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The Influence of Atropine Dose on Recovery from Vecuronium-induced Neuromuscular Blockade

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To determine whether the dose of atropine affects the rate of neostigmine-induced recovery from vecuronium-induced neuromuscular blockade, the authors monitored isometric adductor pollicis mechanical activity in 36 anesthetized (thiopental, fentanyl, nitrous oxide) adult patients (ASA physical status 1 or 2). Once surgery was completed and twitch height had spontaneously regained 25% of its initial value, the patients were randomly allocated into three groups (A10, A15, A20; n = 12 in each group) according to the dose of atropine (10, 15, or 20 μg/kg) that was mixed with 40 μg/kg neostigmine. Twitch height, train-of-four, and 50- and 100-Hz tetanic fade were recorded for 15 min after the administration of the reversal agents. No significant differences were found among the three groups in the final twitch height (95% ± 2%), train-of-four (87% ± 1%, 88% ± 2%, 89% ± 1%), and 50-Hz tetanic fade (90% ± 1%, 94% ± 1%, 93% ± 1%) (mean ± SEM). Fifteen minutes after reversal, fade in response to 100-Hz tetanus was statistically greater in the A10 group than in the two other groups (70% ± 3% of control *versus* 84% ± 4% and 81% ± 2%) (mean ± SEM, $P < 0.05$). The present results demonstrate that larger doses of atropine facilitate neostigmine's reversal of vecuronium neuromuscular blockade. The clinical implications of the differences observed in this study remain to be determined. (Key words: Antagonists, neuromuscular relaxants: neostigmine. Neuromuscular relaxants: vecuronium. Parasympathetic nervous system: atropine.)

ATROPINE OR ATROPINE-LIKE DRUGS are used to block undesirable muscarinic effects of anticholinesterase agents, given to reverse the residual neuromuscular blockade produced by muscle relaxants. Regarding its antimuscarinic effects, there is no consensus about the ideal dose of atropine: doses from 7 to 20 μg/kg are recommended.[1,2] Regarding its neuromuscular effects, no report describes the potential influence of atropine dose variations on the quality of reversal of nondepolarizing muscle relaxants.

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However, *in vitro* experiments[3] have shown that atropine influences the evoked release of labeled acetylcholine by acting at the prejunctional level. Furthermore, some clinical and experimental data have demonstrated that the administration of atropine or atropine-like drugs, even in the absence of anticholinesterases, influences tetanic fade recovery.[4]

In humans, atropine enhanced the 1-s tetanic contractions, elicited at 50 or 100 Hz, after a 5-min delay.[5] In cats, prior administration of atropine reduced the recovery time for the tetanic fade induced by neostigmine given alone or by subparalyzing doses of *d*-tubocurarine and hexamethonium.[4] A similar response was also seen when atropine was injected prior to neostigmine for reversal of paralyzing doses of *d*-tubocurarine.[4]

These results suggest that atropine might modify the action of an anticholinesterase agent given for reversal of nondepolarizing agents.

The purpose of this study was to describe, in anesthetized patients, the neuromuscular effects of different atropine doses mixed with a fixed dose of neostigmine during the reversal of vecuronium-induced neuromuscular blockade in highly standardized conditions.

Materials and Methods

Thirty-six adult patients (ASA physical status 1 or 2) undergoing elective surgery were studied after obtaining informed consent. The study was approved by the hospital ethical committee for human research. None of the patients had clinical or biochemical evidence of hepatic or renal damage. All were free from neuromuscular diseases and drugs that may interfere with the neuromuscular function. Demographic details of the patients included in this study are shown in table 1.

The patients received 0.2 mg/kg diazepam orally 1 h before anesthesia. A force-displacement transducer (UC3 cell Statham®), fitted with a tension attenuator (UL4-20, Statham®) and incorporated in a hand grip, was secured with adhesive tape in the patient's left hand to measure isometric contraction of the adductor pollicis. Two pediatric surface electrodes were placed near the ulnar nerve at the wrist. After induction of anesthesia, mechanical activity was induced in the adductor pollicis by square-wave pulses of 0.2 ms duration at supramaximal intensity, delivered at 0.1 Hz from a DigiStim III® stimulator. The resulting analog signals were amplified and registered on a polygraph recorder.

TABLE 1. Demographic Data

	A10	A15	A20
Age (yr)	39.8 ± 4.5	39.7 ± 4.5	39.6 ± 4.9
Weight (kg)	71.1 ± 4.5	67.1 ± 3.1	65.4 ± 2.5
Height (cm)	172.7 ± 2.6	169.6 ± 2.8	168.5 ± 1.3
Vecuronium administered ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.87 ± 0.12	0.62 ± 0.09	0.74 ± 0.12
Duration until reversal (min)	78 ± 10	96 ± 14	81 ± 11

Results are expressed as mean ± SEM (no significant differences between the three groups studied).
A10, A15, and A20 = 10, 15, and 20 mg/kg atropine, respectively.

