Pharmacokinetics and pharmacodynamics of vecuronium in children receiving phenytoin or carbamazepine for chronic anticonvulsant therapy

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The pharmacokinetics and time course of action of vecuronium in normal children and children receiving anticonvulsant drugs for prolonged periods were characterized. A bolus dose of vecuronium 0.15 mg kg⁻¹ was administered i.v. to 10 non-epileptic children and to 10 children on phenytoin and 10 children on carbamazepine, who were matched for age and weight. Plasma concentrations of vecuronium, 3-OH desacetylvecuronium (the primary metabolite of vecuronium) and α₁-acid glycoprotein (AAG) were determined. Pharmacokinetic variables were derived from plasma samples collected before and after administration of vecuronium. Neuromuscular transmission was monitored by evoked compound electromyography. Recovery of the first twitch of the train-of-four (T₁/T₀) and the recovery index (RI), the time for 25–75% recovery of T₁/T₀, were determined. The elimination half-life of vecuronium was significantly reduced in both anticonvulsant groups compared with control [control 48.2 (SD 40.3), phenytoin 23.5 (13.1), carbamazepine 18.4 (16.6) min, P<0.05]. Vecuronium clearance was increased in both anticonvulsant groups [control 9.0 (3.6), phenytoin 15.1 (8.9), carbamazepine 18.8 (13.1) ml kg⁻¹ min⁻¹, 0.05<P<0.1]. Children on chronic anticonvulsant therapy had a significantly shorter RI than control [control 21.8 (11), phenytoin 12.5 (8.3), carbamazepine 10.6 (5.9) min, P<0.05]. Concentrations of vecuronium at different degrees of recovery of T₁, volumes of distribution and AAG concentrations were not different between groups. Our data confirm anticonvulsant-induced resistance to vecuronium in children and support a pharmacokinetic component contributing to the resistance.

Br J Anaesth 2001; 86: 223–9

Keywords: complications, epilepsy; neuromuscular block, vecuronium; children

Accepted for publication: October 5, 2000

Phenytoin and carbamazepine have been the mainstay of anticonvulsant therapy in children for decades. Several clinical studies have demonstrated resistance to the neuromuscular effects of non-depolarizing neuromuscular blocking drugs (NDNMB), particularly NDNMB steroidal relaxants, in patients receiving chronic anticonvulsant drug therapy. Phenytoin and carbamazepine are potent inducers of hepatic microsomal enzymes. Enhanced hepatic metabolism of NDNMB may account for accelerated inactivation and clearance of these drugs. Recently we reported resistance to rocuronium, a steroidal NDNMB, in children receiving chronic anticonvulsant therapy. Alloul and colleagues demonstrated in adults that a single dose of vecuronium can be metabolized rapidly in patients receiving chronic carbamazepine therapy. These authors concluded that carbamazepine-induced resistance to vecuronium neuromuscular blockade was due to an increase in hepatic clearance. Furthermore, most anticonvulsant drugs currently in use have been shown to increase α₁-acid glycoprotein (AAG) concentrations. An increased concentration of AAG can increase the protein binding of cationic drugs and alter their distribution. These drug-induced changes in the pharmacological effects of NDNMB could also be confounded by age-related variability. Normal
children aged 3–10 yr have increased vecuronium requirements and also recover faster than infants, older children and adults.\textsuperscript{12, 13}

We tested the hypothesis that, in children, long-term phenytoin or carbamazepine therapy alters vecuronium kinetics as a result of hepatic enzyme induction. By measuring plasma vecuronium concentration and its pharmacodynamic effects, we attempted to characterize the pharmacokinetic contribution to the accelerated recovery from vecuronium-induced paralysis occurring in children receiving chronic anticonvulsant therapy.

### Materials and methods

#### Subjects

This study was approved by the institutional Human Studies Committee. Children undergoing neurosurgical or orthopaedic procedures were enrolled after informed consent from the patient and/or their parents. Exclusion criteria included patients taking more than one anticonvulsant drug or patients with coexisting hepatic, renal, cardiac or neuromuscular disease. The study patients were assigned to one of three groups (Table 1). The children receiving phenytoin ($n=10$) or carbamazepine ($n=10$) had been taking it for more than 1 month. The control group consisted of 10 patients who had no history of epilepsy and were not on chronic medication affecting neurotransmission. Plasma concentrations of phenytoin (5–20 \(\mu\)g ml\(^{-1}\)) and carbamazepine (6–10 \(\mu\)g ml\(^{-1}\)) were within the therapeutic range immediately before the study for all patients.

