Effect of smoking on dose requirements for vecuronium

H. TEIRIÄ, P. RAUTOMA AND A. YLI-HANKALA

Summary
We have compared the potency of vecuronium given to 12 smokers and 12 non-smokers during propofol–alfentanil–nitrous oxide anaesthesia. After obtaining individual dose–response curves, bolus doses of vecuronium were given to maintain neuromuscular block at 90–98 % for 60 min. Adductor pollicis EMG was used to monitor neuromuscular block. Mean ED₉₅ values were 61.38 μg kg⁻¹ and 47.49 μg kg⁻¹ for smokers and non-smokers, respectively (P < 0.01). The dose of vecuronium to maintain 90–98 % neuromuscular block was 25 % higher in smokers than in non-smokers (96.80 vs 72.11 μg kg⁻¹ h⁻¹; P < 0.01). These data reflect the effects of smoking on neuromuscular block induced by vecuronium. The effect may be at the receptor level, although possible increased metabolism of vecuronium in smokers cannot be excluded. (Br. J. Anaesth. 1996; 76: 154–155)

Keywords
Neuromuscular block, vecuronium. Complications, smokers.

Smoking changes the potency of many drugs [1]. The effect of smoking on the pharmacodynamics of neuromuscular blockers is poorly understood. A recent study suggested that cigarette smokers are more sensitive to atracurium than non-smokers, possibly because of down-regulation of receptors [2]. However, our clinical impression is that smokers seem to consume more vecuronium than non-smokers. Therefore, we designed a study to evaluate the effect of smoking on the pharmacodynamics of vecuronium.

Methods and results
The study was approved by the Ethics Committee of the hospital. All patients were white, ASA I–II. Twelve smokers (six female; median age 35 (range 19–49) yr; weight 69 (55–91) kg) and 12 non-smokers (eight female; median age 41 (20–47) yr; weight 65 (59–85) kg) gave informed consent. Exclusion criteria were: body weight index more than 27; any disease or medication known to affect neuromuscular block; and weekly alcohol consumption more than 20 units (1 unit = one drink, a glass of wine or a bottle of beer). Smokers inhaled more than 10 cigarettes per day.

Patients were premedicated with midazolam 15 mg orally. An antecubital vein was cannulated for i.v. infusion. Neuromuscular function was monitored by adductor pollicis EMG (Relaxograph, Datex/Instrumentarium, Finland). The stimulating surface electrodes were placed over the ulnar nerve, the recording electrode over the adductor pollicis muscle and the reference electrode on the proximal area of the second finger. The forearm and thumb were attached to a dorsal splint to maintain immobility. The hand was covered with an aluminium sheet to prevent cooling. Skin temperature of the hand was maintained at more than 33 °C.

Anaesthesia was induced with alfentanil 10–20 μg kg⁻¹ and propofol 2–3 mg kg⁻¹, and maintained with an infusion of propofol 6–10 mg kg⁻¹ h⁻¹, 66 % nitrous oxide in oxygen and bolus doses of alfentanil up to 50 μg kg⁻¹ h⁻¹. The neuromuscular monitor was calibrated after induction of anaesthesia and before administration of the neuromuscular blocker (supramaximal train-of-four stimulation, 2 Hz every 20 s). Calibration was continued until unchanged EMG responses were recorded for more than 2 min.

After calibration, the first dose of vecuronium 20 μg kg⁻¹ was given. The ensuing block was monitored until stabilization. The ED₉₅ for vecuronium was calculated by creating an individual dose–response curve. For this purpose, vecuronium was given according to the two-dose technique described previously [3]. Tracheal intubation was performed when the EMG response was <15 % of baseline. Neuromuscular block was maintained at 90–98 % for 60 min by administering vecuronium boluses (20 % of the estimated individual ED₉₅ dose) when needed. The dose of vecuronium was recorded and calculated later. Analysis of variance, followed by Scheffe’s post hoc test, was used to compare means. P < 0.05 was considered statistically significant.

