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Short communication

Pharmacokinetic profile of cocaine following intravenous administration in the female rabbit

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Abstract

Prenatal cocaine exposure in a rabbit intravenous model has revealed selective disruption of brain development and pharmacological responsiveness. We therefore examined the pharmacokinetic properties of cocaine in this model. Dutch-belted rabbits were surgically implanted with a catheter in the carotid artery, allowed to recover, and then injected intravenously with a cocaine bolus. Cocaine and benzoylecgonine concentrations were measured in arterial blood plasma and analyzed by nonlinear regression and noncompartmental analyses. Peak cocaine concentration occurred by 30s, was transient, and distribution was rapid. The profile of cocaine in the rabbit is similar to that observed in humans using cocaine at recreational doses.

Keywords: Cocaine; Pharmacokinetics; Plasma; (Rabbit)

1. Introduction

Cocaine abuse among pregnant women has been a public health concern for several decades. Studies conducted in the late 1980s and middle 1990s estimated prevalence rates of cocaine or crack use during pregnancy at 3–5% in the overall population (Ebrahim and Gfroerer, 2003; National Institute on Drug Abuse, 1996), with some at risk populations possessing incidence rates approaching 20% (Day et al., 1993; Frank et al., 1988). Although cocaine use has since declined significantly, the 2002 National Household Survey on Drug Abuse estimated that at least 1 in 300 children are born that have been exposed to cocaine during pregnancy (Office of Applied Studies, 2003), resulting in approximately 12,000 new births of *in utero* cocaine exposed children each year.

Given the complexity of the human situation where cocaine is often used alongside other illicit drugs and in a context of poor nutrition and prenatal care, establishing well-controlled animal models represents an important complement to the human research. Complexities, however, also arise in the interpretation of effects in animal models based in different species, doses of cocaine, frequency of dosing, and administration method (Malanga and Kosofsky, 2003; Stanwood and Levitt, 2004). Administration methods that produce pharmacokinetic patterns congruent with patterns of human self-administration are thus of high importance. In this regard, inhalation and smoking allow the most rapid delivery of cocaine to the brain, while intravenous (i.v.) injection maximizes its bioavailability (Quinn et al., 1997). These routes of administration produce rapidly peaking cocaine blood levels in human subjects (Cone, 1995; Evans et al., 1996; Javaid et al., 1983; Jenkins et al., 2002) and in animal models (Boni et al., 1991; Booze et al., 1997; Robinson et al., 1994; Saady et al., 1995; Zhou et al., 2001).

We and others have utilized a rabbit i.v. model of *in utero* cocaine exposure (Stanwood and Levitt, 2004). Cocaine-exposed progeny exhibit a host of permanent alterations in brain structure and function, such as reduced dopamine D_1 receptor signaling (Jones et al., 2000), altered cerebral cortical morphology (Jones et al., 2000; Stanwood et al., 2001), and a blunting of subsequent stimulant-induced responses (Stanwood

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and Levitt, 2003). Interestingly, only cerebral cortical areas receiving high dopaminergic innervation such as the medial prefrontal and anterior cingulate cortices show alterations in circuitry (Jones et al., 2000; Stanwood et al., 2001). Cocaine-exposed progeny also exhibit deficits in attentional processes (Gabriel et al., 2003; Romano and Harvey, 1996; Thompson et al., 2005). Cognitive disruptions have also been reported in other animal models of gestational exposure to cocaine (Chelonis et al., 2003; Gendle et al., 2003; Morrow et al., 2002; Wilkins et al., 1998). Prenatal cocaine exposure in the rabbit thus appears to reproduce several features that are found in clinical populations. However, it is important in the development of any animal model of drug abuse to reproduce the pharmacokinetics of the drug observed in humans. In the current study, we investigated the pharmacokinetic properties of cocaine and its metabolite benzoylecgonine, in unanesthetized, non-gravid female rabbits given a bolus injection of i.v. cocaine.

