

## COCAINE IN BLOOD OF COCA CHEWERS\*

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### Summary

Coca leaves (*Erythroxylum coca* Lamarck) and powder (5 - 10 g) were taken orally by human subjects in the same way as South American natives do. The cocaine, as measured by mass fragmentography, was immediately detected in the blood, reached peak concentrations from 10 - 150 ng/ml plasma at 0.38 - 1.95 hours, and persisted in the plasma for more than 7 hours. Half-lives of the elimination of cocaine were calculated and ranged from 1.0 to 1.9 hours. The absorption half-lives ranged from 0.2 to 0.6 hours. The shape of the curves fits with the subjective effects reported. There is no reason to believe that the stimulating effect achieved by the use of either coca leaves or powder is not due to cocaine.

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### Introduction

Although the use of cocaine, either by sniffing or injection, is considered harmful by some medical authorities, considerable controversy exists as to whether the chewing of coca (*Erythroxylum coca* Lamarck), as practiced by South American Indians, is detrimental or not. Coca chewing has been said to be physiologically beneficial for Andean Indians in terms of their adaptation to hunger, cold and fatigue at high altitudes (Hanna and Hornick, 1977). Some authors have concluded that coca chewing does not seem to result in obvious physical and mental deterioration among the Indians (Murphy *et al.*, 1969; Grinspoon and Bakalar, 1976). Zapata-Ortiz, on the other hand, maintains that chronic coca chewing produces a progressive deterioration of intelligence, decrease in attention, torpidity, and deterioration of reaction time (Zapata-Ortiz, 1970). He quotes earlier work using psychological and psychophysiological tests of dubious applicability to the Andean Indian.

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Coca chewers exhibit a general stimulation for about an hour after chewing. This stimulation has been equated by some investigators with that produced by cocaine. As a result, coca leaf chewing and cocaine-sniffing have been regarded as one and the same problem (Wolf, 1952). Some research workers maintain that cocaine ingested during chewing is, in the greater part, decomposed in the gastrointestinal canal before it is absorbed. They believe that ecgonine and other alkaloids — but not cocaine — play the most important role in the use of the drug by the “coquero”. These workers suggest that coca chewing could be of importance in glucose metabolism at high elevations (Burchard, 1975; Nieschulz, 1971). Other studies have shown that coca leaves contain appreciable amounts of vitamins and minerals, and may contribute significantly to the nutritionally deficient diet of the Andean Indian (Duke *et al.*, 1975; Machado, 1972).

Coca chewing thus has both defenders and detractors, and as a consequence vehement polemics have resulted. These observations are not cited to obscure the potential danger of coca chewing nor to advocate coca use in the high Andes, but rather to stress the need for a thorough awareness and understanding of the interlocking nature of the components of a people’s long-standing adaptation to their environment.

The purpose of the present study, as a contribution to our knowledge of coca use, is to determine the amount of cocaine in blood upon administration of coca by the two distinct methods practiced by Indians of the Peruvian Andes and those of the Amazon region.

(1) A number of toasted coca leaves are placed, together with an alkaline material called *llipta*, in the mouth and are “chewed” (actually only rolled around with the tongue and wetted) into a wad or quid which is held in the cheek and periodically “rechewed”. The juice is swallowed and some of the leaf material may occasionally be ingested.

(2) The second method of use, consisting in taking coca leaves in powdered form (as described below in detail), is restricted to the western Amazon region in Brazil, Peru, Ecuador, and Colombia. This variation of coca use is practiced by numerous tribes (Schultes, 1957).

During Phase VII of the Alpha Helix Amazon Expedition 1976 - 1977 we had occasion to study both methods of administration and to determine the amount of cocaine in blood *versus* time by an unequivocal method of analysis\*. Much of the controversy in the older literature seems to be attributable to the lack of determinations of cocaine in blood from coca chewers (Montesinos, 1965).

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\*The RV Alpha Helix is a ship owned by the National Science Foundation (U.S.A.) and administered by Scripps Institute of Oceanography. It accommodates twelve scientists and has three air-conditioned laboratories. The scientific crew of Phase VII of the Alpha Helix Amazon Expedition 1976 - 77 (March 15 - May 15, 1977) consisted of botanists, zoologists, chemists, and medical men. We had at our disposal during the two-month period a gas chromatograph-mass spectrometer for qualitative work on components of toxic plants and animals. The instrument was also equipped with a multiple ion detector for quantitative work and was used for the determination of cocaine in blood.

