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COCAINE PHARMACOKINETICS IN HUMANS

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Summary

Cocaine was given by intravenous administration to human subjects and the concentrations in plasma were measured by gas chromatography–mass spectrometry. Many pharmacokinetic parameters were found to have a strong dose dependence over the range 1 - 3 mg/kg. The terminal plasma half-life in minutes is given by the equation $t_{1/2(\beta)} = 13.5 + 24.5$ dose ($r = 0.946$). The total plasma clearance in liters/kg per h is $2.51 - 0.67$ dose ($r = -0.973$). From analysis of previously published data the absorption half-life $t_{1/2(ab)}$ is approximately 8 min for gastrointestinal and for nasal inhalation absorption. The bioavailability for nasal inhalation is approximately 60%. While routes of administration for modern recreational use could lead to unexpected drug accumulation in the blood it is not likely to occur from chewing coca leaves.

Introduction

Coca chewing is known to have occurred for centuries in the altiplano of South America. While it is well known that cocaine is one of the constituents of the coca leaf it was only recently demonstrated that chewing the leaf does produce measurable concentrations of cocaine in human blood (Holmstedt, *et al.*, 1979). Cocaine consumption in modern society has become increasingly common to the point that it is currently considered by some as a public health hazard. Until recent technological developments permitted the measurement of nanogram concentrations of cocaine in biological fluids, the vast majority of studies on coca and cocaine use were of a descriptive nature. With these recent improvements a dramatic increase can be expected in our basic understanding of how this natural compound interacts with the human organism.

Methods

Chemical analysis

Analytical measurements were performed by application of gas chromatography–mass spectrometry (GC–MS) using a Finnigan 1015 or Finnigan

3200 equipped with a four-channel selected ion monitoring system and a chemical ionization source. The glass column (150 mm × 2 mm I.D.) was packed with 1% OV-1 and operated at 220 °C with an injection port temperature of 260 °C. The helium carrier gas flow was 25 ml/min which created a source pressure of 800 μm Hg. The source temperature was 250 °C. The system was calibrated to monitor quasi-molecular ions (M+1) of cocaine (304), d_3-cocaine (307) and the most prominent fragment ion of each (182 and 185, respectively). Standard curves and subsequent quantitation was done on the basis of the peak ratio 304/307 and confirmatory checks done by examination of the 182/185 peak ratios.

Cocaine hydrochloride and *N*-[C^2H_3]cocaine of 98% purity were obtained from NIDA. Standard acetate buffer (pH 4) was prepared at a concentration of 0.1 M. All solvents were reagent grade.

Standard curves were prepared with every batch of clinical samples by adding known amounts of cocaine (range 2 - 500 ng/ml) to plasma obtained from each subject prior to cocaine administration. The standard samples were worked-up along with the clinical samples by the procedure described below. The standard curve was then obtained by performing a linear regression of the peak ratios 304/307 against known concentrations. The correlation coefficient for the standard curve, using three samples at each of five concentrations, was considered acceptable if greater than 0.980.

Aliquots of 0.5 ml of plasma were placed in 13-ml centrifuge tubes followed by 1.0 ml of acetate buffer containing 100 ng of d_3-cocaine. The tubes were vortexed for 30 sec and placed in an ice-bath. Each tube was extracted with 2 ml of ethyl acetate on a shaker for 15 min, centrifuged and the solvent aspirated. The aqueous layer was neutralized with 1.5 ml of saturated $NaHCO_3$ and extracted with 1.5 ml of cyclohexane. The solvent was transferred to a 3-ml tube and evaporated in a nitrogen stream. The residue was dissolved in 20 μl of methanol and 0.5 - 2 μl were injected onto the GC–MS column.

Clinical protocol

The human subjects were four male volunteers who had documented histories of frequent self-administration of cocaine during the preceding 6 months at doses comparable to those used in the present study. All subjects had refrained from cocaine use for a minimum of 48 h prior to an experimental session. All subjects met FDA requirements for participation in experimental studies with cocaine and signed an informed consent.

They were constantly monitored for vital signs throughout the duration of the study. Three subjects received a 100-mg dose. One of the three subjects and one additional subject received a 200-mg dose in a separate experimental session.

Cocaine dissolved to a volume of 1.5 ml was administered via intravenous infusion over a period of approximately 1.5 to 3 min. Blood samples (10 ml) were periodically withdrawn from the other arm into heparinized tubes containing 100 μl of 0.5% NaF solution. Samples were obtained every 5 to

60 min over a 3 - 6-h period. The tubes were immediately centrifuged, the plasma was transferred to a separate tube and the samples were then frozen until the time of chemical analysis. The use of NaF prevented *in vitro* hydrolysis as indicated by repeat sample analysis over a one-year period.