2. Methods

2.1. Animals and surgery

Adult (1.5–2.5 year old) female Dutch-belted rabbits (Myrtles Rabbitry, Thompson Station, TN; $n=7$) were housed individually on a 12 h light:dark cycle and given *ad libitum* access to food and water. Animals were weighed and allowed to acclimate to the facility (1–2 weeks) before surgery. At least 30 min before the start of the procedure, rabbits were injected with Buprenex (0.1 mg/kg, i.m.) as an analgesic. Cephazolam (15 mg/kg) was administered prophylactically as an antibiotic. Aseptic technique was used for all surgeries. The portion of the animal undergoing surgery was shaved and washed with povidone iodine/alcohol. Anesthesia was induced with ketamine (35 mg/kg) and xylazine (5 mg/kg) and maintained with isoflurane vapor (2.0–2.5%) via a face mask. A small ventral midline incision in the animal's neck revealed the right carotid artery, which was catheterized with Silastic tubing (Technical Products, Inc., Decatur, GA). The catheter was inserted into the cephalic end of the artery, advanced to the point of the aortic arch (approximately 6 cm), and filled with heparinized glycerin (500 U/ml). The catheter was secured to the vessel with 4–0 silk and the free end was knotted and then routed to the scapula through subcutaneous tissue. Incision sites were closed first with 3–0 chromic gut (subcutaneous) and then with 3–0 nylon monofilament (skin; both from Ethicon, Somerville, NJ). After full recovery from anesthesia was observed (approximately 1 h after the start of surgery), animals were returned to their home cages. All experimental procedures conformed to the guidelines set forth in the Vanderbilt University School of Medicine Institutional Animal Care and Use Committee.

2.2. Sample collection

Animals were allowed to recover from surgery at least 3 days prior to sampling. After injecting lidocaine (1% solution; Abbott Labs, Chicago, IL) into the wound site, the arterial catheter was excised from the back of the animal. The catheter was flushed with heparinized saline until blood was observed in the line then clamped with a hemostat. Cocaine HCl (NIDA) was diluted to 3 mg/ml with saline and injected using a pediatric butterfly needle (Terumo SURFLO winged infusion tubing, 25G×3/4″, Fisher Scientific) at 3 mg/kg via the marginal ear vein over approximately 10 s. An additional 0.4 ml was added to each injection volume to account for the residual volume of the tubing. The midpoint of the injection was designated as time 0 min. The following time points were sampled: Pre-injection, 0.5, 1, 1.5, 2, 3, 5, 10, 20, and 30 min post-injection. Blood samples were obtained in volumes of 1 ml in syringes pre-coated with heparinized saline, with about 200 μl of blood taken to waste between each time point (the approximate volume of the catheter). Samples were added to 1.5 ml microfuge tubes pre-coated with 0.1 M EDTA (to prevent hemolysis) with protease inhibitor (Sigma, catalog number P8340, St. Louis, MO) added at a final concentration of 1:1000. In preliminary experiments in which known concentrations of cocaine were spiked into control rabbit plasma, we found that this inhibitor cocktail completely blocked *ex vivo* catabolism of cocaine in the test tube (data not shown). In contrast, the more commonly used enzymatic inhibitor sodium fluoride was ineffective in rabbit plasma. After collection, samples were stored on wet ice and taken immediately to the Vanderbilt Neurochemistry Core for plasma extraction and subsequent HPLC detection. Plasma was isolated by spinning blood samples at 15,500 *g* (Eppendorf 5415D microcentrifuge) for 10 min at 4 °C.

