Nondepolarizing neuromuscular blocking drugs and train-of-four fade

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The aim of this study was to examine differences in prejunctional effects of different relaxants by measuring the train-of-four (TOF) fade during the onset and recovery of neuromuscular block. The relaxants studied were atracurium (225 $\mu g \cdot kg^{-1}$), mivacurium (65 $\mu g \cdot kg^{-1}$) rocuronium (300 $\mu g \cdot kg^{-1}$) and vecuronium (40 $\mu g \cdot kg^{-1}$). The TOF ratios were measured at approximate heights of T_1 (first response in the TOF) of 90, 75, 50, and 25%. The TOF fade (as shown by lower TOF ratios) increased with a decrease in the T_1 during onset of neuromuscular block. Although there was a slightly greater fade with atracurium and rocuronium during the onset of block, the differences among the relaxants were insignificant. It is concluded that the relative prejunctional effects of these relaxants are similar.

Ce travail cherche à évaluer la différences entre les effets préjonctionnels de plusieurs myorelaxants par la mesure de l'affaiblissement (fade) de la réponse au train-de-quatre (TOF) pendant l'établissement et la récupération du bloc neuromusculaire. Les relaxants étudiés sont l'atracurium (225 $\mu g \cdot kg^{-1}$), le mivacurium (65 $\mu g \cdot kg^{-1}$), le rocuronium (300 $\mu g \cdot kg^{-1}$) et le vécuronium (40 $\mu g \cdot kg^{-1}$). Les rapports du TOF sont mesurés avec la hauteur approximative du T_1 (première réponse au TOF) de 90, 75, 50 et 25%. L'affaiblissement du TOF (montré par la baisse du ratio) augmente avec la baisse de T_1 pendant l'établissement du bloc neuromusculaire. Bien que l'affaiblissement soit plus grand avec l'atracurium et le rocuronium pendant l'établissement du bloc, les différences entre myorelaxants ne sont pas significatives. On conclut que les effets préjonctionnels relatifs de ces myorelaxants sont identiques.

Key words
MONITORING: train-of-four;
NEUROMUSCULAR TRANSMISSION: prejunctional effects;
NEUROMUSCULAR RELAXANTS: atracurium, mivacurium, rocuronium, vecuronium.

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Although the site of action of nondepolarizing relaxants is predominantly postjunctional, they may also have a prejunctional site of action.[1-4] Different neuromuscular blocking drugs, however, have been shown to have different degrees of prejunctional effects as shown by different degrees of fade in response to a train-of-four (TOF) stimulation.[2,5-7] The relative prejunctional effects of the newer muscle relaxants, mivacurium and rocuronium, as measured by TOF fade, particularly in relation to agents like atracurium and vecuronium, are not well known, nor is it known if this activity is related to the rate of onset of block. This has been investigated in the present study.

Methods

Forty adult patients, of ASA grades I or II, were included in the study after obtaining their written informed consent and approval of the Regional Ethics Committee. All were scheduled to undergo elective operative procedures requiring the use of nondepolarizing neuromuscular blocking agents. Following premedication with oral temazepam 10–20 mg, 60–90 min preoperatively, anaesthesia was induced with fentanyl 2–3 $\mu g \cdot kg^{-1}$ and thiopentone 5–6 $mg \cdot kg^{-1}$, and maintained with 66% nitrous oxide in oxygen and further increments of fentanyl and/or thiopentone as required. Heart rate, arterial blood pressure, oxygen saturation, end-tidal CO_2 and temperature were monitored in every patient. Ventilation was adjusted to maintain the end-tidal carbon dioxide between 4.5 and 5.0% and the arm was wrapped in cotton wool to keep the skin temperature above 32°C. No volatile agents were used during the study period. Neuromuscular monitoring consisted of stimulation of the ulnar nerve at the wrist with supramaximal stimuli of 0.2 msec duration in a train-of-four (TOF) mode at 2 Hz every 12 sec and recording the force of contraction of the adductor pollicis

muscle using a force transducer and a neuromuscular function analyzer (Myograph 2000, Biometer Ltd, Denmark).

