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Facilitation of Rapid Endotracheal Intubations with Divided Doses of Nondepolarizing Neuromuscular Blocking Drugs

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The authors sought to determine whether prior administration of a small, subparalyzing dose of nondepolarizing muscle relaxant would shorten the onset time of an intubating dose of muscle relaxant. Initially, in 60 anesthetized patients, twitch response of adductor pollicis to ulnar nerve stimulation was studied after a small dose of pancuronium 0.015 mg·kg^{-1}, metocurine 0.03 mg·kg^{-1}, or *d*-tubocurarine 0.04 mg·kg^{-1}, followed 3 min later by pancuronium 0.08 mg·kg^{-1} or atracurium 0.4 mg·kg^{-1} administered iv. After 60 s, the minimum neuromuscular block, in all patients was 79.0 ± 5.0%. A 95% depression or twitch tension occurred between 59.1 ± 5.3 and 86.1 ± 5.9 s. In another 60 patients, intubating conditions under similar regimen were studied, except the small dose of muscle relaxant was given immediately prior to induction of anesthesia. At the end of 60 s, good to excellent intubating conditions were present in 100% of the patients following the second dose of pancuronium and in 83% of the patients following atracurium. In 17% of the patients, after atracurium intubating conditions were fair. When nondepolarizing neuromuscular blocking drugs are administered in divided doses, neuromuscular blockade adequate for endotracheal intubation is achieved in less than 90 s. This facilitates rapid endotracheal intubation in a time comparable to using succinylcholine, without undesirable effects of the depolarizing neuromuscular blocking drugs. (Key words: Intubation: endotracheal. Neuromuscular relaxants: atracurium; d-tubocurarine; metocurine; pancuronium.)

ONE OF THE MEASURES employed to reduce the chance of aspiration of gastric contents is a rapid induction of anesthesia and endotracheal intubation. Succinylcholine (1 mg·kg^{-1}) iv produces good intubation conditions in approximately 60–90 s followed by rapid recovery from neuromuscular blockade.[1] Though succinylcholine is the best available neuromuscular blocker for rapid intubation of the trachea because of its short onset time of neuromuscular blockade, undesirable side effects may result. When atracurium is administered in divided doses, there is significantly faster onset of neuromuscular blockade than when the same dose of drug is administered as a single bolus.[2,3] This study was designed to compare the rate of onset and degree of neuromuscular blockade when a small dose of one nondepolarizing neuromuscular blocking drug was followed by a larger dose of 1) the same, or 2) different nondepolarizing neuromuscular blocking drug.

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Methods

One hundred twenty, ASA I or II patients, aged 18–60 yr undergoing elective surgery were studied. The protocol for the study was approved by the institution's human research committee, and informed consent was obtained from each patient.

The first 60 patients were premedicated with morphine 0.05–0.15 mg·kg^{-1} im and scopolamine 0.003–0.004 mg·kg^{-1} im 45–60 min prior to induction of anesthesia. Anesthesia was induced with fentanyl 50–100 μg iv, thiopental 4–5 mg·kg^{-1} iv and maintained with 70% nitrous oxide and incremental doses of thiopental and fentanyl. The twitch response of adductor pollicis to ulnar nerve stimulation was elicited by supramaximal square wave pulses of 0.2 ms duration, at 0.15 Hz, and quantitated continuously by an FT-10 transducer. Once a steady state twitch was established, the patients were assigned randomly to one of six groups (table 1). The initial, small dose of pancuronium 0.015 mg·kg^{-1}, metocurine 0.03 mg·kg^{-1}, or *d*-tubocurarine 0.04 mg·kg^{-1} iv was administered to mimic the pretreatment dose of the particular agent when used to ameliorate some of the undesirable side effects of succinylcholine.[1,4,5] Three minutes[6] later, the second dose of muscle relaxant pancuronium 0.08 mg·kg^{-1} or atracurium 0.4 mg·kg^{-1} iv was administered. The second dose represents 2 × ED_{90} of pancuronium (unpublished data) or atracurium.[2] The degree of neuromuscular blockade 60 s after the second dose, time to 95% neuromuscular blockade, and degree of maximum blockade following the second dose were observed. The tracheas of all patients were intubated when maximum

blockade was achieved, and the time for the twitch to recover from the maximum blockade to 25% and 50% of the control were observed.

