CHANGES IN RESISTANCE TO MOUTH OPENING INDUCED BY DEPOLARIZING AND NON-DEPOLARIZING NEUROMUSCULAR RELAXANTS


SUMMARY
Mouth opening was measured in 43 children anaesthetized with isoflurane and paralysed with vecuronium or suxamethonium. Measurements of mouth opening were made for up to 10 min after loss of the adductor pollicis twitch and cessation of muscle fasciculations. In 22 patients receiving suxamethonium, a significant (P < 0.001) reduction in mean mouth opening occurred in the 60 s after loss of twitch and cessation of fasciculations. Mouth opening reductions could last for up to 10 min after the loss of twitch, beyond the return of the twitch. One patient experienced "masseter spasm"; he did not develop malignant hyperpyrexia during 2.5 h of isoflurane anaesthesia. Patients receiving vecuronium showed a significant (P < 0.0006) increase in mouth opening. In 20 subjects, mouth opening was generated with a small (1.67 N) and a larger (4.32 N) force. Proportionally equal reductions in mouth opening were obtained with either force after suxamethonium administration. Relatively equal increases with either force followed vecuronium administration. Isolated masseter spasm is not pathognomonic for malignant hyperpyrexia. If the diagnosis of malignant hyperpyrexia is contemplated, signs of hypermetabolism, such as increases in end-tidal carbon dioxide concentration during constant minute ventilation, should be sought.

KEY WORDS

Administration of suxamethonium during halothane anaesthesia is used widely in children to relax jaw musculature to facilitate tracheal intubation. In a recent study we have demonstrated that jaw muscle tone increases after administration of suxamethonium [1]. This unexpected behaviour raises a number of unanswered questions. For example, what mechanism underlies this response; is this behaviour dependent on the presence of halothane; does it occur when the mouth is opened by large as well as small test forces, and may it be caused by jaw muscles which were slow to relax?

The present study was designed to examine the first two questions by comparing the effects of two dissimilar neuromuscular blockers, suxamethonium and vecuronium, administered under isoflurane rather than halothane anaesthesia. The last two questions are examined by using two test forces and continuing measurements for an extended period of time.

PATIENTS AND METHODS
We studied patients of ASA physical status I or II, who required general anaesthesia and tracheal intubation for an elective surgical procedure. Those with known temporomandibular joint (TMJ) or muscle disease or cranio-facial disproportions were excluded. Ethics approval was granted by the local committee for human ex-

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performation and informed parental consent was obtained. Subjects were not premedicated. Anaesthesia was induced with increasing concentrations of isoflurane and 66% nitrous oxide in oxygen. End-tidal carbon dioxide ($\varepsilon_{\text{CO}_2}$) concentration was measured. Breath sounds, arterial pressure, electrocardiogram and temperature were monitored and an i.v. infusion was started. The adductor pollicis muscle twitch was evoked by transcutaneous stimulation of the ulnar nerve using supramaximal, square wave stimuli (frequency 1 Hz, 0.2 ms duration) and was monitored visually. The offset and onset of the twitch and of fasciculations were noted by an observer blinded to the neuromuscular blocker used. General anaesthesia was administered by a separate anaesthesia team, not by the investigators. Anaesthesia was deepened to a level sufficient for the patient’s trachea to be intubated as judged by clinical criteria such as heart rate, arterial pressure, rate of ventilation, tidal volume, pupillary size, and the response to manipulation of the mandible and direct laryngoscopy. When the desired anaesthetic level was obtained, the concentrations of anaesthetic gases were not changed until the end of the study period. The patient’s head was placed in the “sniffing” position.

Forty-three patients were studied in the first part of this study. The mouth was opened for a baseline measurement (at time $T_1$) by means of a constant test force of 1.67 N, applied via a traction device positioned over the central mandibular incisors, as described previously [1]. The test force was directed in the mid sagittal plane perpendicular to the mandibular plane. The separation of the maxillary to mandibular central incisors ($D_1$) was measured in the mid sagittal plane [1]. Either suxamethonium 1.5 mg kg$^{-1}$ i.v. or vecuronium 0.1 mg kg$^{-1}$ i.v. was administered i.v. randomly over 15 s. Ventilation was controlled.

When the twitch was suppressed totally and after cessation of fasciculations (at $T_2$), mouth opening ($D_2$) was measured again, followed 45 s later (at $T_3$) by a third measurement, $D_3$. Intubation was performed usually at approximately 90 s after $T_2$.