Anesthesia was induced with intravenous thiopental 3–5 mg/kg. After loss of consciousness, ventilation was manually controlled (50% oxygen in nitrous oxide) until the trachea was intubated. Thereafter, ventilation was controlled mechanically until the end of the surgical procedure (open circuit, 35% oxygen in nitrous oxide). Ventilation was adjusted to produce normocapnia (end-tidal carbon dioxide about 36 ± 2 mm Hg).

After a 3-min recording of control twitch height, vecuronium 100 μg/kg was given intravenously, and the trachea was intubated once the twitch height was abolished. Thereafter, every time the twitch height regained 25% of its baseline height, vecuronium 20 μg/kg was given until completion of surgery.

Anesthesia was maintained with 5 μg/kg intravenous fentanyl and 100 μg/kg intravenous dehydrobenzperidol, followed by reinjections of 2 μg/kg intravenous fentanyl when clinical evidence of inadequate analgesia was observed. Heat loss from the body surface and the exposed left arm was controlled by using a heated mattress and surgical sheets. Plasma potassium, sodium, and calcium were checked every 30 min and maintained within normal values with intravenous infusion of the corresponding electrolyte when necessary.

For the reversal of vecuronium paralysis, the patients were randomly divided into three groups of 12 patients each to receive 10, 15, or 20 μg/kg atropine mixed with a fixed dose of 40 μg/kg neostigmine. Vecuronium neuromuscular blockade was antagonized at the end of the surgical procedure, when twitch tension spontaneously returned to 25% of the control twitch height. Atropine and neostigmine were injected simultaneously and manually over a 30-s period into a rapidly flowing perfusion of saline. No patient received atropine or any other anticholinergic drug before that time.

After administration of the neostigmine/atropine mixtures, twitch height was measured every 10 s during a 15-min period, and the train-of-four (2 Hz) ratio was measured every 3 min. After the 15-min period, 15 s after measurement of the last train-of-four ratio, tetanic fade (50 and 100 Hz, 5 s duration, 1 min apart) was assessed sequentially in a random fashion. The degree of tetanic fade was calculated as the ratio between the residual muscular activity observed after 5 s of stimulation and the maximal response registered.

Statistical analysis of the data was performed with the Kruskal-Wallis test.[6] The statistical comparisons were considered significant at the $P = 0.05$ level.

Results

There were no significant differences among the patients of the three groups regarding age, weight, and height (table 1). The final mean twitch height recovery was similar in the three groups and greater than 95% for each patient. Vecuronium administered consumption and duration of anesthesia until antagonist administration (table 1) were also similar in the three groups (no significant differences).

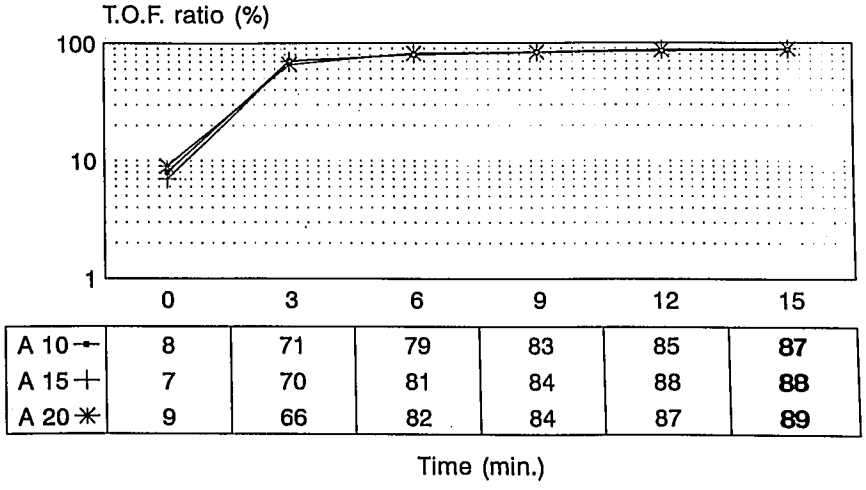
Before administration of the neostigmine/atropine mixtures, the mean train-of-four ratios were respectively: 8% (A10 group), 7% (A15 group), and 9% (A20 group) (no significant differences). Fifteen minutes later (fig. 1), the mean train-of-four ratios were 87% ± 1% (A10 group), 88% ± 2% (A15 group), and 89% ± 1% (A20 group) (mean ± SEM, no significant differences).

