Title: UPTAKE AND DISTRIBUTION OF ETIDOCAINE IN THE FETAL LAMB

Authors: R.L. Kennedy, M.D., R.P. Miller, Ph.D., H. de Sousa, M.D., J.U. Bell, Ph.D., D.M. Doshi, M.D., D.L. Heald, M.S., M.J. Kennedy, B.S., Y. David, M.S.

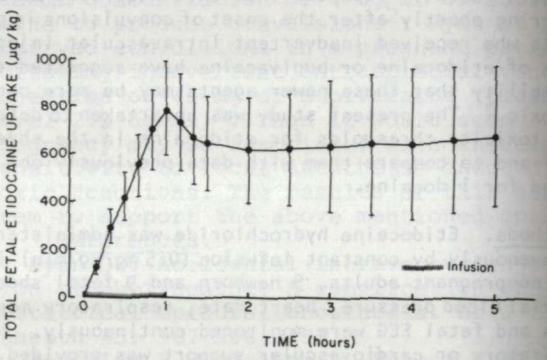
Affiliation: Departments of Anesthesiology, Pharmacy, and Pharmacology and Toxicology West Virginia University Medical Center, Morgantown, West Virginia, 26506

Introduction. Etidocaine is of interest in obstetrics because of its very high lipid solubility demonstrated by its partition coefficient of 141 in N-heptane compared to 2.9 of lidocaine. A high fetal absorption is thought to result despite a low fetal blood concentration that is related to plasma protein binding.[1] To determine actual fetal uptake that occurs following maternal administration, we have utilized a chronic pregnant ewe preparation instrumented to evaluate continual fetal uptake and then to determine distribution to fetal vital organs.[2]

Methods. Five ewes, each with a single fetus of 120-125 days gestation, were surgically prepared by positioning sampling catheters in the umbilical vein (UV), distal fetal aorta (FA), fetal bladder, and maternal artery (MA). In addition, an electromagnetic flow transducer was placed on the common umbilical artery. On the third postoperative day after the maternal and fetal pH blood gases, blood pressure and fetal heart rate were found to be within normal limits, etidocaine HCl, 4mg/kg (3.5 mg/kg of base), was infused at a constant rate for the first hour of a 5 h observation period. Blood samples, 0.5 ml, were drawn simultaneously from the MA, UV and FA at intervals of 5 min for 45 min, 15 min for 1 h 15 min, 30 min for 1 h, and 60 min for the remainder of observation. Umbilical blood flow was recorded continuously as were maternal and fetal blood pressures and fetal heart rate. Total uptake was determined from the product of the UV-FA blood concentration differences and the flow rate. Uptake was determined by integration with respect for time. At hourly intervals pH and blood gases were determined and urine was collected. At 5 h the fetus was killed and the brain, heart, lung, liver, and kidneys were obtained for analysis. Levels of etidocaine and three of its metabolites, 2-N-propylamino-2'-butyroxylidide (PBX), 2-N-2' butyroxylidide (ABX), and 2-N-ethylamine-2'-butyroxylidide (EBX), were determined in all specimens by HPLC.

Results. During the infusion period the mean fetal uptake rose to a peak of 775 µg/kg of which 162 µg were returned to the fetus. The fetal share of the total dose was 22% (fetal uptake/kg ÷ total dose/kg x 100).

Appearance of PBX at 5 min was evidence of rapid metabolism while ABX lagged and was always lower. Only a trace of EBX was occasionally noted in the blood. The fetal UV and FA concentrations paralleled the maternal concentration with fetal-maternal ratios of 0.5 to 0.7. The fetal uptake varied from 278 to 1502 µg/kg. Correlating the total uptake vs the peak metabolite concentration in maternal blood at 70 min we found a significant inverse relationship: ABX r= -0.93 ($P<0.05$), PBX r= -0.88 ($P<0.05$). No metabolite was seen in maternal or fetal blood in the animal which exhibited the highest fetal uptake.




The highest mean tissue etidocaine concentration was found in the heart and the lowest in the brain. ABX was highest in the lung and lowest in the heart. The mean PBX concentrations were lower and EBX was the lowest.

Tissue Concentrations (ng/g)

| | | Liver | Heart | Lung | Kidney | Brain |
|---|---|---|---|---|---|---|
| Etid | $\bar{x}$ | 77 | 88 | 44 | 71 | 28 |
| | sem | 18 | 20 | 9 | 17 | 5 |
| ABX | $\bar{x}$ | 181 | 89 | 306 | 257 | 139 |
| | sem | 71 | 28 | 101 | 50 | 49 |
| PBX | $\bar{x}$ | 20 | 16 | 28 | 24 | 10 |
| | sem | 10 | 5 | 10 | 11 | 5 |
| EBX | $\bar{x}$ | 6 | -- | 16 | 11 | 4 |
| | | 4 | -- | 7 | 7 | 2 |

Discussion. Compared to our previous report,[2] the fetal uptake of etidocaine exceeds bupivacaine but both are less than half of that of lidocaine. Therefore, lipid solubility does not appear to be a major factor in fetal uptake. Variations in uptake were very large which can be inversely related to maternal metabolism. The main metabolite found was ABX.

References.

1. Finster, M: Toxicity of local anesthetics in the fetus and the newborn. Bull NY Acad Med 52:222-225, 1976

2. Kennedy, RL, deSousa, H, Bell, JV, et al: Quantitative Uptake of Local Anesthetics in Fetal Lambs. Anesthesiology 55:A314, 1981

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/57/3/A400/630712/0000542-198209001-00400.pdf by guest on 23 May 2022