either dasotraline or matching placebo, and 2 capsules of either methylphenidate or matching placebo. Methylphenidate was supplied as 20 mg tablets of immediate-release Ritalin® that were encapsulated on site into AAel gel capsules; matching placebo was supplied as lactose 100 mg placebo tablets, also encapsulated into AAel gel capsules. Dasotraline (and matching placebo) was supplied as 2 mg Size #1 Swedish orange opaque hard gelatin capsules. Based on the long $t_{1/2}$ of dasotraline (47–77 h), the minimum washout period between doses in the treatment phase was 21 days.

2.3. Study phases

2.3.1. Qualification phase. To confirm eligibility for the treatment phase of the study, subjects first completed a randomized, 4-day, double-blind, crossover qualification phase, in which they received single oral doses of immediate-release methylphenidate (60 mg) or matching placebo, separated by a 24 h washout. A subject was eligible for the treatment phase only if the following eligibility criteria were met in the qualification phase: (1) their peak score on the Drug Liking Visual Analog Scale (VAS) was 10-points higher in response to methylphenidate versus placebo response; placebo response was required to be in the range of 45 to 55 on the Drug Liking VAS (so that subjects neither endorsed liking nor disliking of placebo); and (2) safety data at the 60 mg dose methylphenidate suggested that the subject would be able to tolerate the 80 mg dose of methylphenidate in the treatment phase.

2.3.2. Treatment phase. Subjects who met eligibility criteria based on the results of the qualification phase were randomized to single oral doses in 1 of 6 treatment sequences based on a computer-generated randomization schedule, according to a 6 × 6 Williams square design (Williams, 1949). Subjects received their assigned dose, in the order specified, using a double-dummy procedure. Each treatment visit was 5 days to collect PK and pharmacodynamic measures up to 72 h postdose, with a 21-day washout period between each treatment visit. Subjects returned for a safety follow-up visit within 14 days after the last administration of study drug.

2.4. Pharmacodynamic measurements

Subjects underwent initial training and practice sessions. Visual analog scale (VAS) measures were scored on a 0–100 scale (Food Drug Administration, 2010, 2013). The VAS for Drug Liking (at this moment), Overall Drug Liking, and Alertness/Drowsiness ("my mental state is") used bipolar VAS scoring, with 50 as a neutral score, and 0 = strong disliking (or drowsiness), and 100 = strong liking (or alertness). The VAS for Good Effects ("I can feel good drug effects"), Bad Effects ("I can feel bad drug effects"), Any Effects ("I can feel any drug effect"), Take Drug Again ("I would take this drug again"), and Drug Similarity, used unipolar VAS scoring, with 0 = definitely not, and 100 = definitely yes. Drug Similarity VASs ("how similar is the drug you most recently received to [drug name]?") provided an estimate of similarity between dasotraline and drugs of other classes with which the subject was familiar, including placebo. Subjects were asked about cocaine (including crack), caffeine, ecstasy (MDMA), D-amphetamine or methamphetamine, phencyclidine (PCP), codeine or morphine, heroin, LSD, nicotine, pseudoephedrine, THC, benzodiazepines, ketamine, and about their "overall familiarity" with each drug. The 49-item Addiction Research Center Inventory (ARCI) was also administered (Martin et al., 1971). Four ARCI scales were used in the current study: MBG (euphoria), A and BG (stimulant effects), and LSD (dysphoria). An assessment of the Subjective Drug Value (SDV) was performed based on a procedure adapted from Griffiths et al. (2003); the permissible payment range was $0.25 to $50. Measures were administered and data were captured electronically using computerized proprietary software (Scheduled Measurement System, INC Research Toronto, Inc.).

The timing of assessments were as follows: VAS scales and ARCI measures were performed pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 9, 10, 10.5, 11, 11.5, 12, 13, 14, 24, 36, 48, and 72 h post-dose (and then repeated at the same intervals on Days 2 and 3; Drug Liking