TITLE : PLASMA CONCENTRATION-RESPONSE RELATIONSHIP OF PANCURONIUM FOR THE DIAPHRAGM AND THE ADDUCTOR POLLICIS IN ANESTHETIZED MAN.

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The diaphragm (Δ) requires twice as much pancuronium as the adductor pollicis (AP) for an identical block (1). Duration of action of muscle relaxants is shorter for Δ than for AP (2). However, differences in Cp50 remain to be established.

Eight patients were studied after obtaining informed consent. Anesthesia was induced with thiopental (8 $mg.kg^{-1}$) and fentanyl (3 $\mu g.kg^{-1}$), and maintained with N_2O and fentanyl. The trachea was intubated, and ventilation was adjusted to maintain end-tidal PCO_2 at 4-5%. The left ulnar and the right phrenic nerves were stimulated with train of four stimulation every 20 s. Electromyographic (EMG) responses of the two muscles were monitored through surface electrodes. When EMG responses were stable, incremental doses of pancuronium were administered until 95% depression of the first twitch (T1) was obtained for Δ. During spontaneous recovery, arterial blood samples were drawn when T1 reached 10%, 25%, 50%, 75% and 90% of control for each muscle. Pancuronium plasma concentration was measured using a modified fluorometric assay (3). Individual linear regressions were obtained between logit transformation of T1 depression and the logarithm of plasma concentration. Mean plasma concentration-paralysis curve was constructed for each muscle The slope of the curves and the expected concentration of pancuronium 50% paralysis (Cp50) were derived. Data from Δ and AP were compared using a Student's t test. Results are expressed as mean ± SEM.

The cumulative doses of pancuronium were 120 ± 8 $\mu g.kg^{-1}$. Time course of recovery after the last injection is shown on Fig.1. Mean plasma concentration-response curves are shown on Fig.2: the slopes of these curves did not deviate significantly from parallelism. Cp50 for Δ and AP were 122 ± 7 and 74 ± 6 $ng.ml^{-1}$ respectively ($P < 0.05$). The higher Cp50 of pancuronium for Δ gives an explanation to the lower potency and the shorter duration of action of muscle relaxants for the diaphragm than for the adductor pollicis.

References : 1- Anesthesiology 65: 1-5; 1986
2- Anesthesiology 67: 326-330; 1987
3- Clin Chim Acta 44: 59-66; 1973

Fig. 1: **Time to T1 recovery**

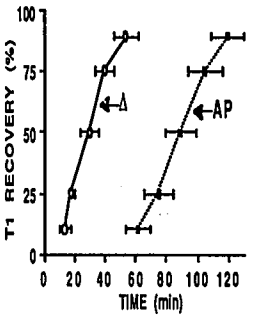
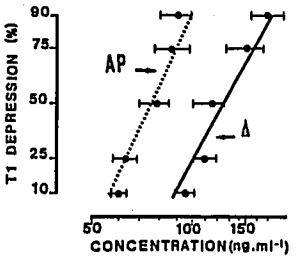


Fig. 2: **Mean plasma concentration-response curves.**

—●—: measured concentrations



TITLE: INTERACTION OF ORG9426 AND OTHER NON-DEPOLARIZING MUSCLE RELAXANTS IN LIVE RATS

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It has been observed in both in vitro animal experiments[1,2] and in clinical studies,[3] that interaction of two different nondepolarizing muscle relaxants (MR) can be more than additive. In this study the interactions of ORG9426 with other MR were investigated in live rats.

Rats anesthetized with i.p. pentobarbital and urethane were tracheostomized and mechanically ventilated with O_2. Drugs were administered through catheters in the jugular vein. Sciatic nerves were stimulated at the gluteal region with supramaximal square wave impulses of 0.2 ms duration at 0.1 Hz. The force of contraction (P) of the tibialis anterior muscle was quantitated by force displacement transducers and recorded on a polygraph. After control measurements, 20-30% steady state neuromuscular (NM) block was established by the continuous infusion of one of the MR (see Table). Subsequently the NM effect of a single 0.1 mg/kg dose of ORG9426 was observed. The effect of the same dose of ORG9426 administered in the presence of a steady state NM block produced by ORG9426 was used as a control.

Results summarized in the Table indicate that only d-tubocurarine (d-Tc) significantly potentiated the NM effect of ORG9426 ($p < 0.05$).

The potentiation of the NM effect of ORG9426 by d-Tc may be due to differences in the affinity of these two compounds to pre- and postsynaptic nicotinic receptors. It has also been suggested that the affinity of the same MR to the ACh binding sites on the alpha-1 and alpha-2 subunits of postsynaptic cholinergic receptors may be different.[2] If d-Tc would have greater affinity for one of these ACh binding sites and ORG9426 for the other, it could be expected that the combined effect of the two MR will be more than additive.[2] Since the onset time of ORG9426 is more rapid than that of other nondepolarizing MR (unpublished observations), the combination of a priming dose of d-Tc with ORG9426 may facilitate rapid tracheal intubation.

References
1. Anesth Analg 70:S131, 1990
2. Anesthesiology 63:4-15, 1985
3. Anesth Analg 59:604-609, 1980

Muscle Relaxant	P1*	P†	P1-P2
ORG9426	78.0±1.0	24.0±5.9	54.0±5.1
Vecuronium	76.3±1.4	25.5±7.8	50.8±6.2
Pancuronium	75.3±0.6	14.2±2.7	61.1±2.7
Pipecuronium	75.9±2.0	11.3±3.7	64.5±3.5¶
d-Tubocurarine	77.0±1.2	6.7±3.1	70.3±3.4¶

*P after establishment of steady state block by the infusion of the MR indicated (Mean±SEM; n=5).
†P after the administration of 0.1 mg/kg ORG9426.
¶Significantly different from control ($p < 0.05$, ANOVA followed by Duncan's test).