DIFFERENTIAL EFFECTS OF VECURONIUM ON DIAPHRAGM AND GENIOHYOID MUSCLE IN ANAESTHETIZED DOGS

S. ISONO, T. KOCHI, T. IDE, K. SUGIMORI, T. MIZUGUCHI AND T. NISHINO

SUMMARY
We have examined the sensitivity of the geniohyoid, an upper airway dilating muscle, to vecuronium in 12 anaesthetized dogs undergoing mechanical ventilation of the lungs and compared it with that of the diaphragm. Dogs were allocated randomly to two groups: pentobarbitone alone (group 1, n = 7); pentobarbitone combined with 0.2 MAC (0.44%) of enflurane anaesthesia (group 2, n = 5). Supramaximal single twitch stimulations (0.1 Hz) were applied to the phrenic nerves in the upper thorax and the geniohyoid branches of the hypoglossal nerves at the neck. The evoked responses were assessed by the transdiaphragmatic pressure (Pdi) and the isometric force of the geniohyoid muscles (Tgh) until complete recovery of these variables after i.v. administration of vecuronium 0.02 mg kg\(^{-1}\). In both groups, the magnitude of the depression of twitch response was greater and time required to reach control amplitude was longer in the geniohyoid than the diaphragm. The depression of Tgh was significantly greater in group 2 than in group 1, whereas no change was observed in Pdi between the two groups. We conclude that the geniohyoid is more sensitive to vecuronium than the diaphragm and the differential effects of vecuronium are facilitated by a low concentration of enflurane.

KEY WORDS

It has been recognized that non-depolarizing neuromuscular block has differential effects on different muscles [1-5]. It has been demonstrated, in humans, that the diaphragm requires 1.4–2.0 times as much myoneural blocker as adductor pollicis muscle for the same degree of block [5]. In the case of upper airway muscles, Pavlin, Holle and Schoene reported that, despite adequate ventilation, upper airway muscle function is impaired greatly during tubocurarine-induced paralysis [6]. As upper airway muscles are responsible for various airway functions such as the maintenance of a patent airway and swallowing, impairment of these muscles may cause upper airway obstruction and aspiration of pharyngeal contents. Despite the clinical importance of the upper airway muscles, the difference in the effects of non-depolarizing neuromuscular block on the diaphragm and the upper airway muscles has not been examined systematically.

It is well recognized that volatile anaesthetics depress muscle function [7-9] and enhance the neuromuscular blocking properties of non-depolarizing myoneural blockers [10-14]. To our knowledge, it is not known if small concentrations of volatile anaesthetics less than MAC-awake enhance the blocking properties, or facilitate the differential effects of neuromuscular block on different muscles.

Accordingly, this study was undertaken to examine the effect of vecuronium on the diaphragm and geniohyoid muscles in pentobarbitone-anaesthetized dogs. In addition, enhancement of the neuromuscular blocking properties and facilitation of the differential effects by a low concentration of enflurane equivalent to 0.2 MAC were examined, to mimic the clinical situation during emergence from anaesthesia.

MATERIALS AND METHODS

Institutional approval for the study was obtained from the Animal Care and Use Committee of Chiba University School of Medicine. Twelve mongrel dogs weighing 5-19 kg were anaesthetized in the supine position with pentobarbitone 30 mg kg\(^{-1}\) i.v. and anaesthesia was maintained with a continuous infusion of pentobarbitone 2 mg kg\(^{-1}\) h\(^{-1}\). An oral cuffed tracheal tube (i.d. = 8.5 or 9.0 mm) was inserted and mechanical ventilation with 100% oxygen commenced. The femoral artery was cannulated to monitor arterial pressure and to permit blood sampling for measurement of arterial blood-gas tensions (Instrumentation Laboratories, model 1302). The femoral vein was cannulated also for administration of saline 100-200 ml h\(^{-1}\), bicarbonate to correct any metabolic acidosis, pentobarbitone and neuromuscular blocking agent.
Via a midline submandibular incision, both hypoglossal nerves were identified and isolated from the surrounding tissue. All branches to the hypoglossal nerves, excluding the branches to the geniohyoid, and all muscles attached to the hyoid bone, except for the geniohyoids, were divided. A stimulating electrode was positioned on each hypoglossal nerve. Supramaximal stimuli (0.1 Hz; 0.2 ms duration) were delivered continuously using a nerve stimulator (Biometer MYOTEST), and the isometric contraction of the geniohyoid muscle (Tgh) was measured by a force transducer (Biometer Myograph 2000) attached to a metal frame fixed to the experimental table and connected with a heavy silk thread to the hyoid bone. The initial load applied to the transducer was set at 300 g because, from a preliminary experiment, maximal force was obtained with this preload.