2.3. Detection of cocaine and BE

High-Performance Liquid Chromatography (HPLC) was used to detect concentrations of cocaine and BE. Methods are modifications of those previously published (Rofael and Abdel-Rahman, 2002). All drug standards and other reagents were obtained from Sigma (St. Louis, MO). The HPLC system consisted of a Waters 717+ Autosampler, a Waters 510 pump, a Waters 474 scanning fluorescence detector and Waters Millennium 32 Data system (Water Associates, Milford, MA). Mobile phase (pH 6.9) consisted of 100 mM monobasic phosphate and 30 mM triethylamine in water combined with a mixture of 60% acetonitrile and 40% methanol (75:25, v:v). The mobile phase was vacuum filtered (0.45 μm filter) to remove particulates and de-gas the solvent. After filtration, the mobile phase was pumped through a Waters Nova-pak C18 analytical column (4 μm, 3.9×150 mm; Waters Associates, Milford, MA) at 1.0 ml/min at room temperature. Column elutant was monitored at 225 nm (UV) and 235 nm excitation and 315 nm emission (fluorescence). Cocaine and benzoylecgonine were diluted with mobile phase to a final concentration of 1000 ng/ml, then diluted serially to the following concentrations: 500, 250, 125, 62.5, 31.25, 15.65, 7.83, and 3.91 ng/ml. Each standard (100 μl) was mixed with control plasma (100 μl) and extracted as follows. In a 1.5 ml microfuge tube, 100 μl of plasma sample, standard or blank was added with 200 μl of 0.5 M borate buffer

(pH 9.0), 400 ng lidocaine (internal marker) and 1 ml of isopropanol:chloroform (1:9). Samples were vortexed for 1 min and centrifuged at 4 °C for 5 min at 15,500 *g*. The organic layer was aspirated, transferred to a new 1.5 ml microfuge tube and dried down under a stream of dry air. Samples were resuspended in 100 µl of mobile phase and 50–75 µl was injected onto the chromatographic column. Calibration curves for cocaine and benzoylecgonine were highly significant and linear within the tested range (r=0.999). Sensitivity of measurement detection for each assayed compound was 3.9 ng/ml. We failed to obtain a 30 s sample for one rabbit and in this case data are modeled on the other time points only.

2.4. Data analysis

The mean and standard error of the mean (S.E.M.) of plasma concentration levels were calculated in Microsoft Excel and plots were drawn in SigmaPlot version 7.0 (Systat Software Inc., Point Richmond, CA). Noncompartmental analyses of pharmacokinetic data were performed using WinNonlin 5.0.1 (Pharsight Corporation, Mountain View, CA).

3. Results

The intravenous injection of cocaine with carotid artery sampling produced a pronounced and transient peak in arterial concentrations of cocaine (Fig. 1). The pharmacokinetic parameters for the bolus intravenous injection of cocaine (3 mg/kg), as determined by noncompartmental analysis, are given in Table 1. Cocaine distribution was extremely rapid and occurred with a $T_{1/2\alpha}$ of approximately 30 s (Table 1). The peak of plasma cocaine occurred at the 30 s sample time for most animals, producing a peak of 1606±363 ng/ml (mean±S.E.M.) cocaine at this time point (Fig. 1). The $T_{1/2\beta}$ was approximately 6 min (Table 1). The AUC_{0-30} represented nearly 98% of the AUC_{inf}. Please note that the C_{max} is calculated based on modeling of pharmacokinetic data from individual animals, thus it differs slightly from the peak value at 30 s presented in Fig. 1. As expected, the metabolic profile of benzoylecgonine revealed a much lower peak value and slower kinetics (Fig. 1) with a $T_{1/2}$ of 25.9 min and a C_{max} of 429 ng/ml based on noncompartmental analysis of the mean data.

