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Chronic Continuous Cocaine Infusion in Rats: Effect on Urine Cocaine, Ecgonine Methylester and Benzoylecgonine Concentrations and Bolus-dose Cocaine Pharmacokinetics

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Abstract

The aim of this study was to determine the effect of chronic cocaine infusion on urine cocaine, ecgonine methylester and benzoylecgonine concentrations to establish if they varied with dose and duration of cocaine administration.

Male rats were continuously infused with cocaine at either 6 or 18 mg kg^{-1} daily for 13 days. Three urine samples taken over the course of the infusion period showed that cocaine, ecgonine methylester and benzoylecgonine concentrations varied with the dose administered and the duration of administration. Cocaine, ecgonine methylester and benzoylecgonine concentrations were 2–3 times greater in the high-dose group than the low-dose group at each sampling time point. These decreased, respectively, from $7{\cdot}0 \pm 1{\cdot}1$, $26{\cdot}7 \pm 4{\cdot}5$ and $29{\cdot}5 \pm 5{\cdot}4$ $\mu g\,mL^{-1}$ to $2{\cdot}5 \pm 0{\cdot}5$, $10{\cdot}5 \pm 1{\cdot}8$ and $11{\cdot}8 \pm 1{\cdot}5$ $\mu g\,mL^{-1}$ in the high-dose group and from $1{\cdot}0 \pm 0{\cdot}2$, $7{\cdot}8 \pm 1{\cdot}5$ and $6{\cdot}3 \pm 0{\cdot}1$ $\mu g\,mL^{-1}$ to $0{\cdot}5 \pm 0{\cdot}1$, $4{\cdot}0 \pm 0{\cdot}6$ and $3{\cdot}1 \pm 0{\cdot}4$ $\mu g\,mL^{-1}$ in the low-dose group ($P < 0{\cdot}05$) over the infusion period. We also studied the pharmacokinetic and metabolic profile of an intravenous bolus dose of $2{\cdot}5$ mg kg^{-1} cocaine hydrochloride after a similar cocaine infusion in rats. Cocaine pharmacokinetics and the profile of ecgonine methylester, benzoylecgonine and norcocaine were no different from rats chronically infused with saline for the same period. Altered cocaine metabolism could not explain the effect of the duration of cocaine infusion on altered metabolite concentrations in urine. Ecgonine methylester/benzoylecgonine urine concentration ratios did not alter with duration of infusion ($1{\cdot}2 \pm 0{\cdot}2$ and $1{\cdot}1 \pm 0{\cdot}2$ in the high-dose group at the first and last time point) and were not affected by the dose of cocaine ($1{\cdot}3 \pm 0{\cdot}6$ and $1{\cdot}2 \pm 0{\cdot}1$ at corresponding times in the low-dose group ($P > 0{\cdot}05$)).

We conclude that chronic cocaine infusion does not alter cocaine metabolism. This was not reflected by absolute cocaine metabolite urine concentrations, which varied with time, but was represented by urine ecgonine methyl ester/benzoylecgonine concentration ratios.

Recently we demonstrated that a cocaine-specific catalytic antibody can protect from cocaine reinforcement and toxicity (Mets et al 1998). This beneficial effect on sequelae from cocaine ingestion was effected through the ability of this antibody to enhance the metabolism of cocaine to the less toxic metabolite, ecgonine methylester (Mets & Virag 1995). Urine analysis of ecgonine methylester and benzoylecgonine may serve as a non-invasive indicator of the effect of this catalytic antibody in enhancing cocaine metabolism during chronic cocaine administration. In-vivo studies have shown altered cocaine (and benzoylecgonine) disposition with chronic cocaine administration (Nayak et al 1976; Pettit et al 1990; Pettit & Pettit 1994; Robinson et al 1994). Thus urine metabolite concentrations (and their ratios) may alter with chronic cocaine administration. To establish baseline data, preliminary to experiments evaluating the chronic use of the catalytic antibody, we studied the effect of chronic continuous cocaine administration for 13 days on the urine metabolite profile of

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cocaine. As this profile altered with time, we assessed whether chronic cocaine administration altered cocaine pharmacokinetics and metabolite profile after intravenous bolus-dose administration.

