**SIMULTANEOUS PHARMACOKINETIC MODELING OF COCAINE AND ITS METABOLITES, NORCOCAINE AND BENZOYLECгонINE, AFTER INTRAVENOUS AND ORAL ADMINISTRATION IN RATS**

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**ABSTRACT:**

To accurately assess the mechanism of involvement of the active metabolite norcocaine in the effects of oral cocaine, it is essential to determine the rate and extent of the formation of norcocaine. Although this study was designed specifically for this aim, it was also of interest to characterize the metabolite kinetics of benzoylecgonine for comparative purpose. We first characterized the pharmacokinetics of cocaine, norcocaine, and benzoylecgonine by the i.v. route of administration; all three drugs decayed biexponentially. These pharmacokinetic estimates were then used for determination of the formation of norcocaine and benzoylecgonine after i.v. and p.o. (20–40 mg/kg) cocaine administration. Although $t_{1/2}$ and $t_{1/2}$ were similar across the three compounds, the values of volume of distribution in the central compartment and clearance for benzoylecgonine were much smaller than those of cocaine and norcocaine.

Norcocaine was not detected following i.v. cocaine; however, serum norcocaine concentrations were as high as those of oral cocaine. Both routes of cocaine administration produced benzoylecgonine. A pharmacokinetic model for the metabolite kinetics was proposed by sequentially adding the models that most adequately described the formation of each metabolite to the model of cocaine. For oral cocaine, the absolute bioavailability was 3.48%, whereas 6.04 and 2.26% of cocaine were converted to benzoylecgonine and norcocaine, respectively, during first-pass absorption regardless of dose. Furthermore, the majority of norcocaine and 92% of benzoylecgonine were formed during the first-pass absorption, leaving 8% of benzoylecgonine produced in systemic circulation. The profile of norcocaine as a metabolite confirmed the involvement of norcocaine in cocaine’s behavioral effects.

Cocaine, a psychomotor stimulant, is known to produce behavioral activation, to serve as a discriminative stimulus, and to support i.v. cocaine self-administration (Woolverton and Balster, 1982; Johanson and Fischman, 1989). Cocaine is extensively metabolized in humans and animals. Benzoylecgonine and ecgonine methyl ester are the major hydrolytic metabolites formed by hepatic and plasma esterases (Stewart et al., 1977, 1979; Inaba et al., 1978). Both metabolites are pharmacologically inactive and are often used for forensic purposes. Cocaine is demethylated to an active metabolite, norcocaine, by cytochrome P450 enzyme systems (Hawks et al., 1974; Leighty and Fentiman, 1974; Misra et al., 1974, 1975). Benzoylecgonine and ecgonine methyl ester are further hydrolyzed to ecgonine (Jatlow, 1987), whereas norcocaine is hydrolyzed to benzoylecgonine (Nayak et al., 1976). Among these compounds, cocaine and norcocaine are hepatotoxic, whereas benzoylecgonine and ecgonine methyl ester are not (Thompson et al., 1979).

In previous studies, we found that p.o. cocaine (20 mg/kg) was three times more effective than i.v. cocaine (2 mg/kg) in disrupting an operant behavior as reflected in pharmacodynamic (PD) estimates (Ma et al., 1999). One plausible explanation is that the active metabolite norcocaine exerted cocaine-like behavioral effects, since norcocaine was detected after oral but not i.v. cocaine administration. The contribution of norcocaine to cocaine’s effects was made even more evident by the use of escalating multiple oral cocaine dosing, which generated higher, lasting norcocaine concentrations (Lau et al., 2000). Although the effects of norcocaine on behavior have been compared with those of cocaine (Spealman et al., 1979; Bedford et al., 1980; Elliott et al., 1987), the role of norcocaine as a metabolite on the effects of cocaine has not been explored to the best of our knowledge. To determine its extent of involvement, it is essential to analyze the rate and extent of formation of norcocaine after cocaine administration. The PK of cocaine has been extensively characterized in humans (Inaba, 1989; Jeffcoat et al., 1989; Ambre et al., 1991) and in animals (Nayak et al., 1976; Benuck et al., 1987; Booze et al., 1997; Mets et al., 2000) after various routes of administration. However, a simultaneous characterization of the PK of cocaine and its metabolites has not been reported with the exception of a PK model developed to analyze the formation and excretion of benzoylecgonine in plasma and urine in humans (Ambre et al., 1991).

