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Title: THE PRE- AND POSTSYNAPTIC EFFECTS OF ORG9426 DURING ONSET OF AND RECOVERY FROM NEUROMUSCULAR BLOCKADE

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Introduction. During indirect stimulation with trains-of-four (TOF) supramaximal impulses at 2 Hz, after administration of a muscle relaxant (MR), the decrease of the force of contraction (P) elicited by the first impulse (T1) is caused by the postsynaptic and the decrease of the ratio of P elicited by T4 and T1 (T4/T1 ratio) is caused primarily by the presynaptic effect of the MR.[1] In the present study the relative contribution of the pre- and postsynaptic component to the NM effects of ORG9426 has been compared with those of other MR.

Methods. In this study, the sciatic nerves of rats, anesthetized with intraperitoneal pentobarbital + urethane, were stimulated indirectly with TOF, supramaximal impulses and P of the tibialis anterior was continuously recorded. A single dose of one of 6 MR (see table) was administered and the T4/T1 ratios were determined, when T1 was 50% of control during onset and recovery of NM block from the tracings.

Results. During onset of NM block, when T1 was 50% of control, the T4/T1 ratios with different MR were similar (Duncan's multiple range test) (see table). When during recovery T1 reached 50% of control the T4/T1 ratios were lower than those during onset of NM block ($p < 0.01$; paired t test). Furethermore, the T4/T1 ratio of vecuronium was significantly lower ($p < 0.05$; Duncan's test) than those of ORG9426, pipecuronium or pancuronium and that of metocurine was lower ($p < 0.05$) than those of ORG9426 or pipecuronium.

Discussion. The findings presented confirm, that at equal T1, the depression of the T4/T1 ratio, caused by various MR is less during onset of than during recovery from NM blockade. Furthermore, during recovery the presynaptic effect of vecuronium or metocurine appear to be greater than those of pipecuronium or ORG9426. These findings indicate that it is unlikely that presynaptic inhibition contributes significantly to the rapid onset of action of ORG9426.[2]

Muscle Relaxant	T4/T1 ratio at 50% NM block during Onset of block	Recovery from block
ORG9426 (8)	0.64±0.07*	0.03±0.05
Vecuronium (8)	0.51±0.02	0.12±0.02†
Pipecuronium (8)	0.54±0.02	0.31±0.04
Pancuronium (8)	0.56±0.05	0.26±0.06
d-Tubocurarine (9)	0.62±0.04	0.21±0.03
Metocurine (8)	0.61±0.04	0.14±0.05‡

*Mean±SEM of number of observations in parenthesis.
†Significantly different from ORG9426, pipecuronium and pancuronium.
‡Significantly different from ORG9426; and pipecuronium.

References.
1. Anesth Analg 59:935-943, 1980
2. Anesthesiology 73:A890, 1990

A799

TITLE: MUSCLE RELAXANT EFFECTS IN THE THUMB, LARYNX, AND DIAPHRAGM: A NOVEL PHARMACODYNAMIC ANALYSIS

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Previous investigations and clinical experience have suggested that the larynx and the diaphragm are resistant to the effects of nondepolarizing muscle relaxants compared to the adductor pollicis (AP). However, a recent report described that some patients given vecuronium, 70 μg/kg, developed 100% depression of the diaphragm but not of the AP.(1) To reconcile these findings, we developed a novel pharmacodynamic model to analyze these published data to determine the relative sensitivities of these muscle groups (C_{50}) and the rate constant for equilibration between the muscle groups and plasma (k_{eo}).

Methods: The pharmacodynamic model is an adaptation of the muscle relaxant pharmacokinetic/phamacodynamic model of Sheiner *et al.*(2) in which plasma concentration (Cp) is expressed as the sum of exponentials and twitch tension is a function of Cp, C_{50}, k_{eo}, and the Hill factor (γ) to explain the sigmoid relationship between effect and concentration in the effect compartment. This model can be reparameterized as:

$$\text{Effect} = \frac{Ce^{\gamma}}{(Ce^{\gamma} + C_{50}^{\gamma})}$$

where: $Ce = \text{dose} \cdot k_{eo} \cdot \left[\frac{A \cdot (e^{-\alpha t} - e^{-k_{eo}t})}{k_{eo} - \alpha} + \frac{B \cdot (e^{-\beta t} - e^{-k_{eo}t})}{k_{eo} - \beta}\right]$

Data were obtained from Donati *et al.*(1,3) Briefly, 36 subjects were anesthetized with propofol and alfentanil. Twitch tension of the AP was measured using a force transducer; the phrenic nerve was stimulated at the neck and the diaphragmatic EMG was recorded; or the superior laryngeal nerve was stimulated and the tension measured from the cuff of an endotracheal tube. Subjects were given bolus doses of vecuronium, 40 or 70 μg/kg. Data for the AP and either the larynx or the diaphragm were fit to the pharmacodynamic model. For each subject, values for C_{50} and k_{eo} for the two muscle groups were compared. $P < 0.05$ was considered significant.

Results: For one subject, C_{50}(diaphragm)/C_{50}(AP) was 0.99 and k_{eo}(diaphragm)/k_{eo}(AP) was 1.9; for the remaining subjects C_{50} and k_{eo} for the larynx or diaphragm were greater than for the AP (table). For several subjects, C_{50}(larynx) or C_{50}(diaphragm) were greater than C_{50}(AP) despite more intense peak effect in the larynx or diaphragm than in the AP.

Discussion: Our results indicate that, consistent with clinical observation, the larynx and diaphragm are resistant to the effects of vecuronium compared to the AP. In addition, k_{eo} is higher for the larynx and diaphragm, presumably because of higher blood flow to these muscles; this results in an earlier, higher, peak concentration in the larynx and diaphragm, so that their peak neuromuscular blockade can be more intense than in the AP, despite their greater resistance. Our results are consistent with clinical observations and explain the early paralysis of the larynx and diaphragm following bolus administration of muscle relaxants despite the known resistance of these muscles compared to the AP.

References:
1. Anesthesiology 65:1-5, 1986
2. Clin Pharmacol Ther 25:358-371, 1979
3. Anesthesiology 1991, in press

Table. Ratio of larynx or diaphragm to AP for C_{50} and k_{eo} (mean ± SD, range)

	C_{50}	k_{eo}
Larynx	1.37 ± 0.23, 1.05-1.83	2.5 ± 0.8, 1.2-4.3
Diaphragm	1.17 ± 0.15, 0.99-1.59	2.2 ± 1.0, 1.4-5.5

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