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TITLE : TUBOCURARINE REQUIREMENT AND CHRONIC HYPOKALEMIA

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Introduction: Acute hypokalemia decreases the concentration of tubocurarine or pancuronium needed to produce neuromuscular block.[1] However, studies on the effect of chronic hypokalemia have produced conflicting results. Chronic treatment with chlorothiazide reduced dose requirement for a neuromuscular blocking agent[2], while chronic treatment with furosemide produced no change.[3] It is difficult to tell from such experiments whether the variability reflects a difference between diuretics or the difficulties inherent in controlling in vivo assay systems. Therefore, the effect of chronic hypokalemia of dietary and of drug-induced origin was examined in an in vitro system. The effect of acute replacement of potassium was determined in a parallel series of experiments.

Methods: Five groups of guinea pigs were studied. Each group contained some animals receiving normal diets and some animals receiving low potassium diets. One group served as controls and the remaining four groups received daily intraperitoneal injections of one of the following drugs; furosemide (1 mg/Kg), ethacrynic acid (3 mg/Kg or 10 mg/Kg), chlorothiazide (15 mg/kg), and deoxycorticosterone acetate (1 mg) from 4 to 30 days. Following the pretreatment, the animals were anesthetized and plasma potassium was measured. Isolated nerve-lumbrical muscle preparations were prepared in two 50 ml baths of Krebs' solution, the composition of which were identical except that one had a potassium concentration of 5.9 mM (the usual value for Krebs' solution), and the other equal to the plasma potassium determined earlier. The baths were bubbled with oxygen 95% and carbon dioxide 5%, and maintained at 37° C. The isometric twitch response to indirect stimulation was measured at 10 sec. intervals with a supramaximal stimulus of 0.3 msec. duration. Once the twitch response had stabilized, d-tubocurarine was added in graded doses to generate twitch height vs. d-tubocurarine concentration-response curves. At the end of the experiment, the d-tubocurarine was washed out to confirm that the twitch responses had returned to control levels. A sigmoid curve was fitted to the results by an iterative non-linear least squares technique, and concentrations reducing the twitch responses by 50% (ED50's) were determined.

Results: Potassium deficient diets lowered plasma potassium from normal range of 3.7-5.4 mEq/l to 1.5-4.8 mEq/l. The ED50 for d-tubocurarine was markedly changed in the potassium depleted animals: the lower the plasma potassium, the lower the ED50 ($p<.01$). When observations from animals on normal diet were added to those from animals on low potassium diet, the resulting regression was indistinguishable from that obtained with the latter group alone. Therefore, both the groups were pooled (figure 1) to give a control population with a wider range of potassium values. The groups treated with diuretics yielded regressions with similar slopes to that obtained with diet alone. However, the heights differed among the groups; the regression in the chlorothiazide treated group was higher, and the regression in the ethacrynic acid treated group was lower than the remaining regressions (furosemide, deoxycorticosterone acetate and the control).

Measurement of ED50 in Krebs' solution with normal potassium levels, rather than levels chosen to match the in vivo plasma values, gives an indication of the degree of acute reversibility of the effect of chronic potassium depletion. Considerable reversal was seen in all groups, although only in the chlorothiazide group, did the ED50 return to normal values.

Conclusions: Chronic hypokalemia reduces dosage requirement for d-tubocurarine. The extent of the effect varies with the choice of intervention used to produce the hypokalemia. Acute replacement of potassium can significantly reverse the effects of chronic depletion.

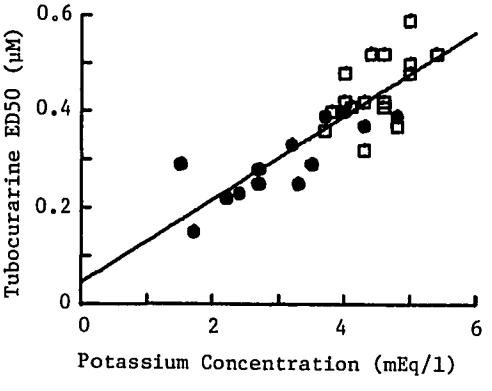

Figure 1. Relation of tubocurarine ED50 to in vivo potassium. • low potassium diet, ▫ normal diet

References:
1. Waud, BE: Interaction of potassium and calcium with neuromuscular blocking agents. Proc. Amer. Soc. Anesthesiologists 403-404, 1978
2. Miller, RD, Roderick, LL: Diuretic induced hypokalemia, pancuronium neuromuscular blockade and its antagonism by neostigmine. Br. J. Anaesth. 50:541-544, 1978
3. Hill, GE, Wong, KE, Lynn, SC, et. al.: Acute and chronic changes in intra- and extracellular potassium and responses to neuromuscular agents, Anesth. Analg. 51:417:421, 1978