The results of the study are presented in table 1. The response after the last individual incremental dose of vecuronium was 95–98 % of maximum and it averaged 12.1 min (no significant difference between groups). Mean end-tidal carbon dioxide concentration was 5.04 % (ns). Skin temperature averaged 34.8 °C (ns).

HELENA TEIRIÄ, MD, PERKA RAUTOMA MD, ARVI YLI-HANKALA MD, PHD, Department of Anaesthesia, Helsinki University Central Hospital, Haartmaninkatu 4, FIN-00290 Helsinki, Finland. Accepted for publication: August 1, 1995.
Correspondence to H.T.
Vecuronium and smoking

Our study suggested that smokers are more resistant to vecuronium than non-smokers. The site of this action is not clear. Both ED95 values and the hourly consumption of vecuronium were increased in smokers. Increased ED95 values probably reflect altered pharmacodynamics at the receptor site. Increased hourly consumption of vecuronium may indicate either increased plasma concentration of the drug, i.e. increased requirement of vecuronium at the receptor site to maintain neuromuscular block, or increased metabolism. The ED95/consumption ratio of vecuronium did not differ between groups, nor did the slopes of the dose–response curves. The similar slopes of the dose–response curves may indicate that the metabolism of vecuronium during construction of the dose–response curve did not differ between groups.

Small doses of nicotine (<100 ng ml⁻¹) stimulate the neuromuscular junction directly (acetylcholine-like action) and facilitate transmission of impulses. Larger doses (>10 µg ml⁻¹) block transmission because of persistent depolarization (acute effect) or desensitization of the receptor site (chronic effect) [4]. Based on the routine procedures of our hospital, patients were not allowed to smoke for 6 h before anaesthesia. Even heavy smoking does not increase blood nicotine concentrations to more than 75 ng ml⁻¹ [5]. Low blood concentrations of nicotine might, therefore, partly explain our results. Tobacco smoke, however, is a mixture of more than 3000 different compounds [1]. It has enzyme-inducing properties; enhanced biotransformation of many drugs sharing the cytochrome P-450 mixed function oxidase pathway has been correlated with cigarette smoking [1]. Therefore, factors other than directly nicotine-induced mechanisms may play a role in increased resistance of vecuronium in smokers.

We measured the ED95 for vecuronium over a period of 12 min. If metabolism of vecuronium were increased, this relatively long measurement time might result in inaccurately increased ED95 values in smokers [6]. Our measurement method was therefore not ideal. However, the difference in ED95 value between smokers and non-smokers was more than 20%. This probably cannot be explained solely by increased metabolism of the drug. An altered mechanism of action on the neuromuscular junction may also be involved therefore.

In the report of Kroeker, Beattie and Yang [2], smokers appeared to require less atracurium than non-smokers. This contrasts with the results presented here. More studies are needed to elucidate the mechanism of the effects of cigarette smoking on the neuromuscular junction and clarify this difference.

References


Table 1  Mean (95% confidence limits) values of hourly consumption of vecuronium (Cons), slope of the dose–response (Slope), ED95 and ED95/hourly consumption of vecuronium (Ratio) between smokers and non-smokers. **P < 0.01 between groups (ANOVA and Scheffe’s test).

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<tr>
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<th>Smokers</th>
<th>Non-smokers</th>
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<tr>
<td>Cons (µg kg⁻¹ h⁻¹)</td>
<td>96.80**</td>
<td>72.11</td>
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<td>(88.49, 105.10)</td>
<td>(64.46, 79.77)</td>
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<td>Slope (probit log⁻¹)</td>
<td>6.48</td>
<td>7.33</td>
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<td>(5.66, 7.29)</td>
<td>(5.80, 8.86)</td>
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<tr>
<td>ED95 (µg kg⁻¹)</td>
<td>61.38**</td>
<td>47.49</td>
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<td>(53.27, 69.49)</td>
<td>(42.16, 52.82)</td>
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<td>Ratio</td>
<td>1.65</td>
<td>1.53</td>
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<td>(1.43, 1.87)</td>
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