Pharmacokinetic analysis of plasma data

Data were processed by performing nonlinear regression fitting of the concentration *versus* time data to an equation of the general form

$$C = Ae^{-\alpha t} + Be^{-\beta t} \tag{1}$$

For most of the intravenous studies the data were well described by a single exponential function, $C = Be^{-\beta t}$ where β is the disposition rate constant. In some cases it was necessary to use the biexponential function to best fit the experimental data and α describes the distribution phase of the plasma curve. The biexponential function was also sufficient for the studies of oral and nasal absorption but in this case α is actually the absorption rate constant k_{ab} and $A = -B$. In all cases the best fit of the mathematical function to the experimental data was obtained when each data point C was weighted by $1/C^2$ (Boxenbaum *et al.*, 1974). From the regression analysis we obtain the constants A, α, B, β and their respective percentage coefficients of variation. From these constants the following pharmacokinetic parameters are obtained (Gibaldi and Perrier, 1975). The plasma biologic half-life is

$$t_{1/2(\beta)} = 0.693/\beta \tag{2}$$

and the absorption half-life is

$$t_{1/2(ab)} = 0.693/\alpha \tag{3}$$

The total plasma clearance is

$$\text{clearance} = (F \times D)/(\text{a.u.c.}) \tag{4}$$

where D is the amount of dose administered, F is the fraction of the dose that reaches the systemic circulation, and a.u.c. is the area under the plasma curve where

$$\text{a.u.c.} = \int_0^\infty C\,dt = A/\alpha + B/\beta \tag{5}$$

The fraction of dose after oral absorption, F_o, or after nasal absorption, F_n, is obtained from a ratio of dose-normalized a.u.c. values for the absorption curve with intravenous curve. For example, using eqn.(4)

$$F_n = \frac{\text{a.u.c.(nasal)}}{\text{a.u.c.(i.v.)}} \times \frac{\text{dose(i.v.)}}{\text{dose(n)}} \tag{6}$$

since $F = 1$ for intravenous administration and the plasma clearance is assumed to be the same for the two routes of administration and two doses

given. For intravenous data the body volume of distribution V_B is given by

$$V_B = \frac{D}{\beta(\text{a.u.c.})} \tag{7}$$

The initial concentration after intravenous administration is $C_0 = B$ for a monoexponential function, and $C_0 = A + B$ for a biexponential case.

Review of literature

Several studies on the effects of cocaine in humans have been reported which include data that contribute to the data base for our pharmacokinetic analysis.

Van Dyke *et al.* (1978) report plasma concentrations after administration of 2 mg/kg cocaine by both oral and nasal routes to the same four subjects. The blood sampling protocol for the oral administration was especially well designed for kinetic analysis. The nasal dose was administered by topical application. The analytical method used for analysis of cocaine in plasma was gas chromatography with a nitrogen–phosphorus detector and introduction of an internal standard, the n-propyl ester of benzoylecgonine, before extraction. The method is sensitive down to a cocaine concentration of 2 ng/ml of plasma (Jatlow, 1976). Their data will be analyzed and discussed further below. The same group (Van Dyke *et al.*, 1976) reported an earlier nasal study which was carried out before the *in vitro* hydrolysis problem had been controlled (Jatlow and Bailey, 1975).

Intravenous and nasal inhalation studies were carried out on ten volunteer subjects by Javaid *et al.* (1978b) in which they used doses of 32 mg and 16 mg for intravenous administration and 96 mg, 64 mg and 16 mg for nasal inhalation with the same subjects. These investigators also used a gas-chromatographic method with electron-capture detection for analysis of cocaine in plasma (Javaid *et al.*, 1975, 1978a). However, they did not use an internal standard and they have not established the range for quantitative analysis in biological fluids, although they did demonstrate the excellence of the procedure in solvent systems. As a result we have decided to use only their high-dose data since we estimate the lower limit of reliability of their analytical assay to be in the 50 - 100 ng/ml range. Inspection of the plasma data shows that concentration ratios of the high doses to the lower doses are erratic at the lower concentrations, thus supporting our conservative approach.