Accordingly, the major aim of the present study was to determine...
the rate and extent of the formation of norcocaine after i.v. and p.o. routes of cocaine administration in rats, for a subsequent delineation of the role of norcocaine in cocaine’s effects. Additionally, the metabolite kinetics of benzoylecgonine was investigated. We first characterized separately the PK of both norcocaine and benzoylecgonine as parent compounds by the i.v. route of administration. These PK parameters were then fixed for the estimation of the metabolite kinetics for norcocaine and benzoylecgonine, with the assumption that the distribution and elimination of a metabolite did not differ from those when the metabolite was administered intravenously. Because cocaine is subject to hepatic first-pass metabolism (Hawks et al., 1974; Leighty and Fenitman, 1974; Misra et al., 1974, 1975), the fraction of cocaine directly metabolized to norcocaine or benzoylecgonine due to first-pass metabolism was determined with various PK models.

This PK study is the second part of a continuing series of experiments for the characterization of norcocaine’s contribution to the observed overall PD effects using two behavioral paradigms following i.v. and p.o. cocaine administration (Wang et al., 2001). To minimize group differences between the PK and PD studies, this PK study was conducted using animals of the same species, age, and gender and under the same food regimen as those used in the PD study. A follow-up PK-PD study will combine the PK results presented here with those of the PD study using the most appropriate PD models developed for drug interactions to delineate how norcocaine modulates cocaine’s effects.

Materials and Methods

Animals. Nine male, albino, Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN) with a mean initial body weight of 382 g (range 378–386 g) were housed individually in a temperature-regulated room with a 12-h light/dark cycle (lights on at 7:00 AM). Animal body weights were reduced to 80% of free-feeding levels by limiting daily food rations (5 g for the first day, 10 g for the next 5 days) and were then maintained at their weights with a daily food supplement (range 14–16 g). Water was made continuously available in the living cages. They were held at this weight for 2 to 3 months before the start of the experiment, a time period required to train and establish baseline performance for operant behavior. All experiments were executed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication 85-23, revised 1996).

Drug. Cocaine hydrochloride (HCl), benzoylecgonine, and norcocaine were obtained from the Research Triangle Institute (Research Triangle Park, NC) through the National Institute on Drug Abuse. Cocaine HCl and benzoylecgonine were dissolved in 0.9% NaCl. Norcocaine (5 mg) was dissolved in 25 μL of 1.2 N HCl and was further diluted to a working concentration with 0.9% NaCl solution. Cocaine and norcocaine were administered either i.v. or orally by gavage in a volume of 1 mL/kg of body weight. Benzoylecgonine was administered only by the i.v. route. All cocaine doses were expressed in terms of salts and were corrected to base for the calculation of PK parameters, whereas doses of norcocaine and benzoylecgonine were expressed in terms of base. When an i.v. bolus dose was administered, the drug solution was delivered in 30 s and was followed by 0.3 mL of 0.9% saline in 30 s. For oral administration, feeding needles with 4-mm ball-tipped stainless steel no. 14; 7.7 cm were used.

Catheterization. Animals were weighed prior to surgery and then anesthetized with a mixture of ketamine and xylazine, as described previously (Ma et al., 1999). Right jugular and femoral vein cannulation was performed under sterile conditions. The jugular vein catheters were composed of polyethylene tubing (PE 50, 0.58-mm i.d. × 0.97-mm o.d.; Becton Dickinson, Parsippany, NJ) attached to silicone tubing (0.51-mm i.d. × 0.94-mm o.d.; Silastic; Dow Corning, Midland, MI). The femoral vein catheters were composed of Renathane tubing (0.64-mm i.d. × 1.02-mm o.d.; Braintree Scientific, Inc., Braintree, MA). The proximal end of the silastic catheter or the Renathane catheter was inserted into the vein. The distal end of the catheters were externalized subcutaneously and connected to two metal outlets of a plastic pedestal (Value Plastics, Inc., Fort Collins, CO) cemented to the skull. The dual catheters accommodate the administration of drug solution via the femoral vein catheter and blood sampling via the jugular vein catheter to avoid contamination of the blood samples with dosing solution. The animals were allowed to recover from catheterization for at least 3 days before drug administration. The catheter was flushed with 0.9% saline containing 50 units of heparin per milliliter and was sealed with fishing line (0.6 mm) when not in use.

