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Urinary Excretion of Ecgonine Methyl Ester, a Major Metabolite of Cocaine in Humans*

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Abstract

In this study, cocaine, benzoylecgonine, and ecgonine methyl ester excretion in urine was measured after intravenous and intranasal administration of cocaine at 16, 32, 48, and 96 mg doses to healthy cocaine users. Ecgonine methyl ester and cocaine were analyzed by gas chromatography/mass spectrometry. Benzoylecgonine was measured by immunoassay (EMIT) and liquid chromatography. Urinary ecgonine methyl ester accounted for 26 to 60% of the cocaine dose. Ecgonine methyl ester had an elimination halflife of 4.2 hr, compared with 5.1 hr for benzoylecgonine. These results indicate that ecgonine methyl ester accounts for most of the previously unidentified urinary metabolic products of cocaine. The time course of ecgonine methyl ester excretion is such that its detection can substitute for benzoylecgonine detection as a marker of cocaine use.

Introduction

The resurgence of cocaine as a drug of abuse has stimulated new interest in studying its metabolism in humans and in developing methods to detect the cocaine user.

Previous studies have indicated that cocaine administered to humans is excreted into the urine, almost entirely in the form of metabolites (1,2). Benzoylecgonine is known to be a major urinary metabolite and to account for approximately 40% of the cocaine dose (1). Small amounts of ecgonine (3) and norcocaine (4) have been found in human urine. Until recently, however, the rest of the urinary products had not been identified. A study in two subjects given cocaine orally indicated a large portion of the urinary product was ecgonine methyl ester, a cocaine metabolite resulting from cholinesterase hydrolysis (2). Also, random urine samples from cocaine users were found to contain high concentrations of ecgonine methyl ester (5).

The primary aim of this study was to determine the extent and time course of ecgonine methyl ester urinary excretion after intravenous and intranasal administration of cocaine. Urinary benzoylecgonine was also measured to show that these two metabolites account for most of the administered cocaine, and to compare directly the rates of benzoylecgonine and ecgonine methyl ester excretion.

Methods

Four healthy adults, ages 21 to 25, with a history of cocaine use participated in the study. They signed consent forms after being given a description of the study and its potential hazards. A general medical history and physical exam was done. The subjects were housed in the Clinical Research Center at the University of Chicago. The study protocol was approved by the Institutional Research Committees of both Northwestern University and the University of Chicago.

Cocaine hydrochloride dissolved in physiological saline was administered intravenously over a one-minute interval. Intranasal cocaine was administered over a one-minute interval. Intranasal cocaine was administered as 100-mg powder consisting of the appropriate dose of cocaine mixed with lactose. The powder mixture was inhaled through a 5-cm straw within one minute.

Urine samples were collected by spontaneous voiding. For the timed samples, the subject emptied his/her bladder, and urine voided 30 min later was collected for analysis. For the recovery study, total urine output during the study interval was collected, the volume was measured and, after mixing, an aliquot was taken for analysis. Samples were frozen for storage.

Ecgonine methyl ester and cocaine were measured by gas chromatography/mass spectrometry (GC/MS), as described previously (5). Benzoylecgonine was measured by enzyme-multiplied immunoassay (EMIT) (6) and the high-pressure liquid chromatographic (HPLC) method of Jatlow, *et al.* (7).

Elimination halflives of the metabolites in urine were calculated, using standard methods, by plotting metabolite excretion rates at the midpoint of the urine collection period against time on a semilog graph (8). Elimination halflives for benzoylecgonine were also calculated from the data of Hamilton, *et al.* (9) in the same manner, using derived excretion rates plotted at 6, 10, 18, 36, and 60 hr.

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Results

Ecgonine methyl ester concentrations in 30-min (timed voiding) samples of urine at various times after a cocaine dose are shown in Table I. Concentrations were generally highest at 4 hr, and declined rapidly thereafter. Concentrations were low but still detectable at 24 hr. The EMIT test for benzoylecgonine was negative in 7 of 8 samples at 24 hr and in some earlier samples.

Benzoylecgonine and cocaine concentrations measured in the urine recovery experiments are shown with the ecgonine methyl ester concentrations in Table II to allow direct comparison. Concentrations of ecgonine methyl ester and benzoylecgonine are generally similar in the first 8-hr samples.

Semilog plots indicated that benzoylecgonine and ecgonine methyl ester excretion rates were declining logarithmically by 4 to 8 hr after the dose. The elimination halflives for the metabolites in urine are shown in Table III. Ecgonine methyl ester concentrations declined more rapidly. The halflife of ecgonine methyl ester excretion was approximately 4 hr, somewhat shorter than the halflife of benzoylecgonine after 48 and 96 mg cocaine doses.

Recovery data (Table IV) indicated that total recovery averaged 93% of the dose, and that ecgonine methyl ester in the urine accounted for 26 to 60% of the cocaine dose. Inquiry into the sources of variation in these experiments indicated that the limiting factor was the accuracy of the recorded urine output.

There was no apparent effect of increasing cocaine dose on the pattern of metabolite excretion within the dose range (16 to 96 mg) studied.

