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The alpha-1 adrenergic antagonist doxazosin for treatment of cocaine dependence: A pilot study

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ABSTRACT

Background: Medications decreasing central noradrenergic activity have been associated with attenuation of cocaine effects.
Aims: This pilot study examined the efficacy of doxazosin versus placebo for reducing cocaine use in treatment-seeking cocaine dependent persons.
Methods: We screened 108 cocaine dependent subjects and assigned 35 participants to receive either doxazosin (8 mg/day) or placebo for 13 weeks. Participants were titrated on the study medication according to two different schedules. During the initial phase of the study, patients were titrated onto the study medication over an 8-week period (DOX-slow). After reviewing data from our human laboratory study, a second phase was initiated, wherein titration was accelerated to a 4-week period (DOX-fast). All participants received weekly cognitive behavioral therapy. Urine toxicology was performed thrice weekly.
Results: Baseline subject characteristics were comparable. Thirty subjects entered the study: 8 subjects in DOX-slow, 9 subjects in DOX-fast, and 13 subjects in placebo. Total number of cocaine-negative urines was significantly increased in the DOX-fast group; and percentage of total cocaine-negative urines by group were 10% for DOX-slow group, 35% for DOX-fast group, and 14% for placebo ($\chi^2 = 36.3$, df = 2, $p < 0.0001$). The percentage of participants achieving two or more consecutive weeks of abstinence by group was 0% for DOX-slow group, 44% for DOX-fast group, and 7% for placebo ($\chi^2 = 7.35$, df = 2, $p < 0.023$).
Conclusions: This pilot study suggests the potential efficacy of doxazosin when rapidly titrated in reducing cocaine use.

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1. Introduction

Cocaine use disorders are a significant cause of morbidity and mortality throughout the world. Estimates from the 2010 National Survey on Drug Use and Health (NSDUH) indicate that 1.5 million Americans aged 12 years or older are current (i.e., "past month") users of cocaine, and 1.0 million Americans meet criteria for past year abuse or dependence (Substance Abuse and Mental Health Services Administration (SAMHSA), 2011a). Further, according to the annual report of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), an estimated 4 million Europeans aged 15–64 years have used cocaine in the past year (EMCDDA, 2010). Cocaine use is associated with numerous acute and chronic medical and psychiatric complications (Devlin and Henry, 2008). Additionally, cocaine use is associated with increased utilization of emergency department (ED) services, as reports from the Drug Abuse Warning Network (DAWN) indicate that cocaine was involved in over 420,000 ED visits, or almost half (43.4%) of visits involving illicit drugs in 2009 (SAMHSA, 2011b).

Cocaine binds and blocks the activity of the dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT), causing reuptake inhibition and subsequent increase in synaptic levels of these catecholamines (Rothman and Baumann, 2003). The rewarding effects of cocaine are attributed primarily to the resulting activation of dopaminergic neurons, initiated through its activity at the mesolimbic DAT (Koob, 2000). However, it is important to note that DAT knockout mice continue to self-administer cocaine, suggesting that blockage of DAT alone cannot account for the rewarding/reinforcing effects of cocaine and that other neurotransmitter systems must play a contributing role (Carboni et al., 2001).

Both preclinical and clinical trials indicate that activity within the noradrenergic system contributes significantly to the biochemical effects of cocaine. Functionally, the noradrenergic system is coupled to that of dopamine (DA), and it is has been demonstrated that stimulation of alpha-1 receptors (1) on DA neurons in the ventral tegmental area (VTA) and (2) in prefrontal

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cortex (PFC) results in increased firing of VTA dopaminergic neurons (Paladini and Williams, 2004; Blanc et al., 1994). Conversely, antagonism in the noradrenergic system results in decreased activity in the dopaminergic system, evidenced by the effect of prazosin, an alpha-1 adrenergic antagonist, which demonstrated the ability to decrease burst activity of VTA dopaminergic neurons (Grenhoff et al., 1993).