#### Anaesthetic management

Anaesthesia was induced with halothane, nitrous oxide and oxygen or thiopental. Vital signs were monitored in all patients with a sphygmonomanometer, electrocardiogram, precordial stethoscope, pulse oximeter and temperature probe. Anaesthesia was maintained with an infusion of fentanyl (3 \(\mu\)g kg\(^{-1}\) h\(^{-1}\)), and isoflurane (0.2–0.5%) with \(N_2O\) and \(O_2\) (2:1 ratio). Oesophageal temperature was maintained at 36.5 (SD 0.5)\(^\circ\)C by using a force hot-air blanket and a mattress blanket. After obtaining baseline neuromuscular data over 5 min, vecuronium (0.15 mg kg\(^{-1}\)) was administered i.v. to facilitate tracheal intubation. The trachea was intubated and the lungs were ventilated mechanically to maintain end-tidal carbon dioxide at 3.3–4.0 kPa.

#### Pharmacodynamics of vecuronium

After induction of anaesthesia, the patient’s hand was secured to a splint in order to minimize movement artefacts during neuromuscular monitoring. Supramaximal square-wave stimuli were delivered to the ulnar nerve via surface electrodes at 2 Hz for 2 s and repeated every 20 s (train-of-four), and the evoked compound electromyogram (EMG) of the adductor pollicis muscle was recorded (Relaxograph NMT; Datex, Minneapolis, MN, USA). The maximal suppression of the EMG with vecuronium and time to recovery of T\(_1\)/T\(_0\) to 0.1, 0.2, 0.25, 0.5, 0.75, 0.8, 0.9 and 1.0 were recorded. The recovery index (RI), calculated as the time taken for T\(_1\)/T\(_0\) to recover from 25–75\%, was also measured.

#### Measurement of plasma vecuronium and 3-\(\text{OH}\) desacetylvecuronium concentrations

Blood samples were collected before and 5, 10, 15, 30, 60, 90, 120 and 240 min after administration of vecuronium. Plasma was separated, frozen immediately at –80\(^\circ\)C and analysed later for concentrations of vecuronium and its principal metabolite, 3-\(\text{OH}\) desacetylvecuronium, using high-performance liquid chromatography with an electrochemical detector.\textsuperscript{14} Organon 7465 was used as the internal standard. The lower limit of the assay was 4 ng ml\(^{-1}\) and the coefficient of variation was less than 10\%.

Plasma vecuronium and 3-\(\text{OH}\) desacetylvecuronium concentrations were analysed by iterative non-linear least-squares regression techniques on observed concentrations, as described previously (Sigma Plot, Windows, version 4, Jandel, Sunnyvale CA, USA).\textsuperscript{15} The slope (beta) of the terminal log-linear phase of each plasma concentration–time curve was determined by linear regression analysis. This slope was used to calculate the apparent elimination \(t_{1/2}\). The area under the plasma concentration–time curve from time zero until the last detectable concentration was determined by the linear trapezoidal method. The residual area extrapolated to infinity was calculated as the final concentration divided by beta. These two areas were added to yield the total area under the plasma concentration–time curve. The peak plasma concentration (C\(_{\text{max}}\)) and the time at which the peak concentration occurred (t\(_{\text{max}}\)) were used as measures of the rate of appearance of drug in the systemic circulation. Coefficients and exponents from the fitted functions were used to calculate the following kinetic variables: total volume of distribution using the area method (V\(_d\)); and total clearance (Cl). The plasma concentration of vecuronium was also plotted against the percent inhibition of T\(_1\)/T\(_0\).

### Table 1 Patient characteristics. Data are mean (sd). No significant differences between groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Phenytoin</th>
<th>Carbamazepine</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>10.2 (4–14)</td>
<td>11.0 (5–17)</td>
<td>12.1 (4–22)</td>
</tr>
<tr>
<td>Males/females</td>
<td>6/4</td>
<td>5/5</td>
<td>6/4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>42 (6)</td>
<td>39 (6)</td>
<td>43 (4)</td>
</tr>
</tbody>
</table>

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Clinical pharmacokinetic–pharmacodynamic modelling

The time-averaged concentration data was fitted to a standard biexponential pharmacokinetic model. Using the models determined for each of the three data sets, the plasma vecuronium concentrations at the times corresponding to each effect level (a given recovery of $T_1/T_0$) were calculated. The resulting concentration–effect pairs were plotted. A sigmoid pharmacokinetic–pharmacodynamic model was chosen, and the following equation was used to describe the concentration–effect relationship. $E_{\text{max}}$ was assumed to equal 100% twitch depression.

$$E = 100 - \frac{E_{\text{max}}C^A}{EC_{50}^A + C^A}$$

where $E_{\text{max}}$=maximum effect, $EC_{50}$=effect compartment concentration at 50% block and $A$=slope factor of the sigmoid curve.