Table 1
Summary of pharmacokinetic analysis for intravenous cocaine (3 mg/kg) in the rabbit

Parameter	Mean	S.E.M.
N	7	n/a
Body weight (kg)	2.28	0.053
$T_{1/2\alpha}$ (min)	0.553	0.055
$T_{1/2\beta}$ (min)	5.58	1.59
T_{max} (min)	0.571	0.077
C_{max} (ng/ml)	1377	337
AUC_{inf}	1963	296
$AUMC_{inf}$	12600	4400
MRT (min)	6.11	2.18
Cl_{tot} (L/min/kg)	4.13	0.882
V_{dss} (L/kg)	18.3	6.67

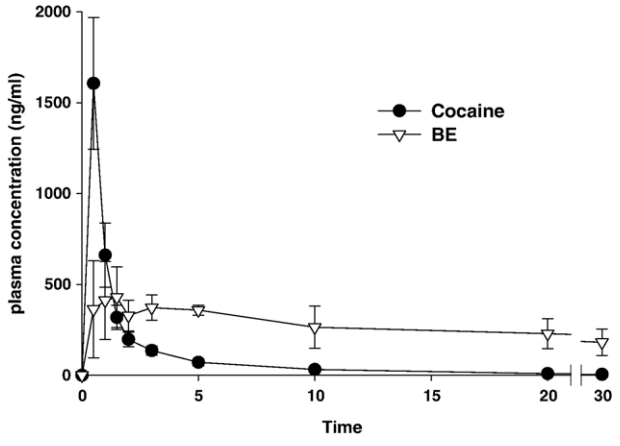

Fig. 1. Graph depicts the concentration (mean±S.E.M.) of cocaine and its major metabolite benzoylecgonine in arterial samples from adult female Dutch-belted rabbits following a bolus intravenous injection (3 mg/kg via marginal ear vein).

4. Discussion

The most common routes of cocaine abuse by humans are by inhalation, snorting and i.v. injection. Inhalation and i.v. injection of cocaine each produce very rapid pharmacokinetic, cardiovascular, and subjective effects (Evans et al., 1996), which in turn increase its euphoric properties, its ability to produce neuroadaptations, and thus its potential for addiction (Samaha and Robinson, 2005; Withers et al., 1995). The current experiment evaluated the arterial plasma levels of cocaine and benzoylecgonine in female rabbits given a bolus i.v. injection of the drug. Our data reveal a pharmacokinetic profile characterized by a rapidly peaking cocaine concentration (C_{max} of 1377 ng/ml at approximately 30 s) and subsequent decline in drug distribution ($T_{1/2\beta}$ of 6.2 min). These values are strikingly similar to those observed in human arterial blood (Evans et al., 1996), though we note that this study was performed in male subjects with previous cocaine history. Evans and colleagues show maximum cocaine levels of approximately 1400 ng/ml at 15 s after infusion (16 mg dose i.v., arterial sampling), followed by a rapid decrease in plasma concentration. This dose is on the lower end of the range corresponding to typical cocaine abuse and produces specific physiological and subjective effects (Fischman and Foltin, 1992; Fischman and Schuster, 1982; Jenkins et al., 2002). The pharmacokinetic dynamics of the Evans model should therefore mimic that observed in clinical populations and serve as a reference point for animal models of cocaine abuse. To our knowledge, this is the only study to assess arterial blood concentrations in humans following intravenous administration, although several studies have examined venous blood samples (Cone, 1995; Javaid et al., 1983; Jenkins et al., 2002), and obtained data that confirm the venous sample data of Evans et al. (1996). Thus, their arterial data are likely to be quite accurate.

In addition to its tight correlation with the human literature, our data in the rabbit complement pharmacokinetic studies performed in other animal models. Early work exploring the pharmacokinetics of cocaine administration frequently utilized high-dose, subcutaneous or intraperitoneal injections (10–80 mg/kg) in rats (Collins et al., 1999; Dow-Edwards et al., 1989; Miller et al., 1996; Spear et al., 1989). Other studies have employed intramuscular, intranasal or oral delivery methods (Binienda et al., 1993; Duhart et al., 1993; Fattinger et al., 2000; Zhou et al., 2001). These reports have measured the levels of both cocaine and benzoylecgonine in fetal brain and plasma and have provided a crucial foundation for future experiments, although these regimens do not accurately recapitulate the pharmacokinetic profile seen in the majority of cocaine abusers (peak cocaine levels are typically much later with a slower decrease in plasma levels in the aforementioned animal models).