Materials and Methods

Animals

Adult male Sprague–Dawley outbred rats (14–15 weeks old, approx. 400 g, n = 37) were cared for and studied according to a protocol approved by the Institutional Animal Care and Use Committee of Columbia University (Mets et al 1999).

Rats were weighed and then anaesthetized with intraperitoneal 80 mg kg^{-1} ketamine hydrochloride and 8 mg kg^{-1} xylazine. The right internal jugular vein was cannulated by surgical incision using PE 60 intramedic polyethylene tubing, (Clay Adams, Parsippany, NJ) cut to 8 cm in length and flushed with 8 U mL^{-1} heparinized saline. The catheter was tied securely and then connected to an Alzet osmotic infusion pump (ALZA Corporation, CA) primed at least 4 h in advance with a cocaine or saline solution. A tight ligature was placed around the catheter-pump connection. The pump was then tunnelled subcutaneously to lie at the nape and the incision was closed with sutures; no antibiotics were administered. Rats were returned to the vivarium and received a continuous infusion of either cocaine or saline for 13 days using the Alzet infusion pump.

Preparation of infusion pumps

Alzet infusion pumps were supplied with information on the mean pumping rate of the pump as determined in-vitro for the batch supplied. With this information, and the known weight of the rat on the day before pump insertion, the concentration of cocaine hydrochloride required to infuse 6 mg kg^{-1} (low-dose group) or 18 mg kg^{-1} (high-dose group) cocaine per day was determined. The pump was then primed with 2 mL of this solution. In control rats the pumps were filled with saline solution. The pump was then incubated for at least 4 h in sterile saline solution so that it would start immediately on implantation (the deadspace of the added catheter inserted into the internal jugular vein was 6·0 μL and pump infusion rates were 4·75–5·19 μL h^{-1}) . At the end of the study the pumps were removed and the residual volume in the pumps aspirated and measured to confirm that an appropriate volume of cocaine or saline solution had been administered.

Evaluation of urine cocaine and metabolite profile

Rats were weighed and randomly divided into two groups to receive either high-dose (n = 12) or low-dose (n = 11) cocaine hydrochloride continuously by means of the infusion pump described. Four or five rats were studied simultaneously. Urine was collected three times during the 13-day period, on day 3 or 4, day 7 or 8 and day 12 or 13. On these days rats were placed in metabolic cages for 5 h (10 00–15 00 h) with no food or water. Urine collected (3–5 mL) was mixed with 200 μL saturated NaF and stored at −20°C for subsequent analysis. At the end of the study under pentobarbital anaesthesia, the central venous catheter was checked to ensure it had remained securely tied to the infusion pump and was in the right internal jugular vein.

Effect of chronic cocaine on cocaine disposition and metabolite profile after subsequent bolus-dose administration

Rats were weighed and randomly divided into two groups to receive either low-dose cocaine by continuous infusion (n = 5) or saline (n = 6). On day 14, rats were anaesthetized, as above, and the femoral artery and vein catheterized for the pharmacokinetic study (Mets et al 1999). A femoral arterial blood sample was taken for later analysis to determine steady-state cocaine and metabolite concentrations from continuous cocaine infusion. The next day, the rats were weighed and patency of the catheters was confirmed by the back flow of blood. An arterial sample (0·4 mL) was taken after removal of deadspace (0·2 mL) and this and all subsequent samples were replaced with an equivalent volume of saline. Cocaine hydrochloride (2·5 mg kg^{-1} diluted into 1 mL of saline) was injected over 60 s and the catheter (deadspace 0·15 mL) flushed with a further 1 mL saline over 30 s (time 0). Arterial blood samples (0·4 mL) for cocaine and metabolite analysis were then taken at 0·5, 1, 2, 5, 10,15, 20, 25, 30, 45, 60, 90, 120, 150 and 180 min. All blood samples were injected into heparinized Eppendorf tubes pretreated with 20 μL saturated NaF and stored on ice before blood injection. The samples were then stored on ice until centrifugation, which took place within 1 h of sampling, and the pipetted plasma was stored at −80°C until analysis.

