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Importance of the Level of Paralysis Recovery for a Rapid Antagonism of Atracurium Neuromuscular Blockade with Moderate Doses of Edrophonium

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Edrophonium, 500 μg · kg⁻¹ or more, effectively antagonizes paralysis induced by long-acting muscle relaxants such as d-tubocurarine and pancuronium.¹⁻⁴ Because of the high rate of spontaneous recovery from paralysis produced by atracurium in normal⁵⁻⁶ patients and those patients with various pathologic conditions,⁷⁻⁸ atracurium neuromuscular blockade should be reversed rapidly by edrophonium. Nevertheless, as shown recently by Rupp and coworkers,⁹ the prerreversal level of neuromuscular blockade influences markedly the speed of the antagonism induced by edrophonium even for the new muscle relaxants of intermediate duration of action.

The goal of this study was to antagonize atracurium-induced paralysis with 500 μg · kg⁻¹ of edrophonium from three predetermined levels of twitch height recovery (i.e., zero, 10, and 25%) in order to select the prerreversal twitch height level at which a 2-Hz train-of-four (TOF) ratio of 75% can be obtained within 15 min. The value of 75% of TOF is widely used as the adequate criterion to indicate that at least the power for respiratory muscles is returned near the preanesthetic state.¹⁰,¹¹

PATIENTS AND METHODS

Thirty adult patients (ASA Class I or II) undergoing elective surgery were studied after informed consent was obtained. The study was approved by our Ethical Com-

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mittee. None of the patients had clinical or biochemical evidence of hepatic or renal damage. One hour before anesthesia, all patients received 10 mg diazepam orally. Anesthesia was induced with thiopental 4 mg·kg⁻¹, fentanyl 5 µg·kg⁻¹, and droperidol 40 µg·kg⁻¹ iv. When unconsciousness resulted, ventilation was controlled until the tracheal intubation, which was performed after the administration of atracurium. Thereafter, ventilation was controlled to maintain end-tidal carbon dioxide between 33 to 35 mmHg or venous P CO₂ between 38 and 42 mmHg. In addition to 66% N₂O, supplementary iv doses of fentanyl were administered if there were clinical evidence of inadequate analgesia. Heat loss was decreased by the use of a warming mattress. Neuromuscular transmission was monitored with a force-displacement transducer (UC3 cell Statham™) fitted with a tension attenuator (U1.4.20, Statham™) incorporated in a hand grip secured with adhesive tape in the hand of the patient in order to measure the isometric contraction of the adductor pollicis. After the induction of anesthesia, the ulnar nerve was stimulated at the wrist by square-wave pulses of 0.2 ms duration and supramaximal intensity, delivered at 0.1 Hz through surface electrodes. The resulting analog signals were amplified and registered on a polygraph recorder. When a consistent control tension was achieved, a bolus injection of 0.5 mg·kg⁻¹ atracurium was administered. Thereafter, 0.1 mg·kg⁻¹ of atracurium was injected each time the twitch height reached 25% of its baseline reading.

Edrophonium 0.5 mg·kg⁻¹ and atropine 8 µg·kg⁻¹ were given either at a twitch height of zero % (ten patients had a posttetanic count [PTC] between 1 and 7), a twitch height of 10% (eight patients), or a twitch height of 25% (12 patients) of spontaneous recovery. In the twitch height zero % series, edrophonium was injected 3 min after the PTC recording, which was observed 5 min after the last atracurium 0.1 mg·kg⁻¹ reinjection. Twitch height and TOF ratios were noted 3, 6, 9, 12, and 15 min after administration of edrophonium. To detect statistical differences between the three groups of patients, one-way or three-way variance analysis, followed for time-period comparisons by Bonferroni t test, was performed. According to the analysis executed, the data were considered significant if F values less than 0.05 and t values less than 0.01 were observed.

RESULTS

Age and weight of the patients allocated in the three groups were not significantly different (variance analysis). The durations of the anesthesias before the edrophonium administration ranged from 60 to 100 min, the number of 0.1 mg·kg⁻¹ atracurium reinjections varied from two to four, and intergroup differences were not significant (variance analysis). In all patients, an increase of twitch height was observed within the first minute following the edrophonium injection. Thereafter, the twitch height regularly increased to reach after 15 min the values of 99% ± 3%, 95% ± 3%, and 94% ± 6% of the initial control values in the twitch height 25%, twitch height 10%, and twitch height zero % groups, respectively. The twitch height values of the twitch height 25% patients were not significantly different from those of the two other groups (Bonferroni t test) (fig. 1). At each period of observation, the TOF ratios of the twitch height 25% group were significantly higher (P < 0.001, Bonferroni t test) than those recorded in the twitch height zero % and twitch height

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Fig. 1. Recovery characteristics of atracurium twitch height (TH) after the administration of 500 µg·kg⁻¹ edrophonium (associated with 8 µg·kg⁻¹ atropine) at three different reversional twitch height values: zero %, 10%, and 25% obtained in standardized conditions in N₂O-fentanyl-anesthetized adult patients.
10% patients (fig. 2). Fifteen minutes after edrophonium injection, the TOF ratios reached 0.88 ± 0.06 in the twitch height 25% patients, 0.72 ± 0.10 in the twitch height 10% patients, and 0.68 ± 0.10 in the twitch height zero % patients, respectively.