Kogan *et al.* (1977) reported plasma data for intravenous administration of 100 mg of cocaine to three subjects. They claimed that pharmacokinetic analyses required multiexponential descriptions of the data and reported half-lives of 20 - 40 min for a distribution phase and 2.8 h for a terminal phase. Our pharmacokinetic analysis of their reported data clearly established a single exponential function as the best fit for all three subjects. When a two-exponential analysis was attempted some of the constants, especially β, had coefficients of variation in the range 100 - 300%, thus rendering their reported analysis questionable. The analytical method used on the plasma

samples had a reported sensitivity of 10 ng/ml, but the authors present precision and accuracy data to a lower limit of only 250 ng/ml. Therefore these data were not used in our analysis.

Results and discussion

Intravenous data

The results of our intravenous (i.v.) studies with four subjects are reported as cocaine plasma concentrations *versus* time in Table 1. For the 100 mg dose, subjects W, X, and Y had maximum plasma concentrations, the first blood sample drawn 5 min after i.v. injection, of approximately 700 - 1000 ng/ml. The concentration decreases to about 200 - 500 ng/ml at 1 h post injection and down to 100 - 200 ng/ml at 2 h. The 200 mg dose gave maximum values of 2530 ng/ml and 3868 ng/ml which decreased to about 1000 ng/ml at 1 h. Generally the plasma–time curves for the lower dose are parallel and log-linear. The high-dose curves tend to have some positive curvature in the early portion of the curves for concentrations above 1000 ng/ml, and the terminal slopes, while parallel, are different than those of the lower doses. For our 100 mg i.v. study the results of the nonlinear regression analysis reported in Table 2 yielded a monoexponential function

TABLE 1

Cocaine plasma concentrations after intravenous administration[a]

Time (min)	Subject (weight/dose)				
	W (68 kg/100 mg)	X (95 kg/100 mg)	Y (58 kg/100 mg)	W (68 kg/200 mg)	Z (86 kg/200 mg)
5	921	682	1005	3868	2530
10	–	–	–	–	1460
15	815	569	810	–	963
20	–	–	–	2476	1149
30	667	254	736	–	1093
39	–	–	–	2031	–
45	352	290	663	–	–
60	430	170	477	1222	990
120	190	88	199	–	–
128	–	–	–	696	–
180	75	25	105	–	333
192	–	–	–	453	–
240	28	0	37	–	146
250	–	–	–	219	–
300	16	0	12	–	118
309	–	–	–	145	–
360	8	0	0	–	–
369	–	–	–	94	–

[a] Values are expressed in ng/ml. – indicates no measurement made.

TABLE 2

Computer constants for fit of $C = Ae^{-\alpha t} + Be^{-\beta t}$

The computer estimates for A, α, B, β are reported. The percentage coefficient of variation for each constant is given in parentheses beneath. - indicates $A = \alpha = 0$ as the best description is monoexponential.

Study*	A (ng/ml)	α (min^{-1})	B (ng/ml)	β (min^{-1})
i.v. 100 mg (a)	-	-	860	0.0135
subject W			(9)	(4)
i.v. 100 mg (a)	-	-	558	0.0172
subject X			(15)	(10)
i.v. 100 mg (a)	-	-	1139	0.0147
subject Y			(6)	(3)
i.v. 200 mg (a)	2482	0.0532	1997	0.00842
subject W	(26)	(43)	(16)	(7)
i.v. 200 mg (a)	-	-	1432	0.00879
subject Z			(11)	(9)
i.v. 32 mg (b)	-	-	309	0.0167
mean data, $n = 10$			(7)	(7)
n.i. 96 mg (b)	−295	0.0827	276	0.00766
mean data, $n = 10$	(31)	(72)	(28)	(38)
p.o. 2 mg/kg (c)†	−577	0.0969	307	0.0118
mean data, $n = 4$	(16)	(20)	(7)	(3)
n.t. 2 mg/kg (c)	−428	0.0340	337	0.00942
mean data, $n = 4$	(45)	(61)	(68)	(34)

*References to the plasma data: (a) this work; (b) Javaid *et al.* (1978b); (c) Van Dyke *et al.* (1978).

†A lag-time of 20 min assumed for absorption.

as the best fit in all three cases. For the 200 mg dose, subject Z is well described by a single exponential but the subject W experimental data are better described by a biexponential function. In this case the early portion of the curve is described by an apparent first-order rate constant α and the terminal portion of the curve is described by the rate constant β. With one exponential the β value is slightly larger and the early time data are not as well represented as by the biexponential fit. In Fig. 1 the 100 mg and 200 mg doses are compared for subject W.

