DOES A SUBPARALYSING DOSE OF VECURONIUM ENHANCE DIAPHRAGM FATIGUE?

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SUMMARY
We have examined, in six healthy volunteers, the effect of a subparalysing dose of vecuronium on the development of diaphragm fatigue. Vecuronium was given as a 0.5-mg bolus i.v. followed by 0.5 mg infused over 30 min; as a control, saline was given in random order. Diaphragm strength was assessed by measuring transdiaphragm pressure and by electromyography. Diaphragm fatigue was induced by breathing against an inspiratory resistance. The plasma concentration of vecuronium varied between 15 and 30 ng ml⁻¹ 15 min after administration of vecuronium was started. Peripheral neuromuscular block was not detected in any subject. Diaphragm fatigue developed within the same period in both groups: mean 324 (SD 166) s after saline and 345 (190) s after vecuronium. The electromyographic pattern of diaphragm fatigue and the time constant of relaxation of transdiaphragm pressure after fatigue were similar in both groups. We conclude that, at low plasma concentrations of vecuronium, similar to those present in the postoperative period, there was no predisposition to diaphragm fatigue.

KEY WORDS

A fraction of postsynaptic receptors of the neuromuscular junction may be occupied by a neuromuscular blocking agent without clinical sign of neuromuscular blocking effect, provided the fraction of receptors occupied is within the safety margin [1]. However, the safety margin varies according to the mode of nerve stimulation: the greater the frequency, the narrower is the safety margin [2]. During maximal contractions, there is an increase in the firing rate of motor neurones [3]. A small residual concentration of neuromuscular blocking drug may not affect muscle strength at rest, but may favour development of muscular fatigue. For respiratory muscles, Gal and Golberg observed that low doses of tubocurarine did not alter quiet breathing, but impaired maximal inspiratory capacity [4]. During recovery from anaesthesia, work of breathing may increase because of upper airway obstruction or shivering, and it is questionable if a residual concentration of blocker may hasten development of diaphragm fatigue. In order to test this hypothesis, we have evaluated the effect of a low dose of vecuronium on diaphragm strength and endurance.

SUBJECTS AND METHODS
Assessment of diaphragm strength
We studied six healthy male volunteers, aged 25–45 yr, with the approval of our local Clinical Investigation Committee. All subjects were scated during the study.

Diaphragm strength was assessed by measuring the transdiaphragm pressure (Pdi)—the difference between abdominal (Pga) and pleural pressure (Ppl). Pga and Ppl were measured using two balloon catheter systems connected by polyethylene tubing to the two ports of a differential pressure transducer (Validyne DP 15). One balloon, filled with 0.5 ml of air, was positioned in the middle one-third of the oesophagus [5] to measure changes in pleural pressure; the second, filled with 1 ml of air, was positioned in the stomach to determine changes in gastric pressure. Pdi was recorded during voluntary contractions produced by sniffing (Pdi_sniff) [6]. Subjects were instructed to make the sniff short and sharp, to achieve but not sustain peak Pdi_sniff as indicated on an oscilloscope. The Pdi_sniff curve was analysed in two ways: peak Pdi_sniff value was measured and considered an index of maximal diaphragm strength, and the time constant of diaphragm relaxation, τ, was calculated from the later position of the Pdi decay curve [6] by plotting the pressure signal on a logarithmic scale [6]. This yielded a straight line over the 50–70 % lower part of the curve. The time constant τ of this exponential position is equal to the reciprocal of the slope of this line [6].

Electrical muscle activity (EMG) of the diaphragm was recorded by an oesophageal electrode [7], from which the myoelectric potentials were passed to a Disa 15 G01 differential amplifier with band-pass filtering of 10–1000 Hz. The signal from the ampi-
LOW-DOSE vecuronium and diaphragm fatigue

Pneumotachograph
Gastric pressure
Pleural pressure
Oesophageal electrode
Inspiratory resistance
Oscilloscope

Fig. 1. Experimental design. Subjects inspired through resistance to be able to produce a predetermined transdiaphragm pressure (Pdi). Pdi was measured with two balloons as the difference between gastric and oesophageal pressure (expressed as % of Pdi
100), and displayed on an oscilloscope, together with tidal volume. EMG of the diaphragm was measured by an oesophageal electrode.