To establish how long mouth opening reductions may last, we studied patients from the first part of this study who demonstrated a mouth opening reduction after suxamethonium at $T_3$ which was of the same magnitude or more than that measured at $T_2$. Ten of 22 patients fulfilled this criterion. In these patients, measurements were continued at 1-min intervals until mouth opening had returned to 2 mm from baseline.

For the third part of this study, 10 randomly selected patients received suxamethonium 1.5 mg kg$^{-1}$ i.v. and 10 patients in an age-matched group received vecuronium 0.1 mg kg$^{-1}$ i.v. during isoflurane anaesthesia as described above. Mouth opening was produced at baseline ($T_1$) by the application of the 1.67-N test force designated as $D_1$, followed immediately by a second test force of 4.32 N (approximately one pound of force), designated as $D_1'$. These double measurements were repeated after the loss of twitch and fasciculations ($T_2$) and 45 s later ($T_3$) with the incisal distances designated as $D_2$ and $D_2'$, and $D_3$ and $D_3'$, respectively.

In the first part of this study, analysis of variance (ANOVA) was used to compare the two groups of patients. Their mouth opening values were compared by two-factor repeated measures ANOVA (rm-ANOVA). When significant interactions of the blocking drug and the repeated measures factors occurred, mouth opening was compared between the two relaxant groups by ANOVA and within each relaxant group over time by one-population repeated measures ANOVA (or-ANOVA). Probability values were adjusted for pairwise multiple comparison (Scheffé). Changes in mouth opening with respect to baseline ($D_2-D_1$, $D_3-D_1$) were compared by ANOVA. In view of the variation in mouth opening, mouth opening values were normalized with respect to the patient’s baseline values ($D_1$). Thus normalized mouth opening at $T_1$, $T_2$ and $T_3$ equal $D_1/D_1$, $D_2/D_1$ and $D_3/D_1$, respectively; subsequently they were compared by ANOVA.

For analyses of the third part of this study, the differences in mouth opening, produced by the two consecutive forces, were calculated for each patient at each time (e.g. delta-$D_1 = D_1' - D_1$), and were compared between relaxant groups by ANOVA. The effects of vecuronium and suxamethonium on the relative changes in mouth opening produced by the two forces at $T_2$ and $T_3$ were compared by rm-ANOVA.

RESULTS

The group of patients receiving suxamethonium did not differ significantly from those receiving vecuronium (table I). Because of inter-subject variability, the effects of the neuromuscular blockers and of the repeated measures were not
TABLE I. Details of patients receiving vecuronium or suxamethonium from the first and second part of this study (mean (sd)). No significant differences between groups (ANOVA)

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Sex (M:F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suxamethonium</td>
<td>6.3(3.3)</td>
<td>117.7(24.6)</td>
<td>25.0 (12.0)</td>
<td>13:9</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>7.2(3.4)</td>
<td>126.7(24.6)</td>
<td>30.9 (17.9)</td>
<td>14:7</td>
</tr>
</tbody>
</table>

TABLE II. Mean (sd) mouth opening (mm) during isoflurane anaesthesia before administration of neuromuscular blocker (D1) immediately after the loss of twitch and fasciculations (D2) and 45 s later (D3). One-population repeated measures ANOVA demonstrated a significant difference of D2 and D3 with respect to D1 in patients receiving suxamethonium (F = 52; *P < 0.0001, corrected for pairwise multiple comparison) and in the group receiving vecuronium (F = 11.2; †P < 0.05; ††P < 0.0001, corrected for multiple comparisons). Mean differences in changes of mouth opening (D3-D1, D2-D1) and in normalized mouth opening, D3/D1 and D2/D1, were significant between groups.

<table>
<thead>
<tr>
<th></th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D2-D1</th>
<th>D3-D1</th>
<th>D3/D1</th>
<th>D2/D1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suxamethonium</td>
<td>19.8(4.9)</td>
<td>14.9 (5.9)*</td>
<td>15.2 (6.0)*</td>
<td>-4.9 (2.4)</td>
<td>-4.5 (2.9)</td>
<td>0.73 (0.16)</td>
<td>0.76 (0.17)</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>16.6 (3.9)</td>
<td>17.4 (4.0)†</td>
<td>18.0 (4.1)††</td>
<td>+0.81 (1.5)</td>
<td>+1.5 (1.7)</td>
<td>1.06 (0.12)</td>
<td>1.10 (0.12)</td>
</tr>
<tr>
<td>P (ANOVA)</td>
<td>&lt; 0.025</td>
<td>&lt; 0.114</td>
<td>&lt; 0.085</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Ten patients in the first part of the study demonstrated a mouth opening reduction at T3 equal to or more than that at T2 following administration of suxamethonium. Their mean values are graphed separately in figure 1. These patients did not differ significantly (P > 0.05) in height, weight, age or baseline measurements from the other patients receiving suxamethonium.