Cocaine and cocaine metabolite assays

Urine cocaine and metabolite concentrations were measured using a method adapted from an assay developed in our laboratory for plasma analysis of these congeners (Virag et al 1995). The lower limit

of quantitation for this assay was 25 ng mL^{-1} for cocaine, norcocaine and benzoylecgonine and 50 ng mL^{-1} for ecgonine methylester. Within-day precision (n = 5) was 4·1, 5·5, 5·5 and 3·1% at 1000 ng mL^{-1} respectively; extraction efficiency was 78–90% for cocaine and its metabolites and 90% for the internal standard bupivacaine.

Plasma cocaine and metabolite concentrations were determined with a highly sensitive method using stable isotope dilution liquid chromatography-atmospheric pressure chemical ionization-selected reaction monitoring-mass spectrometry (Singh et al 1999). The lower limit of quantitation for this assay was 2 ng mL^{-1} for cocaine, norcocaine and benzoylecgonine and 5 ng mL^{-1} for ecgonine methyl ester. The intra- and inter-assay precision for all congeners was 0·8–4·1%, while the percentage error of back-calculated values for the calibration standards from their theoretical values were 88–112%.

Pharmacokinetic analysis

Pharmacokinetic analysis of plasma concentrations was performed using WinNonlin (SCI software, NC) in the Gaus-Newton (Levenberg & Hartley) mode. Plotting of data points suggested that data would be appropriately fitted to a bi-exponential equation. To establish whether the pharmacokinetic disposition of cocaine and its metabolites could be better described by a one- or three-compartment model rather than a two-compartment model, mean data points for the different sampling times in each treatment group were fitted to mono- bi- and tri-exponential equations using WinNonlin (Hull 1991). In each case the models were subjected to the criteria of Boxenbaum et al (1974), Akaike (1974) and Schwarz (1978). A more complex model was only considered an improvement if the latter two criteria were lower and if there was a significant improvement in the weighted sum of squared residuals using the F-test at the $P < 0{\cdot}05$ level after Boxenbaum et al (1974). All analyses showed acceptable conditioning. The above criteria for analysis justified a bi-exponential equation, but not a tri-exponential equation to fit the data points. Thus the plasma concentrations of cocaine for each rat were separately fitted to a bi-exponential equation and the derived pharmacokinetic parameters determined for each rat.

Statistical analysis

Statistical analysis was performed using Graph Pad Prism, Version 3 (San Diego, CA). Data are presented as mean ± s.e.m. Two sample-between-group analyses were performed using a two-tailed unpaired t-test and pharmacokinetic data were assessed using the Mann-Whitney U-test. The effect of time on urine concentrations of cocaine and its metabolites was evaluated using repeated-measures analysis of variance and where significant differences were found at $P < 0{\cdot}05$, a post-hoc analysis was performed using the Newman-Keul's multiple comparison test. The statistical relationship between urine pH and volume and urine concentrations of cocaine and its metabolites was tested using Pearson's correlation coefficient.

Results and Discussion

This study aimed to establish whether urine concentrations of cocaine, ecgonine methylester and benzoylecgonine altered with dose and duration of chronic cocaine administration.