Literature data

As seen in Table 2, the 32 mg i.v. mean data of Javaid *et al.* (1978b) are very well represented by a single exponential function and the 96 mg n.i. (nasal, inhalation) mean data are reasonably well described by the two-exponential function of eqn. (1) although the CV values are rather large. In fact the constant α is poorly estimated with a CV of 72%. Also reported in Table 2 are the computer constants for the p.o. (per os) and n.t. (nasal, topical) mean data of Van Dyke *et al.* (1978). For fitting the p.o. data we assumed a lag time of 20 min since they detected no cocaine in plasma at 15 min and 20 min after administration. These data contained a considerable

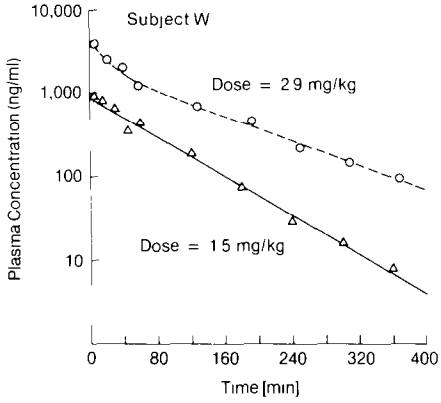

Fig. 1. Comparison of log plasma concentration *versus* time curves for cocaine doses of 2.9 mg/kg and 1.5 mg/kg for subject W.

number of samples during the early phase of the concentration–time curve as well as samples until 6 h post dose. As a result the mean data are well described by a biexponential function as can be seen from the CV values: 16% (A), 7% (α), 7% (B) and 3% (β). It was difficult to obtain a fit of the n.t. data, since too few data points were available, as can be seen from the large CV values which range from 34% to 61%.

Wilkinson, Van Dyke *et al.* (1980) recently published a followup study to the earlier work on oral and nasal topical administration (Van Dyke *et al.* 1978). They found mean $t_{1/2(\beta)}$ values of 75 min and 48 min for the oral and nasal data respectively. This is essentially in agreement with our analysis of their earlier data. The differences are attributed in part to the fact that they report an average of the $t_{1/2(\beta)}$ values from the individual subjects while we were able to analyze only their reported mean plasma–time curve. Also, they weighted the experimental plasma–time data points by $1/C$ while we found $1/C^2$ to be the best weighting factor in all our cocaine calculations. They did not discuss the lack of agreement between the $t_{1/2(\beta)}$ values of 48 min (p.o.) and 75 min (n.t.), but from the CV values for β reported in Table 2 we can say that the difference between our calculated $t_{1/2(\beta)}$ values of 59 min (p.o.) and 74 min (n.t.) is not significant.

Pharmacokinetic parameters

Plasma half-lives [$t_{1/2(\beta)}$] obtained from the terminal slope of the plasma concentration *versus* time curves reported in Table 3 show values ranging from 40 to 91 min. The $t_{1/2(\beta)}$ estimates from both nasal studies are much longer and have much larger CVs. In both of these studies the absorption process was lengthy and, more important, plasma sampling was done to only 1.5 h post dose in the n.i. study while only three samples were obtained after the peak plasma concentration in the n.t. study. For these reasons it is clear that the time of the peak concentrations, t_p, and $t_{1/2(\beta)}$ are not good estimates in the nasal studies. The p.o. absorption study was sufficiently well designed to obtain a β value with a CV of 3% and a correspondingly good estimate of

$t_{1/2(\beta)}$. The larger $t_{1/2(\beta)}$ values obtained in the 200-mg studies raise the possibility of dose-dependent behavior which will be discussed below.

Volume of distribution [V_B] is obtained for our i.v. data from eqn. (7) and reported in Table 3. The values range from 84 l to 179 l, all larger than total body water, thus indicating that substantial binding to extravascular tissues occurs. On a per kilogram of body weight basis the V_B values are in quite good agreement with a range of 1.2 - 1.9 l/kg.

Total plasma clearance values for the three 100-mg studies, calculated from eqn. (4), are also in reasonably good agreement at 1.3, 1.4 and 1.9 l/h per kg. The clearance values obtained from the 200-mg i.v. doses were approximately one-half those obtained from the 100-mg doses.

Absorption half-life [$t_{1/2(ab)}$] values, calculated from eqn. (3), are less accurately estimated than $t_{1/2(\beta)}$. The $t_{1/2(ab)}$ values for the n.i. and n.t.