In the third part of the study the group of

**FIG. 1.** Mean (SEM bars) normalized mouth opening in 43 children undergoing isoflurane anaesthesia. Baseline measurements were obtained at time T1, following which suxamethonium 1.5 mg kg⁻¹ (n = 22) or vecuronium 0.1 mg kg⁻¹ (n = 21) was administered i.v. Immediately after the complete loss of the neurally evoked adductor pollicis twitch and fasciculations (T2), mouth opening was measured again, followed by a third measurement 45 s later (T3). In patients whose mouth opening at T3 was reduced to the same magnitude or more as at T2, measurements were continued at 1-min intervals. This subgroup is plotted separately, in addition to the total suxamethonium group. RT = time of return of the adductor pollicis twitch. Vecuronium administration was followed by a significant increase in mouth opening while suxamethonium was followed by a reduction. †P < 0.05; *P < 0.0001.
Table III. Details of patients in the third part of the study (mean (SD)). No significant differences between groups (ANOVA).

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Sex (M:F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suxamethonium (n = 10)</td>
<td>7.6 (3.0)</td>
<td>129.4 (17.9)</td>
<td>29.1 (10.6)</td>
<td>6:4</td>
</tr>
<tr>
<td>Vecuronium (n = 10)</td>
<td>7.9 (3.6)</td>
<td>129.8 (26.5)</td>
<td>32.1 (18.0)</td>
<td>7:3</td>
</tr>
</tbody>
</table>

The time required to achieve a level of anaesthesia sufficiently deep to permit intubation of the trachea, as determined by the anaesthesia team, was 8–14 min of inhalation with 3–5% isoflurane. The adductor pollicis twitch was abolished in all patients, in 40.7 (18) s (mean (SD)) following suxamethonium administration and in 83.5 (23) s in those receiving vecuronium. Sixty-eight percent of patients receiving suxamethonium showed fasciculations starting at 12.7 (8) s. The reductions in mouth opening in subjects receiving suxamethonium occurred when limb and abdominal muscles were flaccid. Isoflurane anaes-

patients receiving suxamethonium did not differ from that receiving vecuronium (table III). The differences in mouth opening for the two consecutive forces (delta-Di) between the relaxant groups were not significant (ANOVA, P > 0.05) at T1, T2, or T3 (fig. 2). The effect of suxamethonium on the relative change in mouth opening differed significantly from that of vecuronium (F = 36; P < 0.0001, two factor rm-ANOVA) (table IV). The proportional changes observed with the low test force did not differ from those observed with the greater force (two factor rm-ANOVA, P > 0.05).
Resuscitation to mouth opening after neuromuscular block was continued in all patients as indicated by the surgical procedure, which lasted in excess of 1 h in the majority of patients. Temperature and $\text{E}^{'\text{CO}_2}$ values stayed within the limits for normal clinical anaesthesia for the duration of the operative procedures. No patient developed a hypermetabolic state.

The mouth of one patient stayed closed shut for 2.5 min following administration of suxamethonium. After 11.5 min, his incisal distance had not returned to the baseline opening. Tracheal intubation was undertaken approximately 13 min after administration of suxamethonium. His vocal cords could not be visualized, but the trachea was intubated successfully at the third attempt. General anaesthesia with isoflurane was continued for 2.5 h without changes in $\text{E}^{'\text{CO}_2}$ or temperature. The changes in this patient's mouth opening are included in figure 1.

**DISCUSSION**

Optimal conditions for tracheal intubation include relaxation of the jaw muscles and vocal cords, and immobilization of the body, providing unhindered access to the larynx. These conditions can be attained by deep general anaesthesia with isoflurane or by light general anaesthesia supplemented by neuromuscular block. During isoflurane anaesthesia, neuromuscular blockers may increase the magnitude of relaxation and mouth opening depending on the depth of anaesthesia [2]. In this study, vecuronium administration increased mouth opening, a finding which is consistent with loss of tone in human limb and abdominal muscles [3] and with non-depolarizing block of neuromuscular transmission in twitch fibre muscle [4]. However, administration of suxamethonium was followed by a reduction in mouth opening, representing an increase in stiffness of jaw muscles [1]. These changes are contrary to those expected on the basis of the empirically established effects of neuromuscular blockers on the tone of normal human limb and abdominal muscles and to the effects of vecuronium on jaw muscle tone.

