Thenar muscle blood flow and neuromuscular effects of vecuronium in patients receiving balanced or isoflurane anaesthesia

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SUMMARY
We have tested the hypothesis that isoflurane potentiates non-depolarizing neuromuscular block via an increase in muscle blood flow. Anaesthesia was induced with thiopentone 4–5 mg kg⁻¹ in 30 adult male patients of ASA physical status I or II and was maintained with 70% nitrous oxide in oxygen supplemented with either a bolus dose of fentanyl 4 μg kg⁻¹ followed by an infusion of 1 μg kg⁻¹ h⁻¹ (balanced anaesthesia group, n = 15) or 1.1% end-tidal isoflurane (isoflurane group, n = 15). Vecuronium 0.1 mg kg⁻¹ was given for neuromuscular block. The force of contraction of the adductor pollicis of the thumb in response to ulnar nerve stimulation was recorded. Thenar muscle blood flow was measured continuously with a laser Doppler flowmeter. Times required for the first twitch in the train-of-four (T1) to recover to 25%, 75% and 90% of its control value were mean 26.3 (SD 5), 35.3 (10), 43.5 (7) min and 39.2 (15), 53 (12.5), 61.2 (10) min in the balanced anaesthesia and isoflurane groups, respectively (P < 0.01). Recovery index (time between T1 25% and 75%) was prolonged significantly in the isoflurane group. Administration of thiopentone significantly increased thenar muscle blood flow from 2.6 (SD 5), 35.3 (10), 43.5 (7) ml min⁻¹/100 g to 19.2 (14) and 21.7 (16) ml min⁻¹/100 g in the balanced anaesthesia and isoflurane groups, respectively (P < 0.001). The addition of fentanyl (balanced) or isoflurane to the anaesthetic mixture produced further increases in thenar muscle blood flow to reach, respectively, 26.2 (16) and 26.8 (13.6) ml min⁻¹/100 g during steady state anaesthesia. Thenar muscle blood flow was comparable in the two groups throughout the study. We conclude that isoflurane prolonged vecuronium-induced neuromuscular block. This prolongation was not related primarily to increase in muscle blood flow. (Br. J. Anaesth. 1994; 72: 650-653)

KEY WORDS

Volatile anaesthetics augment neuromuscular block produced by non-depolarizing neuromuscular blocking agents [1–5]. Several mechanisms have been proposed to explain this type of drug interaction. The hypothesis that inhaled anaesthetics increase muscle blood flow, so that a greater fraction of the injected blocker may reach the neuromuscular junction, is frequently quoted as the primary mechanism underlying isoflurane-induced potentiation of non-depolarizing block [1]. However, direct correlation between the magnitude of muscle blood flow and augmentation of non-depolarizing neuromuscular block during isoflurane anaesthesia has not been confirmed in controlled clinical studies in humans. Further, Hartman and colleagues [6] reported recently a dose-related reduction in intestinal and skeletal muscle blood flow in dogs anaesthetized with halothane and isoflurane.

The present study was designed to examine the effects of anaesthesia induced with thiopentone and maintained with either nitrous oxide–fentanyl or nitrous oxide–isoflurane on the clinical course of vecuronium-induced neuromuscular block and on thenar muscle blood flow in humans.

PATIENTS AND METHODS
We studied 30 male patients, ASA I or II, undergoing low-risk elective surgery. This study was approved by the hospital Ethics Committee and all patients gave written informed consent. Patients with cardiac, vascular, respiratory, hepatic, renal or neuromuscular disorders were excluded. Chronic smokers, patients at risk of regurgitation and patients receiving medications known to interfere with normal cardiovascular or neuromuscular functions were also excluded.