TABLE 3

Pharmacokinetic parameters for cocaine in humans*

Study**	$t_{1/2(\beta)}$ (min)	V_B		Clearance		$t_{1/2(ab)}$ (min)	F
		(l)	(l/kg)	(l/h)	(l/h per kg)		
i.v. 100 mg (a) subject W	51.5	116	1.71	93.9	1.38	–	–
i.v. 100 mg (a) subject X	40.3	179	1.88	185	1.95	–	–
i.v. 100 mg (a) subject Y	47.2	87.8	1.51	77.3	1.33	–	–
i.v. 200 mg (a) subject W	82.3	83.7	1.23	42.3	0.62	–	–
i.v. 200 mg (a) subject Z	78.9	140	1.63	73.6	0.86	–	–
i.v. 32 mg (b) mean data, n = 10	41.5	104	–	104	–	–	–
n.i. 96 mg (b) mean data, n = 10	90.5	–	–	–	–	8.4	0.6
p.o. 2 mg/kg (c)† mean data, n = 4	58.6	–	–	–	–	7.2†	(0.3)
n.t. 2 mg/kg (c) mean data, n = 4	73.6	–	–	–	–	20.4	(0.3)

*Parameters are calculated from data reported in Tables 1 and 2.
**References (a), (b) and (c) as given in Table 2.
† A lag-time of 20 min assumed for absorption.

studies are 8 min and 20 min, respectively, but both have large CVs. The p.o. value is better estimated with a $t_{1/2(ab)}$ of 7 min following a 20-min lag-time. Since the nasal inhalation route of administration is so common, we at-

tempted to improve the estimate of the α parameter of eqn. (1). The observed t_p is between 20 min and 60 min; thus, using this range of values and a β value of 0.017, the expression

$$t_p = \frac{2.303}{(\alpha - \beta)} \log \frac{\alpha}{\beta}$$

was solved iteratively in search of a self-consistent α value. Unfortunately, the sparseness of plasma data points around t_p in the n.i. data prevented us obtaining a better estimate of α and thus of $t_{1/2(ab)}$.

Fraction of dose absorbed [$F_{n.i.}$] in the n.i. study can be estimated since the same ten subjects were used in both the i.v. and the n.i. study. Taking the appropriate a.u.c. ratio and using eqn. (6), we found $F_{n.i.} = 0.6$, or approximately 60% of the dose was absorbed into the systemic circulation based on averaged plasma data. The remaining 40% is either not absorbed from the nasal pathways, is metabolized during its transport across the absorbing tissues or involves dose dependence. We obtained a relative F value for the p.o. and n.t. studies by making use of the i.v. mean data of Javaid *et al.* The calculated $F_{p.o.}$ and $F_{n.t.}$ values are similar; however, the validity of this comparison is questionable as different laboratories, analytical methods, subjects and doses were involved in the comparisons with i.v. data.

Dose dependence

The possibility of dose-dependent behavior for the cocaine pharmacokinetic parameters was investigated using the i.v. data from our studies. The comparison in Fig. 1, for subject W, shows $t_{1/2(\beta)}$ values of 82 min for the 200-mg dose and 51 min for the 100-mg dose. We carried out a linear regression analysis of $t_{1/2(\beta)}$ *versus* i.v. dose in mg/kg, which ranges over 1.05 - 2.94 mg/kg for the data in Table 3. The result is the strong positive correlation ($r = 0.946$) presented in Fig. 2. There was a weaker negative correlation for the total body volume of distribution V_B with dose, $r = -0.89$. Therefore it is not surprising to find the negative correlation is strong ($r = -0.973$) for the total plasma clearance, as seen in Fig. 3, since

$$\text{clearance} = 0.693 V_B / t_{1/2(\beta)}$$

The less-efficient clearance of cocaine from the body, which ranges from 1.95 l/h per kg at a dose of 1.1 mg/kg down to 0.6 l/h per kg at a dose of 2.9 mg/kg in these studies, is dramatic. The resulting effect on initial plasma concentration C_0 is demonstrated in Fig. 4. A strong linear correlation between C_0 and D (dose) was found over the range 1.1 to 2.3 mg/kg. The experimental value (from the theoretical computer fit) of C_0 is 140% greater than the extrapolated prediction at the 2.9 mg/kg dose. The best correlation over the entire dose range, 1.1 - 2.9 mg/kg, is an exponential dependence

$$C_0 = 185e^D$$

which is also shown in Fig. 4. On the basis of our i.v. data it appears that a threshold effect occurs within the range 2.3 - 2.9 mg/kg which is approxi-