Plasma AAG concentrations

AAG concentrations were assayed by radial immunodiffusion plates as described previously. Plasma was incubated for 24 h in wells treated with rabbit AAG antiserum in an agarose gel. This solution yielded a precipitin ring. The quantity of AAG in plasma was calculated from the standard curve of AAG 100–2000 µg ml$^{-1}$. This AAG assay was highly specific and had no cross-reactivity with other proteins, including albumin, haemopexin and $\alpha_2$-macroglobulin. Correlation between individual AAG concentrations and the corresponding recovery index was analysed.

Statistical analysis

Neuromuscular recovery and the pharmacokinetic data of the three groups were compared by analysis of variance followed by Dunnett’s multiple comparisons post hoc test. The Pearson product–moment correlation coefficient was calculated to assess the affect of AAG concentrations on the corresponding recovery indices. Data are presented as means (SD). $P<0.05$ was considered significant.

Results

The physical characteristics of the patients in the three groups are listed in Table 1. There were no differences between groups with respect to age, sex or weight.

Pharmacokinetic–pharmacodynamic modelling of vecuronium

The concentration–time data for the parent compound and the metabolite (3-OH desacetylvecuronium) in the three groups are shown in Fig. 1. Volumes of distribution were not different between the three groups. The elimination half-life was significantly shorter for the phenytoin and carbamazepine groups compared with control. There was increased clearance of vecuronium in the phenytoin and carbamazepine groups compared with control, which reached statistical significance in the carbamazepine group (Table 2). As indicated in Fig. 1b, the active metabolite, 3-OH desacetylvecuronium, was detected in all three groups at 1% of the parent drug concentration. The plasma concentration of vecuronium (parent drug only) plotted against recovery of $T_1/T_0$ to 10, 25, 50, 75 and 100% did not differ between groups (Fig. 2). Sigmoidicity in the pharmacodynamic analysis was evident, and thus a sigmoid pharmacokinetic–pharmacodynamic model was used to describe the concentration–effect relationship. However, examination of the plots revealed no hysteresis, and thus an effect site distinct from the central compartment was not postulated (Fig. 2). There was also no difference in the $EC_{50}$ and slope factor ($A$) between groups (Table 3).

Vecuronium pharmacodynamics on EMG

Bolus administration of vecuronium 0.15 mg kg$^{-1}$ abolished the twitch response in all patients. The recovery indices from vecuronium-induced block for the children on antiepileptic drugs were significantly faster than those for the control group (Table 3). Recovery $T_1/T_0$ was also significantly faster in the treatment groups than in the controls (Fig. 3).

Plasma AAG concentrations

The AAG concentrations for the three groups were as follows: control 36.7 (4.6) µg ml$^{-1}$, phenytoin 44.4 (5.0) µg ml$^{-1}$, carbamazepine 52.3 (5.4) µg ml$^{-1}$. These values did not differ significantly. There was no correlation between individual plasma AAG concentration and the corresponding recovery index (Fig. 4).

Discussion

Phenytoin and carbamazepine have direct depressant effects on the neuromuscular junction by a presynaptic and postsynaptic mechanism. Acute administration of an anticonvulsant drug either suppresses the post-tetanic potentiation of the muscle and endplate potential or leads to a decrease in the release of acetylcholine quanta at the nerve terminal. Thus, in the presence of acute exposure to anticonvulsants, the neuromuscular effects of NDNMBs are enhanced. With chronic exposure, however, there is resistance to the neuromuscular effects of NDNMBs. This resistance has been observed with steroidal relaxants (pancuronium, vecuronium, pipercuronium, rocuronium). Evidence exists for increased elimination of steroidal relaxants in the presence of chronic carbamazepine
or phenytoin therapy\(^7\)\(^{21}\). This resistance, however, is less common with benzoylisoquinolones (tubocurarine, meto-
curine, atracurium).\(^2\)\(^{22}\)\(^{23}\) Resistance to the neuromuscular
effect of mivacurium in patients taking anticonvulsants has
not been observed.\(^24\)\(^{25}\)

Our study in children confirms previous studies in adult
patients that chronic administration of either of the anticonvulsants phenytoin and carbamazepine induces resistance
to the neuromuscular effects of vecuronium. The resistance
was evidenced as a faster recovery of \(T_1/T_0\) to given endpoints and a shorter recovery index relative to controls.

