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Cocaine: Analysis, Pharmacokinetics, and Metabolic Disposition

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The ability to measure concentrations of cocaine in body fluids can contribute substantially to any investigation of cocaine's pharmacological effects. Design of research which involves the administration of cocaine must take into account current knowledge regarding the drug's pharmacokinetics. Cocaine's very rapid elimination from the body should be considered in attempting to understand patterns of cocaine abuse, and such phenomena as bingeing and acute tolerance. Accurate analysis of cocaine and/or its metabolites is essential to the diagnosis and evaluation of cocaine use whether for medical or forensic purposes. Appropriate selection of methods for analysis of cocaine depends upon the intended purpose of the assay, and correct interpretation of the data obtained upon knowledge of cocaine's kinetics and metabolic disposition.

The measurement of cocaine and its metabolites has considerable relevance to cocaine research, both clinical and basic, and to that controversial and fuzzy interface between medicine and social policy defined as drug abuse screening. Investigations of the clinical effects of cocaine, and the differing consequences of various routes of administration, are clearly enhanced by the ability to determine concentrations of cocaine and its time course within the body. Any attempt to develop a method for the analysis of body fluids to detect use or abuse of cocaine, whether for clinical or forensic purposes, and any attempt to obtain intelligible information from the data obtained, also require knowledge of cocaine's metabolic disposition and of its pharmacokinetics.

METABOLIC DISPOSITION OF COCAINE

With its low concentrations in body fluids, very rapid and complete metabolic disposition, and susceptibility to enzymatic and spontaneous hydrolysis both *in vivo* and *in vitro,* accurate measurement of cocaine represents an interesting challenge to the toxicologist and pharmacologist. If cocaine is incubated with human plasma or with liver homogenates, it is rapidly hydrolyzed with formation of ecgonine methyl ester, one of cocaine's two major metabolites [1–4]. We were initially concerned with this aspect because of our need to preserve cocaine for future analysis in plasma samples obtained from experimental subjects. We found that the addition of sodium fluoride or physostigmine to plasma prevented its decomposition, suggesting that serum cholinesterase was responsible. We also observed that sera from subjects who by history were sensitive to succinylcholine, and whose dibucaine numbers indicated that

Abbreviations: EMIT: enzyme immunoassay technique gc/ms:gas chromatography-mass spectrometry RIA: radioimmunoassay TLC:thin-layer chromatography

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they were either homozygous or heterozygous for inheritance of the atypical esterase, failed to hydrolyze cocaine or hydrolyzed it at an intermediate rate, respectively [1]. Similar findings were reported by Stewart et al. [3], who also demonstrated that cocaine was metabolized by liver homogenates to the same product. While the homozygous state for inheritance of the atypical enzyme occurs with a frequency of only about 1 in 2,500, about 4 percent of the population are heterozygous. The relative importance of serum cholinesterase and other liver esterases in the actual disposition of cocaine *in vivo* has not been established. An intriguing question that remains unanswered is whether or not individuals who either have reduced activity of the normal cholinesterase, or who have inherited the atypical form, are at increased risk for toxicity or fatal overdose following cocaine use, especially following the extremely large cumulative doses that are administered during binges. Chronic liver disease and pregnancy are events in the drug-abusing population that can reduce activity of cholinesterase, aside from inheritance of the atypical enzyme.

Cleavage of the methyl ester group yields benzoylecgonine, which is the other major metabolite of cocaine. This compound is of particular interest because most cocaine immunoassays used for urine drug screening employ an antibody directed at benzoylecgonine rather than the parent compound. This method is used because very little unchanged cocaine is excreted in the urine, while approximately 50 percent of an administered dose of cocaine appears in the urine as benzoylecgonine. It has been suggested that spontaneous chemical hydrolysis may be responsible for the appearance of this metabolite [3], and, as yet, an enzymatic pathway for the formation of benzoylecgonine has not been identified.

Approximately 85–90 percent of an administered dose of cocaine is recovered in the urine, only about 1–5 percent of which is eliminated as the unchanged parent compound. About 75–90 percent is eliminated as ecgonine methyl ester and benzoylecgonine combined [5–8]. Both of these metabolites are inactive as regards their ability to block the re-uptake of monoamines into presynaptic neurons and the production of pharmacological effects in animals.

Hepatic mixed function oxidases play only a minor role in the metabolic disposition of cocaine in humans, although they are more important in some other species. N-demethylation of cocaine in hepatic microsomes produces norcocaine, the only pharmacologically active metabolite of cocaine as yet identified [9]. Although very little norcocaine is produced in humans, this microsomal pathway is of some interest in that it can result in the formation of hepatotoxic-reactive intermediate metabolite(s) in some species of rodents [10–13]. Although hepatotoxicity as a direct consequence of cocaine use has not been demonstrated in humans, its occurrence is difficult to discriminate in the framework of polydrug and alcohol abuse and a high incidence of hepatitis.