Cocaine's activity at NET, which serves to increase synaptic levels of norepinephrine (NE) in both PFC and on DA neurons through the process of feedback in the above described circuit, further enhances the activation of the dopaminergic system (Sofuoglu and Sewell, 2008). This effect has been mimicked with systemic administration of reboxetine, a specific inhibitor of NET, which demonstrated the ability to increase burst firing of VTA dopaminergic neurons (Linner et al., 2001). Antagonism of the noradrenergic system has been shown to limit the behavioral effects of psychostimulants, such as d-amphetamine (D-AMPH) or cocaine. Prazosin injected into mPFC completely blocks locomotor hyperactivity induced by intra-accumbens injections of D-AMPH (Blanc et al., 1994). Darracq et al. (1998) demonstrated through microdialysis studies in rats the locomotor activating effects of D-AMPH are caused by stimulation of cortical alpha-1 adrenergic receptors. Prazosin, when administered either locally or systemically, has demonstrated the ability to inhibit D-AMPH induced dopamine release and locomotor activity in mice (Blanc et al., 1994; Darracq et al., 1998; Drouin et al., 2002; Wellman et al., 2002). Additionally, knockout mice lacking alpha-1B NE receptors demonstrate significantly decreased locomotor activity and behavioral sensitization in response to D-AMPH, morphine, and cocaine (Drouin et al., 2002).

Pharmacologic antagonism of the noradrenergic system and its subsequent impact on cocaine use has been the subject of preclinical study by our group. Prazosin attenuates cocaine-induced reinstatement of extinguished drug-seeking behavior in rats (Zhang and Kosten, 2005). Further, prazosin, when co-administered with cocaine pre-treatment, attenuated subsequent self-administration of cocaine under a fixed ratio (FR) schedule and blocked the effect entirely under a progressive ratio (PR) schedule (Zhang and Kosten, 2007). These results further suggest the contribution of the noradrenergic system to the neurochemical and behavioral effects as well as the implications of decreasing alpha noradrenergic stimulation for treatment of cocaine dependence.

This pilot study evaluated the safety and efficacy of doxazosin, a long acting and selective alpha-1 adrenergic antagonist, in reducing cocaine use among cocaine-dependent individuals. We selected doxazosin because of its extended half-life ($t½$ up to 22 h), which is not influenced by age, renal function, or dose, and which is also significantly longer than that of prazosin ($t½ = 2–3$ h; Jaillon, 1980; Rubin et al., 1981). We hypothesized that doxazosin treatment, in comparison to placebo, would decrease cocaine use behavior as measured by cocaine urine toxicology.

2. Methods

2.1. Participants

One hundred eight individuals seeking treatment for cocaine dependence were recruited from the greater Houston area and attended clinic at the Outpatient Clinical Trials Research group at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC). At the time of screening, subjects underwent a full physical examination, psychiatric evaluation, and assessment of laboratory values. Subsequently, each participant met the following inclusion criteria: (a) male or female, (b) aged 18–64 years, (c) any race or ethnic origin, (d) current use of cocaine with self-reported use of cocaine at least once weekly for at least one month preceding study entry, toxicology confirmation of cocaine-positive urine, and a score of three (3) or greater on the Severity of Dependence Scale (SDS; Kaye and Darke, 2002; Gossop et al., 1995, 1997), (e) diagnosis of cocaine dependence, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000). Exclusion criteria included current diagnosis of alcohol or other drug abuse or dependence (other than nicotine); significant medical conditions (i.e., major cardiovascular, renal, endocrine, or hepatic disorders), such as abnormal liver function (with laboratory findings of SGOT or SGPT greater than three times normal), hypotension or hypertension, a current cardiac condition, or seizure disorder; lifetime diagnosis of schizophrenia, bipolar disorder, or other psychotic disorders; active suicidality or homicidality; current prescription for psychotropic medication; and pregnancy or breastfeeding.