An additional 60 patients, randomly assigned to one of the six groups similar to those above, were studied under conditions mimicking rapid sequence induction of anesthesia. All patients breathed oxygen for 5 min via a mask. One minute after beginning breathing oxygen was given, 50–100 μg of fentanyl was given, and 1 min later the small dose of muscle relaxant was administered iv (table 1). Three minutes later, anesthesia was induced with thiopental 4–5 $mg \cdot kg^{-1}$ iv, followed by the second dose of muscle relaxant being studied (table 1). Intubation was attempted 60 s after the injection of the second dose of muscle relaxant, and intubating conditions were categorized as indicated in table 2.

Statistical analysis was performed by one-way analysis of variance and chi-square test for homogeneity where appropriate. $P < 0.05$ was indicative of statistical significance.[7]

Results

The degree of neuromuscular blockade 60 s after the second dose, time to 95% neuromuscular blockade, and maximum blockade achieved following the second dose of muscle relaxant are shown in table 3. There was no significant difference in the degree of neuromuscular blockade achieved among any of the groups. The recovery of twitch height from the maximum blockade to 25% of control following pancuronium was 75–100 min, while atracurium was 40–50 min. There was significant ($P < 0.05$) prolongation of recovery of twitch to 25% of control when pancuronium was preceded by metocurine (table 3).

None of the patients receiving small doses of relaxant prior to induction of anesthesia complained of significant symptoms attributable to profound muscle weakness. At end of 60 s, good to excellent intubating conditions were obtained in all patients following the second dose of pancuronium and in 83% of the patients following atracurium. In the remaining 17% of the patients in the atracurium group, intubation was graded as fair (table 4). There was significant difference in the intubating conditions ($P < 0.05$) between the groups receiving pancuronium or atracurium as their second dose.

Discussion

Succinylcholine is currently the drug of choice to facilitate rapid intubation of trachea during anesthesia but frequently is associated with some undesirable effects such as muscle fasciculations,[4] postoperative muscle pain,[4] hyperkalemia,[8] increased intraocular pressure,[9] increased intragastric pressure,[10] and malignant hyperthermia.[11] In instances when succinylcholine has been contraindicated or undesirable, use of larger doses of nondepolarizing neuromuscular blocking drugs have been suggested.[12] Increasing the dose of nondepolarizing neuromuscular blocking drugs decreases the time to complete neuromuscular blockade but also increases the potential of such side effects as tachycardia with pancuronium[13] or hypotension with *d*-tubocurarine[14] and atracurium[15] and prolongation of neuromuscular blockade.[12]

TABLE 1. Group and Drug Dosage

Group	Initial (Small) ($mg \cdot kg^{-1}$)		Second dose ($mg \cdot kg^{-1}$)	
A	Pancuronium	0.015	Pancuronium	0.08
B	Metocurine	0.03	Pancuronium	0.08
C	*d*-Tubocurarine	0.04	Pancuronium	0.08
D	Pancuronium	0.015	Atracurium	0.4
E	Metocurine	0.03	Atracurium	0.4
F	*d*-Tubocurarine	0.04	Atracurium	0.4

A control group of patients receiving a bolus dose of the drug equal to the sum of the two doses given in this study might well have been included. However, several published reports[2,12,16–19] indicate that time in excess of 2 min is required to produce more than 95% block of neuromuscular transmission with doses of nondepolarizing neuromuscular drugs similar to those used in this study. Although not ideal, we accepted these published reports as a control for this study.