Our data give further evidence that changes in the elimin-
ation half-life (\(t_{1/2}\)) are at least partly responsible for the
observed resistance to vecuronium. The trend for increased
clearance of vecuronium was apparent in both groups and
was statistically significant in the carbamazepine group.

Age-related differences in vecuronium pharmacology in
normal patients have been reported.\(^12\)\(^{13}\) When compared

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**Fig 1** Vecuronium (A) and 3-desacetylvecuronium (B) plasma concentrations are plotted against time (semilogarithmic plot) after a single bolus dose of vecuronium 0.15 mg kg\(^{-1}\). Mean (SD) are plotted for each group. The metabolite 3-desacetylvecuronium could be detected within 5 min of the bolus of vecuronium. There were no significant differences between groups.

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**Fig 2** Plasma concentrations of vecuronium are plotted against degree of neuromuscular block. Mean values and the predicted curves are plotted for each group. There were no significant differences between the groups in the hysteresis in the concentration–effect curves.
with infants and adults, young children aged 3–10 yr had a higher ED95 for tracheal intubation.26 Furthermore, they had significantly shorter recovery times than infants and adults.\textsuperscript{12, 13} The ED50 of vecuronium to produce depression of adductor pollicis twitch tension reported by Fisher and Miller was 19.0 \text{mg kg}^{-1} for children and 15.0 \text{mg kg}^{-1} for adults.\textsuperscript{12} These authors concluded that the increased volume of distribution in children mediated the increased requirement for vecuronium. In our study, the average age of the patients was 11 yr and the age distribution was similar between groups. Thus, age-related differences in elimination or distribution kinetics are not the cause of the faster recovery observed in the treatment groups.

The aetiology of the decreased sensitivity to NDNMB after prolonged anticonvulsant therapy may be multifactorial. Phenytoin and carbamazepine are both potent inducers of hepatic microsomal enzymes by induction of cytochrome P-450 isoenzyme III A4, resulting in enhanced elimination of many drugs.\textsuperscript{18, 27, 28} The decreased half-life and the trend for increased clearance in the anticonvulsant-treated group is consistent with the reports of Alloul and colleagues\textsuperscript{7} and Szenohradszky and colleagues\textsuperscript{21} in adults, where enhanced elimination kinetics of vecuronium or rocuronium was observed in patients on anticonvulsants.

The potential for anticonvulsants to induce qualitative or quantitative changes at the neuromuscular junction, and therefore resistance to NDNMBs, is also present. A known side-effect of anticonvulsants is muscle weakness resulting from a decrease in the spontaneous and evoked quantal release of acetylcholine.\textsuperscript{5, 18} In addition, these drugs also have effects that simulate the actions of curare-like drugs on the prejunctional membrane nerve terminal.\textsuperscript{29, 30} Therefore, these anticonvulsant drugs behave prejunctionally like botulinum toxin and postjunctioanlly like NDNMBs. Thus, chronic exposure to anticonvulsant drugs may induce a ‘denervation syndrome’ in which the expression of immature receptor isoforms leads to upregulation of acetylcholine receptors.\textsuperscript{31} These upregulated acetylcholine receptors can either increase the effective dose or have altered sensitivity to NDNMB because of the expression of immature isoforms of the receptors.\textsuperscript{30} Animal and human studies have provided direct and indirect evidence for upregulation of acetylcholine receptors after chronic anticonvulsant therapy.\textsuperscript{8, 32} Kim and colleagues reported a proliferation of acetylcholine receptors at the muscle membrane after chronic phenytoin therapy in rats.\textsuperscript{8} Furthermore, patients on anticonvulsant therapy had increased sensitivity to succinylcholine, consistent with the possibility of upregulated acetylcholine receptors.\textsuperscript{32}

