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(Accepted for publication December 9, 1996.)

Anesthesiology
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Pharmacokinetic Considerations for the Use of the Ovine Model in Cocaine Research

To the Editor:—In a recent study by Bernards *et al.*, the authors report that chronic cocaine administration reversibly increases isoflurane minimum alveolar concentration in sheep.[1] This study illustrates the dilemma often encountered by researchers when trying to answer a clinically relevant question with a less than ideal animal model.

The authors do acknowledge that no animal metabolizes cocaine in a manner identical to humans, and that the clearance of cocaine in sheep is significantly more rapid than in humans. However, there are other pharmacokinetic considerations that were not mentioned by the authors that are essential whenever using this species for cocaine and drug interaction research. Specifically, the metabolism of cocaine in sheep is quite different from its metabolism in humans and other commonly used laboratory animals.[2] The primary metabolite of cocaine in sheep is ecognine methyl ester, whereas in other species (*e.g.,* human, subhuman primate, rat, guinea pig), benzoylecgonine is the major metabolite. These metabolites are cleared more slowly than the parent compound, and, consequently, would be expected to accumulate in a chronic situation. Because it is unclear as to whether the accumulation of these metabolites alters minimum alveolar concentration, ideally, an animal model in which benzoylecgonine, rather than ecognine methyl ester, would be expected to accumulate would be preferable.

In addition, the investigators used a subcutaneous osmotic pump in this study to deliver cocaine continuously so as to maintain a steady, low background plasma cocaine concentration, ranging from 15 to 69 ng/ml. Although the authors state that this background cocaine infusion was intended to mimic heavy cocaine use, the pharmacodynamic rationale behind this "chronic exposure" with such pharmacologically ineffective low plasma concentrations is unclear. In addition, because of the drug's short elimination half-life in this species, a cocaine infusion rate of 0.4 mg/kg/min over 10 min without an initial loading dose would not produce a pattern of plasma drug concentrations or hemodynamic responses similar to that observed in human "binge" abusers. As previously demonstrated in our continuous intravenous administration study in sheep, the plasma cocaine concentration decreased rapidly when the cocaine infusion was terminated, whereas the benzoylecgonine concentration continued to increase (note that ecognine methyl ester was not determined in this early study). The elimination half-life of cocaine in this study was 5 min.* In addition, in this species, "binge" cocaine doses at 1-h intervals probably do not mimic one important aspect of human "binge" abuse, namely cocaine accumulation. It is unfortunate that the authors did not measure cocaine concentrations during the "binge," because this might have provided more information in regard to drug accumulation.

Based on this knowledge, the investigators similarly should have kept plasma cocaine concentrations in a range occurring in human "binge" abusers by administering a programmed constant intravenous infusion at a high initial rate followed by a gradual decrease in rate.

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(Accepted for publication December 12, 1996.)

Supported, in part, by NIDA grants RO1 DA06648 and RO1 DA07588 and NIH grant T32 GM08464.

* Morishima HO, Chao CR, Matsuo M, Abe Y, Cooper TB: Placental transfer and disposition of cocaine in the pregnant sheep (abstract). ANESTHESIOLOGY 1992; 77:A1038.