Rats given high-dose and low-dose cocaine were similar in weight at the time of pump implantation (400 ± 9 g vs 420 ± 7 g, respectively). Table 1 shows that there were significantly higher cocaine, ecgonine methyl ester and benzoylecgonine concentrations in timed urine samples from rats administered 18 vs 6 mg kg^{-1} per day. Table 1 also demonstrates that there was significant variation in cocaine, ecgonine methylester and benzoylecgonine concentrations with time. These time-dependent changes in urine metabolite concentration could be the result of altered distribution of these congeners in the body or changes in metabolism of cocaine with time. To investigate this we evaluated the effect of continuous chronic cocaine infusion on the subsequent pharmacokinetic profile of cocaine after bolus-dose administration. Arterial blood samples taken during continuous cocaine infusion on day 14 of cocaine administration confirmed continuous cocaine administration. Plasma cocaine and metabolite concentrations at this time were: cocaine, 31·6 ± 8·9 ng mL^{-1}; norcocaine, 0 ng mL^{-1}; ecgonine methylester, 13·2 ± 2·9 ng mL^{-1}; and benzoylecgonine, 35·8 ± 4·6 ng mL^{-1}. Plasma concentrations of these congeners just before cocaine bolus-dose administration the following day were 3·6 ± 1·6 ng mL^{-1}, 0 ng mL^{-1}, 1·5 ± 1·5 ng mL^{-1} and 4·8 ± 0·9 ng mL^{-1}, respectively. Figure 1 shows that the pharmacokinetic profiles of cocaine, norcocaine, ecgonine methylester and benzoylecgonine were not altered by chronic cocaine administration. Table 2 shows that the derived pharmacokinetic parameters for cocaine elimination were no different from the saline control group. This suggests that the altered urine

Table 1. Urine concentration of cocaine, ecgonine methylester and benzoylecgonine in 5 h urine samples taken at three different times during a 13-day period of continuous cocaine infusion at two different dose rates in rats.

Urine sample	Cocaine congener	Urine concn of congener ($\mu g\,mL^{-1}$)	
		High-dose cocaine ($18\,mg\,kg^{-1}$/day)	Low-dose cocaine ($6\,mg\,kg^{-1}$/day)
Day 3–4	Cocaine	7·0 ± 1·1	1·0 ± 0·2
	Ecgonine methylester	26·7 ± 4·5	7·8 ± 1·5
	Benzoylecgonine	29·5 ± 5·4	6·3 ± 0·1
Day 7–8	Cocaine	2·5 ± 0·4*	0·6 ± 0·1
	Ecgonine methylester	14·8 ± 3·0*	6·9 ± 1·8
	Benzoylecgonine	15·8 ± 1·5*	4·8 ± 1·0
Day 12–13	Cocaine	2·5 ± 0·5*	0·5 ± 0·1
	Ecgonine methylester	10·5 ± 1·8*	4·0 ± 0·6*
	Benzoylecgonine	11·8 ± 1·5*	3·1 ± 0·4*

Urine concentrations are expressed as mean ± s.e.m. *$P < 0·05$, compared with day 3–4.