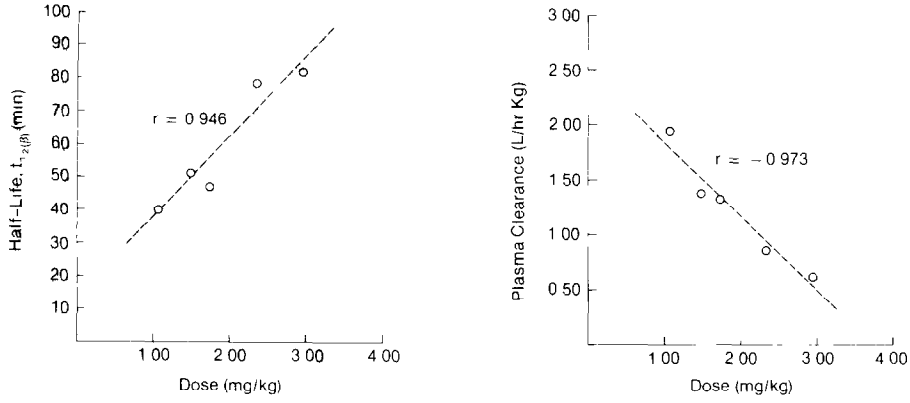

Fig. 2. Plasma disposition half-life $t_{1/2(\beta)}$ *versus* i.v. dose administered. Points are individual values. Solid line represents linear regression analysis with correlation coefficient $r = 0.946$; $t_{1/2(\beta)} = 13.5 + 24.5\ D$.

Fig. 3. Total plasma clearance *versus* i.v. dose administered. Points are individual values. Solid line represents linear regression analysis with correlation coefficient $r = -0.973$; clearance $= 2.51 - 0.67\ D$.

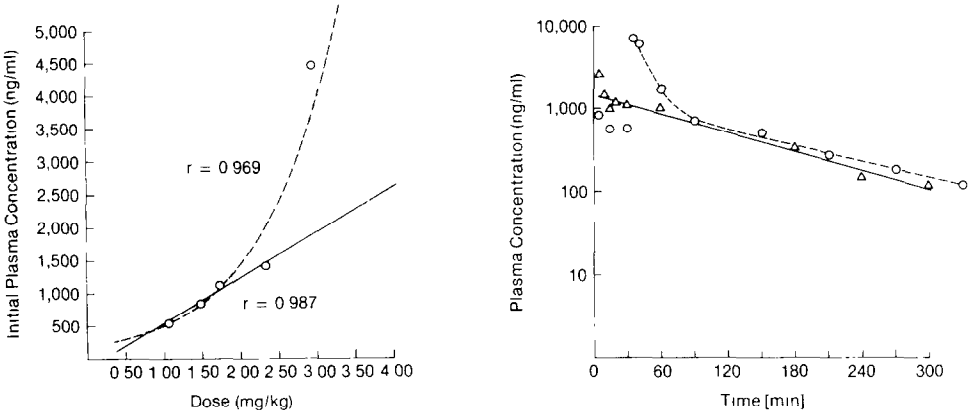

Fig. 4. Initial plasma concentration *versus* i.v. dose administered. Straight line is linear regression analysis with correlation coefficient $r = 0.987$ for dose range 1.1 - 2.3 mg/kg; $C_0 = -137 + 691\ D$. Curved line is exponential regression analysis of C_0 for dose range 1.1 - 2.9 mg/kg, with correlation coefficient, $r = 0.969$; $C_0 = 185e^D$.

Fig. 5. Comparison of log plasma concentration *versus* time curves for subject Z receiving both a 200-mg i.v. dose and, in a subsequent experiment, 100 mg i.v. followed by a second 100-mg i.v. dose 30 min later.

mately described by an exponential dose dependence, although it underestimates by 33% the value of C_0 at 2.9 mg/kg. The two studies with subject W present an excellent opportunity for intrasubject comparison of changes in pharmacokinetic parameters. With a 100% increase in the i.v. dose from

1.47 to 2.95 mg/kg, there is a 60% increase in $t_{1/2(\beta)}$, and decreases of 28% in V_B and 55% in plasma clearance. Thus, while our observations of dose-dependent behavior in general is based on only five sets of data, this intra-subject observation lends additional strength to the findings.

