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A single-day paradigm of self-regulated human cocaine administration

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ABSTRACT

Prior work by our group has shown the feasibility, safety, and validity of a multi-day, multi-dose paradigm of self-regulated cocaine administration in humans. The current work sought to consolidate these methods in a single-day design focused on reducing logistical complexity, decreasing research burden to human subjects, and increasing suitability for medication development designs.

Methods: Eleven experienced cocaine users participated in a 6-hour, single-day design, consisting of one safety/eligibility and three experimental cocaine periods (during which subjects were allowed to self-administer 8, 16, and 32 mg/70 kg cocaine doses under a fixed-ratio 1:5 minute timeout schedule). Changes in cocaine-induced cardiovascular response, self-administration behavior, and subjective effects were assessed.

Results: Procedures were well tolerated by participants, and no significant adverse events were noted. Significant ($p<0.05$), changes in measures of cocaine self-administration (e.g., responses, infusions, interinfusion intervals, consumption, and plasma levels), cardiovascular response (HR), and subjective effects ("high") were observed. In contrast, cocaine-induced increases in other vital signs (e.g., SBP, DBP) and subjective effect measures (e.g., paranoia) did not differ between doses.

Conclusions: These data support the safety, tolerability and validity of our single-day design. Depending on the application, such methods may afford advantages for assessing the self-regulation of cocaine administration behavior in humans (e.g., including medication development designs).

1. Introduction

Human laboratory studies involving cocaine administration have contributed significantly to our understanding of the drug's pharmacology, including cardiovascular effects (Fischman et al., 1976; Foltin et al., 1995), drug tolerance (Foltin and Fischman, 1991a), subjective states (Lynch et al., 2006; Sughondhabirom et al., 2005; Foltin et al., 2003; Fischman and Foltin, 1992; Fischman, 1989), abuse liability (Fischman et al., 1983a,b; Foltin and Fischman, 1991c), regulation of drug intake (Angarita et al., 2010), effects on neuropsychological functioning (e.g., sleep and cognition) (Matuskey et al., 2011; Morgan and Malison, 2008; Morgan et al., 2006; Pace-Schott et al., 2008), and in conjunction with neuroimaging, brain mechanisms (Martinez et al., 2004, 2007; Risinger et al., 2005; Schlaepfer et al., 1997; Breiter et al., 1997). Moreover, human laboratory studies have played an increasingly important role in the development of improved treatments for cocaine dependence, including investigations of preliminary safety (e.g., potential drug–drug interactions) and efficacy (Penetar et al., 2006; Collins et al., 2006; Oliveto et al., 2001; Sofuoglu et al., 2005; Grasing et al., 2010; Hart et al., 2006, 2008; Rotheram-Fuller et al., 2007; Rush et al., 2010; Walsh et al., 2001; Evans et al., 2001; Newton et al., 1999; Fischman et al., 1990; Haberny et al., 1995; Haney et al., 1998, 1999, 2001; Kalayasiri et al., 2007a).

Our group has developed a multi-day paradigm of "self-regulated" (i.e., ad libitum) cocaine administration (Sughondhabirom et al., 2005; Lynch et al., 2006) in which experienced users are allowed flexibility in the control of the frequency of cocaine intake. Current procedures require several daily sessions of self-administration (e.g. 2 hour 'binge' sessions on successive days) to allow for the testing of multiple cocaine doses (e.g., 8–32 mg/70 kg IV). Using four and five day designs, we have shown these methods to be safe and well-tolerated, pharmacologically valid (i.e., dose responsive with respect to cardiovascular, behavioral and subjective effects) and test–retest reliable (Sughondhabirom et al., 2005; Lynch et al., 2006; Kalayasiri et al., 2006). We have previously

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used these methods to study the effects of candidate pharmacotherapies (e.g., disulfiram; Kalayasiri et al., 2007a), gender (Lynch et al., 2008) and genetics (Kalayasiri et al., 2007b) on cocaine-related effects, as well as potential differences in the self-regulation of drug administration by humans (Angarita et al., 2010).

While advantages of reliability, validity, and full-dose response remain, our procedures, as currently implemented, are time-intensive and require participants to undergo multiple test sessions spread over several (e.g., 4–5) days. The latter has also provided challenges of logistics and/or feasibility for medications development (e.g., due to research burden placed upon human subjects and institutional/facility resources), with dose-finding designs typically employing multiple doses of the drug candidate (e.g., a placebo-controlled study of two active medications and three active cocaine doses would require 12–16 laboratory sessions, as currently implemented). Therefore, in the current study, we assessed whether salient features of our methods (e.g., self-regulation and full cocaine dose–response curves) could be preserved in the context of a more practical, single-day design, maintaining essential elements of safety, subject tolerability, and pharmacologic validity.

2. Methods

2.1. Subject population

Participants were medically healthy, non-treatment seeking cocaine-dependent individuals who were recruited through local newspaper advertisements and by word-of-mouth referrals. Initial screening evaluations were typically conducted on an outpatient basis and individuals underwent an unstructured psychiatric interview, physical and neurological examinations, ECG, and routine laboratory testing (i.e., blood chemistries, hematology, and urinalysis). Participants were required to meet DSM-IV criteria for cocaine abuse or dependence, be between the ages of 18 and 50 years, report cocaine use via smoked and/or IV routes of administration (although all participants preferred smoked use and only one admitted to past IV cocaine use), have a history of regular, recent use greater than the maximum employed in the study (i.e. ≥728 mg in a day), and provide objective evidence of recent use (i.e., benzoylecgonine positivity) on urine toxicology testing.