Following a ten-minute period of stabilization of control TOF responses, ten patients each were randomly allocated to receive atracurium 225 $\mu g \cdot kg^{-1}$, vecuronium 40 $\mu g \cdot kg^{-1}$, mivacurium 65 $\mu g \cdot kg^{-1}$ or rocuronium 300 $\mu g \cdot kg^{-1}$, these being the approximate ED_{95} doses of these relaxants. The TOF ratios, i.e., the ratio of the heights of the fourth (T_4) to the first (T_1) twitch in the same train, were calculated at approximate heights of T_1 of 90, 75, 50 and 25% of control during both the onset of the block and spontaneous recovery. The time to attain 90% block of the T_1 and the degree of maximum block attained was also recorded.

The statistical significance of the results was tested using analysis of variance followed by t tests with Bonferroni correction if required. A P value of <0.05 was taken to represent a significant difference.

Results

The patients in the four groups were comparable with regard to age, weight and height (Table I).

The TOF ratios with the four relaxants at 90, 75, 50 and 25% of T_1 during the onset of block are given in Table II. The end-points could not be recorded at all times, particularly with rocuronium as the T_1 sometimes decreased in height rapidly. It is clear that fade increases as the height of the T_1 decreases from 90 to 25% of control with all four relaxants as shown by decreasing TOF ratios with increasing block. Although TOF ratios with rocuronium and atracurium were slightly lower, particularly at T_1 of 50 and 25%, the differences were not statistically significant. The time to 90% depression of T_1 was shorter with rocuronium than with the other three relaxants, being 52 sec compared with 128, 147 and 136 sec with atracurium, mivacurium and vecuronium respectively ($P < 0.01$). All but one patient receiving atracurium and two receiving mivacurium developed 90% or greater block (Table II). The T_1 depression in these patients was 68, and 40 and 54% respectively. The mean values, however, were not significantly different.

The TOF ratios during recovery of neuromuscular block (Table III) were lower in comparison with the ratios during onset of block at each of the measured heights of T_1. However, there was no significant difference between the relaxants at any of the assessment points.

TABLE I Demographic data (mean ± SD)

	n	*Age (yr)*	*Weight (kg)*	*Height (cm)*
Atracurium	10	35 ± 13.5	63 ± 11.7	162 ± 6.8
Mivacurium	10	36 ± 15.9	68 ± 10.6	167 ± 9.8
Rocuronium	10	46 ± 14.8	65 ± 11.1	163 ± 11.6
Vecuronium	10	39 ± 10.4	66 ± 9.6	166 ± 9.1

Discussion

During repetitive nerve stimulation, nondepolarizing relaxants, in addition to depressing the amplitude of contractions, also cause varying degrees of fade in response to TOF or tetanic stimulation.[3] Fade produced by non-depolarizing neuromuscular blocking drugs in intact muscles in response to higher rates of stimulation (such as TOF and tetany) has been suggested to be due to prejunctional actions of the drugs causing inhibition by a nicotinic receptor-mediated positive feedback of transmitter release.[3,8] Therefore the greater the fade, the greater is thought to be the prejunctional effect. The mechanism of the prejunctional effect is perhaps, decreased transmitter output.[2,8,9]

The present study has shown no differences among the four relaxants examined in the relative degree of fade. A previous study showed greater fade with atracurium than with vecuronium.[7] Although the TOF ratios in the present study were also lower with atracurium than with vecuronium, the differences were smaller and not statistically significant, when an overall comparison of all four drugs was made. Of the newer relaxants, rocuronium showed slightly greater fade, but in general there were no differences which suggests relatively similar prejunctional effects with them. It is possible that this may be due to rapid onset of block with rocuronium allowing little time for development of fade. However, absence of any greater prejunctional effect with rocuronium has also been shown in a more controlled *in-vitro* study.[10] Greater fade during recovery of block than during onset of block is well known. This phenomenon was observed in the present study and has been reported with other relaxants also.[11]

