TITLE: A STRUCTURE-ACITVITY-RELATIONSHIP (SAR) DIFFERENCE BETWEEN PRE-JUNCTIONAL AND POST JUNCTIONAL NICOTINIC RECEPTORS

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Transmitter mobilization and release are maintained by a mechanism in which prejunctional nicotinic receptors are involved. Transmitter reduction occurs when these receptors are blocked resulting in tetanic fade (TF). Postjunctional receptor block causes loss of peak tetanic tension (PTT). Disparity in the affinities of the prejunctional and postjunctional have been proposed for differences in the effects of muscle relaxants on PTT and TF. The purpose of this study was to determine other pharmacological differences between the two receptors.

A soleus nerve-muscle preparation was made in Sprauge Dawley rats. The soleus nerve was supramaximally and continuously stimulated with rectangular pulses of 0.15 msec duration at 0.2 Hz except when interrupted for 5 sec trains of 30, 50, 100 and 200 Hz. Controls were obtained before the administration of one of 5 muscle relaxants studied: atracurium (ATRA), dimethyl tubocurarine (DMTC), d-tubocurarine (dTC), pancuronium (PAN) and vecuronium (VEC). The contractile responses were recorded with the PTT and TF being quantitated.

All muscle relaxants depressed PTT and tetanic maintenance (TM) in a dose-related manner at all frequencies. Their effects on PTT and TM were not equal, but differed. At higher frequencies, higher doses of dTC and VEC evoked a greater loss of tetanic maintenance than at lower frequencies, while higher doses of ATRA, DMTC and PAN were more constant, separating the relaxants into 2 groups. To elucidate further this possible division, the ratio of the percent loss of PTT and the percent loss of TM (PTTL/TML) was determined. The results showed dTC and VEC had similar values and differed from those of ATRA, DMTC and PAN. The order was dTC VEC DTMC ATRA PAN.

That PPTL/TML was not constant for each relaxant adds further evidence that muscle relaxants act at prejunctional and postjunctional sites. ATRA, DMTC and PAN, all bisquaternary compounds, have lesser prejunctional action while dTC and VEC, monoquaternary compounds, have greater prejunctional action. This SAR difference may reflect a variation in the prejunctional and postjunctional receptor binding sites.

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TITLE : PHARMACODYNAMICS OF VECURONIUM IN PATIENTS WITH AND WITHOUT RENAL FAILURE.

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Pharmacodynamics of vecuronium (V) has long been known as unaffected by chronic renal failure (CRF). Recently some authors reported different results (1,2). This study was designed to compare pharmacodynamics of V in patients with and without CRF.

Twenty two patients, free from hepatic disease, participated in the study : 11 anephric patients (AP) undergoing renal transplantation and 11 normal patients (NP) undergoing urological surgery. Anesthesia was achieved with flunitrazepam (3 $\mu g.kg^{-1}$), propofol (2,5 $mg.kg^{-1}$ bolus then 6 $mg.kg^{-1}.h^{-1}$) fentanyl (2,5 $\mu g.kg^{-1}$ bolus then 2,5 $\mu g.kg^{-1}.h^{-1}$) and N20 50%. Ventilation was controlled mechanically and ajusted to produce end-tidal pCO2 at 30-40 mmHg. Esophageal temperature was maintained at 35-37°C. Supramaximal stimuli of 0.1 ms duration were delivered in a train of four (TOF) sequence (2Hz) to the ulnar nerve at the wrist every 20s, and electromyographic evoked response of the hypothenar muscles recorded. All patients received V 0.1 $mg.kg^{-1}$ IV. After first twitch (T1) recovered to 25% of control, they received an incremental dose (0.03 $mg.kg^{-1}$). Variables measured were : onset time, time from initial injection (DUR 25) and from subsequent injection (DUR Rep25) until T1 recovered to 25%, time from subsequent injection until T1 recovered to 90% (DUR 90), time from 25% to 75% recovery (R.I.) and time until TOF ratio = 75% (TOF 75).

	NP	AP
Onset time (sec)	145.9 ± 40.3	139 ± 47.7 NS
DUR 25 (min)	35.3 ± 5.3	46.5 ± 10.9**
DUR Rep25 (min)	25 ± 4.2	39.7 ± 10.8**
DUR 90 (min)	47.6 ± 12.9	118 ± 33.6***
R.I. (min)	13.9 ± 4.5	48.7 ± 32.9**
TOF 75 (min)	60.5 ± 14.1	128.6 ± 24.9***

*p<0.05 **p<0.01 ***p<0.001

The T1 tension values were compared using Kruskall-Wallis rank test. The results are expressed as mean ± SD.

Results are summarized in the table. All the variables, but onset time, were significantly prolonged in AP.

DISCUSSION : CRF increases neuromuscular blockade of V. These results are different from those of other studies (3,4) exepted some recent ones (1,2). Renal clairance of V is poor and its suppression by CRF cannot explain such an increase in neuromuscular blockade. We assume that CRF might alter the liver extraction of V and the interaction between V and nicotinic muscular receptors.

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