Exclusion criteria included nonsubstance related Axis I psychiatric disorders, cardiac conditions, seizures, diabetes, any current systemic medications, sedative hypnotic or opiate dependence, and for females, a positive serum β-HCG (i.e., pregnancy) test.

All participants provided voluntary written informed consent, and all study-related procedures were approved by both the Yale University Human Investigation Committee and the Yale Center for Clinical Investigation's Safety and Science Committee. A certificate of confidentiality was obtained from the National Institute on Drug Abuse (NIDA), and the study was conducted under the auspices of an Investigational New Drug (IND) application to the U.S. Food and Drug Administration (RTM, physician sponsor). All study participants were compensated for their participation.

Of the 16 individuals that consented to the study, two were excluded after an abnormal screening ECG and two individuals did not complete the study: both passed the safety/eligibility assessments but one had sustained blood pressure elevations above safety criteria in response to repeated cocaine, and the other subject withdrew electively (stating he was not comfortable being observed while using cocaine). Additionally, one subject (completer) responded at very low levels on each of the test sessions (two or fewer responses) and was excluded on statistical grounds (>3 standard deviations below mean self-administration rates).

2.2. General study design

Cocaine dependent subjects participated in a single, approximately 6-hour (5 h and 50 min) cocaine self-administration study, composed of an initial safety/eligibility phase (80 min) followed by a subsequent experimental component (4 h and 30 min; see Fig. 1). The initial/safety component was composed of three, serial (at 20 min intervals), bolus, fixed order, escalating dose injections of 8, 16, and 32 mg/70 kg IV cocaine hydrochloride via patient-controlled analgesia (PCA) pump. Given the time constraints inherit in the current one-day design, in conjunction with our clear prior demonstration of differences in active vs. placebo response (Lynch et al., 2006; Sughondhabirom et al., 2005), we opted to exclude a placebo session in the current design (with the primary goal of establishing the capacity of the current procedures to reproduce pharmacological dose–response relationships without placebo).

The purpose of the safety/eligibility phase was two-fold: 1) to familiarize subjects with the experimental methods (PCA pump, cocaine doses, experimental environment), and 2) to minimize chances of unsafe cardiovascular responses by establishing each subject's ability to tolerate IV cocaine over the full range of doses tested in subsequent experimental components. Subjects who exhibited elevations in vital signs above safety thresholds and/or evidence of clinically significant cardiac ectopy, arrhythmias, or symptoms were excluded from further

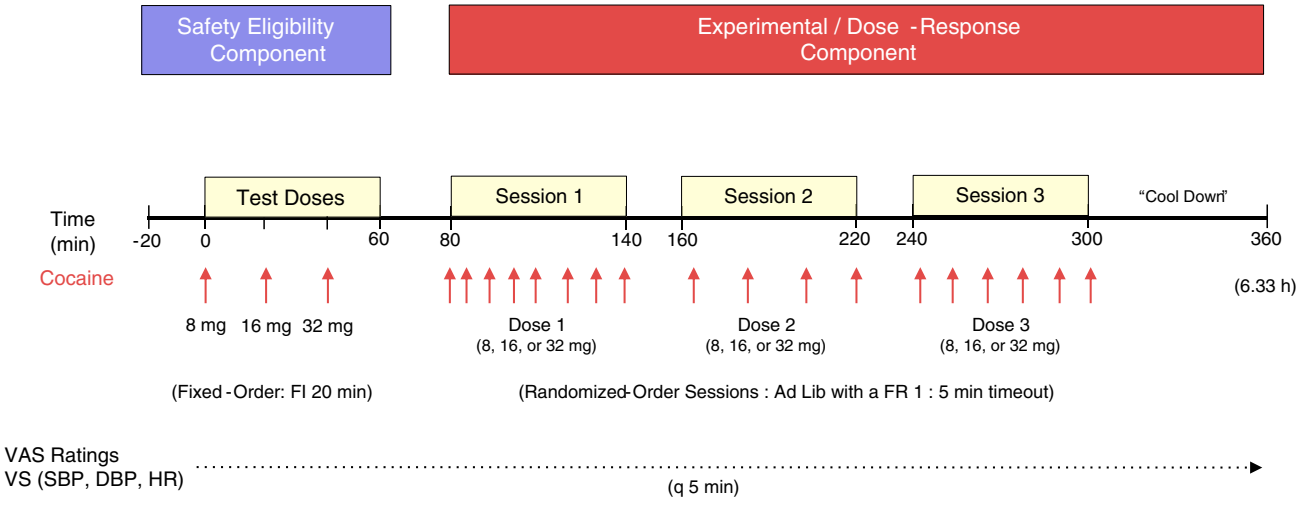

Fig. 1. A schematic representing the cocaine self-administration day. See text for full description of the study design.