**DISCUSSION**

Patterns of reversal of the paralysis induced with non-depolarizing neuromuscular blocking drugs by acetylcholinesterase inhibitors, even in the normal subjects, depend on numerous factors: 1) the degree of spontaneous recovery before injection of the antagonist, 14 2) pharmacokinetic and pharmacodynamic properties of the muscle relaxant to be antagonized; 3) the type of cholinesterase inhibitor molecule used; and 4) the dosage of the antagonist.

We found that even though quite similar final twitch height values were observed for all groups, the final TOF ratios remained markedly influenced by the prereversal twitch height level. In the twitch height 25% series, the reversal of atracurium paralysis was marked and rapid, as a mean TOF ratio of 75% was already obtainable within a 6-min delay after 500 µg · kg⁻¹ of edrophonium. In contrast, more than 15 min were required in the present work to obtain the 75% TOF level when 500 µg · kg⁻¹ edrophonium was injected i.v. at prereversal levels less than twitch height 25%.

Nevertheless, the mean TOF values observed after 15 min (68% and 72%, respectively, in the twitch height zero % and the twitch height 10% groups) are probably sufficiently high to predict restoration of normal respiratory movements at rest—including nearly normal vital capacity—in all subjects, and fade (in the head lift test) would be restricted to a small percentage of the patients. The present results point out that with moderate edrophonium dosage, a correct estimation of at least 25% of prereversal twitch height level is important in practice. This level is, fortunately, easy to quantify routinely either by spot manual monitoring of TOF to see if the fourth twitch of the train is present or even by clinical observation. If respiratory depression is absent, net diaphragmatic movements are often manifest at this level of neuromuscular blockade.

In conclusion, at the twitch height 25% level, paralysis resulting from repeated injections of 0.1 mg · kg⁻¹ of atracurium is rapidly—within a 15-min period—antagonized to a mean TOF ratio above 75% by 500 µg · kg⁻¹ of edrophonium during fentanyl-N₂O-thiopental anesthesia. With such a dose of edrophonium, more than 15 min were necessary to obtain a TOF ratio above 75% if the antagonism of an atracurium paralysis was attempted at a prereversal twitch height level equal to or less than 10%.

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Biotransformation of Halothane and Enflurane in Patients with Hyperthyroidism

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Halogenated anesthetics are commonly administered to patients undergoing thyroid surgery. Their main advantages are that recovery is rapid, which is important in patients susceptible to postoperative airway obstruction, and that they cause only a moderate increase in concentrations of plasma thyroid hormones.1,2 Although hepatic necrosis has not been reported in patients with hyperthyroidism receiving halogenated anesthetics, administration of halothane, enflurane, and isoflurane has resulted in hepatic necrosis in triiodothyronine (T₃) pretreated rats.3,4 For this reason, and because patients with Graves' disease often are treated with several drugs that have an effect on the hepatic microsomal enzyme system, we examined the biotransformation of halogenated anesthetics by patients undergoing thyroid surgery. Specifically, we measured halothane and enflurane metabolites after anesthesia in: 1) euthyroid patients having surgical removal of a nonsecreting thyroid tumor; 2) patients with Graves' disease treated preoperatively with propranolol, carbimazole, and phenobarbital; and 3) untreated patients with mild to moderate hyperthyroidism secondary to a toxic adenoma of the thyroid gland.

MATERIALS AND METHODS

Forty patients scheduled for thyroid surgery were assigned to one of three groups according to the type of thyroid disease they had; within each group, patients were randomly assigned to receive either halothane or enflurane. Group 1 consisted of 14 euthyroid patients undergoing surgical removal of a nonsecreting thyroid tumor; five patients received halothane and nine were administered enflurane. Group 2 consisted of 19 patients with Graves' disease undergoing subtotal bilateral thyroidectomy after preoperative preparation with propranolol (30–120 mg · day⁻¹), carbimazole (20–60 mg · day⁻¹) and phenobarbital (80–500 mg · day⁻¹); 11 patients received halothane and eight were given enflurane. All of these patients were considered clinically euthyroid at the time of surgery. Group 3 consisted of seven patients with clinically mild to moderate hyperthyroidism and with laboratory evidence of thyroid dysfunction (mean serum thyroxine [T₄] level [±SD], 14.4 ± 3.4 μg · 100 ml⁻¹; serum T₃, 315 ± 85 ng · 100 ml⁻¹; normal values, less than 12.5 μg · 100 ml⁻¹ and 200 ng · 100 ml⁻¹, respectively) under-