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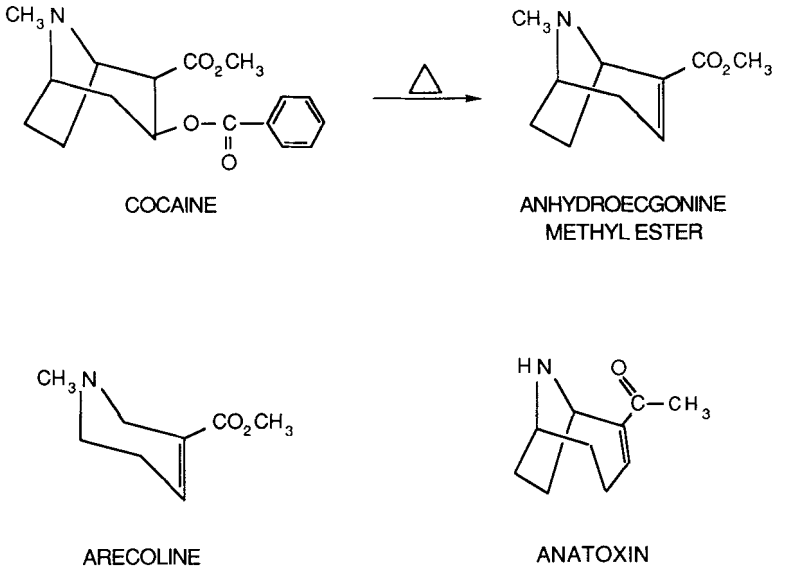
LETTER TO THE EDITOR

COCAINE SMOKERS EXCRETE A PYROLYSIS PRODUCT, ANHYDROECGONINE METHYL ESTER

Smoking free-base cocaine ("crack") is a serious drug abuse problem in many countries. Typically, cocaine is smoked mixed with tobacco or marijuana in cigarettes, or it is inhaled as an aerosol produced by heating the base in a pipe. Presumably, this route of administration is popular because of rapid pulmonary absorption and rapid onset of action. Cocaine is not particularly volatile, and it would be expected to undergo significant decomposition during the process of smoking. Several pyrolysis products, including benzoic acid, methyl benzoate, N-methyl benzamide, methyl cycloheptatriene carboxylate isomers, methyl-4-(3-pyridyl)-butyrate, and isomers of the product resulting from the elimination of benzoic acid from cocaine (anhydroecgonine methyl ester and isomeric compounds) have been reported (1). Whether these substances contribute to the pharmacology or toxicology of cocaine smoking is unknown. A recent study has indicated that *in vitro*, under conditions designed to mimic cocaine smoking, anhydroecgonine methyl ester (methylecgonidine) is the major pyrolysis product (2). We have also found that under a variety of conditions, anhydroecgonine methyl ester (AEME) is the major thermal decomposition product of cocaine (3). Consequently, it appeared likely that significant amounts of this substance would be absorbed by cocaine smokers.

As a part of studies of cocaine pharmacokinetics and pharmacodynamics, we obtained urine samples from nine human subjects who had inhaled the aerosol produced by 100 mg cocaine base placed in an electrically heated glass apparatus designed to mimic a "free-basing" pipe.



All urine voided during the 48 hours following cocaine smoking was collected and analyzed for AEME and cocaine by GC-MS. Most of the subjects excreted substantial amounts of AEME, averaging 0.85 micromoles with a range of 0.093 to 3.7 micromoles. Cocaine excretion (4) in these subjects averaged 1.6 micromoles with a range of 0.25 to 4.3. Consequently, AEME excretion was of the same order of magnitude as cocaine excretion, the mean of the molar ratios of AEME/cocaine being 0.58. We also measured AEME and cocaine in urine of subjects given cocaine by intravenous and nasal routes since a report has suggested that AEME is a cocaine metabolite (5). In six subjects given intravenous cocaine (0.6 mg/kg bolus), AEME excretion averaged 0.0077 micromoles (range 0 to 0.034) while cocaine excretion averaged 3.0 micromoles (range 0.74 to 7.31). The corresponding amounts for six subjects given cocaine intranasally (2 mg/kg) were 0.042 micromoles AEME (range 0 to 0.14) and 4.1 micromoles cocaine (range 1.3 to 14). Whether the small amounts of AEME determined following intravenous and intranasal administration were due to metabolic formation from cocaine or

an artifact is not clear, since a small percentage (~ 0.30%) of cocaine is converted to AEME under the conditions of the analysis.

Cocaine smoking has been associated with various medical problems, including lung damage and neurological disorders (6-9). It is generally assumed that the effects of "crack" smoking are due to cocaine per se. However, the pathophysiology of these cocaine-induced disorders is unknown. Since pharmacologic and toxicologic studies of AEME have not been reported, the possibility that AEME contributes to the adverse effects of cocaine smoking or possibly even to the effects desired by the user must be considered. Based on its structural similarity to arecoline and anatoxin (Figure), one might expect AEME to be a cholinergic agent (10-12). Further research will be necessary to determine to what extent anhydroecgonine methyl ester is absorbed by cocaine smokers and whether it plays a role in the effects resulting from cocaine smoking.

A manuscript describing the analytical methodology has been submitted to the *Journal of Analytical Toxicology*.

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