TITLE: CHANGES IN LIDOCAINE PROTEIN BINDING MAY EXPLAIN ITS INCREASED CNS TOXICITY AT ELEVATED CO_2 TENSIONS

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INTRODUCTION: High serum lidocaine concentrations are associated with signs and symptoms of central nervous system toxicity. Since only uncharged molecules are able to cross the blood-brain barrier (BBB), respiratory acidosis would be expected to decrease the toxicity of lidocaine, a weak base with a pKa 7.86. However, Engelsson demonstrated that high values of carbon dioxide tensions are associated with increased rather than decreased lidocaine toxicity[1]. In their attempts to resolve this paradox, previous investigators failed to account for the fact that to cross the BBB, a substance must be both nonionized and unbound to plasma proteins. We designed this study to determine the effect of carbon dioxide tension on lidocaine plasma protein binding.

METHODS: We added sufficient lidocaine to two 25-ml aliquots of pooled human plasma from normal volunteers to yield concentrations of 2 and 7 µg/ml respectively. We then divided each aliquot into 5 samples which we placed in stoppered glass test tubes and warmed to 37°C. With appropriate venting we bubbled either 0, 3, 6, 9, or 12 percent carbon dioxide in oxygen through each sample for 30 min. After removing the needles from the stoppers, we took the tubes to a constant temperature room which had been pre-heated to 37°C. We anaerobically removed serum from the tubes and transferred duplicate samples to ultrafiltration devices (Syva, Palo Alto, CA) which we had prefilled with corresponding mixtures of carbon dioxide in oxygen. The samples were centrifuged for 15 min at 5000 x g to obtain a protein-free ultrafiltrate. To determine if there was significant nonspecific binding of lidocaine to the filters themselves, the process was repeated using a protein-free plasma filtrate in place of whole plasma. We determined the lidocaine concentration of the ultrafiltrate as well as the original samples using the Emit-cad® kit (Syva, Palo Alto, CA). This immunoassay is optimally sensitive in the range of 1-12 µg/ml with a coefficient of variation of < 5% in our laboratory. A portion of each sample was analyzed for PCO_2 with a Corning #168 pH/blood gas analyzer® which was calibrated before each determination. Using linear regression we determined the relationship between fraction of free-lidocaine and carbon dioxide tension; we used a t-test to determine if the correlation coefficient differed significantly from 0. $P<0.05$ indicated statistical significance.

RESULTS: When lidocaine containing (2.3 and 7.1 µg/ml) protein-free filtrate passed through the ultrafiltration devices, there was 91±2 percent ($\bar{X}$±SEM) recovery of lidocaine. Binding of lidocaine to the filters did not vary with carbon dioxide tension. We corrected our measurements of lidocaine binding in the plasma samples to compensate for this non-specific binding. Total lidocaine concentrations for the whole plasma lidocaine samples were 2.2 and 6.8 µg/ml. These values are within the therapeutic and preconvulsive ranges previously recorded for lidocaine[2]. Measured CO_2 tensions ranged from 1.0 to 80.5 mmHg, while the associated unbound lidocaine fraction varied from 15 to 48%. The data obtained at the two lidocaine concentrations did not differ significantly (fig 1); therefore we pooled the data before performing the regression analysis. Least squares linear regression demonstrated a strong positive correlation between PCO_2 and the fraction of unbound lidocaine ($r=0.93$, $P<0.001$).

DISCUSSION: Because lidocaine is a weak base, respiratory acidosis decreases the concentration of nonionized lidocaine available to cross the BBB; on this basis, hypercarbia should decrease the CNS toxicity of lidocaine. However, respiratory acidosis has been shown to increase the CNS toxicity of lidocaine. The results of the present study explain this apparent paradox. Only unbound lidocaine is able to cross the intact BBB; respiratory acidosis increases unbound lidocaine. Therefore, respiratory acidosis should increase the CNS toxicity of lidocaine. Conversely, by increasing lidocaine protein binding, hypocarbia decreases the amount of lidocaine available to cause CNS toxicity. Our data emphasize the importance of maintaining adequate ventilation in the face of impending local anesthetic toxicity; by decreasing the fraction of unbound lidocaine available to cross the BBB, early hyperventilation may actually prevent lidocaine-induced seizure activity.

REFERENCES: 1. Engelsson S: The influence of acid-base changes on central nervous system toxicity of local anesthetic agents. Acta Anaesthesiol Scand 18:79-87, 1974. 2. Gianelly R, von der Groeben J, Spivack A, Harrison D: Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease. N Engl J Med 277:1215-1219, 1967.

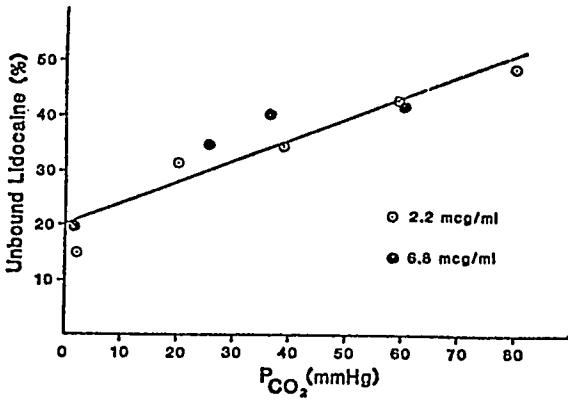

Fig. 1. CO_2 tension vs. fraction of unbound lidocaine