Discussion

Surprisingly, little is known about the metabolism and excretion of cocaine, a drug that has been in medical use for more than a century. In 1969, Fish and Wilson (1) identified benzoylecgonine as a major urinary metabolite and found that unchanged cocaine excretion accounted for less than 10% of the dose. In a 1976 review of the literature, Lemberger and Rubin (10) noted that only 40 to 50% of the administered cocaine dose had been accounted for by the known urinary products. In 1978, however, Inaba, *et al.* (2), in a study of two subjects given ^{14}C-labelled cocaine orally, found that 75% of the radioactivity appeared in the urine in 28 hr. In addition to the benzoylecgonine, they found that ecgonine methyl ester identified by thin layer chromatography accounted for a major portion of the urinary radioactivity. The results of the study reported here indicated that ecgonine methyl ester is a major metabolite after intravenous and intranasal administration of cocaine, and that it probably accounts for most of the previously unidentified urinary drug products.

In this study, the time course of ecgonine methyl ester excretion was defined in four subjects. The elimination halflife of ecgonine methyl ester averaged 4.2 hr. Decline in benzoylecgonine concentrations occurred more slowly, the elimination halflife averaging 5.1 hr in two subjects. The halflives for benzoylecgonine calculated from the data of Hamilton, *et al.* (9) averaged 7.0 hr after similar intranasal cocaine doses in six subjects. The difference is probably due to the smaller number of subjects in the present study.

Analytical methods for the detection of the cocaine user have been aimed at identification of benzoylecgonine in urine (11). Assay of ecgonine methyl ester is simpler than that for benzoylecgonine (5), and detection of ecgonine methyl ester could provide an analytically more convenient marker of cocaine use. It was of interest, therefore, to compare directly the elimination rates of ecgonine methyl ester and benzoylecgonine. Given

Table I. Ecgonine Methyl Ester Concentrations (μg/ml) in 30-Minute (Timed) Urine Samples

Cocaine Dose	Subject	Collection Point (time after dose) 4 hrs	8 hrs	12 hrs	24 hrs
48 mg IN	C	2.0*	4.2	0.5*	0.1*
32 mg IV	C	4.5	7.7	1.9	0.1*
		19.0	3.5	2.3*	0.1*
	D	9.5	3.0	0.4	0.2*
		2.5	0.7	0.2	0.5*
16 mg IV	C	10.0	0.9	0.1	0.4*
		3.6	0.8	1.0	0.2
	D	6.5	1.6	0.2	0.3*

IN = intranasal
IV = intravenous
*EMIT negative

Table II. Ecgonine Methyl Ester (EME), Benzoylecgonine (BZ), and Cocaine (C) Concentrations (μg/ml) in Total Urine Collections

Cocaine Dose		Subject A Collection Period 0-8 hr	8-16	16-24	24-48	Subject B Collection Period 0-8 hr	8-16	16-24	24-48
	EME	36.2	2.8	1.5	0.2	28.5	18.1	9.3	0.1
96 mg IN	BZ	45.0	22.0	15.0	1.3	19.0	19.0	22.0	3.0
	C	1.9	—	—	—	11.3	0.2	—	—
	EME	6.9	7.6	0.9	0.1	4.3	7.4	@	0.1
48 mg IV	BZ	9.5	9.5	2.3	0.4*	19.0	17.0	@	1.1
	C	0.3	0.1	—	—	5.4	0.2	@	—
	EME	11.2	2.9	1.9	0.2	22.3	5.0	2.7	0.2
48 mg IN	BZ	1.7	5.2	2.7	0.9*	10.0	24.0	11.0	2.1
	C	1.3	—	—	—	6.3	0.1	—	—

— = none detected
@ = missing sample
*EMIT negative

Table III. Elimination Halflives (T ½) of Cocaine Metabolites in Urine

Cocaine Dose	Subject	Ecgonine Methyl Ester T ½ (hrs)	Mean	Benzoylecgonine T ½ (hrs)	Mean
96 mg IN	A	4.8		6.0	
	B	3.5	4.2	4.0	5.0
48 mg IN	A	3.9		4.5	
	B	3.9		5.0	4.8
	C	3.0	3.6		
48 mg IV	A	4.1	4.1	5.5	5.5
32 mg IV	C	3.2			
	C	31.4*			
	D	2.5			
	D	2.6	2.8		
16 mg IV	C	5.1			
	C	5.8			
	D	7.6	6.2		

*omitted

Table IV. Recovery of Ecgonine Methyl Ester (EME), Benzoylecgonine (BZ), and Cocaine (C) in Urine

Cocaine Dose	Subject	Percent of Dose			
		EME	BZ	C	Total
96 mg IN	A	26	44	1	71
	B	44	47	13	104
48 mg IN	A	36	33	3	72
	B	60	55	15	130
48 mg IV	A	37	52	1	90
	B	incomplete collection			

similar initial concentrations and assays of similar sensitivity, the longer elimination halflife of benzoylecgonine indicates that it will be detectable somewhat longer. Ecgonine methyl ester was easily detectable, however, beyond the time that the EMIT screening test became negative. Therefore, its identification can substitute for benzoylecgonine in confirmation of most EMIT-positive urine specimens.

Acknowledgments

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