All patients were premedicated with oral diazepam 10 mg, 90 min before surgery. In the operating room, lactated Ringer's solution with 5% glucose was administered at a rate of 4 ml kg⁻¹ h⁻¹ through a peripheral arm vein. ECG was monitored continuously and mean arterial pressure (MAP) was measured every 2 min using an electronic oscillotonometer (Dinamap). Anaesthesia was induced in all patients with thiopentone 4–5 mg kg⁻¹ and maintained with 70% nitrous oxide in oxygen delivered via a face mask. Ten minutes after induction, patients were allocated randomly to receive one of two

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ISOFLURANE AND THENAR MUSCLE BLOOD FLOW

anaesthetic agents (n = 15 in each group). In group I, anaesthesia was maintained with an initial i.v. bolus dose of fentanyl 4 μg kg⁻¹ followed by an infusion of 1 μg kg⁻¹ h⁻¹. In group II, anaesthesia was maintained with 1.1% end-tidal concentration of isoflurane (1 MAC excluding nitrous oxide). The infusion rate of fentanyl and the concentration of isoflurane were not altered during the course of anaesthesia, provided that MAP and heart rate (HR) were maintained within ±20% of awake baseline values. Patients were also observed closely for other clinical signs of inadequate anaesthesia (e.g. sweating, lachrymation, slight movement). After at least 20 min of stable anaesthesia, vecuronium 0.1 mg kg⁻¹ was given and the airway was maintained with a size 3 or 4 laryngeal mask, as appropriate. Ventilation was controlled to maintain normocapnia (end-tidal carbon dioxide partial pressure of 4.6–5.3 kPa). Nasopharyngeal temperature was maintained at 35.5–37 °C by warm blankets and heated i.v. fluids. End-tidal concentration of isoflurane, nitrous oxide, carbon dioxide and oxygen saturation were measured continuously by a multiple gas analyser (Capnomac, Datex Instrumentarium Corporation, Helsinki, Finland).

The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2-ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz, repeated every 10 s, using a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). The resultant contractions of the adductor pollicis muscle were recorded using a force displacement transducer and a neuromuscular function analyser (Myograph 2000, Biometer International, Odense, Denmark). The muscle response to vecuronium was recorded on graph paper and the following variables were determined: (1) onset time: the time interval between the end of administration of vecuronium and the development of maximum block; (2) time required for the first twitch in the TOF (T1) to recover spontaneously to 25%, 75% and 90% of its control value; (3) recovery index: time for recovery of T1 from 25% to 75%. The study was terminated at this stage and anaesthesia and further neuromuscular block, if necessary, were maintained as appropriate for surgery.

A laser Doppler flowmeter (Laserflo BPM³, Vasamedics Inc, MN, U.S.A.) was used to measure thenar muscle blood flow. A sterile 19-gauge needle type laser flowmeter probe was inserted percutaneously in the thenar muscle to a depth of 0.5–1.0 cm from the skin surface. Painless skin puncture was ensured by the use of EMLA cream. A sterile transparent dressing was used to cover the skin puncture site, to secure the needle probe in place and to allow for inspection and detection of inadvertent extrusion. The hand contralateral to the site of neuromuscular and arterial pressure monitoring was used for monitoring blood flow to avoid the possible effects of muscle movement or contractions on the blood flow signal [7]. The hand was wrapped in a sterile towel to minimize heat loss and skin temperature over the thenar muscle was maintained above 33 °C. Monitoring of blood flow started in all patients before induction of anaesthesia and 15 min was allowed for stabilization of the flow signal. The baseline awake value was taken as the mean of three successive readings recorded at 2-min intervals. During the course of anaesthesia, thenar muscle blood flow was monitored continuously and recorded every 1-min during induction and every 5 min during maintenance of anaesthesia.

Statistical analysis was performed by analysis of variance (for repeated measures) within each anaesthetic technique group and by unpaired Student's t test for comparisons between the two groups. Differences were considered significant when P < 0.05.

RESULTS

All results are expressed as mean (sd). The balanced anaesthesia and isoflurane groups were comparable in age (mean 36.4 (range 18–55) y vs 33.1 (18–49) y), weight (mean 68.8 (sd 15) kg vs 65 (19) kg), ASA status and duration of surgery (83.6 (28) min vs 77.5 (31) min).

All patients developed complete neuromuscular block after administration of vecuronium. Onset time was 3.3 (0.77) and 2.7 (0.96) min in the balanced anaesthesia and isoflurane groups, respectively (ns). The clinical duration (time required for 25% spontaneous recovery of T1) times to T1 75% and T1 90%, and the recovery index were prolonged significantly in the isoflurane group. The neuromuscular characteristics of the two groups are shown in table I.