Fifteen minutes after administration of the neostigmine/atropine mixtures, no significant differences in tetanic fade to 50 Hz were observed among the three groups: 90% ± 1% (A10 group), 94% ± 1% (A15 group), and 93% ± 1% (A20 group). However, after 100-Hz stimulation, the mean value of 70% ± 3% observed in the A10 group was significantly less ($P < 0.05$) than the values of 84% ± 4% and 81% ± 2% (mean ± SEM), respectively, recorded in the A15 and the A20 groups.

Discussion

Results from this study suggest that the response of neuromuscular junction to neostigmine in patients paralyzed with vecuronium is influenced by the size of the dose of concurrently administered atropine.

Experimental data demonstrate in *in vitro* rat phrenic nerve–hemidiaphragm preparations that atropine alone influences the neuromuscular function.[7] *In vivo,* in anterior tibial muscle preparations of anesthetized cats, prior administration of atropine alone reduces the recovery time from the tetanic fade induced by neostigmine or by subparalyzing doses of *d*-tubocurarine or hexamethonium.[4] A similar response was observed when atropine was administered prior to neostigmine administration for reversal of paralyzing doses of *d*-tubocurarine.[4]



A 10 -•-	8	71	79	83	85	**87**
A 15 -+-	7	70	81	84	88	**88**
A 20 -✳-	9	66	82	84	87	**89**

Time (min.)

FIG. 1. Evolution of train-of-four (TOF) ratio recorded at 3-min intervals after administration of 40 μg/kg neostigmine once the twitch height level regained 25% of its initial value. $P < 0.05$, Kruskal-Wallis test.

In anesthetized patients (oxygen–nitrous oxide, halothane 1% or enflurane 1–2%, without muscle relaxants), Wali *et al.*[5] showed that atropine alone enhanced the 1-s tetanic contractions. Five minutes after atropine (1–10 μg/kg) administration, the values of 50- and 100-Hz tetanic contractions were greater (50 Hz, 27%; 100 Hz, 43%) than before atropine administration.

Several studies have suggested that some cholinergic synapses, including the motoneuron, contain presynaptic nicotinic[8] and muscarinic[9,10] receptors. Blockade of these presynaptic nicotinic receptors by nondepolarizing neuromuscular relaxants decreases[11] whereas blockade of the muscarinic receptors by atropine increases[3] acetylcholine output from neuromuscular preparations. According to some experimental hypotheses, acetylcholine acts also on such presynaptic muscarinic receptors by feedback mechanisms to regulate the release of neuromuscular transmitter, by changing the acetylcholine mobilization process.[12–14]

At high rates of stimulation, acetylcholine release seems also to be modulated by presynaptic nicotinic and muscarinic cholic feedback mechanisms.[4] Activation of presynaptic nicotinic cholinoceptors increases the output of acetylcholine from readily releasable stores,[15] whereas activation of muscarinic receptors leads to inhibition of the metabolic reactions involved in mobilization of the transmitter.[10]

In addition to its well-known anticholinesterase effect, neostigmine can directly depolarize the motor nerve terminal, because of interactions with the acetylcholine receptor–ion channel complex.[16] Tetanic fade may also follow nerve stimulation at different physiologic frequencies (30–80 Hz) if muscle is treated with neostigmine.[17] According to these experimental results, it is conceivable that blockade by atropine of the muscarinic feedback mechanism would antagonize the fade induced by nondepolarizing or anticholinesterase drugs.[4]

The present study states that 15 min after different atropine doses mixed with 40 μg/kg neostigmine, fade associated with 100 Hz tetanus was greater when the smaller dose of atropine (10 μg/kg) had been used than with larger doses (15 and 20 μg/kg), despite the same degree of train-of-four ratio recovery (87% to 89%) and of tetanic fade to 50-Hz tetanus (90%–94%); *i.e.*, the mechanical responses elicited at 100 Hz were the only differences among the observed parameters.

In previous studies performed in many different conditions, 100-Hz tetanic fade was also found to be more sensitive than train-of-four fade as an index of residual paralysis in either clinical studies, when recovery occurred either spontaneously[18,19]; after administration of anticholinesterases[20,21]; in the presence of a therapeutic plasma concentration of disopyramide[22]; or in animal studies when drugs other than neuromuscular blocking agents (atropine, hexamethonium, neostigmine) were also present.[4]

In conclusion, the present investigation demonstrates that atropine, given in larger doses than previously mentioned for edrophonium,[1] facilitates the reversal of vecuronium-induced neuromuscular blockade. The clinical implications of the differences observed in this study remain to be determined. The effects of atropine doses and atropine-like drugs are still to be analyzed with longer-acting muscle relaxants, smaller doses of anticholinesterase, other prereversal levels, or other muscular groups.

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