This study demonstrates that onset of neuromuscular blockade is faster (<90 s) when a nondepolarizing neuromuscular blocking drug is preceded by a small dose of the same or another nondepolarizing neuromuscular blocking drug. This finding agrees with Nagashima *et al.*,[5] Foldes,[20] and Gergis *et al.*,[3] that when nondepolarizing blocking drugs are administered in divided doses, the onset of neuromuscular blockade is shorter. A small (usually subparalyzing) dose of nondepolarizing neuromuscular blocking drug partially may occupy the postjunctional receptors[21] and/or inhibit presynaptic release of acetylcholine,[22] allowing more rapid and profound effect of the second dose. Perhaps differing abilities of neuromuscular blocking drugs to inhibit neuromuscular transmission by blocking the ionophores on postjunctional membranes[23] may have some role in shortening

TABLE 2. Grading of Intubation Condition

Grade	Definition
1	Excellent (easy passage of tube without coughing)
2	Good (passage of tube with slight coughing or bucking or both)
3	Fair (passage of tube with moderate cough or bucking or both)
4	Not possible

TABLE 3. Percent Depression of Twitch Tension at 60 s, Time to 95% Blockade, and Maximum Block Achieved Following the Second Dose and Recovery of Twitch Height to 25 and 50% from Maximum Blockade of Nondepolarizing Neuromuscular Blocking Drug

	Groups					
	Pancuronium			Atracurium		
	A	B	C	D	E	F
Percent block at 60 s	89.2 ± 3.5	89.8 ± 2.4	79.0 ± 5.0	90.7 ± 2.7	94.0 ± 2.2	81.5 ± 2.8
Time to 95% Block (s)	79.9 ± 5.7	69.3 ± 4.3	85.9 ± 9.6	65.1 ± 5.7	59.1 ± 5.3	86.1 ± 5.9
Maximum Block (%)	100	99.4 ± 0.3	99.4 ± 0.3	98.8 ± 0.3	98.8 ± 0.3	99.0 ± 0.3
Recovery to 25% Twitch (min)	75.0 ± 7.6	100.81 ± 10.0*	77.5 ± 3.7	49.5 ± 2.7	50.1 ± 2.7	40.6 ± 1.9
Recovery time 25–50% (min)	29.7 ± 3.3	23.7 ± 3.1	22.5 ± 3.3	7.9 ± 0.9	8.6 ± 0.9	8.0 ± 0.9

Mean ± SE. N = 10. * $P < 0.05$.

the onset of neuromuscular blockade when combinations of these drugs are used.

The disadvantage of small subparalyzing dose administered to an awake patient is a subjective feeling of discomfort.[24] This is due to the wide variation in sensitivity of patients to muscle relaxant.[25] Occasional patients who are very sensitive to nondepolarizing neuromuscular blocking drugs can be paralyzed profoundly by the small dose used in this study.

Crul[26] has suggested that adequate intubating conditions may be present at 50% twitch inhibition of the adductor pollicis. Agoston *et al.*[27] and Gergis *et al.*[3] have observed that good intubating conditions are present at 40–60% and 70% twitch inhibition of the adductor pollicis, respectively. In this study, 79% or greater twitch inhibition of the adductor pollicis at the end of 1 min was seen with all the groups ($P > 0.05$), still in 17% of the patients following atracurium the intubating conditions were graded as only fair. Although the sensitivity of different muscles to different muscle relaxants varies, the contribution of depth of anesthesia and technical proficiency of the person performing the intubation are the most likely causes of the differences in grading the intubating conditions between the two groups.

In conclusion, this study demonstrates that when a nondepolarizing neuromuscular blocking drug is preceded by the same or another subparalyzing dose of nondepolarizing muscle relaxant, there is a shorter onset of neuromuscular blockade. This method may be used to facilitate rapid endotracheal intubation when use of succinylcholine is contraindicated or undesirable. Further studies with different neuromuscular blocking drugs, dose regimen, and variation of the time between doses are necessary to arrive at one that supplies the best intubating conditions in the shortest period of time.

TABLE 4. Intubating Condition 60 s Following the Second Dose of Nondepolarizing Neuromuscular Blocking Drug

	Groups					
	Pancuronium			Atracurium*		
	A	B	C	D	E	F
Excellent	7	7	7	4	6	3
Good	3	3	3	3	4	5
Fair	0	0	0	3	0	2
Not possible	0	0	0	0	0	0

N = 10.
* $P < 0.05$.

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