The thorax was opened through a median sternotomy and both phrenic nerves identified and isolated in the upper thorax. The nerves were protected carefully by intermittent application of Vaseline and stimulated supramaximally (Nihon Koden SEN-3201). A catheter with a thin-walled latex balloon (5.0 cm length, 1.0 ml air) was positioned in the abdominal cavity beneath the costal part of the diaphragm via a small midline abdominal incision and connected to a differential pressure transducer (Nihon Koden TP-601T). The surgical incision was closed in layers. As the thorax was open throughout the experiment, pleural pressure remained unchanged and Pdi was equal to the changes in abdominal pressure. Constancy of diaphragm geometry and muscle length during contraction was achieved by placing a closely fitting plaster cast around the abdomen and lower one-third of the rib cage.

Intramuscular temperatures in both the diaphragm and the geniohyoid were monitored continuously by a digital thermistor (Baxter Monathermo 6700) and maintained at physiological values throughout the experiment. The end-tidal concentration of enflurane was measured continuously using an anaesthetic gas analyser (Datex Normac). The experimental design is schematically illustrated in figure 1.

Animals were allocated randomly to two groups: pentobarbitone alone (group 1, n = 7) and pentobarbitone combined with 0.44% enflurane (0.2 MAC) (group 2, n = 5). In group 1, vecuronium 0.02 mg kg⁻¹ was administered i.v. after confirming stable responses of the diaphragm and the geniohyoid to twitch stimulation. Both Pdi and Tgh were recorded continuously using an eight-channel recorder (Nihon Koden Thermal Array Recorder) until they recovered completely. Maximal neuromuscular block (Pdi,max, Tgh,max), time to maximal depression (tPdi,max, tTgh,max), and time to recovery (tPdi,rec, tTgh,rec) (defined as the duration from maximal block effect to 95% recovery) were determined in each muscle. The time course of the changes in Pdi and Tgh was determined. Before and after these measurements, arterial blood-gas tensions, mean arterial pressure (MAP) and temperatures of the diaphragm (Temp_d) and the geniohyoid (Temp_gh) were measured. In group 2, enflurane was inhaled after Pdi and Tgh became stable, during which the end-tidal concentration of 0.2 MAC enflurane was kept constant for at least 30 min. The measurement of all variables was performed before and after inhalation of enflurane. Thereafter, the same procedure as in group 1 was followed.

Statistical analysis was performed using a two-way analysis of variance and Tukey's test. Some results were also analysed using Student's t test. All values are expressed as mean (SEM). P < 0.05 was considered to be statistically significant.

RESULTS

Table I shows the average (SEM) values of hydrogen ion concentration ([H⁺]), Paco₂, PacO₂, Temp_d, Temp_gh, MAP and Pdi in both groups of animals. Although PacO₂ and Temp_d changed significantly during the course of the experiment, the changes were minimal and the values remained within the physiological range. Therefore, changes in acid–base state, blood supply and muscle temperatures would not have affected the functions of the diaphragm and the geniohyoid.

The depression in response to twitch stimulations after administration of vecuronium in group 2 was greater in the geniohyoid than in the diaphragm (fig. 2). The time to maximal depression and time to recovery were shorter in the diaphragm than in the geniohyoid (fig. 2).
Differential Effects of Vecuronium

Table I. Average (SEM) values of mean arterial pressure (MAP), hydrogen ion concentration ([H+]), PaCO2, PaO2, diaphragm temperature (Tempd), geniohyoid temperature (Tempg), and Pdi in groups 1 (pentobarbitone) and 2 (pentobarbitone + 0.44% enflurane). Vec. = vecuronium; rec. = recovery; enf. = enflurane. *P < 0.05 compared with before administration of vecuronium.

<table>
<thead>
<tr>
<th>Group 1 (n = 7)</th>
<th>Group 2 (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>120 (7.0)</td>
</tr>
<tr>
<td>[H+] (umol litre−1)</td>
<td>40.3 (1.3)</td>
</tr>
<tr>
<td>PaCO2 (kPa)</td>
<td>4.32 (2.1)</td>
</tr>
<tr>
<td>PaO2 (kPa)</td>
<td>48.7 (2.4)</td>
</tr>
<tr>
<td>Tempd (°C)</td>
<td>37.7 (0.4)</td>
</tr>
<tr>
<td>Tempg (°C)</td>
<td>36.7 (1.0)</td>
</tr>
<tr>
<td>Pdi (cm H2O)</td>
<td>10.8 (1.2)</td>
</tr>
</tbody>
</table>

FIG. 2. Effect of vecuronium on transdiaphragmatic pressure (Pdi) and isometric force of the geniohyoid muscles (Tgh) in one animal from group 2. Arrow = i.v. injection of vecuronium 0.02 mg kg−1.