In Fig. 5 a comparison is made for subject Z who received a 200-mg i.v. dose and at a later time received a 100-mg i.v. dose followed by a second 100-mg dose 30 min later. The terminal portions of the two curves have similar concentrations while $t_{1/2(\beta)}$ values are 78.9 min and 94.9 min for the 200 mg and 100 mg + 100 mg studies, respectively. For the 100 mg + 100 mg curve the concentration at 35 min, $C(35)$, which is 5 min after the second injection, might be predicted as approximately equal to the sum of $C(5)$ = 820 ng/ml *plus* $C(30)$ = 554 ng/ml. However, the experimental result $C(35)$ = 6990 ng/ml is 400% above this prediction. This experimental observation lends further support to the findings of Fig. 4; *i.e.* a surprising accumulation of cocaine in blood may occur. For the 100 mg + 100 mg case the α-phase is clearly distinguished with $t_{1/2(\alpha)}$ = 8.6 min, to be compared with 13.0 min in the high-dose curve of Fig. 1. Thus, for concentrations above 1000 ng/ml an α-phase can be distinguished although its physiological significance is a question in need of further study (McNamara *et al.*, 1979).

A final qualitative observation is made on the relative shapes of the curves in Fig. 1. Perrier *et al.* (1973) reported computer simulations for model systems where drug elimination occurs only by a saturable biotransformation process, which may approximate the case of cocaine. They generated curves very similar in shape to those of Fig. 1 for a model where drug elimination is subject to inhibition by the metabolic products. This allows a drug that is normally described by a monoexponential function to display both longer $t_{1/2(\beta)}$ values and convex curvature in early times, an apparent α-phase, for higher dose curves.

Conclusions

The results of our study serve to clarify many aspects of the time-course of the fate of cocaine in the human body. Nevertheless these findings must be viewed as tentative in that our intravenous studies were carried out on a small number of subjects and the findings from our analysis of the literature are based on averaged data.

Our major finding is that the disposition of cocaine by the human body has a pronounced dose dependence over the dose range studied. Thus many pharmacokinetic parameters are dose-dependent over the range of 1.1 - 2.9 mg/kg for intravenous administration. The plasma biologic or terminal phase half-life $t_{1/2(\beta)}$ must be expressed in terms of the linear equation

$$t_{1/2(\beta)} = 13.5 + 24.5\,D$$

where $t_{1/2(\beta)}$ is given in minutes and D (dose) in mg/kg. This correlation of $t_{1/2(\beta)}$ with i.v. dose is very high, r = 0.946, as seen in Fig. 2. For a dose of 1 mg/kg the half-life is $t_{1/2(\beta)}$ = 38 min, and for a dose of 3 mg/kg, $t_{1/2(\beta)}$ =

87 min. The total plasma clearance of cocaine likewise has a strong dose dependence thus

$$\text{clearance} = 2.51 - 0.67\,D$$

where clearance is in units of l/kg per h and dose (D) in mg/kg. Here the correlation, which is negative, is also high, $r = 0.973$, as seen in Fig. 3. At a dose of 1 mg/kg the plasma clearance of cocaine is 1.8 l/kg per h, while for a dose of 3 mg/kg it is 0.5 l/kg per h. Thus, at the higher dose the body is only 28% as efficient at clearing cocaine from the body volume, V_B. Since clearance is via urinary and metabolic pathways the observed dose dependence strongly suggests that the relatively large doses used in our study have reached saturable levels for metabolism.

From computer analysis of our experimental data we obtained theoretical values for the initial plasma concentration C_0, which corresponds to the concentration immediately after administration of the i.v. bolus of drug. As seen in Fig. 4, C_0 was found to have an exponential dependence on dose for the full range studied but a linear dependence for the lower range of 1.1 - 2.3 mg/kg. For a one-compartment pharmacokinetic model $C_0 = D/V_B$, while for a two-compartment model $C_0 = D/V_c$, where V_c is a central or plasmatic compartment which is usually smaller than V_B. Since the extreme value for C_0 is from subject W, which is the only case where a two-compartment fit was required, one would describe the extreme value as a computational artifact. However, the data of Fig. 5, which were discussed above, support the extreme value, and thus the exponential dose dependence for C_0, as being reasonable.

The resolution of the dose-dependent disposition of cocaine will clearly require further study. Such studies should include measurements of both drug and metabolites in plasma, analysis of both in urine, and consideration of an extended dose range.