## Materials and methods

### Chemicals

Cocaine hydrochloride was obtained from Karolinska Apoteket, Stockholm. Deuterated cocaine was synthesized as previously described (Holmstedt *et al.*, 1977).

### Plant materials

Descriptions of the voucher specimens used in this study are given in Table 1.

The RV Alpha Helix was anchored during the two-month period at the small village of Pebas, where the Río Ampiyacu flows into the Amazon. The

TABLE 1

Voucher specimens for chemical analyses and biological experiments

Plowman, Schultes & Tovar No.	Locality*	Date	Description**
6663	A	5 April 1977	<i>Erythroxylum coca</i> , herbarium specimens (USM, ECON)
6663A	A	5 April 1977	Coca powder prepared from dried leaves of <i>Erythroxylum coca</i> (6663) and ashes of leaves of <i>Cecropia sciadophylla</i> (6664A) (ECON)
6664	A	5 April 1977	<i>Cecropia sciadophylla</i> , herbarium specimens (USM, US, ECON)
6664A	A	5 April 1977	Ashes of burned, dead leaves of <i>Cecropia sciadophylla</i> (ECON)
6750	A	12 April 1977	<i>Erythroxylum coca</i> , herbarium specimens (USM, ECON)
7113	B	24 April 1977	<i>Erythroxylum coca</i> , dried leaves purchased in market (ECON)
7115	B	24 April 1977	<i>Llipta</i> , hardened ball of ash prepared from stems of <i>quinua</i> ( <i>Chenopodium quinoa</i> Willd.) (ECON)

\* A = Peru: Dept. Loreto, Prov. Maynas, Río Ampiyacu. B = Peru: Dept. Cuzco, Pisac.  
 \*\* Voucher specimens are deposited in the herbaria cited: Economic Herbarium of Oakes Ames (ECON), Botanical Museum, Harvard University, Cambridge, MA; Museo de Historia Natural "Javier Prado", Universidad Nacional Mayor de San Marcos (USM), Lima, Peru; U.S. National Herbarium (US), Smithsonian Institution, Washington, DC.

surrounding Indian tribes, Boras and Witotos, both cultivate coca in their house gardens. The ingredients for the coca experiments were obtained from the Indians in the upper Ampiyacu.

The use of coca leaves in powdered form is found in several areas of the northwest Amazon in Colombia, Ecuador, Peru, and Brazil in a number of unrelated tribes. The preparation of the powder is essentially the same throughout the area. The fresh leaves of *Erythroxylum coca* are gathered in the late afternoon and carried to the main "maloca" (communal house). The leaves are immediately toasted to dryness over a fire in a large hemispherical ceramic bowl made especially for this purpose or on a flat ceramic "fariña" (*Manihot*-flour) plate. The leaves are constantly turned by hand to prevent burning. When completely dried, they are placed in a large wooden mortar (*pilón*) and thoroughly pounded to a fine powder with a pestle. At the same time, fallen dead leaves of *Cecropia sciadophylla* Martius (or certain other species of *Cecropia* or *Pourouma*) are gathered into a large pile and burned to ashes.

The coca powder is removed from the mortar and placed in a cloth bag for sifting, a little at a time. The bag is shaken in a large bowl or tin can with a cover to prevent loss of the powder. The powder, sifted through the cloth to remove any fibrous material, is very fine and light green in color.

The clean grey ash is added to the coca powder little by little until the right proportions are reached. The ratio of coca powder to ash varies from 1:1 to 2:1. The powder is often chewed after the evening meal by the men. The greater part is stored in a bamboo tube or tin can for use during work the following day. As the powder does not keep well, it is usually prepared each day.

The prepared powder is taken in tablespoonful doses. It is held between the cheek and the gum for a few minutes until it absorbs sufficient quantity of saliva to become pasty in consistency. It is then worked with the tongue into the recesses of the cheeks and gums, where it is allowed to remain for one to several hours. By the time most of the juices are sucked from the quid, very little coca powder remains, and the greater part is swallowed gradually. Indians working in the forest may take coca powder numerous times during a day. It is often used after the evening meal during discussions and story telling.

