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Title : PHARMACOKINETICS OF INTRATHECAL LIDOCAINE IN THE MONKEY

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INTRODUCTION:

The development of a non-human primate model for spinal anesthesia will aid in the determination of the efficacy associated with many new drugs and pain management techniques, such as intrathecal narcotics and continuous epidural infusion of local anesthetics. The viability of extrapolating the data from such a model to the human situation hinges on both pharmacodynamic and pharmacokinetic responses. This paper compares the pharmacokinetics of subarachnoid lidocaine in the rhesus monkey with recently reported human data[1].

METHODS:

Adult rhesus monkeys were used throughout the study. After fasting overnight, the animals were sedated with ketamine (10 mg/kg IM). Aortic and inferior vena cava (IVC) cannulae were placed at the L4-5 levels via a femoral artery and vein. Positions were verified by radiographs. For studies utilizing a peripheral venous line, a distil femoral vein cannula was placed contralateral to the arterial and venous cannulae. All cannulations were accomplished under light general anesthesia, consisting of 60/40 nitrous oxide/oxygen supplimented with 0.5% halothane as required. Spinal tap was accomplished at the L5-6 interspace in the lateral decubitus position. Free flow of clear CSF was judged proof of entrance into the subarachnoid space. 5% lidocaine (7.5, 15 or 30 mg) in 7.5% dextrose was injected. 3 ml blood samples were obtained at t = 0, 5, 10, 15, 20, 30, 45 and 60 minutes in the case of the 15 mg experiments (N=12) for absorption studies, and at 0, 30, 60, 120, 180, 240 and 300 minutes for the 7.5 and 30 mg doses (N=6) for elimination studies. For overall pharmacokinetic studies (N=6), 3 ml arterial samples were taken at t = 0, 4, 7, 10, 15, 20, 25, 30, 45, 60, 120, 180, 240 and 300 minutes. Serum, obtained by allowing the blood to clot followed by centrifugation, was extracted and lidocaine concentrations were determined by gas chromatography. Estimation of pharmacokinetic parameters was accomplished using standard computer programs. Data were subjected to statistical analysis using either paired t, student's t test and/or analysis of variance. $p<.05$ were considered significant.

RESULTS:

The peak serum concentrations of lidocaine in all studies represents an absorpiton of $2.4 \pm 0.3\%$ of the infused dose. There appears to be a slow increase in serum lidocaine concentration from 5 to 30 minutes. Normal disappearance kinetics are observed after 30 minutes. In all cases, inferior vena cava concentrations were significantly higher than aortic concentrations ($p<.05$). Peripheral venous concentrations were found to be significantly lower than arterial ($p<.05$) and IVC ($p<.01$) concentrations. After 240 minutes, all blood concentrations had begun to converge. Figure 1 is a representative pharmacokinetic plot for arterial lidocaine concentrations. These data fit an open one compartment model for extravascular administration. The data fit the blood concentration equation for this model given by:

$$C_p = Ae^{-k_{el}\cdot t} - Be^{-k_a\cdot t}$$

The following data were derived form Figure 1:

$$A=B=C_p^{o} = 1.7 \text{ ug/ml}; \; k_{el} = 0.6308h^{-1}; \; k_a = 3.32h^{-1}.$$

Corresponding half-lives of 1.09h for elimination and 0.21h for absorption are consistent for those reported for man.[2]

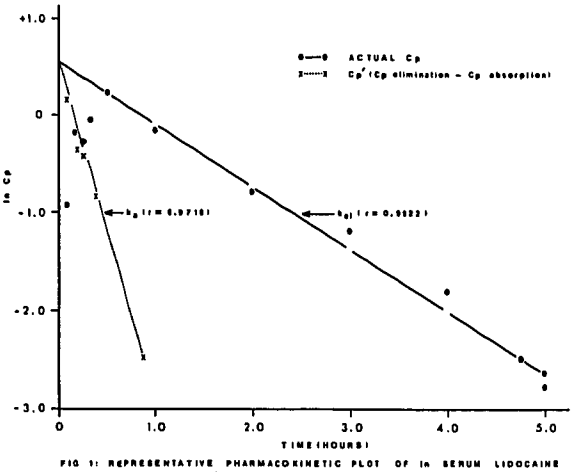

FIG 1: REPRESENTATIVE PHARMACOKINETIC PLOT OF ln SERUM LIDOCAINE CONCENTRATIONS AS A FUNCTION OF TIME FOLLOWING INTRATHECAL INJECTION.

DISCUSSION:

The absorption of 2.4 + 0.3% of the administered dose is in excellent agreement with the human data reported by Giasi, D'Agostino and Covino.[1] The pharmacokinetic data is consistent with that suggested by Tucker and Mather for man.[2] Our findings that IVC concentrations were higher than aortic levels support the hypothesis proposed by Tucker and Mather that systemic absorption from the subarachnoid space occurs prior to entering the hepatic circulation. Our results support the hypothesis that the rhesus monkey is a viable pharmacokinetic model for predicting the human response to intrathecal local anesthetics.

REFERENCES

1. Giasi RM, D'Agostino E, Covino BG: Absorption of lidocaine following subarachnoid and epidural administration. Anesth and Anal 58:360-363, 1979.
2. Tucker GT, Mather LE: Pharmacology of local anesthetic agents - Pharmacokinetics of local anesthetic agents. Br J Anaesth 47:213-223, 1975.