Title: BRAIN UPTAKE OF FENTANYL IN FETAL LAMBS

Authors: J. H. Eisele, Jr., M.D., B. W. Goetzman, M.D., Ph.D., J. M. Milstein, M.D., R. G. Bickers, M.D., S. H. Bennett, M.S., and R. W. Martucci, M.A.

Affiliation: Departments of Anesthesiology and Neonatalogy
University of California, Davis, Sacramento
Medical Center, Davis, California 95616

In evaluating the fetal effect of narcotic drugs administered to the mother, the measurement of the umbilical vein (U.V.) concentration or the fetal/maternal ratio of drug may not reflect the fetal drug effect or disposition. It is more relevant in studying CNS acting drugs to know the uptake and elimination of drug by CNS tissues. This can be accomplished either directly by measuring brain tissue samples or indirectly by CNS arterial-venous differences in drug concentrations, assuming flow is constant.

Studies on meperidine estimate fetal brain equilibration and elimination rates from fetal brachiocephalic arterial and sagittal venous concentration curves.[1] This study is a similar attempt to quantitate fetal brain uptake and elimination of fentanyl in the pregnant sheep model.

Methods. Seven near term pregnant ewes under spinal anesthesia were instrumented with exteriorized catheters leading to fetal brachiocephalic artery (FA), fetal sagittal vein (SV), fetal femoral artery (FFA) and fetal femoral vein (FFV), and maternal artery (MA) and vein (MV). After complete recovery, the awake ewes and fetuses were studied following MV bolus injection of fentanyl (24 μg/kg) while monitoring FFA pressures and blood gases. Sequential blood samples for MA, FA, and SV were taken from 1 to 360 minutes and analyzed for drug with R.I.A. technique.

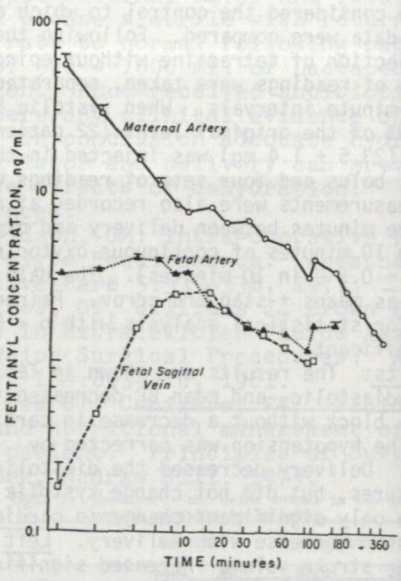
Results. FFA pressure remained constant following drug injection indicating no change in blood flow. FA fentanyl peaked in 5 minutes and declined exponentially and parallel to MA fentanyl, but appreciably lower with F/M fentanyl ratio of 0.3. SV fentanyl lagged well below FA fentanyl for 15 minutes then peaked, exceeding FA and remaining higher than FA for 30 minutes, then declined similar to the MA and FA decline. FA and SV fentanyl curves intersected in 15 minutes at a concentration of 2-3 ng/ml which represents brain equilibration of drug. At 90 minutes, SV fentanyl was still above 1 ng/ml.

Discussion. The large arteriovenous difference means rapid uptake of fentanyl by brain tissue which continues until drug entering equals drug emerging which is the point of brain equilibration. This occurs after FA fentanyl has fallen to 50% of its peak value and shows how serum concentrations underestimate brain levels.

Compared to human fentanyl elimination half-times,[2] pregnant sheep elimination rates are somewhat faster which indicates that human fetal brain equilibration of fentanyl would take longer than sheep. Specifically, human fetal brain uptake may exceed 20 minutes, a time when analgesia in the mother is decreasing. This should have a bearing on the use and timing of short acting potent narcotics in clinical obstetrics.

References.

1. Szeto HH, Clapp JF, Abrams R, et al: Brain uptake of meperidine in the fetal lamb. Amer J Obs Gyn 138:528, 1980
2. Schleimer R, Benjamini E, Eisele J, et al: Pharmacokinetics of fentanyl as determined by radioimmunoassay. Clin Pharmacol Ther 23(2):188-194, 1978



Logarithmic plot of time versus fentanyl concentrations in MA, FA, and SV following MV bolus injection.