LOCAL ANESTHESIA AND PAIN—POSTER

Title: PLASMA PROTEIN BINDING OF BUPIVACAINE AND LIDOCAINE IN THE DOG
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Introduction: Recent reports of cardiovascular system and central nervous system toxicity following inadvertent intravenous injection of bupivacaine in man have spirited renewed interest in animal research to glean a further understanding of cardiovascular and neural toxicity of local anesthetics. A study addressing the cardiotoxicity of the amide local anesthetics has been reported in the dog. (1) It is difficult to relate the findings of this study to the human clinical situation because of the lack of data on the extent of plasma protein binding in the dog. The present study was designed to evaluate the extent of protein binding for lidocaine and bupivacaine in the dog, and to examine the effects of pH on the extent of protein binding.

Methods: Heparinized blood (10 U/ml) was obtained from 5 dogs. Plasma was separated by centrifugation, pooled, separated into 10 ml aliquots, and frozen at -20°C until used. Two pH's were studied for each drug. These were the normal physiological pH for the dog (7.36) and a pH representing moderate acidosis (6.96). The extent of protein binding was studied over a range of five concentrations for each drug. For lidocaine, 1.25, 5, and 20 ug/ml were studied, while 0.5, 1.25, and 10 ug/ml were studied for bupivacaine. Six replicates were performed for each drug at each pH. Plasma protein binding was determined using Spectrapor dialysis membrane No. 2 (Spectrum Medical Industries, Inc.) in Teflon cells. 1 ml aliquots of plasma adjusted to the appropriate pH at 37°C were exchanged against an equal volume of isotonic Sorensen's phosphate buffer containing the desired concentration of local anesthetic and adjusted to the appropriate pH at 37°C. Preliminary experiments verified equilibrium was achieved at 3 hours. For the present study, dialysis cells were slowly rotated in a water bath at 37°C for 4 hours. Following dialysis, the plasma half and the buffer half of each cell were removed and analyzed for local anesthetic by gas chromatography. Binding capacities (nPr) and affinities (K) for lidocaine and bupivacaine at each pH were estimated from plots of bound/free versus bound. These techniques assume only one class of binding site, and are directly comparable to human data. (2) Statistical analysis was accomplished using analysis of variance. p<0.05 were considered significant.

Results: Plots of percent bound versus total anesthetic concentration for both lidocaine and bupivacaine were curvilinear. Decreasing the pH from 7.36 to 6.96 causes a significant decrease in the percent plasma protein binding for lidocaine over the entire concentration range studied. A similar decrease in pH caused minimal decreases in bupivacaine protein binding below 10 ug/ml (Figure 1). Estimations of nPt and K resulted in values which are lower than those reported for man (see Table 1). Discussion: The affinities and binding capacities of dog plasma for both lidocaine and bupivacaine are lower than those expected on the basis of human data. (2) The net result is that the free fraction for both bupivacaine and lidocaine are higher in the dog for a given total plasma concentration. Decreased plasma binding for lidocaine associated with decreases in pH in the dog are in agreement with human data. (3) No human data for bupivacaine binding as a function of pH are available for comparison. Our data suggest acidosis would have little effect on the free fraction for bupivacaine. The data reported here suggest that the cardiotoxicity thresholds reported for the dog are lower than would be found in man if one accepts the premise that only the free fraction is responsible for toxicity. Perhaps the recent suggestions of Moore et al., regarding the influence of hypoxia and acidosis warrant further examination to resolve reported cardiotoxic episodes following local anesthetic administration. (4)

References:

![Graphical representation of data](image)

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**Table 1. Plasma Binding Affinities and Capacities for Bupivacaine and Lidocaine in the Dog**

<table>
<thead>
<tr>
<th>Drug</th>
<th>pH</th>
<th>nPr (molar)</th>
<th>K (1/moles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>7.36</td>
<td>1.48x10^-5</td>
<td>5.4x10^3</td>
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<tr>
<td>Bupivacaine</td>
<td>6.96</td>
<td>1.16x10^-5</td>
<td>7.8x10^3</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>7.36</td>
<td>7.50x10^-5</td>
<td>1.5x10^3</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>6.96</td>
<td>6.89x10^-5</td>
<td>3.8x10^3</td>
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