LOCAL ANESTHESIA AND PAIN I

Title: DIFFERENTIAL SENSITIVITY OF FAST AND SLOW FIBER IN MAMMALIAN NERVE EFFECT OF PH AND PCO2

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INTRODUCTION

We seek a method of blocking pain (small, slow fibers) while permitting normal motor function (large, fast fibers). Studies of local anesthetic drugs (LA) have shown that the large fibers have a greater sensitivity to LA than small fibers but are more protected by diffusion barriers against externally applied drugs. This study investigated the differential effect caused by changes in external pH and PCO2 on large/small fibers in the intact in-vitro nerve trunk. However, in no previous study were differential effects on the nerve groups evaluated. Also, the studies were conducted on desheathed nerves, so there was little relation to the clinical situation where local anesthetic is applied to the outside of the intact nerve.

METHODS

The method has been presented in detail in a recent report. We used the isolated intact rabbit vagus nerve trunk removed following air embolus death, cleaned and stored in HEPES-Lile (HEPES-L) solution at pH 7.4 bubbled constantly with O2. The nerve was mounted in a nerve chamber with outside compartments for stimulation and recording and a central compartment for drug application. Measurements were made from photographs of the oscilloscope. The pH of the HEPES-L solution was regulated by varying the amount of NaOH 0.1N added. We also used the traditional Carbonate-Lile (CO2-L) solution with a CO2-carbonate buffer system aerated with a gas mixture of 5% CO2 and 95% O2. pH of the Carb-L solution was adjusted by varying the NaHCO3 concentration. Bupivacaine HCl powder was made up daily in the appropriate solution and concentration.

Only one nerve was used for each drug concentration. Contaminants lasted the least 30 minutes till action potentials (AP) were stable. PH of the perfusate was repeatedly checked both before and after nerve application. Drugs were dissolved in the selected solution, the middle chamber was then perfused at 0.1 ml/min at room temperatures (20°-22°C).

RESULTS

Bupivacaine dissolved in Carb-L was 2-3 fold more potent in blocking action potentials (AP) than in HEPES-L at the same pH. Only in the HEPES-L is the C fiber blocked before A fiber. We present this in the accompanying figure. Application of bupivacaine in HEPES-L with pH changed from 7.8 to 6.7 showed increased IA potentiation in the alkaline medium.

A systematic evaluation was then made of bupivacaine effect varying HEPES-L pH from 6.6-6.8 to 7.2-7.4 to 7.8-7.9; also in Carb-L at pH 7.3-7.4. Results were evaluated as time needed to reach 50% AP block of the A fiber at each drug concentration. The neutral Carb-L was most potentiating. Different block (early predominant C block, later predominant A block) was seen in the HEPES-L experiments, and most predominantly in the slowly developing blocks. The time needed for A block to equal C block was 87.75 min. in acid HEPES-L, 26.0 min. in neutral HEPES-L, 10.5 min. in alkaline HEPES-L and only 5.0 min. in Carb-L.

DISCUSSION

The results support the thesis that the neutral LA form (increased by an alkaline medium) is the most potent form when applied to the intact fiber. We cannot speak directly to the cationic form being the more potent moiety at the nerve membrane from these experiments.

Comparison of the neutral HEPES-L and the neutral Carb-L showed marked potentiation of the LA in the presence of CO2. The close approximation of the Carb-L effect to that of alkaline HEPES-L effect raises the question of whether this effect is due to CO2 diffusion into the fiber interior or does this response reflect the alkaline pH of the fluid layer left after CO2 diffusion, and thus acts like an alkaline medium? In any case the use of alkaline medium closely simulates the use of carbonated solution and is easier to use technically.

Also to be noted is that differential block is least visible in fast blocks regardless of the use HEPES-L or neutral Carb-L. Differential nerve block is apparent in the same relationship as seen previously. We make a plea that clinical LA blocks should be possible with alkaline solutions so as to minimize total drug dosage rather than the acid solution in which all drugs are now commercially prepared.

REFERENCES