Reagents and High-Performance Liquid Chromatography. Reagents were obtained from standard commercial sources. Serum levels of cocaine and its metabolites (norcocaine, benzoylecgonine) were determined by a fluorometric high-performance liquid chromatography method developed in our laboratory for microsamples (Sun et al., 2000).

Drug Administration and Blood Sampling. The PK experiment in this study was conducted in Plexiglas chambers similar in size to those used for the behavioral experiment (Wang et al., 2001). Each chamber was equipped with a stainless steel food-pellet receptacle into which 45-mg dustless pellets could be delivered. The animals were divided into two groups. Group 1 (n = 4) received a cocaine dosing series (i.v. bolus 2 mg/kg and p.o. bolus 20 and 40 mg/kg), and group 2 (n = 5) a norcocaine dosing series (i.v. bolus 2 mg/kg and p.o. bolus 10 and 40 mg/kg). For both groups, the i.v. dose was administered as the first dose, and the successive p.o. doses were given in random order with each drug dose separated by 3 to 5 days. Because the catheters of two animals (one from each group) were still functional after their dosing series, these two animals also received an i.v. bolus dose of 1 mg/kg benzoylecgonine administration for characterizing the PK of benzoylecgonine.

Blood samples (100 μL) were obtained at 5, 10, 20, 30, 60, 90, 120, and 180 min postinjection; an additional blood sample was also obtained at the 2.5-min time point after i.v. route of administration. After each blood sampling, 0.2 ml of sterilized 0.9% NaCl solution was administered to replace the blood sample. For each drug dose, the animals in the present study also received 45-mg food pellets equal in number to the quantity earned during the corresponding behavioral sessions at time points of 15, 30, 45, 60, 90, 120, and 180 min (Wang et al., 2001) to minimize the difference between the PK and PD studies. After 180 min, animals were returned to home cages and given food rations sufficient to maintain their usual, daily criterion weights.

Blood samples were centrifuged for 10 min at 13,700g; serum samples were stored frozen (−50°C) until analysis. Previously, we have found that in vivo rat serum cocaine samples remain stable for at least a month without the presence of sodium fluoride, a cholinesterase inhibitor (Lau et al., 1990). Thus, sodium fluoride was not used in the present study because serum samples were analyzed within a week.

PK Analysis. PK modeling was performed using the SAAM II software system (SAAM Institute, Seattle, WA, 1997), as described previously, using naive pooled concentration-time profiles analyzed in a manner in which all of the individual data were fitted simultaneously (Lau et al., 1999, 2000). We first characterized the PK parameters for each drug (cocaine, norcocaine, and benzoylecgonine) as an independent parent compound (model 1). The PK estimates for each of the two metabolites were then fixed for determination of the metabolite kinetics after i.v. and p.o. cocaine administration (model 2). Finally, the PK models for the formation of norcocaine and benzoylecgonine were combined to build a full model for the two routes of administration (model 3). Model parameters were estimated by visual examination, numerical optimization using Akaike’s information criterion (AIC) as the objective function (Akaike, 1974), and errors in parameter estimation (S.D., expressed as CV%) derived from the covariance matrix of the SAAM II software system to evaluate model order and to perform model discrimination.

Characterization of PK of Cocaine, Norcocaine, and Benzoylecgonine as Parent Compounds: Model 1. An open two-compartment model was used to characterize the concentration-time profiles for each parent compound following i.v. bolus administration with elimination from the central compartment (Fig. 1). The compartmental model parameters, the volume of distribution for the central compartment (Vc), and intercompartmental rate constants (k10, k12, and k21) were used to calculate the parameters in the equation Ct = Ae−αt + Be−βt, using standard formulas, where the terms A and B are the extrapolated zero intercepts, and α and β are the slopes representing the apparent first order distribution and elimination rate constants, respectively. The PK parameters, clearance (CL), volume of distribution at steady state.
PK Model for Intravenous and Oral Cocaine and Metabolites

Fig. 1. PK model 1 describing the disposition of cocaine, norcocaine, and benzoylecgonine after i.v. and/or p.o. routes of administration.