The pharmacokinetic and metabolic profiles of cocaine have previously been reported following i.v. administration in rodents (Booze et al., 1997; Carmona et al., 2000; Pan et al., 1991; Robinson et al., 1994; Tella and Goldberg, 1993) and nonhuman primates (Carmona et al., 2000; Mello et al., 2002; Saady et al., 1995; Zhou et al., 2001). In a comprehensive dose–response study, Mactutus and colleagues administered i.v. cocaine to male rats and measured arterial plasma concentration (Booze et al., 1997). Following 3 mg/kg cocaine, they observed roughly similar peak concentrations and time to peak, with a C_{max} of 2553 ± 898 ng/ml and a $T_{1/2\alpha}$ of < 1 min. Similarly, Tella and Goldberg (1993) observed a $T_{1/2\alpha}$ of < 1 min and a maximal plasma drug concentration (1276 ng/ml at 3 mg/kg, i.v.) that is on scale with our data. In contrast, however, the half-life of cocaine in these paradigms (~ 12 min, (Booze et al., 1997)) was not quite as pronounced as that observed in our experiments ($T_{1/2\beta}$ ~ 5.6 min). Interestingly, when the human arterial data reported in Evans et al. (1996) are modeled, a $T_{1/2\beta}$ value of approximately 4 min is obtained, suggesting that the rapid clearance of cocaine in the rabbit following i.v. administration accurately mimics the human response. Rapid metabolism has also been reported in pregnant sheep (Burchfield et al., 2001; DeVane et al., 1991). Differences in circulation time and metabolic pathways among species may contribute, at least in part, to differences in drug half-life between the rat, rabbit and human (Lin, 1995).

Most previous studies have assessed cocaine pharmacokinetics in males, yet females may be more sensitive to some pharmacodynamic properties of cocaine (Festa et al., 2004; van Haaren and Meyer, 1991; Walker et al., 2005) (though also see Mello et al., 2002). We examined female rabbits in the present study because of our *in utero* exposure model, though we did not use pregnant animals. While it is likely that pregnancy can modulate cocaine responses (Sutliff et al., 1999), parallel experiments that we are conducting in mice suggest that pregnancy does not alter the pharmacokinetic profiles of cocaine or benzoylecgonine following an i.v. bolus of 3 mg/kg cocaine (Parlaman and Stanwood, unpublished data). Further, in a small study comparing pregnant and non-pregnant monkeys, no statistically significant differences in peak level, half-life, or mean residence time were observed, but a potentially large decrease in the observed AUC and an increase in volume of distribution in pregnancy were reported (Duhart et al., 1993). An increase in blood volume has been reported late in gestation in the pregnant rabbit, which would be expected to dilute the plasma concentration of any drug, including cocaine (Prince, 1982). Direct assessment of i.v. cocaine distribution in pregnant rabbits of distinct gestational ages awaits further study. For obvious ethical reasons, however, the only available reference data in the human literature are in the absence of pregnancy (Cone, 1995; Evans et al., 1996; Javaid et al., 1983; Jenkins et al., 2002). Repeated intravenous administration of cocaine might also induce adaptations in drug distribution as compared to a single exposure, although data obtained in rats and sheep argue against this possibility (Burchfield et al., 2001; Pan et al., 1991).

In summary, our data reveal pharmacokinetic parameters that are similar to what is typical of either smoked or i.v. administration of cocaine in humans. Prenatal cocaine-exposed progeny in the rabbit model demonstrate permanent deficits in cognition and attention; similar dysfunctions are seen in cocaine-exposed children, particularly as they grow older and are exposed to a more demanding environment (Leech et al., 1999; Linares et al., 2005; Singer et al., 2004). This pharmacokinetic analysis provides further support for the utility of the rabbit model. Experimental evidence from this (and other) animal model(s) of prenatal cocaine exposure improves our ability to define the developmental and molecular mechanisms that induce permanent disruption of brain structure and function, and to design clinically relevant interventions.

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