Neostigmine-induced reversal of vecuronium in normal weight, overweight and obese female patients

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Background. The purpose of this study was to compare neostigmine-induced reversal of vecuronium in normal weight, overweight and obese female patients.

Methods. In total, 15 each of normal weight (18.5≤BMI<25), overweight (25≤BMI<30) and obese (BMI≥30) patients were enrolled. Anaesthesia was induced and maintained with fentanyl, propofol and nitrous oxide. Neuromuscular block was induced with vecuronium 0.1 mg kg⁻¹ on the basis of the patient’s real body weight (RBW) and was monitored using acceleromyographic train-of-four (TOF) of the adductor pollicis. All patients received neostigmine 0.04 mg kg⁻¹ combined with atropine 0.02 mg kg⁻¹ at 25% recovery of the first twitch (T1) of TOF and were allowed to recover to a TOF ratio of 0.9.

Results. The time from administration of vecuronium to spontaneous recovery of T1 to 25% of control was significantly longer in the obese [mean (SD, range); 68.4 (16.3, 39.8–110.8) min] and the overweight groups [49.3 (6.2, 39.8–60.8) min] as compared with the normal weight group [41.0 (9.0, 27.5–59.5) min]. The times for facilitated recovery with neostigmine to a TOF ratio of 0.7 did not differ among groups. However, the recovery to a TOF ratio of 0.9 in the obese [25.9 (6.7, 13.5–41.0) min] and the overweight groups [14.6 (7.7, 3.3–28.5) min] were significantly longer than that in the normal weight group [6.9 (2.0, 3.0–10.7) min].

Conclusions. Early reversal after neostigmine is prompt; however, recovery to a TOF ratio of 0.9 is slow in overweight and obese patients when vecuronium is dosed on the basis of the patient’s RBW.

Br J Anaesth 2006; 97: 160–3

Keywords: antagonists neuromuscular block, neostigmine; complications, obesity; neuromuscular block, vecuronium

Accepted for publication: April 20, 2006

Previously published studies¹,² demonstrated that the duration of action of vecuronium is significantly longer in obese patients compared with normal weight patients when the dose of vecuronium had been chosen on the basis of the patient’s real body weight (RBW). This prolonged effect in obese patients may be explained by a relative overdosing of vecuronium in relation to the patient’s lean body mass. As the dosage of vecuronium is increased, the duration of action and spontaneous recovery from neuromuscular block is prolonged.³⁻⁵

It is therefore anticipated that, in obese patients, the speed of facilitated recovery with anticholinesterases may also be prolonged when the neuromuscular function is inhibited by vecuronium dosed on the basis of RBW. However, the reversal effect of vecuronium in obese patients has not yet been formally examined. Therefore, this study was designed to compare the efficacy of neostigmine on neuromuscular block induced with the dose of vecuronium based on the patient’s RBW in normal weight, overweight and obese female patients.

Materials and methods

After approval of the protocol by the Hospital Ethics Committee on Human Rights in Research, 45 adult female patients consented to participate in this study. Patients were ASA physical status I or II, 27–57 yr of age undergoing elective gynaecological surgery with general anaesthesia.
None of the patients had neuromuscular, hepatic and renal disorders, or were taking any drug known to interact with neuromuscular blocking agents.

Patients were grouped according to their BMI [BMI=weight (kg)/height² (m)]; the normal weight group (18.5 ≤ BMI <25, n=15), the overweight group (25 ≤ BMI <30, n=15) and the obese group (BMI ≥ 30, n=15).

Patients were not premedicated before the induction of anaesthesia. On arrival at the operating room, ECG, non-invasive blood pressure and pulse oximetry were applied. An i.v. infusion of acetated Ringer’s solution was started in the right forearm and was administered at an infusion rate of 8–10 ml kg⁻¹ h⁻¹. General anaesthesia was induced with fentanyl 2–4 μg kg⁻¹ and propofol 2.5 mg kg⁻¹ while patients received 100% oxygen through an anaesthesia face mask. After loss of consciousness, a laryngeal mask was inserted without the aid of neuromuscular blocking agents. Anaesthesia was maintained by nitrous oxide 67% in oxygen, a propofol infusion 4–8 mg kg⁻¹ h⁻¹, and supplemental fentanyl as clinically indicated. Ventilation was adjusted to maintain end-tidal carbon dioxide between 4.3 and 5.1 kPa using a Multigas Unit AG-920™ (Nihon Kohden, Tokyo, Japan). Rectal temperature was monitored using Mon-a-Therm™ (Mallinckrodt, Anesthesi Products Inc., St Louis, USA) and maintained at ≥36°C using a warming mattress, blanket (Thermacare™ and Medi-Therm II™, Gaymer Industries, Inc., NY, USA) and warmed i.v. fluids. Skin temperature over the thenar muscle was recorded every 15 s throughout the experiment using a surface probe attached in acceleromyographic unit and kept at >32°C.