#### *Gas chromatography-mass spectrometry*

The mass spectrometric analyses were carried out on an LKB 2091 gas chromatograph-mass spectrometer (GC-MS) equipped with a multiple ion detector. The glass column (150 cm × 2 mm i.d.) was packed with 3% SE-30 Ultraphase on Gas Chrom Q (100 - 120 mesh) and maintained at a temperature of 200 °C. Helium was used as carrier gas at a flow rate of 30 ml/min. The temperature of the injection port was 240 °C and the ion source was kept at 250 °C. The ionizing energy and trap current were 50 eV and 50 μA, respectively.

During the mass fragmentographic (MF) analyses, the instrument was adjusted to record the ions  $m/e$  303 and 306 ( $M^+$ ) for cocaine and cocaine- $d_3$ .

In some experiments, the mass spectrometer was set to detect  $m/e$  182 and 185 (base peak) for cocaine and cocaine- $d_3$  in order to check the accuracy.

Standard curves for the determination of cocaine in plasma were obtained by treating, in the same way as described below, a series of blood-blank plasma specimens to which known amounts of cocaine (1 - 200 ng/ml) had been added. The ratio of the peak heights of cocaine and cocaine- $d_3$  was calculated and plotted against the known concentration of cocaine in the standard samples. The  $m/e$  303 and 306 were chosen because a better signal-to-noise ratio was obtained than with the  $m/e$  182 and 185. Nevertheless, concentrations of cocaine were almost identical with both systems.

#### *Cocaine determination in the plant material*

The cocaine content in plants was measured following the procedure already published (Holmstedt *et al.*, 1977), with slight modifications. 0.02 g of coca material — either coca powder, commercially obtained dried leaves, or air-dried fresh leaves — was ground up and mixed with EtOH (5 ml) containing 50  $\mu$ g of deuterated cocaine as internal standard and 0.1 g  $\text{NaHCO}_3$ . The mixture was heated for 2 min at 75 °C and allowed to stand at room temperature for over 5 hours. The sample was centrifuged (2000g, 1 min) and 1 - 3  $\mu$ l of the clear supernatant were injected directly in the GC-MS for MF determinations.

#### *Biological experiments*

All experiments were performed on Eurasians or Indians. Most sampling took place on board the Alpha Helix and occasionally in the "malocas" or communal houses of the Indians. It should be pointed out that the use of coca leaves and preparations thereof, except for cocaine, is legal in Peru.

Weighed amounts of freshly prepared coca powder (voucher specimen 6663A) mixed with *Cecropia* leaf ashes (voucher specimen 6664A) or sun-dried leaves of *E. coca* (voucher specimen 7113) purchased in the market at Pisac (Dept. Cuzco, Peru) mixed with *Quinoa* ash (*Ilipta*, voucher specimen 7115) were given orally (time zero) and kept for various times in the cheek, as indicated in Fig. 1. Blood samples were taken by venous puncture at regular intervals with heparinized green stoppered 10 ml evacuated blood collecting tubes fitted to a syringe (Venoject, Teruma, Tokyo, Japan). \* Physostigmine (eserine) was added immediately to a final concentration of  $10^{-4}$  M, and the tube was shaken for 0.5 min. After centrifugation (5000g, 20 min) the plasma was kept cold ( $-40$  °C, dark) until analysed the next day.

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\*This commercial brand of collection tube does not alter the plasma concentration of drugs as compared with the value obtained from the all-glass system (R. H. Cotham and D. Shand, Spuriously low plasma propranolol concentrations resulting from blood collection methods, *Clin. Pharmacol. Ther.*, 18 (1975) 535 - 538).

### *Extraction*

To 1.0 ml of plasma in a 15 ml glass-stoppered tube 50  $\mu$ l of the internal standard (400 ng cocaine- $d_3$ /ml in ethanol), 0.1 g sodium bicarbonate, and 2.5 ml of anhydrous diethyl ether were added. The tube was shaken by hand for 1 min and then centrifuged at 5000g for 10 min. The organic phase, dried with anhydrous sodium sulphate, was transferred to a 3 ml methanol-washed glass tube and evaporated to dryness at room temperature under a stream of nitrogen. The residue was dissolved in 50  $\mu$ l of toluene and 2 - 4  $\mu$ l of this solution was analysed by mass fragmentography.

