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 334 (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-
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
\textsubscript{total}), and displayed on an oscilloscope, together with tidal volume. EMG of the diaphragm was measured by an oesophageal electrode.

**Results**

No change in the elicited single twitch response or in T4:T1 ratio was observed throughout the study. Pdi\textsubscript{target} and \(\tau\) did not differ significantly after administration of vecuronium or saline (table I). Therefore, the target Pdi of the endurance test (80 % Pdi\textsubscript{target}) 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\textsubscript{target} and \(\tau\) did not differ significantly between the groups.

Because the individual variation in the daily H:L ratio derived from EMG measurements was large,
Table 1. Mean values (sd) of transdiaphragm pressure during sniff test (Pdi\textsubscript{sniff}) and time constants of relaxation (τ) before (t\textsubscript{1}) and after (t\textsubscript{2}) diaphragm endurance test in the saline and vecuronium groups. Significant difference (P < 0.05) between t\textsubscript{1} and t\textsubscript{2} values for all variables.

<table>
<thead>
<tr>
<th>Pdi\textsubscript{sniff} (cm H\textsubscript{2}O)</th>
<th>τ (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saline</strong></td>
<td><strong>Vecuronium</strong></td>
</tr>
<tr>
<td>t\textsubscript{1}</td>
<td>115 (29)</td>
</tr>
<tr>
<td>t\textsubscript{2}</td>
<td>96 (30)</td>
</tr>
</tbody>
</table>

Fig. 2. Individual (•) and mean (□ (sd)) changes in endurance test duration after saline (S) and vecuronium (V) in the six subjects. Solid line = line of identity.

Fig. 3. Mean (sd) value of H:L ratio of diaphragm for all subjects as a function of breath number after saline (•) and vecuronium (□). Each point is the average of three inspirations.

we averaged the H:L ratios of the first three breaths of each run, and assigned to the average a value of 100 %, using the method of Gross and colleagues [8]. The H:L ratios of the subsequent breaths were calculated as a percentage of this value. The mean changes in H:L ratio with time during the endurance test are shown in figure 3. There was a systematic decrease in H:L ratio after the first few breaths. No significant difference in the H:L ratio was noticed between saline and vecuronium throughout the endurance test.

**DISCUSSION**

Vecuronium was detectable in the plasma of all subjects 15 min after the start of vecuronium administration in concentrations of 15 ng ml\textsuperscript{-1} (two subjects), 20 ng ml\textsuperscript{-1} (two) and 30 ng ml\textsuperscript{-1} (two).

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\textsuperscript{-1}, a plasma concentration of vecuronium 15 ng ml\textsuperscript{-1} is present within 90–200 min, and a concentration of 30 ng ml\textsuperscript{-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\textsuperscript{-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\textsuperscript{-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\text{\textsubscript{max}} 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.

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REFERENCES