After having obtained stable depth of anaesthesia, the ulnar nerve was stimulated at the wrist with square-wave, automatically detected supramaximal stimuli of 0.2 ms duration, delivered in a TOF mode at 2 Hz every 15 s and contraction of the ipsilateral adductor pollicis muscle was measured using acceleromyography (TOF Guard™; Organon Teknika NV, Turnhout, Belgium). After control TOF stimuli were administered for at least 20 min and evoked responses had been stable, the first twitch (T1) of TOF and TOF ratio measured at the end of control stimulation was regarded as the baseline value. All patients then received vecuronium 0.1 mg kg⁻¹ on the basis of the patient’s RBW. When the T1 had recovered spontaneously to 25% of control, all patients received RBW-based neostigmine 0.04 mg kg⁻¹ combined and atropine 0.02 mg kg⁻¹ and were allowed to recover to a TOF ratio of 0.9.⁶

The following variables were measured or calculated: lag time (s) from the time of bolus injection of vecuronium to the beginning of depression of T1; onset time (min) from the injection of vecuronium to maximum depression of T1; maximum depression (%) of T1; duration (min) from the injection of vecuronium to spontaneous recovery of T1 to 25% of control (DUR25%); times (min) required for facilitated recovery to TOF ratios of 0.5, 0.7 and 0.9 following neostigmine. All data were collected on a memory card and analysed on a desktop computer off-line.

Data are presented as mean (SD) (range). Statistical analysis was performed using StatView software™ for Windows (SAS Institute, Cary, NC, USA). ANOVA was used for multiple comparisons. If a significant F-value of <0.05 was obtained in multiple comparisons, further group comparisons were made using Bonferroni post hoc test.

**Results**

Age, height and ideal body weight (IBW) of patients were comparable between groups (Table 1). However, statistically significant differences were seen in the RBW and the BMI. Both lag and onset times following vecuronium were significantly shorter in the overweight and the obese groups than the normal weight group (Table 2). Complete block of T1 was obtained in all patients. As the BMI increased, the DUR25% was significantly prolonged (Table 2). The times required for reversal to TOF ratios of 0.5 and 0.7 were comparable between groups; however, the late phase in recovery to a TOF ratio of 0.9 was significantly longer in the overweight and obese groups, when compared with the normal weight group (Table 3).

**Discussion**

This study demonstrated that early facilitated recovery of TOF ratios to 0.7 did not differ among groups. However, late recovery to TOF ratios of 0.9 was prolonged in overweight and obese patients when vecuronium had been administered in a dose calculated by the patient’s RBW.

Although vecuronium has the maximum octanol/buffer distribution coefficient among clinically available neuromuscular blocking agents,⁷⁻⁸ it is basically polar and

**Table 1** Patient characteristics. Data are presented as mean (SD) (range). IBW (kg)=22×height² (m). *P<0.05 compared with the measurements of the normal weight group. †P<0.05 compared with the measurements of the overweight group.

<table>
<thead>
<tr>
<th></th>
<th>Normal weight</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>41.2(30–52)</td>
<td>43.4(32–57)</td>
<td>42.6(28–60)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.60(0.07)</td>
<td>1.54(0.05)</td>
<td>1.57(0.07)</td>
</tr>
<tr>
<td>IBW (kg)</td>
<td>56.3(4.9)</td>
<td>52.3(3.4)</td>
<td>54.5(4.7)</td>
</tr>
<tr>
<td>RBW (kg)</td>
<td>53.0(4.4)</td>
<td>65.7(4.5)*</td>
<td>84.4(7.9)*</td>
</tr>
<tr>
<td>BMI (kg·m⁻²)</td>
<td>20.8(1.4)</td>
<td>27.8(1.0)*</td>
<td>34.3(2.3)*</td>
</tr>
</tbody>
</table>

**Table 2** Comparison in onset and duration of vecuronium-induced neuromuscular block. Data are presented as mean (SD) (range). *P<0.05 compared with the measurements of the normal weight group. †P<0.05 compared with the measurements of the overweight group.