Table II. Effects of vecuronium in groups 1 (pentobarbitone) and 2 (pentobarbitone + enflurane). Maximal neuromuscular block in diaphragm (Pdi,max) and geniodyoid (Tgh,max), time to maximal effect in diaphragm (tPdi,max) and geniodyoid (tTgh,max) and duration from maximal effect to 95% recovery in diaphragm (tPdi,rec) and geniodyoid (tTgh,rec). *P < 0.05, **P < 0.01 vs diaphragm; †P < 0.05, ††P < 0.01 vs group 1.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
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<tbody>
<tr>
<td>Pdi,max (% control)</td>
<td>86.0 (3.5)</td>
</tr>
<tr>
<td>Tgh,max (% control)</td>
<td>66.7 (6.5)*</td>
</tr>
<tr>
<td>tPdi,max (s)</td>
<td>207 (13)</td>
</tr>
<tr>
<td>tTgh,max (s)</td>
<td>274 (23)**</td>
</tr>
<tr>
<td>tPdi,rec (s)</td>
<td>373 (36)</td>
</tr>
<tr>
<td>tTgh,rec (s)</td>
<td>873 (147)*</td>
</tr>
</tbody>
</table>

The effects of vecuronium on the twitch height of the diaphragm and the geniodyoid in all animals of both groups are shown in table II and figure 3. Pdi decreased significantly from control after 2–5 min (P < 0.05–0.01) in group 1 and after 2–8 min (P < 0.01) in group 2. Tgh also decreased significantly from control after 3–8 min (P < 0.01) in group 1 and after 3–12 min (P < 0.05–0.01) in group 2. The magnitude of the depression of twitch response in the geniodyoid was significantly greater compared with that of the diaphragm (group 1: 3–8 min, P < 0.05; group 2: 1–6 min, P < 0.05–0.01). The duration from 95% maximal block to 95% recovery was significantly greater in the geniodyoid than the diaphragm (P < 0.05 in group 1). By contrast, Tgh values from 1 min to 5 min and Tgh,max were significantly different between the two groups (P < 0.01), whereas no significant changes were observed between the groups regarding Pdi values, indicating that changes...
in $T_{gh}$ were more enhanced by enflurane than those in $P_{di}$. 

**DISCUSSION**

The main findings of this study are that the geniohyoid was more sensitive to vecuronium than the diaphragm and that enflurane 0.2 MAC enhanced the neuromuscular blocking properties of vecuronium to a greater extent in the geniohyoid than in the diaphragm.

Comparison between upper airway muscles and inspiratory muscles with regard to their sensitivity to non-depolarizing neuromuscular blocking drugs has been reported previously. However, in most studies, the response in humans was assessed only semi-qualitatively by clinical function of the upper airway and maximum inspiratory pressure [6]. Smith, Donati and Bevan measured the isometric tension in the masseter of anaesthetized patients by stimulating the superficial branches of the mandibular nerve. They showed that the masseter was more sensitive to pancuronium than the adductor pollicis [15]. Our results are compatible with these reports. However, the experimental setting in the present study has obvious advantages over these reports. First, it was possible to assess accurately the isometric force of the geniohyoid, which represents an important muscle in the maintenance of a patent upper airway, swallowing and other upper airway protecting functions. Second, we were able to compare simultaneously the function of the geniohyoid with that of the diaphragm. This yields useful information, as the collapsing force of the upper airway during inspiration is determined by the balance between the inspiratory negative force and the upper airway dilating force [16].

Three possible mechanisms may be responsible for the difference in the effects of vecuronium between the diaphragm and the geniohyoid. First, it has been suggested that slow fibres are more resistant to non-depolarizing blockers [17,18]. The diaphragm is mostly composed of slow fibres [19], whereas the geniohyoid is composed mainly of fast and intermediate fibres [20]. Second, these differential effects may be caused by differences in muscle temperature [21]. However, this is unlikely to account for our present findings, as there were no significant differences in temperature between the two muscles. Third, their function during partial paralysis may be affected by differences in blood flow. Clearly, further studies are needed to elucidate the differential effects of vecuronium on these muscles.

In the present study, 0.44% enflurane facilitated the differential effects of vecuronium on the diaphragm and geniohyoid muscles. Although the underlying mechanisms for this phenomenon are not entirely clear, it may be explained in terms of the margin of safety for neuromuscular transmission [22,23]. In the relationship of the twitch response to the fraction of receptors blocked, twitch height suddenly decreases from 100% to 0% along a non-linear steep curve when approximately 80% of the receptors are blocked [23]. $T_{gh,max}$ of group 1 (66.7%) is placed at a steeper point on this curve than $P_{di,max}$ (86.0%). The greater decrease of twitch response in the geniohyoid than in the diaphragm follows the leftward shift of the curve by enflurane [23].

Our results give us important information related to clinical anaesthesia. A small dose of vecuronium such as might be given for "priming" [24,25] reduced the twitch height of the geniohyoid to 66.7% of control, although that of the diaphragm remained at 86.0% of control. Such a partially paralysed patient may have impaired upper airway function, despite adequate ventilation. In addition, a small concentration of enflurane, less than MAC-awake, facilitated the difference in the effects of vecuronium between the diaphragm (71.0% of control value) and geniohyoid muscles (35.0% of control), suggesting that postoperative residual muscle paralysis [26,27] may be more prominent in the upper airway muscles than in the diaphragm. Therefore, upper airway function including maintenance of a patent upper airway, swallowing and other airway protecting mechanisms may be impaired by priming and by postoperative residual muscle paralysis.

**REFERENCES**

DIFFERENTIAL EFFECTS OF VECURONIUM