Life was recorded simultaneously on a magnetic tape for further analysis. The signal from the tape was passed subsequently through two band-pass filters with ranges of 20–46 Hz for the lower frequency component (L) and 150–350 Hz for the high frequency component (H) [8]. The filtered signals were rectified and integrated and the results displayed on a paper recorder.

Assessment of diaphragm endurance

For the diaphragm endurance test, subjects breathed through a Hans-Rudolf valve with the inspiratory inlet connected to a variable resistance. The inspiratory resistance was adjusted so that the subject could achieve a Pdi equal to 80% of the predetermined Pdi
100. Pdi was displayed on an oscilloscope marked with the target pressure that the subject had to sustain for 2 s (fig. 1). Inspiration was performed without added resistance. Ventilatory frequency was set at 12 b.p.m. and tidal volume at 0.75 litre. The endurance test was continued until the diaphragm fatigued, as defined by failure to sustain 80% Pdi
100 for three or more consecutive breaths. Diaphragm EMG activity was recorded continuously throughout the endurance test. The amplitudes of the H and L signals were measured in arbitrary units, and the mean H:L ratio during three consecutive breaths was taken to give a single value for this time span. The H:L ratio during the endurance test was calculated at the 5th, 10th, 15th, 20th and 30th breaths of the endurance test.

Monitoring of peripheral neuromuscular transmission

The ulnar nerve was stimulated at the wrist (Grass S 88) via surface electrodes, using train-of-four stimuli delivered every 12 s throughout the study. The elicited strength of the adductor pollicis muscle was measured by a force displacement transducer (Statham UC3). The train-of-four ratio (T4:T1) was monitored continuously.

Experimental procedure

After a period of 2 days of training, the subjects were studied on two days separated by 1 week. Vecuronium or saline was given to each subject in a random order. Vecuronium 0.5 mg was given as a bolus, followed by a continuous infusion of vecuronium of 0.5 mg given over 30 min. To avoid diplopia after administration of vecuronium, subjects were blindfolded during the first 10 min.

A venous blood sample (15 ml) was obtained from the antecubital vein of the contralateral arm before and 15 min after the start of the i.v. administration of vecuronium or saline, for measurement of plasma concentration of vecuronium in triplicate, in 2-ml samples using the Rose Bengale fluorimetric method [9]. The smallest detectable concentration of vecuronium was 10 ng ml
-1 in a 2-ml plasma sample. A first set of Pdi
100 values was obtained 10 min after the start of administration of vecuronium or saline (t1), then diaphragm endurance was assessed. A second set of Pdi
100 measurements was made within 15–30 s after the end of the endurance test (t2).

Results are given as mean (SD). Comparisons between group data were evaluated by paired t test. The H:L ratio during the endurance test was compared using repeated measures analysis of variance. For all tests, P ≤ 0.05 was considered significant.

RESULTS

No change in the elicited single twitch response or in T4:T1 ratio was observed throughout the study. Pdi
100 and t did not differ significantly after administration of vecuronium or saline (table I). Therefore, the target Pdi of the endurance test (80% Pdi
100) was set at the same value for both groups.

The duration of diaphragmatic endurance was 334 (166) s after saline and was virtually unchanged after vecuronium: 345 (190) s (fig. 2). After the endurance test, peak Pdi
100 was significantly smaller (P < 0.05), and t significantly greater (P < 0.05) than at t1 after either vecuronium or saline, indicating that the diaphragm was fatigued in both groups. Pdi
100 and t did not differ significantly between the groups at t2.

Because the individual variation in the daily H:L ratio derived from EMG measurements was large,
mean values (SD) of transdiaphragm pressure during sniff test (Pdi sniff) and time constant of relaxation (τ) before (t1) and after (t2) diaphragm endurance test in the saline and vecuronium groups. Significant difference (P < 0.05) between t1 and t2 values for all variables.