Fig. 2. PK model 2 describing the formation of norcocaine or benzoylecgonine after i.v. and p.o. cocaine administration by pathways 1 (via the forming rate constant $k_{m}$) and 2 (with first-pass metabolism).

Table 1 shows the PK parameters of cocaine, norcocaine, and benzoylecgonine following i.v. and p.o. cocaine administration (i.e., pathway 2). Meanwhile, some bioavailable cocaine dose (F) was absorbed through the gut wall, passed the portal vein and liver, and eventually converted to norcocaine or benzoylecgonine in the systemic circulation characterized by $k_{m}$ (pathway 1) as in the case for i.v. cocaine, leaving the fraction of cocaine (1-F) lost in the gastrointestinal lumen (Fig. 2). To test whether pathway 2 could account for the formation of norcocaine for oral cocaine, model 2b was tested by removing pathway 1 from model 2a. The PK parameter values used for $V_{e,c}$, $k_{1,0,m}$, $k_{1,2,m}$, and $k_{2,1,m}$ were those obtained from model 1 for i.v. norcocaine and i.v. benzoylecgonine, assuming that the distribution and elimination of a metabolite remained the same as those when a metabolite was administered systemically (Fig. 1).

No first-pass metabolism: model 2c. Here (model 2c), we assume that norcocaine and benzoylecgonine were formed only by pathway 1 without the presence of pathway 2 after p.o. cocaine administration.

Simultaneous Characterization of PK of Cocaine and Its Two Metabolites: Model 3. By simultaneously optimizing concentration-time profiles of cocaine, norcocaine, and benzoylecgonine following i.v. and p.o. cocaine administration, a full model that combined the most optimal model for the formation of each metabolite was constructed (model 3; Fig. 3). Specifically, for oral cocaine, benzoylecgonine was formed by both of the pathways, whereas norcocaine was only formed by pathway 2. Statistical analyses were performed as appropriate via one- or two-way repeated measures analyses of variance followed by Newman-Keuls tests, using SigmaStat (SPSS Inc., Chicago, IL).

Results

Figure 4, A–C, show the mean serum cocaine (filled circles) and its metabolite concentration-time profiles (open symbols, norcocaine and benzoylecgonine) for the i.v. (2 mg/kg) and p.o. cocaine doses (20–40 mg/kg). Cocaine was not detected after 120 min postinjection. After i.v. cocaine administration, norcocaine was not detected. In contrast, norcocaine appeared immediately after oral cocaine dosing with a $T_{max}$ (i.e., 10 min) equal to that of cocaine, regardless of dose, after which both compounds eliminated in parallel. Furthermore, despite the low F value for oral cocaine (Table 1), norcocaine concentrations were as high as those of cocaine ($p > 0.05$). Benzoylecgonine was detected in serum immediately after both routes of cocaine administration with a $T_{max}$ occurring after 10 min; the concentration levels were significantly higher than those of cocaine and remained relatively high for the duration of the blood sampling.

Characterization of PK of Cocaine, Norcocaine, and Benzoylecgonine as Parent Compounds: Model 1. Table 1 shows the PK parameters of cocaine, norcocaine, and benzoylecgonine administered as parent compounds. The PK parameter values of cocaine estimated simultaneously for the two routes were similar to those estimated separately for the i.v. dose by itself (data not shown), indicating that the PK of cocaine was neither route- nor dose-dependent in the dose ranged used. All three drugs decayed biexponentially following i.v. administration (Fig. 4, A and D). Although $t_{1/2,a}$ and $t_{1/2,B}$ were similar among the three compounds, the values of $V_{e,c}$, $V_{e,m}$, and CL for benzoylecgonine were much smaller than those of cocaine and norcocaine (Table 1). However, the MRT for benzoylecgonine was somewhat longer than those of cocaine and norcocaine.