Both groups had comparable HR and MAP values before operation. HR and MAP were maintained within ±20% of awake values in the two groups during induction and steady state anaesthesia. During operation, MAP was comparable in the two groups while HR was reduced significantly in the balanced anaesthesia group. Alterations in the infusion rate of fentanyl or end-tidal isoflurane concentration were not required in any patient during the study.

Thenar muscle blood flow was comparable in the two groups before induction of anaesthesia. Administration of thiopentone produced a progressive increase in thenar muscle blood flow in all patients. Ten minutes after administration of thiopentone, thenar muscle blood flow increased significantly from 2.6 (1.9) to 19.2 (14) ml min⁻¹/100 g in the balanced anaesthesia group and from 2.2 (1.5) to 21.7 (16) ml min⁻¹/100 g in the isoflurane group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Balanced (n = 15)</th>
<th>Isoflurane (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset time (min)</td>
<td>3.3 (0.77)</td>
<td>2.7 (0.96)</td>
</tr>
<tr>
<td>T1 25% (min)</td>
<td>26.3 (5)</td>
<td>39.2 (15)*</td>
</tr>
<tr>
<td>T1 75% (min)</td>
<td>35.3 (10)</td>
<td>53.0 (12.5)*</td>
</tr>
<tr>
<td>T1 90% (min)</td>
<td>43.5 (7)</td>
<td>61.2 (10)*</td>
</tr>
<tr>
<td>Recovery index (min)</td>
<td>9.8 (6.4)</td>
<td>15.3 (3.3)*</td>
</tr>
</tbody>
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difference between the two groups was not significant. Addition of fentanyl (group 1) or isoflurane (group 2) to the anaesthetic mixture resulted in a further increase in thenar muscle blood flow. During steady state anaesthesia, thenar muscle blood flow increased to 26.2 (16) and 26.8 (13.6) ml min⁻¹/100 g in the balanced anaesthesia and isoflurane groups, respectively. However, this increase was not significant compared with the induction values for blood flow recorded 10 min after thiopentone. The blood flow pattern was comparable in the two groups throughout the study (fig. 1).

**DISCUSSION**

The present study has demonstrated that isoflurane caused prolongation of vecuronium-induced neuromuscular block. Similar findings have been reported by other investigators [4, 5]. *In vitro*, isoflurane and halothane potentiate non-depolarizing neuromuscular block to the same extent [1]. In contrast, *in vivo*, isoflurane produces more potentiation than halothane [8]. This discrepancy was explained by the hypothesis that, *in vitro*, isoflurane increases muscle blood flow and consequently a greater proportion of the neuromuscular blocking agent reaches the neuromuscular junction. This hypothesis, however, was not confirmed by controlled clinical studies.

Assessment of tissue blood flow, including skeletal muscle, is now possible clinically with the use of a laser Doppler flowmeter. Although this technique is used widely in plastic and reconstructive surgery to assess blood flow in skin and musculocutaneous flaps [7], this method is comparatively new to anaesthesia.
neuromuscular block which was prolonged more by constructive criticism during the preparation of this manuscript.

Recent evidence indicates that inhaled anaesthetics have specific effects on acetylcholine receptor channels. Brett, Dilger and Yland [18], using a patch clamp technique, found that isoflurane reduced the average open duration of the acetylcholine receptor channels that remain open for activation. Under such circumstances, the end-plate current is both reduced in amplitude (by neuromuscular block) and also has an accelerated decay (by isoflurane). Both factors reduce the net charge transfer across the end plate, which impairs neuromuscular transmission.

In summary, vecuronium was found to produce neuromuscular block which was prolonged more by isoflurane than by a balanced technique of anaesthesia. However, both anaesthetic techniques were associated with comparable increases in thenar muscle blood flow. We suggest that increased muscle blood flow was not therefore the primary mechanism underlying isoflurane-induced potentiation of vecuronium block.

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REFERENCES


4. Rupp SM, Miller RD, Gencarilli PJ. Vecuronium-induced neuromuscular blockade during isoflurane anaesthesia was related probably to direct neuromuscular effects than to effects on muscle blood flow. *Anesthesiology* 1984; 60: 102-105.