### *Calculations*

Plasma concentrations were used to calculate rate constants for elimination and absorption by linear regression analysis and the method of residuals (*cf.* Gibaldi and Perrier, 1975). Absorption was assumed to be more rapid than elimination, and a simple one-compartment pharmacokinetic model was used even though the possibility of a second, slower elimination phase could not be totally excluded.

## **Results and discussion**

### *Alkaloids in plant materials*

Analyses by GC-MS have shown that the cocaine content of the various plant materials used represents more than 95% of the basic chloroform soluble fraction of the ethanolic extracts. Furthermore, no ecgonine nor benzoylecgonine trimethylsilyl derivatives were detected by MF in the silylated ethanolic extract of those materials. This shows that we were dealing with plant materials containing almost exclusively cocaine. The amount of this alkaloid in freshly harvested leaves (voucher specimen 6750) immediately air-dried and analysed was 0.39%, dry weight. The powder, as prepared by the Indians (voucher specimen 6663A), showed a cocaine concentration of 0.24%, dry weight; the Pisac leaves (voucher specimen 7113), 0.48%, dry weight.

### *Absorption*

Measurable cocaine levels in plasma found 5 min after chewing started indicated rapid absorption (see Fig. 1). Some researchers have pointed out that there may be differences between the use of coca leaves and cocaine. They refer to the fact that cocaine in the leaves may be destroyed in the gastrointestinal tract (Montesinos, 1965; Nieschulz, 1971; Nieschulz and Schmersahl, 1969). Undoubtedly, some cocaine and perhaps even some metabolites are swallowed and may ultimately be hydrolysed in the gut, but this does not imply that a certain amount could not be absorbed in the stomach. It is also conceivable that a certain amount of cocaine in the blood is locally absorbed. No positive evidence for this exists at the moment but appreciable amounts of cocaine in solution are known to be absorbed when the substance is used for

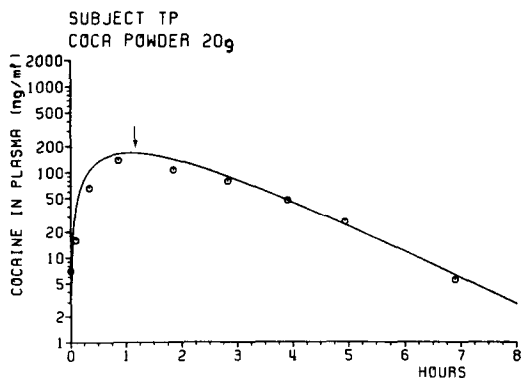


Fig. 1. Cocaine concentration, as determined by mass fragmentography, in the plasma of a volunteer chewing 20 g of coca powder (voucher specimen 6663A) corresponding to 48 mg of cocaine. The arrow indicates time of disappearance of the quid in the mouth. The curve was generated by use of the parameters derived for the pharmacokinetic model (see text).

topical application (Jatlow and Bailey, 1975; Van Dyke *et al.*, 1976; Dvorchik *et al.*, 1977), and synthetic cocaine hydrochloride in a gelatine capsule is not absorbed from the gastrointestinal tract until 30 min after oral administration (Van Dyke *et al.*, 1978).

### Doses

The cocaine doses ranged from 15 - 50 mg total in the administered amount. This dose must be considered low, when compared with the quantities used in topical anaesthesia (Van Dyke *et al.*, 1976), or intravenously injected (Kogan *et al.*, 1977). Much higher doses are known to be illegally used: cocaine addicts may use up to 10 g in a day (Jaffe, 1975).

### Means of administration

In both preparations studied by us, alkali is typically added. In the better known method of use (the highland method employed in the Andes), *llipta* is taken with the leaves. With the powder (the Amazon method), ash of *Cecropia* leaves is used. This contributes to the extraction of the alkaloids when the material is wetted (unpublished results). The effectiveness of the addition of alkali to crude drugs has been discovered by widely different ethnic groups. It occurs among the South American Indians, who mix ashes with their several intoxicating snuffs (Schultes, 1967) and in the East Indies when betel is chewed (Hartwich, 1911). It is also reported among the Australian aborigines when they chew *pituri* (Barnard, 1952).