Simultaneous Characterization of PK of Cocaine and Each of Its Metabolites: Model 2 (i.e., COC-NORC or COC-BE). Table 2 shows the formation rate constants ($k_{1,0,m}$ and $k_{1,2,m}$) and the fraction of cocaine converted to norcocaine and benzoylecgonine during the first-pass metabolism ($F_{NORC}$ and $F_{BE}$) for both routes of administration using model 2a (COC-NORC and COC-BE), and the PK parameters of cocaine, which remained similar to those obtained for model 1 (Table 1, left). This indicated that characterization of the metabolite formation had minimal effects on estimation of the parameters for the parent compound. Upon visual inspection of the fits, model 2a de-
This demonstrated that the formation of norcocaine metabolites. The value of \( k_{1-0} \) remained unchanged (Table 2, models 2a and b, parent compound and the formation of norcocaine. In particular, the norcocaine concentration-time profiles after administration of i.v. cocaine (2 mg/kg) (A), p.o. cocaine (20 mg/kg) (B), and i.v. norcocaine (2 mg/kg) and benzoylecgonine (1 mg/kg) (D). Table 5 shows the formation of benzoylecgonine in concentration-time profiles for the i.v. dose (Fig. 5A) had less between-subject variability compared with those for the two p.o. doses (Fig. 5, B and C). Figure 5D shows the formation of benzoylecgonine in concentration-time profiles for the p.o. 20 mg/kg dose estimated from the full model by simulation. This is, the total benzoylecgonine (symbols and solid lines) was formed by the two pathways of cocaine, in a composition of 8% via pathway 1 (dotted symbols) and 92% via pathway 2 (dashed line).

Determination of the extent of benzoylecgonine from each of the two pathways can be estimated also by the principle of mass balance. For the absorption model, the fraction of the cocaine that reached the systemic circulation \( F \) was estimated as the ratio of the bioavailable dose to the absorbed dose. By pathway 2, 6.04 and 2.26% of absorbed cocaine was converted to benzoylecgonine and norcocaine, respectively. The parameters estimated from model 3 (Fig. 3) were pooled using the first-pass effects (models 2a, 2b, and 2c). As a result, the observed concentration-time profiles for oral cocaine were adequately described for both cocaine and either of the two metabolites obtained from model 3. Figure 3 shows that the predicted concentration-time profiles (solid lines) described well the observed individual concentration-time profiles of cocaine (filled symbols) and its metabolite, norcocaine or benzoylecgonine (open symbols). Although complete metabolite profiles for each cocaine dose are not shown in Fig. 5, it is apparent that the observed individual serum cocaine concentration-time profiles for the i.v. dose (Fig. 5A) had less between-subject variability compared with those for the two p.o. doses (Fig. 5, B and C). Figure 5D shows the formation of benzoylecgonine in concentration-time profiles for the p.o. 20 mg/kg dose estimated from the full model by simulation. That is, the total benzoylecgonine (symbols and solid lines) was formed by the two pathways of cocaine, in a composition of 8% via pathway 1 (dotted line) and 92% via pathway 2 (dashed line).

Determination of the extent of benzoylecgonine from each of the two pathways can be estimated also by the principle of mass balance. The \( k_{1-0} \) was about 6 times slower than \( k_{2-1} \) of cocaine (Table 2, model 2c). As a result, the observed concentration-time profiles for oral cocaine were completely underestimated and neither of the models converged, indicating the importance of inclusion of pathway 2 for estimating the formation of each metabolite.

**Simultaneous Characterization of PK of Cocaine and Its Two Metabolites: Model 3.** Table 2, the rightmost panel, shows the PK parameters (CV%) of COC, NORC, and BE administered as parent compounds using model 1.
The results generated using the two methods of calculation were consistent with each other. One set of parameters accounted for the two oral cocaine doses (Table 1, left), indicating that the PK of cocaine was not dose-dependent in the dose range used.

Thus, the rest of the benzoylecgonine formed by pathway 2 was 92%. The formation of benzoylecgonine and norcocaine across all of the doses, indicating that the metabolite kinetics was not dose-dependent in the dose range used.

