Title : SUBARACHNOID BUPIVACAINE, LIDOCAINE, AND MEPIVACAINE IN THE RHESUS MONKEY: NEURAL BLOCKADE AND PHARMACOKINETICS.

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Introduction: A sensitive and reliable animal model for the objective physiologic and pharmacokinetic evaluation of spinal anesthesia has been developed using lidocaine (1,2). The use of this model to evaluate changes which occur with such things as compounding of local anesthetics, or the effect of adjuvant drugs on rates of absorption and protein binding, hinge on the scope of reliability of the model. The present study was undertaken to evaluate changes in neural blockade and pharmacokinetics associated with equipotent doses of lidocaine, mepivacaine, and bupivacaine in the rhesus monkey.

Methods: Twelve adult rhesus monkeys were used in a two-way crossover design. Each animal received subarachnoid lidocaine and either subarachnoid mepivacaine or bupivacaine. The three study treatments were: (1) 30 mg. lidocaine, (2% in 7.5% dextrose); (2) 30 mg mepivacaine(2% in balanced salt solution); (3) 5 mg bupivacaine (0.375% in 7.5% dextrose). All treatments were hyperbaric.

Fasted animals were sedated with IM ketamine (10 mg/kg) and maintained with light general anesthesia for placement of arterial and venous cannulae, as well as performance of a spinal tap. Upon achieving free flow of clear CSF, one of the three study drugs was administered. Fifteen 4-ml. arterial blood samples were collected over a 5-hour period for lidocaine and mepivacaine, and over an 8-hour period for bupivacaine. Sample volumes were replaced with normal saline in a ratio of 3:1. The level and duration of sensory and motor block were evaluated as previously described (1).

Estimations of the absorption constant, elimination constant (kel), volume of distribution during elimination phase (Vdβ), and total clearance (Cl(tot)) were calculated from the area under the blood-level curve. Detailed pharmacokinetic analysis was accomplished by fitting the data to either a one- or two-compartment model using standard computer programs. The coefficients of determination were determined by comparing actual blood-level data with each computer-generated solution. Parameters were subjected to statistical analysis using either a paired t, Student's t test, and/or Schefe's analysis of variance where appropriate for group comparisons. $p<.05$ were considered significant.

Results: All treatments resulted in statistically equivalent sensory and motor block in terms of both level and duration(Tables 1 and 2). Mean durations of both sensory and motor block tended to increase in the order lidocaine < mepivacaine < bupivacaine. Pharmacokinetic parameters were identical for the lidocaine and the mepivacaine treatments. The bupivacaine treatment resulted in a significant decrease in rate of elimination(Table 3). Equivalent times to peak concentration were found for all three treatments.

Discussion: Our results suggest that mepivacaine and lidocaine are equipotent , and that bupivacaine is approximately six times as potent as either lidocaine or mepivacaine. Elimination constants for lidocaine, mepivacaine and bupivacaine are in agreement with intravenous data reported for man.(3) The finding that all three treatments resulted in statistically equivalent absorption rates support the finding of statistically equivalent durations for neural blockade. Our results expand the scope of reliability of the rhesus monkey model in terms of evaluating neural blockade and pharmacokinetic changes as a function of local anesthetics of varying pKa's, lipid solubilities, and potency, in a manner relevant to the human clinical situation.

References:

1. Denson DD, Bridenbaugh PO, Phero JC et al: Evaluation of lidocaine spinal anesthesia in the rhesus monkey, Anesth Analg 60:756-59,1981.

2. Denson DD, Ritschel WA, Turner PA et al.: A comparison of intravenous and subarachnoid lidocaine pharmacokinetics in the rhesus monkey. Biopharmaceutics and Drug Disposition 2:367-80,1981.

3. Tucker GT, Mather LE: Clinical pharmacokinetics of local anesthetics. Clinical Pharmacokinetics 4: 241-78, 1979.

Table 1: Evaluation of Motor Blockade Following Subarachnoid Bupivacaine, Lidocaine, and Mepivacaine[a]

Drug	Motor Score	Time for Complete Motor Block (min)	Time for Complete Motor Recovery (min)
Bupivacaine	5.4±0.6	113±23	150±33
Lidocaine	6.0±0	61± 8	114±11
Mepivacaine	6.0±0	90±15	137±21

a, mean ± sem

Table 2: Evaluation of Sensory Blockade Following Subarachnoid Bupivacaine, Lidocaine, and Mepivacaine[a]

Drug	Level	Time for 2-Segment Regression (min)	Time for Complete Sensory Recovery (min)
Bupivacaine	T-8±1	48±10	163±30
Lidocaine	T-8±1	55± 9	110±10
Mepivacaine	T-7±1	48± 7	127±19

a. mean ± sem

Table 3: Pharmacokinetic Parameters Following Subarachnoid Bupivacaine, Lidocaine, and Mepivacaine[a]

Drug	ka (1/h)	kel (1/h)	cKtot> (ml/min)	VdB (ℓ)
Bupivacaine	5.4±1.4	0.29±0.04[b]	146±27	31±5
Lidocaine	4.2±0.7	0.46±0.07	182±19	26±4
Mepivacaine	4.2±1.4	o.47±0.06	187± 9	27±4

a. Mean±sem; b. p<.025 when compared to either lidocaine or mepivacaine