PHARMACOKINETICS

The rate of appearance of cocaine in the blood varies, as might be expected, with the route of administration. Following intravenous or pulmonary (smoking—"crack" or freebase) administration, relatively high peak plasma levels are achieved almost instantaneously [14–16]. Systemic bioavailability by the smoking route, if only that cocaine that reaches the respiratory tract is considered, appears to be excellent [16]. Some users state that smoking cocaine produces qualitatively different and/or more intense effects. The intravenous route is, however, considered to be a reasonable

paradigm for cocaine smoking, but with more precise and predictable dosage control. Smoking, on the other hand, provides a noninvasive way to achieve instant access of cocaine to the systemic circulation. Peak plasma levels after intravenous use or smoking of the usual doses appear to be in the range of about 500–1,000 ng/ml [14]. Peak concentrations achieved during binges have not been established but, based upon anecdotal reports of the quantities consumed, may be considerably higher.

Freebase, which can be volatilized at relatively low temperature, is the more potent dosage form, and that most widely employed by smokers. Cocaine is a tertiary amine with a pKa of 8.6. At higher pHs the un-ionized or freebase form predominates, while at more acidic pH cocaine exists as a salt, e.g., hydrochloride. Traditionally, the freebase was prepared by alkalinizing an aqueous solution of the salt and extracting the freebase into an organic solvent such as ether, which was then evaporated. Crack, on the other hand, is prepared by precipitating cocaine from an alkalinized aqueous solution. This innovative and relatively simple street technique for preparation of the freebase avoids the use of organic solvents, with their attendant risks, and associated, sometimes spectacular, accidents. In any event, once in the systemic circulation, cocaine is in the same form, regardless of route of administration or type of dosage preparation.

The first cocaine plasma levels were obtained in surgical patients who received intranasal drug for vasoconstriction and local anesthesia prior to intubation [7]. Cocaine can be detected in the blood very soon after intranasal dosing, but peak levels do not occur until about one hour after administration. Vasoconstriction limits the rate of absorption of cocaine, and thus variable amounts are swallowed. One of the more interesting, although in retrospect not that surprising, outcomes of our studies was the finding that cocaine is absorbed and pharmacologically active following oral administration [18]. In this instance, cocaine appears in the plasma following a lag phase of about 30 minutes.

Andean natives have for years self-administered cocaine by chewing coca leaves. This form of administration is associated with sustained absorption, in contrast to the intermittent administration typical of street use. Plasma cocaine concentrations in samples obtained from Andean natives chewing coca leaves according to their usual custom are in the same range as those seen after administration of modest doses of crystalline cocaine by the oral or intranasal routes [19]. Cocaine's systemic bioavailability by the intranasal and oral routes has been described as 20–60 percent in various reports [20,21]. Peak plasma levels after the "usual" intranasal dosages are in the range of about 100–500 ng/ml [20].

The quality and intensity of cocaine's psychotropic effects vary with route of administration apparently as a function of differences in absorption kinetics or rate of rise in plasma levels [22,23]. Moreover, pharmacological effects associated with any given level of cocaine are greater during the ascending portion of the plasma level vs. time curve than while concentrations are falling [24–27]. This clockwise hysteresis curve is characteristic of acute tolerance [28] and may have relevance to patterns and consequences of cocaine bingeing. These pharmacodynamic aspects are reviewed in greater detail elsewhere in this issue.

Cocaine is rapidly eliminated from the body with a biological half-life of about one hour and total body clearance of about two liters per minute [20,21,27]. Its volume of distribution of approximately two liters per kilogram is small compared to some psychotropic drugs. While cocaine's kinetics do show inter-individual variation, it

appears to be less than is characteristic of many other drugs that are primarily dependent upon microsomal oxidation for their elimination. The major hydrolytic metabolites of cocaine, benzoylecgonine and ecgonine methyl ester, which together comprise about 80–90 percent of a cocaine dose excreted in the urine, are eliminated more slowly, with half-lives of about five and eight hours, respectively [6,8]. This information regarding the kinetics and metabolic disposition of cocaine must be taken into account in the development, selection, and interpretation of tests used for drug abuse screening.

ANALYSIS

The tools available for the analysis of cocaine and its metabolites in biological fluids are no different from those used for most other drugs. (Table 1). They include thin-layer, gas liquid and high-performance liquid chromatography, gas chromatography-mass spectrometry (gc/ms), and various immunoassays—both isotopic and non-isotopic [29]. Selection of methodology for any given application must be consistent with the nature of cocaine's metabolic disposition and kinetics, as described above. For example, a highly specific monoclonal antibody directed toward unmetabolized cocaine is unlikely to be of value in urine screening for cocaine abuse, as little unchanged parent drug is excreted in the urine, and that only for a short time. Similarly, considering cocaine's very short half-life, there would be little rationale for the analysis of cocaine concentrations in plasma in the evaluation of a clinical problem when the ingestion has occurred eight or more hours previously.

