Cocaine- and Cocaethylene-Creatinine Clearance Ratios in Humans

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Abstract

Cocaine (COC)– and cocaethylene (CE)–creatinine clearance ratios (CCR) were determined in five patients. In each case, COC:CCR greatly exceeded CE:CCR, and in four patients the data suggested renal tubular secretion of COC. For all patients, some renal tubular reabsorption of CE was apparent. These findings may be due, at least in part, to the greater hydrophobicity of CE relative to COC and to the lower pKb of CE (8.23) than that of COC (8.60). The pKb of CE was determined by titrimetry and is reported here for the first time. These data may be useful in investigating the pharmacokinetic profiles of COC and CE in humans and may also help to explain the longer plasma half-life of CE relative to that of COC.

Introduction

Cocaethylene (CE) is a pharmacologically important trans-esterification product of cocaine (COC) and ethanol (ETOH) that is formed when they are ingested together (1,2). Like COC, CE binds to the dopamine transporter and inhibits the uptake of dopamine into synaptosomes (1,2). The behavioral pharmacology of CE is similar to that of COC, and both compounds produce essentially the same psychomotor stimulant effects, although COC is more potent in this regard (1,3). The enzyme responsible for this reaction has been purified and characterized as a hepatic carboxylesterase that, in the absence of ETOH, catalyzes the production of benzoylecgonine, the major metabolite of COC in urine (4). The toxicity of CE is greater than that of COC, and its LD50 is considerably lower (5). The plasma half-life of CE is also longer than that of COC, which makes CE toxicologically important in humans (6).

The concept of analyte–creatinine clearance ratios (CCR) is familiar to most clinical laboratory workers and has generally been used to estimate renal tubular secretion versus reabsorption of compounds, most notably amylase (7–9).

In an attempt to explain the longer plasma half-life of CE relative to that of COC, the COC:CCR and CE:CCR ratios were investigated in five patients. The findings were correlated with the relative hydrophobicity of each drug and to the pKb (pKₐ for basic drugs) of each drug. The pKb of CE is reported here for the first time.

Experimental

Patients and Samples

Five patients admitted to the University of California, San Diego (UCSD) Medical Center were included in this study. Blood and urine samples from each patient were submitted to the UCSD Medical Center Clinical Toxicology Laboratory for drug screening for purposes of patient care, and CE was discovered in each patient by thin-layer chromatography of urine (10). Whole blood, anticoagulated with potassium oxalate and preserved with sodium fluoride, was submitted for alcohol analysis. Urine was submitted for drug screening, and serum was provided for additional toxicology studies. All specimens were collected at the time of the admission of the patient to the hospital, and no specimens were obtained specifically for the purposes of this study. Residual fluoride-preserved plasma and urine were used for analysis of COC and CE, whereas residual serum and urine were used for measurement of creatinine (CR). Plasma and urine samples were frozen (−20°C) until the time of analysis, which ranged from three to eight weeks from the time of sample collection. Previous work demonstrated the stability of COC and its metabolites in blood and urine under these storage conditions for more than 100 days (11,12).

Drug screening

Whole blood was analyzed for alcohols by flame-ionization gas–liquid chromatography after dilution with aqueous n-propanol as the internal standard (13). Urine was analyzed for drugs of abuse by various thin-layer chromatographic, immunosassay, spectroscopic, and gas–liquid chromatographic methods previously described (10,14).

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Measurement of COC and CE
Both COC and CE were measured in residual fluoridated plasma and in residual urine (diluted appropriately) using high-pressure liquid chromatography with a UV detector and the n-propyl analogue of COC, cocapropylene, as the internal standard (15). Reference calibrators in drug-free plasma and in water were prepared from COC hydrochloride (Merck, Rahway, NJ) and from CE base (Sigma Chemical, St. Louis, MO). The calibrators were analyzed concurrently with the patient samples and were used for quantitation of the concentrations in each sample.

Analysis of CR
Measurement of CR in residual serum and residual urine was performed on a Beckman CX7 automated analyzer (Beckman Instruments, Fullerton, CA).

Calculation of CCR
Both COC:CCR and CE:CCR were calculated by the following formula (7–9):

\[
\text{COC:CCR or CE:CCR} = 100 \times \frac{[(\text{Urine}_{\text{coc or CE}})(\text{Serum CR})]}{[(\text{Plasma}_{\text{COC or CE}})(\text{Urine CR})]}
\]

It should be noted that urine flow rates are not included because the same urine sample is used for COC or CE clearance and for CR clearance, and the values would cancel one another out. Hence, random (nontimed) urine samples can be used. However, use of random urine specimens precludes the calculation of individual clearance ratios for COC and CE.

Determination of pKb (pKb for basic drugs)
The pKₐ of CE was determined by manual titritymetry (16). A known mass of CE was dissolved in water. A nonsignificant volume of ETOH was added as needed to enhance solubility. The solution was titrated with standardized HCl, 0.010 mol/L (Fisher Scientific, Pittsburgh, PA). This procedure was performed four times at 19.2°C, and more than 50 data points were obtained for each curve. The endpoint of titration was determined as the volume of HCl used from the inflection point of each titration curve. The pH at the halfway point of titration (at one-half of the total volume of HCl used) represented the pKₐ of CE. Blank titration curves (water and ethanol) did not demonstrate inflection points (curves not shown).

Results
The age, gender, and toxicologic findings for each of the five patients are shown in Table I. The concentrations of COC, CE, and CR in plasma or serum and in urine are shown in Table II, along with the calculated CCR. The pKₐ of CE was determined to be 8.23 (mean of four titrations: 8.10, 8.35, 8.20, and 8.30), and a representative titration curve, obtained from 54 data points, is shown in Figure 1. Blank titration curves (ethanol and water with no drug) did not demonstrate inflection points (curves not shown).

Discussion
For all five patients, COC:CCR greatly exceeded CE:CCR (Table II). Also, in each case, some renal tubular reabsorption of CE was apparent because all CE:CCR were less than 100%. In four instances (patients...
Conclusion

Although this is a small series that may not be representative of the population at large, the findings may nonetheless be useful in investigating the pharmacokinetic profiles of COC and CE in humans. They may also help to explain the observed longer plasma half-life of CE relative to that of COC (6). Finally, it is conceivable that the enzymatic degradation of CE may occur at a rate slower than that of COC, although this has not been reported.

References


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