### Discussion

To determine the involvement of norcocaine in cocaine’s effects, it is necessary to assess the rate and extent of the formation of norcocaine after cocaine administration. This study was specifically designed for this purpose, although it was also of interest to characterize the metabolite kinetics of benzoylecgonine for comparative purposes. To the best of our knowledge, this is the first attempt to simultaneously characterize the formation of benzoylecgonine and norcocaine after oral cocaine dosing. The PK estimates for cocaine, norcocaine, and benzoylecgonine after oral cocaine administration were parallel to that of i.v. cocaine, the PK estimates of i.v. cocaine were used as references for interpreting the observed concentration-time profiles of norcocaine for the oral cocaine doses by assuming that norcocaine was formed exclusively from pathway 1. Thus, cocaine was converted to norcocaine mainly during the first-pass absorption (i.e., $k_{BE}$), coinciding with...
administration of the two oral cocaine doses (20–40 mg/kg), indicating that metabolite kinetics for benzoylecgonine and norcocaine was dose-independent in the dose range used. Thus, an estimation of the time course of cocaine and its two metabolites for doses in the linear range can be simulated from the PK parameters shown in Table 2, the rightmost panel. The PK parameters estimated from model 3 for cocaine and/or the formation of norcocaine and benzoylecgonine corresponded to those estimated from models 1 and 2, respectively (Tables 1 and 2). Therefore, simultaneous evaluation of the formation of norcocaine and benzoylecgonine had minimal effect on the PK estimates of both the parent compound and either of the metabolites. Accordingly, the comparative PD data of cocaine and norcocaine (Wang et al., 2001) can be integrated with model 2b (COC-NORC) for delineation of how norcocaine modulates cocaine’s effects as a metabolite in the follow-up PK-PD study.

We characterized the metabolite kinetics with the assumption that the PK parameter values of norcocaine and benzoylecgonine as metabolites were the same as those when both compounds were administered systemically. Although the PK parameters of norcocaine as a parent compound have been characterized in rats (Mets et al., 1999) and in humans (Stewart et al., 1979), the metabolite kinetics of norcocaine has not been characterized. During model formulation, we tried to characterize the metabolite kinetics of norcocaine and benzoylecgonine without the PK estimates of synthetic norcocaine and benzoylecgonine (model 1) as the estimates for the metabolite parameters (i.e., $V_{c,t}$, $k_{1,0,m}$, $k_{1,2,m}$, and $k_{2,1,m}$) in models 2a, 2b, and 3. However, none of the models converged; presumably, these metabolite parameters were unidentifiable. Since simultaneous modeling of cocaine and its metabolites had minimal effects on the PK estimates for the parent compound as described above, we examined whether the metabolite kinetics could be estimated by fixing the PK parameters of cocaine as done by other investigators (Ambre et al., 1991). Again, none of the models optimized. Hence, it is essential to characterize norcocaine and benzoylecgonine as parent compounds by the i.v. route, thereby facilitating the determination of the extent of involvement of the two pathways in the formation of the metabolites with biexponential decays after various doses of cocaine administration. The metabolite kinetics of benzoylecgonine was estimated using the PK estimates of i.v. benzoylecgonine from the two rats due to the short catheter lives with the assumption that the serum drug concentration-time profiles for the i.v. route in general have much less between-subject variability compared with those for the extravascular routes of administration as in the case of cocaine (Fig. 5). The predicted concentration-time profiles for cocaine and its two metabolites generated from model 3 described the observed concentration-time profiles well (Fig. 5), demonstrating the feasibility of simultaneous modeling of the parent compound and its metabolites as used by other investigators (Ogiso et al., 1998).

In summary, a full PK model for the metabolite kinetics of cocaine was proposed by sequentially adding the models that most adequately described the formation of each metabolite to the model of the parent compound. This permitted the dissociation of the effects of norcocaine from those of cocaine after integration of PK with the respective PD profiles. Norcocaine also was detected in rats after i.p. cocaine administration (Booz et al., 1997) and in humans after oral cocaine administration (Inaba et al., 1978; Walsh et al., 2000) and its formation increased with repeated oral dosing (Jufer et al., 1998). Therefore, defining norcocaine’s influence is not only essential to delineate cocaine’s effects in animal research but also clinically relevant to the understanding of norcocaine’s contribution to the physiological and behavioral effects of oral cocaine observed in humans (Epstein et al., 1999; Rush et al., 1999). Recently, chronic oral cocaine dosing has
been evaluated as a possible agonist therapy in the treatment of cocaine dependence in humans (Walsh et al., 2000). Simulation of the concentration-time profiles for both cocaine and its formation of norcocaine after PK modeling would allow the design of the most optimal oral cocaine dose regimens for a more complete evaluation of this possibility and the dissociation of the effects of norcocaine from those of cocaine.

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References