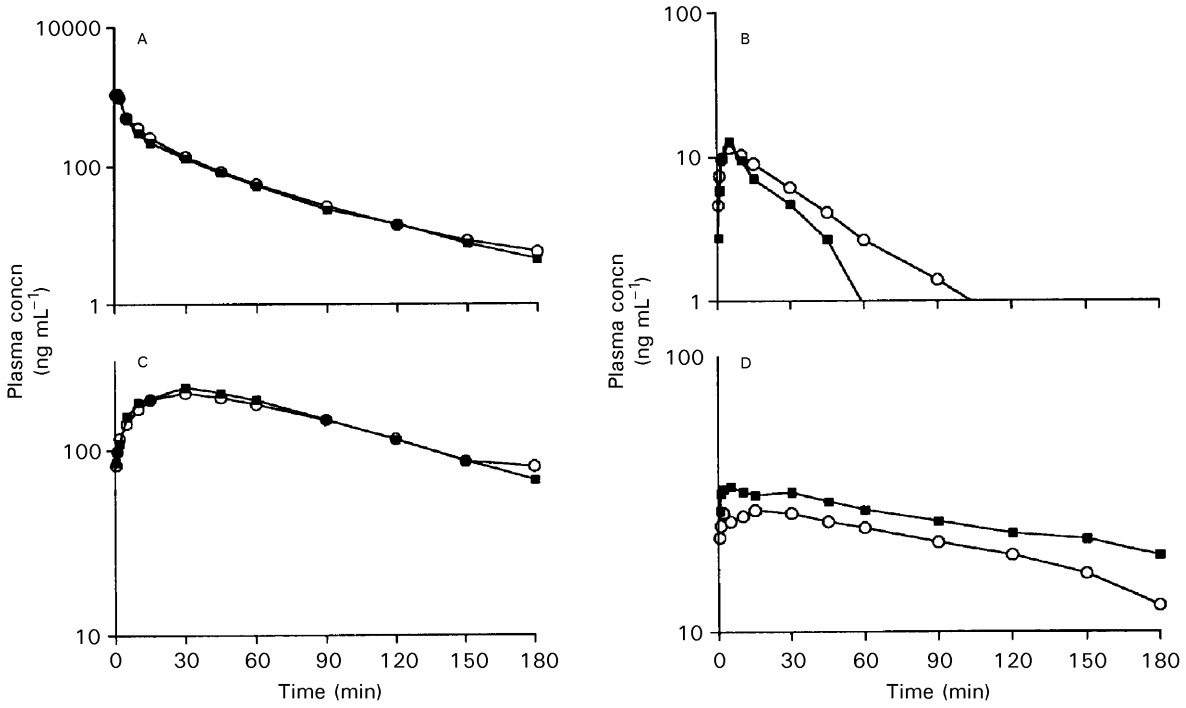

Figure 1. Plasma concentration data for cocaine (A), norcocaine (B), benzoylecgonine (C) and ecgonine methylester (D) after a cocaine bolus dose of $2·5\,mg\,kg^{-1}$ in rats chronically treated with $6\,mg\,kg^{-1}$ cocaine (■) or saline (○) daily for 13 days.

metabolite profiles observed in these experiments were not the result of altered cocaine metabolism or distribution from chronic cocaine infusion.

Further possible reasons for the time-dependent decreases in the absolute concentration of cocaine and its metabolites may be due to altered renal elimination of the congeners due to alterations in urine pH (Jones 1997) or volume (Preston et al 1997) over time, or alteration in renal function or metabolism.

We measured the urine pH and volume of each sample. Urine pH did not alter with time in the cocaine groups (Table 3) and there was no correlation between cocaine and benzoylecgonine concentration with urine pH. There was a significant ($P = 0·018$), but negative correlation ($r = -0·28$, $n = 68$) for urine pH and ecgonine methylester concentration. Urine volume correlated inversely with benzoylecgonine ($P < 0·001$, $r = -0·48$, $n = 69$), cocaine ($P = 0·0012$, $r = -0·38$, $n = 69$)

Table 2. Effect of continuous cocaine infusion on subsequent cocaine-derived pharmacokinetic parameters after bolus-dose cocaine administration to rats.

Parameter	Cocaine (n = 5)	Saline (n = 6)	*P*
Vd ($L\,kg^{-1}$)	1·72 ± 0·11	1·88 ± 0·22	0·90
$t_{\frac{1}{2}}\alpha$ (min)	3·03 ± 0·41	3·52 ± 0·77	0·90
$t_{\frac{1}{2}}\beta$ (min)	27·5 ± 1·3	26·0 ± 1·7	0·94
C_{max} ($ng\,mL^{-1}$)	1323 ± 91	1277 ± 158	0·94
CL ($L\,kg^{-1}$)	0·156 ± 0·014	0·165 ± 0·034	0·90
$AUC_{cocaine}$ ($ng\,mL^{-1}\,min^{-1}$)	14790 ± 1392	15740 ± 2215	0·90
$AUC_{norcocaine}$ ($ng\,mL^{-1}\,min^{-1}$)	328 ± 53	504 ± 218	0·82
$AUC_{ecgonine\ methylester}$ ($ng\,mL^{-1}\,min^{-1}$)	4452 ± 690	3583 ± 422	0·94
$AUC_{benzoylecgonine}$ ($ng\,mL^{-1}\,min^{-1}$)	25710 ± 3641	24910 ± 3592	0·94
Preparation weight (g)	415 ± 10	401 ± 11	0·36
Final weight (g)	423 ± 17	419 ± 18	0·86