### Peak levels

Cocaine was determined in plasma by MF, after addition of physostigmine at the earliest step of the extraction procedure ( $10^{-4}$  M solution final concentration) in order to inhibit all esterase activities *in vitro* (Stewart *et al.*, 1977). The peak levels obtained amount to a maximum 150 ng/ml for 4.4 g

of leaves and 140 ng/ml for 20 g of powder (see Figure). From the limited data available, it would appear that whole leaves and *llipta* provide a more efficient means of administration than the powder-ash mixture. Of more importance are the shape of the curve and the half-lives as related to the subjective effects. The volunteers were asked in a non-provocative way how they felt; in all cases, they reported local anaesthesia in the mouth and a stimulating effect ("amphetamine-like", "I feel fine", "feel much more awake", "feel great", "full of energy", "feel vigorous", "feel stimulated") during the rising phase of the blood curve. During the falling phase, when the quid was still in the mouth, less expressive statements could be extracted from the subjects, but all reported "no more stimulation".

### Pharmacokinetic half-lives

This study was not designed as a pharmacokinetic investigation, but some comments can be made on the disposition pattern of oral cocaine in man. Most of the plasma concentration-time curves obtained can be interpreted according to a one-compartment model, assuming first-order rate constants for absorption and elimination. It has also to be assumed that the absorption is more rapid than the elimination, since the model cannot differentiate between these two parameters. These rates have been approximately estimated yielding half-lives for the elimination from 1.0 to 1.9 hours. The absorption half-life ranged from 0.2 to 0.6 hours. The peak plasma concentration occurred between 0.4 and 2.0 hours after the cocaine dosage was inserted (Table 2).

TABLE 2

Pharmacokinetic data on coca chewing

Subject* weight (kg)/ age (yr)	Plant material (g)	Cocaine (mg)	$k_a$ (h <sup>-1</sup> )	$t_{1/2}$ (h)	$C_{max}$ (ng/ml)	$t_p$ (h)	$k_{el}$ (h <sup>-1</sup> )	$t'_{1/2}$ (h)
BH, 84/58	(powder) n.d.	n.d.	1.32	0.31	23	0.38	0.40	1.72
OT, 62/55	(powder) 10	24	1.19	0.58	59	1.35	0.43	1.62
JEL, 78/46	(powder) 7	16.8	1.15	0.32	31	1.00	0.58	1.19
TP, 75/33	(powder) 20	48	1.11	0.61	139	1.32	0.73	0.95
OT, 62/55	(leaves) 4.4	21	1.17	0.60	140	1.05	0.60	1.22
TP, 75/33	(leaves) 6.4	30.7	1.68	0.41	78	1.95	0.37	1.86

\*BH, JEL and TP are Eurasians, OT is Indian. The age and weight values of the subjects correspond to the time of the experiments (1977).

$k_a$  = absorption rate constant,  $k_{el}$  = elimination rate constant,  $t_{1/2}$  = absorption half-life,  $t'_{1/2}$  = elimination half-life,  $C_{max}$  = maximum cocaine concentration in the plasma,  $t_p$  = time at which maximum concentration of cocaine occurred in the plasma, n.d. = not determined.



## Conclusions

Experimental evidence on coca chewing gathered scientifically in the field has not previously been substantiated by measurements of blood levels of cocaine. We have carried out such experiments and the stimulating effect obtained seems to be well correlated with the rising concentrations of cocaine in the blood. The differences in stimulation between using whole coca leaves or the powder and taking cocaine by local application in the nose or by intravenous injection seem to lie essentially in means of administration and dosage (Van Dyke *et al.*, 1978). There is certainly no need to invoke as an explanation the differences in the formation of metabolites known to be inactive as euphorics and reaching peak concentrations later than cocaine (Kogan *et al.*, 1977).

There is, consequently, no reason to believe that the stimulating effect achieved by the use of either coca leaves or powder is not due to cocaine. As always in pharmacology, effect is dependent upon dose and means of administration.

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