**Table 2** Vecuronium pharmacokinetic parameters. Data are mean (sd).

*P<0.05 vs control.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Phenytoin</th>
<th>Carbamazepine</th>
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</thead>
<tbody>
<tr>
<td>$t_{1/2a}$ (min)</td>
<td>8.4 (3.7)</td>
<td>6.8 (3.8)</td>
<td>6.1 (0.7)</td>
</tr>
<tr>
<td>$t_{1/2b}$ (min)</td>
<td>48.2 (40.3)</td>
<td>22.5 (13.1)*</td>
<td>18.4 (16.6)*</td>
</tr>
<tr>
<td>$V_d$ (litre kg(^{-1}))</td>
<td>0.55 (0.52)</td>
<td>0.54 (0.25)</td>
<td>0.52 (0.13)</td>
</tr>
<tr>
<td>Cl (ml kg(^{-1}) min(^{-1}))</td>
<td>9.0 (3.6)</td>
<td>15.1 (8.9)</td>
<td>18.8 (13.1)*</td>
</tr>
</tbody>
</table>

**Table 3** Vecuronium pharmacodynamic parameters. Data are mean (sd).

*P<0.05 vs control. EC\(_{50}\)=effect compartment concentration at 50% block; $A$=slope factor of the sigmoid curve.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Phenytoin</th>
<th>Carbamazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset time (min)</td>
<td>1.40 (0.16)</td>
<td>1.38 (0.11)</td>
<td>1.21 (0.11)</td>
</tr>
<tr>
<td>Recovery index (min)</td>
<td>21.8 (11)</td>
<td>12.5 (8.3)*</td>
<td>10.6 (5.9)*</td>
</tr>
<tr>
<td>EC(_{50}) (ng ml(^{-1}))</td>
<td>95.6 (4.7)</td>
<td>91.1 (4.1)</td>
<td>104.8 (7.6)</td>
</tr>
<tr>
<td>$A$</td>
<td>5.17 (0.95)</td>
<td>6.15 (1.26)</td>
<td>7.83 (2.85)</td>
</tr>
</tbody>
</table>

**Fig 3** Per cent recovery $T_1/T_0$ is plotted against time after a single dose of vecuronium 0.15 mg kg\(^{-1}\). Data are mean (sd) for all three groups. Recovery times for the phenytoin and carbamazepine groups were significantly different from control.

**Fig 4** Plot of individual plasma $\alpha_1$-acid glycoprotein concentrations against recovery $T_1/T_0$. Pearson product–moment correlation coefficient analysis showed no significant relationship between the two variables.
In our study, plasma concentrations of vecuronium at specific degrees of neuromuscular blockade did not differ significantly between the three groups. At first glance, this finding could be interpreted as a lack of difference between groups in drug–receptor kinetics or target organ sensitivity. This conclusion cannot be reached definitively on the basis of the findings of this study. A major metabolite of vecuronium is 3-OH desacetylvecuronium, which has potent neuromuscular blocking properties that can be additive or synergistic with its parent compound. Thus, it is possible that the concomitant presence of the metabolite in the plasma (and at the target tissues) confounded these observations. However, the plasma concentration of the metabolite was 1% of the parent compound, which would have a negligible effect on neuromuscular blockade.

Another possible cause of the resistance is alterations in plasma protein binding caused by anticonvulsant-induced increases in AAG concentrations. This protein can potentially bind to many cationic drugs, including NDNMBs, and thus reduce their efficacy and alter the unbound concentration. In the rat, long-term phenytoin administration resulted in increased concentrations of AAG and a decrease in the free concentration of metocurine, partially explaining the resistance. In our study, plasma concentrations of AAG in both anticonvulsant groups were not statistically different. The reason for this is unclear. We note that of Hans and colleagues, who reported that elevated concentrations of AAG induced by chronic anticonvulsant therapy did not contribute to the rapid recovery from vecuronium blockade.

In summary, this study confirms previous studies in adults that the resistance to vecuronium in children on chronic anticonvulsant therapy is partly related to increased metabolism. Previous studies have indicated altered drug–receptor kinetics as an additional cause of the resistance to NDNMBs. But the contribution of altered pharmacodynamics to the resistance to vecuronium could not be determined in this study. These results do not exclude the additional possibility of changes in target organ sensitivity to account for the resistance.

Acknowledgements
This work was supported by NIH grants GM 31569–15 and GM55082–4 to J.A.J.M. and MH-34223 to D.J.G.

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