Drug Abuse Screening

As with most other drugs of abuse, one form or another of immunoassay is most commonly used for initial screening of urine for evidence of cocaine use. Radioimmunoassay and a variety of non-isotopic immunoassays can be employed [30,31]. Drug abuse screening provided an important and perhaps major stimulus for the development of immunoassays for drugs and other small molecules (haptens) in general and probably provided the major impetus for the development and refinement of non-isotopic immunoassays. Although the antibodies used vary in specificity to some degree, in all instances they are primarily directed at the detection of benzoylecgonine, which is the major urinary metabolite of cocaine. The widely used homogeneous enzyme immunoassay technique, which bears the acronym EMIT®, utilizes a ligand coupled to an enzyme, glucose-6-phosphate dehydrogenase. When used in a competitive binding immunoassay, analogous to radioimmunoassay (RIA), the enzyme-ligand conjugate that is not bound to antibody is available to act on the added substrate with generation of NADPH. The latter can be monitored spectrophotometrically. Another widely used type of non-isotopic assay employs fluorescence polarization. In this instance, the ligand is conjugated to a fluorophore, and changes in fluorescent polarization resulting from binding of the ligand to the larger antibody molecule can be measured.

A variety of other ingenious non-isotopic assays for cocaine (benzoylecgonine) and other drugs have been described. Many of these assays are characterized as "homogeneous" because, in contrast to classical radioimmunoassay, a step to separate free from antibody-bound ligand is not required. The marvel of these assays is that they can be accomplished in a matter of minutes and can be automated. Thus, laboratories that

TABLE 1
Analysis of Cocaine and Its Metabolites

Method	Sample	Analyte	Approximate Detection Limit	Usual Use
Immunoassay	Urine	Benzoylecgonine	300 ng/ml[a]	Qualitative or semi-quantitative Drug abuse screening Presumptive identification only
Thin-layer chromatography	Urine	Benzoylecgonine Ecgonine methyl ester Cocaine	500 ng/ml	Qualitative Drug abuse screening Presumptive identification only
Gas chromatography	Urine	Benzoylecgonine Ecgonine methyl ester Cocaine	Variable approximately 50 ng/ml	Quantitative Drug abuse screening Presumptive or confirmation
Gas chromatography	Blood	Benzoylecgonine Ecgonine methyl ester Cocaine	Variable 5–50 ng/ml	Quantitative Clinical correlation Kinetics
High-pressure liquid chromatography	Urine	Benzoylecgonine Cocaine	50 ng/ml	Quantitative Limited use for drug abuse screening
High-pressure liquid chromatography	Blood	Cocaine Benzoylecgonine	50 ng/ml	Quantitative Clinical correlation Kinetics
Gas chromatography-Mass spectrometry	Urine	Benzoylecgonine Ecgonine methyl ester Cocaine	5 ng/ml or lower	Quantitative Definitive identification and confirmation
Gas chromatography-Mass spectrometry	Blood	Benzoylecgonine Ecgonine methyl ester Cocaine	5 ng/ml or lower	Quantitative Clinical correlation Kinetics

[a]Can be lower, cutoff set to minimize false positives

devote themselves to drug abuse screening for cocaine, as well as other drugs, can churn out hundreds, even thousands, of sample results per day.

It is reasonable to assume that antibodies with broad specificity that cross-react with both major urinary metabolites of cocaine may be more sensitive and thus preferable for drug abuse screening. For this one application, and in distinction to most assays used for research, or for clinical purposes, narrow molecular specificity is not necessarily an asset. On the other hand, class specificity is important. In view of the forensic and social implications of false-positive data, it is considered axiomatic to confirm any positive with a reference physical assay such as gas chromatography-mass spectrometry. This dictum applies only to drug abuse screening programs. For the rapid medical evaluation of an emergency room patient with seizures or acute psychosis, an immunoassay for cocaine metabolites can be justifiably used by itself.

Benzoylecgonine and ecgonine methyl ester with half-lives of about five and eight hours, respectively, can generally be detected for up to 24 to about 48 hours after cocaine use with the usual immunoassays [29]. Although this time period will depend upon the amount of drug used, and possibly inter-individual differences in its disposition, the metabolites may be detected in urine for a considerable period of time after the acute effects of cocaine have dissipated. Their persistence following cocaine use is, however, still relatively short compared to other drugs of abuse. For example, drug screens may remain positive for cannabinoid metabolites for several weeks after marijuana use in the chronic user. As with other drugs, the finding of cocaine metabolites in urine provides no information about an individual's condition or degree of impairment at the time of urine sampling. On the other hand, a negative urine probably indicates that the subject has probably not used cocaine within the last two to three days.