Data are expressed as means ± s.e.m. Vd = volume of central compartment; CL = clearance; AUC = area under the concentration–time curve. Pharmacokinetic data were analysed using the Mann-Whitney *U*-test.

Table 3. Urine pH and volume of timed urine samples collected over 5 h from rats receiving continuous cocaine infusion.

	Urine sample		
Group	Day 3–4	Day 7–8	Day 12–13
High dose cocaine			
pH	7·41 ± 0·19	7·79 ± 0·22	7·38 ± 0·11
Urine volume (mL)	3·6 ± 0·6	4·0 ± 0·4	6·3 ± 0·3*†
Low dose cocaine			
pH	7·32 ± 0·16	7·17 ± 0·17	7·31 ± 0·12
Urine volume (mL)	4·9 ± 0·6	6·3 ± 0·8‡	6·2 ± 0·54
Saline			
pH	7·58 ± 0·12	7·37 ± 0·11	7·38 ± 0·12
Urine volume (mL)	4·8 ± 0·7	5·4 ± 0·5	5·7 ± 0·5

*$P < 0·05$, compared with day 12–13; †$P < 0·05$, compared with day 7–8. There was no difference between groups at different sampling times except ‡$P < 0·05$, high-dose vs low-dose cocaine. Analysis of variance was with Newman-Keuls multiple comparison test.

and ecgonine methylester concentration ($P = 0·016$, $r = -0·29$, $n = 69$). In the high-dose group, the alteration in urine volume over time (Table 3) might in part explain the decrease in urine concentration with time as urine volume increased. However, this is unlikely to be the whole explanation as the inverse correlations were not strong. In addition, in the low-dose group, urine volumes did not increase significantly with time unlike ecgonine methylester and benzoylecgonine urine concentrations.

An alteration in renal function from cocaine administration is possible (Di Paolo et al 1997) but unusual, as impaired renal function from cocaine is not common and is usually associated with rhabdomyolysis. In this study, rats receiving cocaine did not have different urine volumes or urine pH concentrations compared with the saline controls (Table 2). Another possibility is an alteration in cocaine metabolism in the kidneys as cocaine methylesterases have been found in the rat kidney (Dean et al 1995).

We aimed to determine whether cocaine metabolite urine concentration or metabolite concentration ratios remained stable over time in order to use alterations in metabolite concentrations as a possible monitor of altered metabolism in experiments with a newly developed cocaine-specific antibody (Landry et al 1993). We have shown that this antibody can decrease systemic toxicity from cocaine infusion through enhanced cocaine metabolism to ecgonine methylester while benzoylecgonine formation remains unchanged (Mets et al 1998). Thus alterations in urine ecgonine methylester concentrations might be used to monitor the effects of this antibody. However, this study demonstrated that urine concentrations of benzoylecgonine and ecgonine methylester varied with time and often varied substantially in absolute value. Ecgonine methylester/benzoylecgonine ratios were determined at each sampling time (Table 4). This data demonstrates that this ratio was unaffected by cocaine dose and duration of administration. The metabolite ratio determined from timed urine samples may serve as a monitor of altered cocaine metabolism caused by therapeutic agents such as butyrylcholinesterase (Mattes et al 1997) or the catalytic antibody. However, appropriate dose–response studies are necessary to establish this as a useful monitor.