Coca chewing has been studied by Holmstedt *et al.* (1979), who reported a biexponential curve for cocaine plasma concentration *versus* time. As they properly pointed out, since no i.v. data were then available they were forced to assume that the rapid phase represented the absorption process while the slow phase corresponded to the elimination process. The doses of cocaine administered were 0.22 - 0.64 mg/kg. It is likely, therefore, that the rapid phase, with a half-life range of 25 - 37 min, is the elimination half-life $t_{1/2(\beta)}$. The slow phase, with a range of 57 - 112 min, thus represents a complicated process of buccal and gastrointestinal absorption which occurs during chewing as long as cocaine is being extracted from the quid. Subject OT, who had the highest plasma levels, chewed 4.4 g of leaves containing 21 mg of cocaine (0.34 mg/kg) and reached a maximum concentration of 149 ng/ml. The oral study of Van Dyke *et al.* (1978) gave a maximum concentration only slightly higher, 210 ng/ml, with a six-fold greater dose, thus indicating considerable buccal absorption, which does not undergo first-pass metabolism, during chewing. As the quid size is increased it is likely that less buccal and more

gastrointestinal absorption will occur and a quid size of 30 g would still produce cocaine levels below 1000 ng/ml.

Therefore, on the basis of this new information that has come as a result of technological development we can conclude with a practical obervation. The size of the quid of coca leaves that can be comfortably accommodated by a person is such that it is unlikely that coca chewing, as practiced for centuries in places like Macchu Picchu, presents the dangers that may result from the modern forms of recreational use.

> . . .
> Dadme el silencio, el agua, la esperanza.
> Dadme la lucha, el hierro, los volcanes.
> Apegadme los cuerpos como imanes.
> Acuid a mis venas y a mi boca.
> Hablad por mis palabras y mi sangre.
>
> (Pablo Neruda)

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References

Boxenbaum, H. G., Riegelman, S. and Elashoff, R. M., Statistical estimations in pharmacokinetics. *Journal of Pharmacokinetics and Biopharmaceutics, 2* (1974) 123 - 148.

Gilbaldi, M. and Perrier, D., *Pharmacokinetics*, Marcel Dekker, New York, 1975.

Holmstedt, B., Lindgren, J. E., Rivier, L. and Plowman, T., Cocaine in blood of coca chewers. *Journal of Ethnopharmacology 1* (1979) 69 - 78.

Jatlow, P., Analysis of cocaine and its metabolites in biological fluids. In S. J. Mulé (ed.), *Cocaine: Chemical, Biological, Clinical, Social and Treatment Aspects*, CRC Press, Cleveland, Ohio, 1976, p. 61.

Jatlow, P. and Bailey, D., Gas chromatographic analysis of cocaine in human plasma, with use of a nitrogen detector. *Clinical Chemistry, 21* (1975) 1918.

Javaid, J. I., Dekirmenjian, H., Brunngraber, E. G. and Davis, J. M., Quantitative determination of cocaine and its metabolites benzoylecgonine and ecgonine by gas–liquid chromatography. *Journal of Chromatography 110* (1975) 141 - 149.

Javaid, J. I., Dekirmenjian, J., Davis, J. M. and Schuster, C. R., Determination of cocaine in human urine, plasma and red blood cells by gas–liquid chromatography. *Journal of Chromatography, 152* (1978a) 105 - 113.

Javaid, J. I., Fischman, M. W., Schuster, C. R., Dekirmenjian, H. and Davis, J. M., Cocaine plasma concentration: relation to physiological and subjective effects in humans. *Science, 202* (1978b) 227 - 228.

Kogan, M. J., Verebey, K. G., DePace, A. C., Resnick, R. B. and Mulé, S. J., Quantitative determination of benzoylecgonine and cocaine in human biofluids by gas–liquid chromatography. *Analytical Chemistry, 49* (1977) 1965 - 1969.

McNamara, P. J., Levy, G. and Gibaldi, M., Effects of plasma protein and tissue binding on the time course of drug concentration in plasma. *Journal of Pharmacokinetics and Biopharmaceutics, 7* (1979) 195 - 206.

Perrier, D., Ashley, J. J. and Levy, G., Effect of product inhibition on kinetics of drug elimination. *Journal of Pharmacokinetics and Biopharmaceutics, 1* (1973) 231 - 242

Van Dyke, C., Barash, P. G., Jatlow, P. and Byck, R., Cocaine: plasma concentrations after intranasal application in Man. *Science, 191* (1976) 859 - 861.

Van Dyke, C., Jatlow, P., Ungerer, J., Barash, P. G. and Byck, R., Oral cocaine. plasma concentrations and central effects. *Science, 200* (1978) 211 - 213.

Wilkinson, P., Van Dyke, C., Jatlow, P., Barash, P., and Byck, R., Intranasal and oral cocaine kinetics. *Clinical Pharmacology and Therapeutics, 27* (1980) 386 - 394.