2. Loesberg A, Taylor FC, Awh MH: Dislodgment of inferior vena caval filters during "blind" insertion of central venous catheters. AJR 1993; 161(3):637-8

3. Amesbury S, Vargish T, Hall J: An unusual complication of central venous catheterization. Chest 1994; 105:905-7

4. Marelich GP, Tharratt RS: Greenfield inferior vena cava filter dislodged during central venous catheter placement. Chest 1994; 106:957-9

5. Urbaneja A, Fontaine AB, Bruckner M, Spigos DG: Evulsion of a Vena Tech filter during insertion of a central venous catheter. J Vasc Intervent Radiol 1994; 5:783-5

6. Kaufman JA, Thomas JW, Geller SC, Rivitz SM, Waltman AC: Guide-wire entrapment by inferior vena caval filters: *In vitro* evaluation. Radiology 1996; 198:71-6

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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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References

1. Bernards CM, Kern C, Cullen BF: Chronic cocaine administration reversibly increases isoflurane minimum alveolar concentration in sheep. ANESTHESIOLOGY 1996; 85:91-5

2. Morishima HO, Whittington RA: Species-, gender-, and pregnancy-related differences in pharmacokinetics and pharmacodynamics of cocaine, Biological Mechanisms and Perinatal Exposure to Drugs in NIDA Research Monograph 158. Edited by Thadani PV. Rockville, National Institutes of Health, 1995, pp 2-21

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* 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.