There is little data in the literature on urine concentrations of cocaine and its metabolites in rats after cocaine administration. Nayak et al (1976) demonstrated that excretion of free cocaine in urine was 1–1·5% of $20\,mg\,kg^{-1}$ [^{3}H]cocaine

Table 4. Ecgonine methylester/benzoylecgonine urine concentration ratios from timed urine samples in rats receiving continuous cocaine infusion

Urine sample	Urine concn ratio		P
	High-dose cocaine ($18\,mg\,kg^{-1}$/day)	Low-dose cocaine ($6\,mg\,kg^{-1}$/day)	
Day 3–4	1·2 ± 0·2	1·3 ± 0·6	0·6
Day 7–8	1·0 ± 0·2	1·3 ± 0·3	0·3
Day 12–13	1·1 ± 0·2	1·2 ± 0·1	0·6

Ecgonine methylester/benzoylecgonine ratio did not vary with time (repeated measures analysis of variance).

administered subcutaneously. They identified benzoylecgonine and ecgonine methylester, but not norcocaine, in the urine. Using a validated ion-cluster technique with mass spectometric analysis, Jindal & Lutz 1989 identified cocaine and the three metabolites studied here, and a further 6 metabolites, in rat urine after $20\,mg\,kg^{-1}$ cocaine administered intraperitoneally. Misra et al (1979) noted that only 1% of administered norcocaine was retrieved from urine. In this study, plasma concentrations of norcocaine were close to the limit of detection (LOD) ($2\,ng\,mL^{-1}$) from continuous cocaine infusion ($6\,mg\,kg^{-1}$/day) and we did not detect norcocaine in the urine (LOD $25\,ng\,mL^{-1}$). Matsubara et al (1984) studied urinary cocaine and metabolite elimination after subcutaneous administration of $1\,mg\,kg^{-1}$ cocaine in dogs. Their data revealed substantial variation in urine metabolite concentrations similar to our findings. Five hours after cocaine administration, urine cocaine ($0{\cdot}8\,\mu g\,mL^{-1}$), ecgonine methylester ($11{\cdot}7\,\mu g\,mL^{-1}$) and benzoylecgonine ($10{\cdot}2\,\mu g\,mL^{-1}$) concentrations were comparable with those found in this study in rats where cocaine was infused at $6\,mg\,kg^{-1}$ per day. Ecgonine methylester/benzoylecgonine ratios from their data appear to remain stable over a 48-h period after cocaine administration.

The effect of chronic cocaine administration on its own pharmacokinetics and metabolite profile is not clear. In-vitro, microsomal studies suggest that cocaine pretreatment may enhance cocaine metabolite formation (Sandberg et al 1993; Powers & Shuster 1999). However, we did not observe a change in the pharmacokinetics of cocaine or its metabolite formation after prolonged cocaine infusion. Our findings are similar to other studies in rats (Pan et al 1991) and dogs (Wilkerson et al 1991). In female rats, chronic cocaine ($6\,mg\,kg^{-1}$, i.v., daily for 11 days) administration altered cocaine and benzoylecgonine disposition from bolus-dose cocaine (Robinson et al 1994). Nayak et al (1976) described an increase in cocaine half-life after bolus-dose cocaine injection ($8\,mg\,kg^{-1}$) associated with chronic cocaine administration ($20\,mg\,kg^{-1}$, s.c., twice daily for 23 days). It is not clear why these conflicting findings exist. They may be a function of the dose and duration or route of cocaine administration. This study has confirmed that chronic cocaine administration does not alter its own metabolism and thus this cannot be an explanation for the altered urine metabolite profile seen over time. Further, because we used a highly sensitive assay to determine plasma metabolite concentrations we were able to show that the metabolite profiles for the three major metabolites of cocaine were not altered by chronic cocaine administration.

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