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SHORT COMMUNICATION

# Excretion of cocaine and its metabolites in man

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Little information exists on the metabolism, distribution and excretion of cocaine in persons dependent upon it. We now present results showing the proportions of cocaine excreted unchanged and as its metabolite benzoylecgonine.

## *Experimental*

*Regimen.* The subject was a 23-year-old male who usually administered to himself, by intravenous injection, 120 mg cocaine hydrochloride and 180 mg diacetylmorphine (as hydrochloride), in divided doses as desired. During the study period the drugs were given intramuscularly by nursing staff and a strict check was kept on drug dosage, times of administration, times of micturition, and volumes of urine voided. The pH of each urine sample was measured with a pH meter and the samples stored (−20°) pending analysis.

*Urine analysis.* Analysis for cocaine was made on 1–5 ml aliquots from each urine sample using the method of Fish & Wilson (1969). Cocaine was removed from similar aliquots of the same samples by extraction with diethyl ether (3 × 5 ml) and benzoylecgonine was then extracted by continuous liquid–liquid extraction with chloroform (12 ml) to which internal standard solution (1 ml, 5α-cholestane 1·55 mg % in chloroform) had been added. The extract was concentrated (100 μl) and treated with ethereal diazomethane (0·5 ml): excess reagent was removed (40°) after 5 min. The residue was suspended in saturated sodium bicarbonate solution (1 ml) from which cocaine was extracted with diethyl ether (2 × 1 ml). The extract was concentrated (50 μl) and 1–2 μl analysed by gas chromatography (Fish & Wilson, 1969). Calibration curves were constructed by adding known weights of benzoylecgonine to urine samples and processing these as described above. The curves were linear over the range 1–14 μg/ml.

Confirmation of the identity of benzoylecgonine in the test samples was obtained by extracting larger volumes (50 ml), concentrating the extract and separating by preparative thin-layer chromatography adapted from the system of Noirfalise & Mees (1967). The appropriate band was removed, the compound eluted and its ultraviolet spectrum obtained: this was indicative of benzoylecgonine (Orosoco, 1956).

The system of Noirfalise & Mees (1967) and that of Majlat & Bayer (1965) gave a faint band of characteristic colour with Dragendorff's reagent, and of correct position for ecgonine. The partition characteristics of ecgonine are such (Weast, 1964) that it cannot be recovered from urine by the extraction procedure described, in amounts sufficient for quantitation.

The subject was also taking orally glutethimide, orphenadrine and methadone, but none of these, or their metabolites, interfered with the determinations.

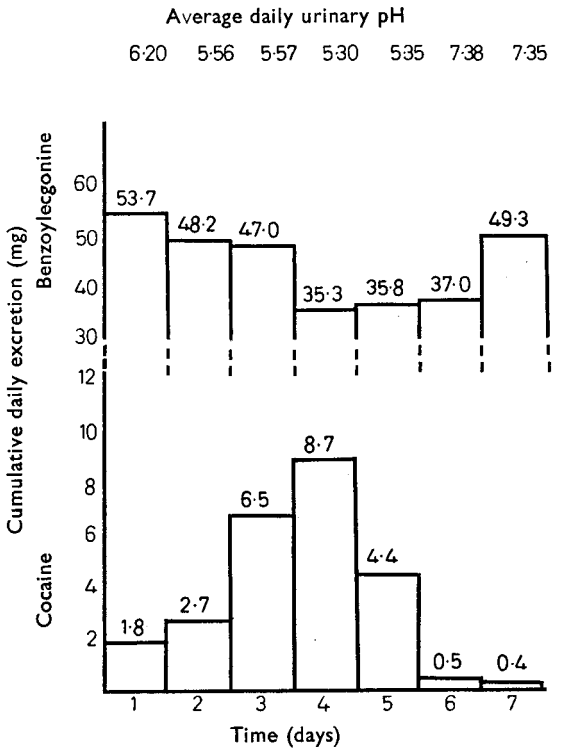


FIG. 1. Excretion (%) of cocaine and benzoylecgonine in urine of different pH values.

