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A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of cocaine dependence

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Abstract

Prior studies have demonstrated inefficacy among dopamine receptor antagonists for treating cocaine dependence. An alternative approach would be to investigate the ability of indirect inhibitors of cortico-mesolimbic dopamine release, such as the 5-HT_3 receptor antagonist ondansetron, to reduce cocaine's reinforcing effects. We hypothesized that ondansetron might be more efficacious than placebo at reducing cocaine intake and promoting abstinence in cocaine-dependent individuals. In a pilot randomized, double-blind, 10-week controlled trial, 63 treatment-seeking, cocaine-dependent men and women received ondansetron (0.25 mg, 1.0 mg, or 4.0 mg twice daily) or placebo. Up to three times per week, participants were assessed on several measures of cocaine use, including urine benzoylecgonine. Cognitive behavioral therapy was administered weekly. Ondansetron was well tolerated, causing no serious adverse events. The ondansetron 4.0 mg group had the lowest dropout rate among all treatment groups and a greater rate of improvement in percentage of participants with a cocaine-free week compared with the placebo group ($p = 0.02$), whereas the ondansetron 1.0 mg group had a lower rate of improvement in percentage of weekly mean non-use days than did placebo recipients ($p = 0.04$). These results suggest the possibility of a non-linear dose–response function, with evidence supporting efficacy for the 4.0 mg group.

Keywords: Ondansetron; Cocaine dependence; Humans; 5-HT_3 receptors; Benzoylecgonine; Cognitive behavioral therapy

1. Introduction

Cocaine dependence and its psychiatric, social, and economic sequelae constitute a major public health problem in the US (Mendelson and Mello, 1996). While behavioral and psychosocial interventions have remained the mainstay of treatment, high relapse rates are typical (Di Ciano and Everitt, 2002), and medical treatments directed at treating the underlying pathophysiology of cocaine-taking offer the promise of greater efficacy. Yet, despite almost two decades of scientific effort, no medication has been approved by the Food and Drug Administration for the treatment of cocaine dependence.

Cortico-mesolimbic dopamine (DA) neurons mediate the reinforcing effects of cocaine that are associated with its abuse liability (Weiss and Porrino, 2002). Nevertheless, the obvious approach of using direct DA receptor antagonists in the treatment of cocaine dependence has not been fruitful (Kreek et al., 2002). While the reasons for this inefficacy are not well understood, it is plausible that central monoaminergic pathways exhibit high adaptability and compensatory mechanisms (Hemby et al., 1997), thereby reversing any early treatment effects or therapeutic gains of direct DA antagonists. In any case, poor compliance with direct DA receptor antagonists, due to their propensity to induce unpleasant adverse events (e.g., extrapyramidal symptoms) by non-selectively altering baseline DA function, limits their practical utility as treatment for cocaine dependence. Hence, an alternative scientific approach is needed. Logically, such an approach should include examination of the

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efficacy of indirect inhibitors of cortico-mesolimbic function, rather than direct DA antagonists, in the treatment of cocaine dependence.

Serotonin-3 (5-HT_3) receptors co-localized with gamma-amino-butyric acid interneurons are indirect inhibitors of cortico-mesolimbic DA release (Bloom and Morales, 1998). It is, therefore, of scientific interest that 5-HT_3 receptor antagonists such as ondansetron, presumably by attenuating the suprabasal release of cortico-mesolimbic DA, have been shown to reduce the reinforcing effects of a variety of abused drugs including alcohol and amphetamines (Costall et al., 1987; Di Chiara and Imperato, 1988; McBride and Li, 1998; Sellers et al., 1992). Direct study of the anti-reinforcing effects of 5-HT_3 antagonists on cocaine-taking has, however, yielded some equivocal results. While 5-HT_3 antagonists reduce cocaine-induced extracellular DA release (Kankaanpaa et al., 1996; McNeish et al., 1993) and locomotion (Kankaanpaa et al., 1996; McNeish et al., 1993; Reith, 1990; Svingos and Hitzemann, 1992), they do not appear to attenuate cocaine-induced self-administration (Kankaanpaa et al., 1996; Lane et al., 1992; McNeish et al., 1993; Peltier and Schenk, 1991; Reith, 1990; Svingos and Hitzemann, 1992). Nevertheless, 5-HT_3 antagonists have been reported to reduce conditioned place preference for cocaine (Suzuki et al., 1992) cf. (Cervo et al., 1996), diminish the development of behavioral tolerance and sensitization to cocaine following a period of acute withdrawal (King et al., 1998) by down-regulation of 5-HT_3 receptors in the nucleus accumbens (King et al., 1999), and decrease discomfort or post-cessation anxiety following psychostimulant withdrawal (Costall et al., 1990a,b). In humans, the 5-HT_3 antagonist, ondansetron, also has been shown to inhibit right orbitofrontal cortex increases in neuronal activation and cerebral blood flow in recently withdrawn cocaine addicts (Adinoff, 2004). It is, therefore, reasonable to propose that when considered with the preclinical data (King et al., 2000), ondansetron might aid the restoration of normative DA function during the period of recent withdrawal from cocaine use, and thus decrease the potential for relapse to drug-taking. Taken together, these data suggest that 5-HT_3 antagonists such as ondansetron might impair the maintenance of preference for cocaine and reduce the likelihood of relapse to cocaine following cessation of its use.