The relevance of prejunctional effects of muscle relaxants is unclear at this stage, apart from explaining the site of their action. The clinical importance of the effect is also not clear but it does not appear to be an important factor in the speed of onset of neuromuscular block. A greater prejunctional effect does not appear to be associated with a more rapid onset since d-tubocurarine, with a greater prejunctional effect, is not more rapid-acting than pancuronium, nor is atracurium any faster-acting than vecuronium even though it has a greater prejunctional effect.[2,6,7,11-13] Since the extent of the prejunctional effects of rocuronium is similar to the other relaxants used in the present study, it is unlikely that prejunctional activity has any relation to the rapid onset of its effect as observed in this study and as reported by others.[14-17] The rapid onset is perhaps related to its

TABLE II TOF ratios during onset of neuromuscular block with atracurium, mivacurium, rocuronium and vecuronium at different heights of T_1; also shown is the time taken for 90% block of T_1 and the degree of maximum block in each group (mean ± SD)

	n	*T_1 90%*	*T_1 75%*	*T_1 50%*	*T_1 25%*	*Time to 90% block (min)*	*Degree of maximum block (%)*
Atracurium	10	83 ± 8.0	74 ± 8.7	57 ± 16.4	47 ± 12.3[a]	128 ± 63.1	96 ± 10.0
Mivacurium	10	86 ± 9.9	76 ± 7.5	69 ± 7.2[a]	52 ± 9.1[b]	147 ± 50.5	87 ± 21.6
Rocuronium	10	87 ± 6.2[c]	70 ± 9.5[d]	59 ± 12.9[e]	47 ± 11.7[f]	52 ± 11.0	99 ± 1.4
Vecuronium	10	89 ± 3.9[a]	82 ± 3.2	70 ± 3.4	52 ± 7.2	136 ± 47.0	98 ± 2.8

[a]$n = 9$; [b]$n = 8$; [c]$n = 6$; [d]$n = 4$; [e]$n = 5$; [f]$n = 7$; in other cases the height of T_1 during the onset of block did not correspond to any of the end-points at which the TOF was recorded.

TABLE III TOF ratios (mean ± SD) during recovery from neuromuscular block with atracurium, mivacurium, rocuronium and vecuronium

	n	*T_1 25%*	*T_1 50%*	*T_1 75%*	*T_1 90%*
Atracurium	10	15 ± 9.3[a]	27 ± 14.7	42 ± 14.6[b]*	61 ± 13.1[b]*
Mivacurium	10	13 ± 4.0[c]	23 ± 5.6[d]	43 ± 12.4	61 ± 12.1
Rocuronium	10	18 ± 9.1[e]	22 ± 13.8	41 ± 13.5	53 ± 14.4
Vecuronium	10	12 ± 4.3[f]	25 ± 14.5	47 ± 17.7	60 ± 16.6

[a]$n = 7$; [b]$n = 9$; [c]$n = 5$; [d]$n = 8$; [e]$n = 3$; [f]$n = 4$; in others the fourth response in the TOF was not present at this stage; *data not recorded for one patient at these points due to mechanical problems.

lower potency.[18,19] The prejunctional effects may be important when a drug with relatively greater prejunctional effects is administered along with a drug with predominantly postjunctional effects, when there may both be a potentiation of effect as well as a more rapid onset with the combination.[20–23] A possible role for the prejunctional effects has also been suggested in an experimental study in the prevention of succinylcholine-induced fasciculations by d-tubocurarine.[24] However, others have observed no difference between d-tubocurarine and vecuronium, two drugs with different relative prejunctional effects, in reducing succinylcholine-induced myalgias and fasciculations.[25]

The extent of prejunctional effects may be related to potency as low potency drugs tend to show greater TOF fade.[7] This is not supported by the findings of the present study and any such relationship needs examination.

A previous study has shown that the degree of fade at any particular height of T_1 is greater with higher doses.[7] In the present study only lower doses of relaxants were used in order to be able to measure the fade (TOF ratios) at various points during the onset of block; higher doses of rocuronium produce a very rapid onset of effect making it difficult to obtain the fade at different heights of T_1.

In conclusion, the present study showed no differences in the TOF fade with atracurium, vecuronium, mivacurium and rocuronium. Any pharmacodynamic differences are therefore related to factors other than their relative prejunctional effects.

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