Cocaine, with its short half-life and relatively complete systemic metabolism, usually disappears from the urine in four to six hours and thus is generally not the focus of drug abuse screening. If, however, unmetabolized cocaine is detected by any of several chromatographic methods, it is reasonable to assume that its use has been fairly recent.

Prior to the introduction of immunoassays for drugs, thin-layer chromatography (TLC) was the mainstay for drug abuse screening. This inexpensive, simple, yet elegant technique has many virtues. Reactions with chromogenic reagents, sometimes functional group-specific, provide identifying information beyond that of chromatographic behavior (migration or elution time); multiple samples can be analyzed for multiple drugs concurrently or in parallel; the appearance of parent drug with metabolites provides characteristic patterns. In regard to cocaine, it is the only method which can easily and concurrently demonstrate the presence of cocaine and its two major urinary metabolites [32]. In the clinical environment, wherein other information about the patient is available, we have found it to be a dependable way to confirm a positive immunoassay for cocaine. Interpretation of TLC does require experience, skill, and some subjective judgment, not unlike other procedures and decision-making processes in medicine. For drug abuse screening, however, when data is interpreted absolutely and *in vacuo,* without clinical information, and may be used for punitive rather than therapeutic purposes, TLC has fallen into disfavor.

While any of the common physical methods for analysis of drugs can be applied to drug abuse screening, none are as efficient or, with the exception of gc/ms, as sensitive as immunoassay. It is increasingly recognized that gc/ms is the most reliable and,

legally, the most defensible method for confirmation of positive immunoassays [33]. In essence, when used in the scan mode, gc/ms can provide a molecular fingerprint of cocaine and its metabolites. When used in the selective ion mode, considerably greater sensitivity can be obtained, and identification is still essentially absolute if several ions are simultaneously monitored and ratioed [34,35]. This type of analysis requires far greater effort, skill, and time than immunoassay, and its use is commonly restricted to confirmation. The cost-benefit ratio to society of applying these elegant technologies to large-scale drug abuse screening remains to be determined.

Analysis of Cocaine in Blood

Facile analysis of cocaine in plasma was first made possible by the introduction of a new, highly sensitive detector for gas chromatography, the nitrogen-phosphorus detector [36,37]. This detector responds selectively to most nitrogen-containing compounds, with a sensitivity considerably greater than the traditional flame ionization detector. Concentrations as low as about 5 ng/ml can be accurately quantified, which is sufficient to determine the elimination kinetics of cocaine after modest doses. Currently, most assays for cocaine used in research still utilize gas chromatography with a nitrogen detector, although gc/ms and, more recently, high-pressure liquid chromatography are also used. As with most drug assays, gc/ms remains the state of the art in regard to specificity. The ability to use deuterated cocaine as an internal standard also enables unparalleled sensitivity and accuracy.

All of the physical assays for cocaine in plasma are considerably more complex and difficult to perform than the immunoassays employed for drug abuse screening. Generally, a multi-step extraction procedure is required adequately to concentrate and separate cocaine from endogenous interferences. Research protocols, as well as clinical and forensic studies, often fail to take into account cocaine's susceptibility to enzymatic and alkaline hydrolysis. Blood samples must be preserved with fluoride or another esterase inhibitor, and prolonged exposure to elevated pH must be avoided. A significant proportion of cocaine concentrations reported in possible cases of overdose are undoubtedly underestimated because of these problems.

Analysis of cocaine's major metabolites will not be discussed in detail except to indicate that extraction and chromatography of these relatively water-soluble hydrolytic products is even more of a challenge than for the parent compound. Gas chromatography and gc/ms require derivatization of the metabolites prior to chromatography. Reversed-phase high-pressure liquid chromatography is particularly useful for benzoylecgonine because a derivatization step is unnecessary [38]. Although these metabolites are pharmacologically inactive, the presence of these more slowly eliminated derivatives may be the only evidence of cocaine use at a time when the parent compound is no longer detectable in body fluids. Aside from drug abuse screening, investigation of cocaine metabolism may provide some insights into whether interindividual differences in the disposition of cocaine may explain differences in susceptibility to its toxicity.

Among the goals of current cocaine research are a better characterization of cocaine's clinical effects and, ultimately, determination of cocaine's mechanism of action. An understanding of cocaine's pharmacokinetics and metabolic disposition and the ability to quantify cocaine and its metabolites in human biological fluids are important for the rational design and performance of research at both the clinical and basic levels. Any constructive use of drug abuse screening for cocaine requires

absolutely accurate assays and interpretations that are consistent with current knowledge about cocaine's kinetics and disposition.

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