Mean mouth opening of the depolarizing muscle relaxant group was larger at baseline than in the non-depolarizing group. It is possible that the former group was anaesthetized more deeply than the latter. Addition of a blocking drug in the depolarizing group would be expected to increase mouth opening to a lesser degree than observed in the non-depolarizing group, if both groups had a similar mouth opening capacity. As the inspired concentrations of isoflurane were not changed during controlled ventilation, the anaesthetic level was either the same or deeper at the time of subsequent measurements. Deepening the level of isoflurane anaesthesia would be expected to decrease muscular tone in a dose dependent manner. As during halothane anaesthesia, jaw muscle tone was increased also after suxamethonium administration during isoflurane anaesthesia in the present study, despite the different effects of these anaesthetic agents on neuromuscular block [5, 6].

An essential difference between depolarizing and non-depolarizing neuromuscular blocking agents is that the former initiate depolarization of the end-plates of twitch fibre muscles which elicits an action potential propagating along the muscle membrane, followed by an initial contraction and subsequent relaxation of that fibre. However, the agonist actions at the acetylcholine receptors continue unabated, action potentials are no longer generated and propagated, no further contractions occur, and the normal twitch fibre muscles demonstrate loss of tone. Neuromuscular transmission is restored when the depolarizing agent has diffused away from the endplate region. Consistent with these phenomena at the cellular level, are the "agonist effects" associated typically with depolarizing agents, including rapid onset, fasciculations and movements of limb muscle. However, profound relaxation of normal mammalian limb muscle and continued inhibition of neuromuscular transmission are caused also by the typical agonist effects. The non-depolarizing neuromuscular blockers lack the typical signs resulting from stimulation of the cholinergic neuromuscular receptors.

It has been suggested that reductions in mouth opening after suxamethonium administration resulted from "normal agonist" effects [7]. Although fasciculations and limb muscle movements may be thought of as normal agonist effects, and which may indeed represent periods of increased muscle tone, they occur usually within two to three circulation times (less than 1 min) after administration of suxamethonium and cease before, during or, occasionally, shortly after the abolition of the neurally evoked adductor pollicis twitch. In this study, mouth opening reductions were present in the 1 min after loss of twitch, after cessation of fasciculations and for up to 10 min.
MHS on the basis of the (no longer accepted) second study [10], all patients were considered on the interpretation of the muscle biopsy test. In susceptibility (MHS) is controversial and that the elective diagnosis of malignant hyperthermia studies [9], the authors acknowledged that the was similar to these reports. In the first of these and specific therapy was not required. Our patient symptoms of hypermetabolism were not present spasm occurred in isolation—that is, signs or clinical data provided to deduce that masseter muscle rigidity. However, it is apparent having experienced "masseter muscle rigidity" [7]. There are only three reports with sufficient clinical data provided to deduce that masseter spasm occurred in isolation—that is, signs or symptoms of hypermetabolism were not present and specific therapy was not required. Our patient was similar to these reports. In the first of these studies [9], the authors acknowledged that the elective diagnosis of malignant hyperthermia susceptibility (MHS) is controversial and that the significance of isolated masseter spasm depends on the interpretation of the muscle biopsy test. In the second study [10], all patients were considered MHS on the basis of the (no longer accepted) calcium uptake test [11]. Anaesthesia was discontinued in the latter two studies. However, in a recent report [12], anaesthesia was continued in 14 of 15 patients for up to 1 h (all patients received halothane except three who received an opioid-relaxant technique). A hypermetabolic state did not develop in any patient. One patient developed wheezing with cyanosis, hypercapnia and mas- seter spasm shortly after induction of anaesthesia with halothane and suxamethonium. Dantrolene was given and the procedure was continued. Other signs or symptoms of hypermetabolism did not develop. All patients recovered uneventfully, while two had subsequent anaesthetics with halothane and suxamethonium or atracurium without untoward events.

It is clear from the latter and the current study that hypermetabolic activity does not necessarily follow isolated masseter spasm even when anaesthesia is continued. Isolated masseter spasm occurs more frequently than the estimated incidence of MH and, although isolated masseter spasm is an uncommon sign, it does not differentiate subjects susceptible to hypermetabolism. If the diagnosis of malignant hyperpyrexia is contemplated, signs of hypermetabolism should be sought. Monitoring of $E'_{CO_2}$ concentrations during constant minute ventilation is a more sensitive and specific test for the early detection of hypermetabolism characteristic of MH.

REFERENCES