Each participant gave written informed consent, as approved by the Baylor College of Medicine and Michael E. DeBakey Institutional Review Boards (IRB).

2.2. Design and procedures

The study was a 17-week, double-blind, placebo-controlled trial in which cocaine dependent individuals were randomly assigned to receive doxazosin (8 mg/day) or placebo. Initially, we began this pilot clinical trial by using the dose titration recommended by the Physicians' Desk Reference (PDR), which suggests starting doxazosin at 1 mg/day and increasing by 1 mg each week to a maximum daily dose of 8 mg (PDR, 2012). After analyzing data from our human laboratory study, it became evident that doxazosin could be safely increased at a more rapid rate (Newton et al., 2012). As a result, the dose escalation schedule was changed so that induction onto the medication would occur at a rate of increase of 2 mg/week, allowing the optimum dose of 8 mg/day to be reached after four weeks. Participants reaching the target dose after an 8-week titration period are labeled as the DOX-slow group, while those reaching the target dose after a 4-week period are labeled as the DOX-fast group. Participants were stabilized on doxazosin or placebo over weeks 4–13 (for DOX-fast group) or 8–13 (for DOX-slow group) and then tapered off doxazosin or placebo over study weeks 14–17.

All participants were asked to attend clinic visits for dosing and completion of research tasks on Monday, Wednesday, and Friday of each week of the study. Research staff administered the study medication or placebo on these days (MWF), and participants were given take-home doses of the medication or placebo to self-administer on Tuesday, Thursday, and weekends. Additionally, all participants were required to participate in 1 h of weekly, individual, manual-guided cognitive behavioral therapy (Carroll et al., 1998) to facilitate treatment retention and medication adherence as well as delivering enhanced treatment to all participants, regardless of medication arm.

2.3. Assessments

Participants were assessed during screening, at baseline, weekly during treatment, and at the end of study (week 17). At intake, each participant was interviewed using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and completed the Addiction Severity Index (ASI-Lite; McLellan et al., 1985). During both intake and at baseline, participants completed the (a) SDS, (b) Cocaine Selective Severity Assessment (CSSA; Kampman et al., 1998; Mulvaney et al., 1999), (c) cocaine craving visual analog scale (Kampman et al., 1998; Mulvaney et al., 1999), (d) Beck Depression Inventory (BDI), and (e) Hamilton Anxiety Scale (HAM-A).

The a priori primary outcome was reduction in percentage of cocaine positive urines as measured by thrice-weekly cocaine urine toxicology results. Samples were obtained Mondays, Wednesdays, and Fridays and tested for the presence of the cocaine metabolite, benzoylecgonine, as well as other drugs (e.g., opiates, benzodiazepines, barbiturates). Following collection, urine samples were immediately tested on site using an Acon DOA-754 5-Panel One Step Drug Screen Test card (coc/amp/thc/opi/benz). Secondary outcome measures included percentage of participants achieving two weeks of abstinence, retention (weeks in treatment), and adverse effects from medication.

2.4. Data analyses

Subject demographics and baseline characteristics of participants assigned to the three conditions were compared using χ^2 and general linear model (one-way) analysis of variance (ANOVA) for ASI-Lite parameters. Urine toxicologic screening results for cocaine-positive urines collected over the total course of the trial were analyzed using χ^2 and repeated measure ANOVA statistical tests with the Least Squares Difference for post hoc two group comparisons. The percentage of cocaine-positive urines per two week period served as the analyzed variable. Urine toxicology was analyzed with consideration of the impact of missing urine results, which were counted as cocaine positive. Comparisons between groups were performed using χ^2 statistical analysis. Treatment retention was examined across all treatment groups by performing one-way ANOVA that compared the total number of weeks each participant stayed in study.

3. Results

3.1. Baseline characteristics

Baseline subject characteristics were comparable across groups, except in regards to race, since participants were predominantly African-American (see Table 1). Thirty-five subjects were