<table>
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<tr>
<th></th>
<th>Saline</th>
<th>Vecuronium</th>
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<tr>
<td>Pdi sniff (cm H2O)</td>
<td>115 (29)</td>
<td>110 (22)</td>
</tr>
<tr>
<td>t1</td>
<td>96 (30)</td>
<td>95 (25)</td>
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<tr>
<td>t2</td>
<td>102 (17)</td>
<td>96 (11)</td>
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**DISCUSSION**

The conditions produced in the present study are consistent with those usually found after spontaneous recovery from neuromuscular block. There was no sign of a neuromuscular blocking effect detectable by the usual methods of monitoring: there was no decrease in the elicited twitch response and no train-of-four fade, throughout the study. By comparing the changes in plasma concentration of vecuronium reported in other studies [10, 11] with our observations, we estimate that, after administration of vecuronium 0.1 mg kg⁻¹, a plasma concentration of vecuronium 15 ng ml⁻¹ is present within 90–200 min, and a concentration of 30 ng ml⁻¹ within 70–150 min. In comparison, the spontaneous recovery to 100 % twitch tension has been shown to occur at 74 min after vecuronium 0.1 mg kg⁻¹ [12]. Thus our study conditions approximately reproduced clinical conditions found up to 30 min after complete spontaneous recovery from vecuronium-induced block.

Several mechanisms may cause postoperative respiratory failure, including the residual depressant effect of anaesthetic agents on respiration, pulmonary regurgitation, pulmonary atelectasis, postoperative pneumothorax and respiratory muscle fatigue [13]. Diaphragm fatigue could be caused by impaired response of the muscle to excitation (contractile fatigue), by impaired neural or neuromuscular transmission (transmission fatigue), or both [3]. Diaphragm fatigue may occur more easily under circumstances when the muscle is weak, as during curarization. Gal and Golberg [4] demonstrated that administration of tubocurarine 0.15 mg kg⁻¹ in normal subjects produced a 37 % decrease in maximum Pdi, which for a given work of breathing increases the ratio of Pdi to maximum Pdi, leading to earlier diaphragm fatigue [13]. However, diaphragm muscle impairment in this situation is associated with important clinical signs of peripheral block, inability to sustain a head lift for 5 s, and marked reduction of the train-of-four ratio of the adductor pollicis muscle in response to ulnar nerve stimulation. Because the dose of vecuronium we administered did not reduce maximal Pdi generation, it is unlikely that this agent favoured development of contractile fatigue.

Although transmission fatigue has been questioned in normal man [3], failure of electrical neuromuscular transmission accompanies the loss of force that occurs during sustained maximal voluntary contraction of the adductor pollicis [14]. This phenomenon has been reported also in a rat model when diaphragm fatigue was induced by repeated phrenic nerve stimulation [15]; transmission fatigue contributes markedly to the fatigue induced by brief high-frequency stimulation, and prolongs that caused by low-frequency stimulation [3]. Neuromuscular blocking agents, even in small plasma concentrations,
produce subclinical changes in neuromuscular transmission which may favour development of diaphragm fatigue. Although diaphragm muscle has a greater margin of safety than peripheral muscle [16], neuromuscular impairment may occur earlier when a sufficient number of receptors are blocked, while this muscle [15] is submitted to a high and sustained activation. Physiological muscle activation is tetanic, and tetanic fade corresponds to a lesser occupancy of postsynaptic receptors by non-depolarizing agents than does train-of-four fade [17, 18]. In our study, neither train-of-four ratio nor Pdi\textsuperscript{\textsubscript{awt}} was altered after administration of vecuronium. However, had sufficient diaphragm neuromuscular receptors been blocked by administration of a small dose of vecuronium, transmission fatigue may have been more likely to develop, especially with large values of Pdi [3].

Our finding that diaphragm fatigue developed similarly after administration of saline or vecuronium indicates that subclinical plasma concentrations of vecuronium do not impair diaphragm function or enhance diaphragm fatiguability.

ACKNOWLEDGEMENT

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REFERENCES