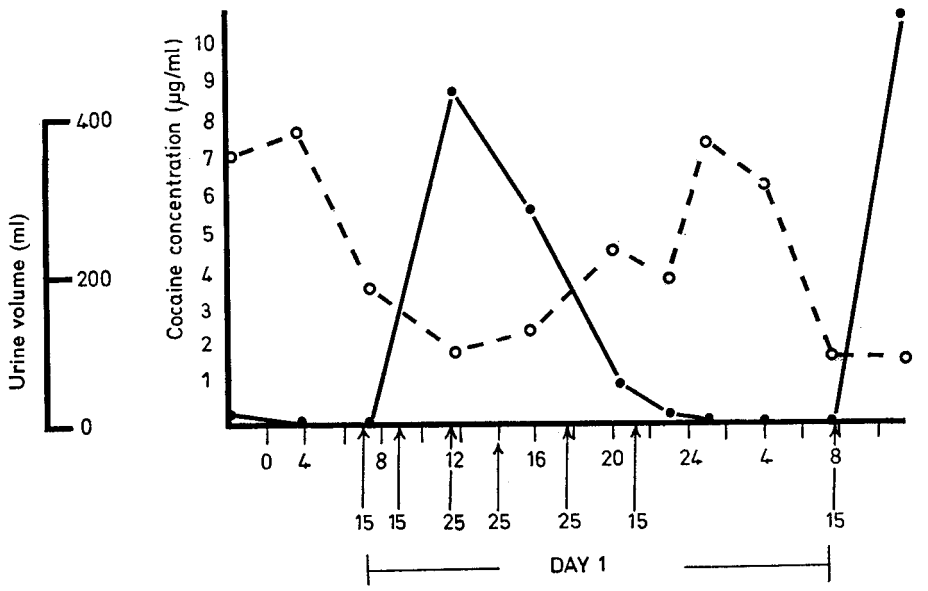


FIG. 2. Plots of total urine volumes and cocained concentration in urine against time of day (B.S.T.). The doses of cocaine hydrochloride (mg) and the times of administration are at the arrows. ●-● Cocaine concn. ○-○ Total urine volume.

*Results and discussion*

Results of analyses for cocaine and benzoylecgonine are summarized in Figs 1 and 2.

Amounts of unchanged cocaine (1–9%) excreted in the addict's urine agree with those previously reported (Woods, McMahon & Seevers, 1951) after submucosal administration (1–21%). The one report (McIntyre, 1936) of a 54% excretion in 12 h following cocaine overdosage is not strictly comparable.

As expected with an amphoteric compound, the cumulative excretion of benzoylecgonine was not pH dependent. Cumulative excretion of cocaine depended on urinary pH (Fig. 1) and this conclusion was supported by our unpublished observations on the buccal absorption of cocaine measured by the method of Beckett & Triggs (1967).

A regime to induce acid urine begun on the fourth day of the investigation was not maintained after one dose of ammonium chloride (4 g) because this caused the patient to become irritable, cold and drowsy; this despite indications of normal liver function as determined immediately before commencing the regime. Moreover, the patient's urine was normally acidic with pH values lower than the average literature values. No side-effects were experienced during the administration of sodium bicarbonate (21 g/day), to induce alkalinuria, during the sixth and seventh days and at no time did the subject describe any quantitative or qualitative variation in drug effect.

Most available data on cocaine metabolism and excretion have come from South American studies and relate to the chewing of coca leaf, which presents fundamental differences due to the rate of administration and time-course of absorption. Elimination of unchanged cocaine from habituées has been conflictingly reported as 6–20% by Ortiz (1952) and negligible by Sanchez (1957) who regarded ecgonine as the final and only urinary excretion product of cocaine. However, figures quoted for ecgonine accounted for only 2–8% of the total cocaine available. Sanchez & Guillen (1949) reported 10–20% urinary excretion of unchanged cocaine, the amount rising to 21–34% when the leaf was chewed with alkalis. In no case was benzoylecgonine considered as an important metabolite and urinary constituent.

Comparisons with data from animal studies must be made with caution because of inter-species variations in detoxification mechanisms (Langecker, 1938), especially in serum esterase activity (Glick & Glaubach, 1942), but it is of interest to note that Ortiz (1966) described cocaine, benzoylecgonine and ecgonine as urinary products in the rat. Greatest excretion occurred within 6 h of a single intraperitoneal injection and significant differences by sex were noted, there being higher urinary benzoylecgonine levels in males.

Of possible forensic significance are the low urinary concentrations encountered at certain times of the day even at the high dosage levels reported in this work. This is due to the antidiuretic side-effect of heroin on micturition, resulting in wide diurnal variations in urine volumes (Fig. 2).

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