<table>
<thead>
<tr>
<th></th>
<th>Normal weight</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lag time (s)</td>
<td>48.0(6.2)*</td>
<td>40.0(10.9)*</td>
<td>39.6(7.5)*</td>
</tr>
<tr>
<td>Onset (min)</td>
<td>2.1(0.2)</td>
<td>1.9(0.4)*</td>
<td>1.7(0.2)*</td>
</tr>
<tr>
<td>DUR25%</td>
<td>41.0(9.0)</td>
<td>49.3(6.2)*</td>
<td>68.4(16.3)*</td>
</tr>
</tbody>
</table>

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hydrophilic and is therefore distributed mainly in lean tissues. In obese individuals, adipose tissue accounts for the most part of the excess of body weight. Therefore, if vecuronium based on the patient’s RBW is administered, it should lead to a relative overdosing for the lean body mass and a higher serum concentration in obese patients compared with normal weight patients. Faster onset and prolonged duration of action of vecuronium-induced block observed in the overweight and the obese groups are consistent with a relative excess of the dosing based on the patient’s RBW. The explanation of relative overdosing is additionally supported by the fact that duration of action of non-depolarizing neuromuscular block in obese patients is similar to that in normal weight patients when the obese are dosed on the basis of the IBW.

The obese patients in our study received 1.5 times doses of the IBW-based vecuronium. Pharmacokinetic and pharmacodynamic studies by Fisher and colleagues revealed that increasing the dose of vecuronium significantly increased the spontaneous recovery from neuromuscular block because of its cumulative effect. Fahey and colleagues found that the average time at which twitch tension recovered spontaneously from 25 to 75% of control increased from 8 to 21 min as the vecuronium dose was increased from 0.07 to 0.14 mg kg⁻¹. Reversal time is determined by two processes which include direct antagonism by anticholinesterase and spontaneous recovery (elimination of neuromuscular blocking agent from the plasma). Reversal effect of neostigmine usually appears within about 1–2 min and the maximum effect occurs in about 6–10 min. It is therefore considered that the early facilitated recovery to a TOF ratio of 0.5 or 0.7 observed in overweight and obese patients may be attributable to competitive antagonism to vecuronium at the neuromuscular junction because of increased acetylcholine concentration. Following peak antagonistic effect of neostigmine, the further recovery of TOF ratios from 0.7 to 0.9 in obese patients is slow like a plateau phase that may represent a balance between spontaneous recovery from overdosed vecuronium-induced neuromuscular block and the waning reversal effect of neostigmine. We did not evaluate the speed of spontaneous recovery without reversal in this study. Based on our previous study, the average time for spontaneous recovery of a TOF ratio from 0.7 to 0.9 was about 15 min (Suzuki T, Fukano N, Kitajima O, Saeki S, Ogawa S; unpublished data). It is therefore anticipated that overdosed vecuronium should prolong more the spontaneous recovery time. It is likely that total reversal time may also be increased when spontaneous recovery time is considerably prolonged by an excess dose of vecuronium in obese patients.

In contrast to vecuronium, it is reported that atracurium-induced neuromuscular block is rapidly antagonized by neostigmine even if atracurium is administered in obese patients based on RBW. As the dose of atracurium is increased, the duration of action should also be increased. However, the spontaneous recovery time is similar following doses that ranged from 0.2 to 0.6 mg kg⁻¹. Therefore, the reversibility of atracurium with neostigmine may not be influenced by obesity.

It is known that the depth of block influences its reversibility. In general, neostigmine 0.04 mg kg⁻¹ should be adequate for prompt reversal of vecuronium-induced block if neostigmine is administered after 25% recovery of twitch. Increasing the neostigmine dose from 0.04 to 0.08 mg kg⁻¹ could not accelerate the recovery of TOF ratios. It is therefore likely that high-dose neostigmine cannot facilitate the late recovery from vecuronium-induced neuromuscular block in obese patients. The ‘ceiling’ is supported by the fact that human acetylcholinesterase activities following neostigmine 0.036 and 0.071 mg kg⁻¹ similarly decrease to the lowest values, 11.3 and 11.4% of baseline, respectively within 2 min. Whereas, it is also accepted that high doses of neostigmine can antagonize neuromuscular block more rapidly than smaller doses. Therefore, the maximum dose of neostigmine (e.g. 0.07–0.08 mg kg⁻¹) may be recommended for reversal of overdosing vecuronium in obese patients. Further investigations may be warranted with regard to the dose–reversal effect relationship of neostigmine in obese patients.

In conclusion, total reversal time following neostigmine 0.04 mg kg⁻¹ is longer in overweight and obese female patients compared with normal weight patients when vecuronium 0.1 mg kg⁻¹ is administered on the basis of their RBW.

Acknowledgement
Financial support: institutional funding.

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