As a proof-of-concept test of this hypothesis, we conducted a pilot randomized, double-blind, 10-week controlled, dose-ranging trial to determine whether ondansetron (0.25 mg, 1.0 mg, or 4.0 mg twice daily) would be more efficacious than placebo at reducing cocaine intake and promoting abstinence among cocaine-dependent individuals.

2. Methods

2.1. Participants

We enrolled 63 men and women with a primary diagnosis of cocaine dependence according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) (American Psychiatric Association, 1994). During a 2-week baseline period, enrolled participants also had to provide up to six urine samples (three per week); at least one out of a minimum of four samples had to test positive for the major cocaine metabolite, benzoylecgonine (BE). We included individuals with secondary diagnoses of alcohol, caffeine, tobacco, marijuana, or amphetamine abuse or dependence as long as the participants could provide urine samples free of these and other drugs and an alcohol-free breath sample without exhibiting any physical signs of withdrawal at the time of enrollment. Other forms of drug dependence were excluded. Participants were treatment-seeking individuals ≥18 years of age who had agreed to attend the clinic three times per week for monitoring and once during one of those visits for psychosocial intervention. They were in good physical health as determined by physical and laboratory examinations (i.e., hematological assessment, biochemistry, and urinalysis) including electrocardiographic studies. We excluded individuals with current diagnoses of bipolar or psychotic disorders or other Axis I disorders requiring treatment, including major depression. We also did not study individuals who were mandated by the courts to be treated for cocaine dependence, were pregnant or not using an acceptable form of contraception (i.e., oral contraceptive, hormonal or surgical implant, sterilization, or spermicide and barrier), were taking psychotropic medication that could interfere with ondansetron, were using opiate substitutes within 6 months of enrollment, were asthmatic, or had AIDS.

Ethics approval was provided by the institutional review board at The University of Texas Health Science Center at San Antonio (UTHSCSA). Participants were recruited between July 2001 and September 2002 by newspaper, television, or radio advertisements.

2.2. General procedures

Within 1 month prior to randomization, participants provided written informed consent and began a screening and baseline period. Their physical health was assessed by medical history, physical examination, vital signs (i.e., blood pressure, pulse, and temperature), 12-lead electrocardiogram, laboratory studies (including hematology, chemistry, drug testing, breath alcohol concentration, urine pregnancy test, infectious disease panel, and optional HIV test), and adverse events. Psychiatric diagnoses were determined by the structured clinical interview for DSM-IV (First et al., 1994), and the measure of cocaine use was the cocaine timeline follow-back (Sobell and Sobell, 1992). Drug-related symptoms and sequelae were assessed by the substance use inventory (SUI) (Sobell et al., 1980), cocaine selective severity assessment (Kampman et al., 1998), cocaine craving questionnaire-now (Tiffany et al., 1993), brief substance craving scale (Mezinskis et al., 1998), clinical global impression-observer (National Institute of Mental Health, 1976), clinical global impression-self (National Institute of Mental Health, 1976), sensation-seeking scale (Zuckerman and Link, 1968), and Barratt impulsivity scale (Barratt, 1965). During the screening and baseline period, participants reported to the clinic 3 days per week, and study entrance criteria – which were made known to the participants – required them to provide four to six urine samples during the 14 days prior to randomization, at least one of which had to be positive for cocaine (i.e., BE). Even if the first urine was positive for BE, an attempt was made to collect all six samples. Participants who failed to provide the required four urine specimens – including at least one positive specimen for BE – during their first 2 weeks were allowed another 16 days to meet this criterion (i.e., for such participants, the baseline period was extended to 30 days).

We enrolled eligible participants for double-blind treatment at the beginning of week 1 after a review of the diagnostic, physical health-related, and urine drug screen data. At that visit, we also collected data on adverse events, concomitant medications, vital signs, cocaine selective severity assessment, clinical global impression-observer, clinical global impression-self, brief substance craving scale, SUI, urine BE, and creatinine, with the latter three being measured two to three times per week. All the measures were repeated weekly for 7 weeks (i.e., through week 8). Additionally, all the physical health-related checks were repeated at weeks 4 and 8. The weekly study requirements were completed during the first visit each week, except for cognitive behavioral therapy (CBT), which could be scheduled on a second or third visit. Participants received US$ 10 as compensation for each visit, plus an extra US$ 10 bonus if they came in for all three visits in a week. Double-blind treatment was concluded at the end of week 8. At week 12, a post-treatment follow-up visit was conducted to ascertain cocaine timeline follow-back, adverse events, concomitant medications, SUI, urine BE, and creatinine.