

Title: Differential Sensitivities of Mammalian Nerve Fibers during Pregnancy in Relation to Different Concentrations of Bupivacaine.

Authors: S. Datta, M.D., H.L. Flanagan, M.D., D.H. Lambert, Ph.D., M.D., A.J. Gissen, M.D., B.G. Covino, Ph.D., M.D.

Affiliation: Department of Anesthesia, Harvard Medical School, Brigham and Women's Hospital, Boston, MA 02115

Introduction. Pregnancy increases the parturients sensitivity to local anesthetics so that less drug is required for a given level of epidural anesthesia.(1) The mechanism of this phenomenon remains unresolved. Suggested mechanisms have been, a) hormonal changes associated with pregnancy which may change the susceptibility of the nerve membrane to the local anesthetic, b) distension of epidural veins resulting in increased spread of the anesthetic given epidurally, c) other biochemical changes that may alter nerve response to local anesthetics.

Using a single concentration of bupivacaine (0.35 mM) we found that the rate of onset of conduction block of the isolated nerve (50%) in the A,B and C fibers occurred much faster in pregnant animals.(2) This suggests either an increased sensitivity of nerve fibers during pregnancy to bupivacaine or an enhanced diffusion of the bupivacaine to the membrane receptor site.

We have studied the effect of pregnancy on neuronal conduction blockade by determining bupivacaine response curves in nerves from pregnant and nonpregnant animals.

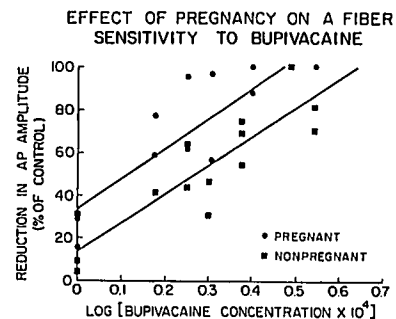
Methods. 17 adult Albino rabbits (3.5-4kg) were used for the study. Pregnant rabbits were at four weeks gestation. Pregnancy was documented by exploring the uterus and plasma progesterone levels were determined.

The vagus nerves were removed; placed in modified Liley solution and then transferred to a nerve chamber. The nerves were stimulated via a Grass S48 stimulator and Grass stimulus isolation unit. Stimulus intensities for A,B and C fibers were individually adjusted for maximum amplitude of the action potential (AP) as displayed on a Tektronix 5113 oscilloscope. A control period of 30 minutes was employed prior to any drug administration to ensure nerve stability. The depression of action potentials of A,B,C fibers from nerves of pregnant and nonpregnant animals were determined after 30 minutes using different concentrations of bupivacaine (0.1mM to 0.35mM)

The data was analyzed by linear regression using least squares analysis. Standard statistical methods were used to determine linearity of regression, coefficients of correlation and the difference between slopes. Differences between parallel lines were determined by analysis of covariance.

Results. Progesterone levels were 7 times higher in the pregnant rabbits than in nonpregnant rabbits ($p < .001$). The A fibers from pregnant animals were significantly more sensitive to bupivacaine (Fig.) The figure shows the least square regression lines for reduction in AP amplitude in A fibers taken from pregnant and nonpregnant animals. The slope of the lines were not statistically different (140 ± 1.4 pregnant vs. 134 ± 1.1 nonpregnant,

$p > 0.05$). The correlation coefficients were 0.85 for pregnant and 0.87 for nonpregnant animals. The reduction in AP amplitude of any given dose of bupivacaine was significantly greater in the pregnant group than in the nonpregnant group ($t = 2.48$, $p < 0.05$, analysis of covariance). However, the B and C fibers were not significantly different between the groups.



Discussion. Bromage initially reported a wider dermatomal spread of anesthesia after epidural administration of local anesthetic in term pregnant patients. He emphasized the need to use smaller doses of local anesthetics in parturients to achieve equal levels of anesthesia. Recently, he reported this difference as early as the first trimester of pregnancy. This later finding cannot be explained on the basis of mechanical factors and suggests hormonal or biochemical effects.

Our present study demonstrates the increase in sensitivity of fibers from pregnant animals to bupivacaine at various concentrations. Notable is that the most difference (statistically significant) occurs in the A fiber rather than the B & C fibers. The difference between the sensitivities between nerves from pregnant and nonpregnant animals explain the marked increase in dermatomal spread of local anesthetics in parturients. Further studies are being done to determine the exact site of action of the pregnancy hormones.

References.

1. Bromage PR.: Continuous lumbar epidural analgesia for obstetrics. *Can Med Assoc J.*: 85:1136-40, 1961.
2. Datta S, Lambert DH, Gregus J, et al.: Differential sensitivities of mammalian nerve fibers during pregnancy. *Anesth Analg* 62:1070-2, 1983.