Target controlled infusion of rocuronium: analysis of effect data to select a pharmacokinetic model

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Background. We aimed to evaluate whether area under the curve (AUC) analysis of pharmacodynamic data can be used to compare pharmacokinetic models taken from the literature, during a target controlled infusion (TCI) of rocuronium.

Methods. Seventy-two patients scheduled for orthopaedic surgery received a TCI of rocuronium (Stanpump) based on one of four pharmacokinetic models: those described by Szenohradszky, Alvarez-Gomez, Wierda, and Cooper. The resulting theoretical plasma concentration versus time curve was calculated for all patients based on all four pharmacokinetic models. Predicted effect versus time curves were calculated following the pharmacokinetic–pharmacodynamic link model (Sheiner and colleagues). Neuromuscular block was evaluated acceleromyographically. The difference between the area under the observed effect (AUCOE) and predicted effect (AUCPE) versus time curves was used for comparison.

Results. AUCPE differed significantly from AUCOE in the Szenohradszky and Alvarez-Gomez models, both with the reference link-pharmacodynamic data and with altered link-pharmacodynamic variables. AUCPE and AUCOE were comparable for the Wierda and Cooper models. The mean AUCOE was 25.1 (SD 11.9)% block×h. AUCPE–AUCOE was significantly larger in the Szenohradszky model when compared with all other pharmacokinetic models. This difference remained when link or pharmacodynamic variables were modified. The smallest AUCPE–AUCOE difference was found with the Wierda model.

Conclusion. It was possible to use AUC analysis for identification of the pharmacokinetic model that best predicted the pharmacodynamic characteristics of our patients.

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Continuous i.v. infusion of drugs can be achieved using computer-based pharmacokinetic software to control a syringe driver. A computer-controlled syringe driver injects the drug accurately and reproducibly, based on the pharmacokinetic properties of the agent. This target controlled infusion (TCI) technique aims for a preset blood concentration, or for a target effect concentration if pharmacodynamic parameters are available. It is intended to provide a stable plasma concentration (Cp) and a stable effect, with minimal intervention by the anaesthetist.

The pharmacokinetic/pharmacodynamic properties of rocuronium make it suitable for continuous administration and for TCI: it has a fast onset of effect, an intermediate duration of action, and no active metabolites. While clinical experience of the administration of neuromuscular blocking agent with such systems is limited, selection of the most appropriate pharmacokinetic model from the literature is of primary importance. We studied a method for comparison of pharmacokinetic models based on effect measurements during and after TCI of rocuronium. The aim of the study was to evaluate if area under the curve (AUC) analysis of pharmacodynamic data can be used to compare pharmacokinetic models from different populations. The influence of altering pharmacodynamic parameters on the results of the AUC analysis was also studied.

Methods

This study was approved by the institutional medical ethics committee. After obtaining written informed consent, 72 patients undergoing elective orthopaedic surgery of the knee or the leg lasting at least 60 min were included. Male and
female patients aged 18–64 yr and ASA physical status I or II were included. The main exclusion criteria were: weight outside 30% of ideal body weight (body length in cm–100), neuromuscular disease, any medication potentially interfering with neuromuscular transmission, pregnancy, or breastfeeding.

A peripheral i.v. catheter was placed in a large arm vein on arrival in the operating room. An Anti-Reflux PCA Y-set (Baxter, Deerfield, IL, USA) was connected to avoid backflow of study medication in the i.v. line. Monitoring consisted of ECG, pulse oximetry, non-invasive arterial pressure, capnography, and body temperature. Anaesthesia was induced with fentanyl 2 mg kg$^{-1}$ i.v. and propofol TCI (Diprifusor, Zeneca Pharmaceuticals, Macclesfield, UK) to a theoretical target blood concentration of 6 μg ml$^{-1}$. Maintenance of anaesthesia was with TCI propofol adjusted to clinical needs. Additional doses of fentanyl were given as judged by the attending anaesthetist. A laryngeal mask airway (LMA) was used to secure a free airway. Manual ventilation of the lungs with a mixture of 50% oxygen in air was effectuated to an end-tidal carbon dioxide concentration of 3.8±4.2%.

Rocuronium 10 mg ml$^{-1}$ was used in 10 ml syringes and was administered with a Graseby 3400 syringe driver. The theoretical Cp and the infusion rate of rocuronium were calculated by the Stanpump$^6$ every 10 s. (Stanpump is freely available from http://pkpd.icon.palo-alto.med.va.gov.)

Stanpump was programmed for rocuronium TCI according to four pharmacokinetic models found in the literature: those described by Szenohradszky and colleagues,$^2$ Alvarez-Gomez and colleagues,$^3$ Wierda and colleagues,$^4$ and Cooper and colleagues.$^5$ Details of these data are summarized in Table 1. Patients were allocated to one of these four calculation algorithms following a randomization list that was made before the start of the study. Rocuronium was administered to a theoretical blood concentration of 2 μg ml$^{-1}$, avoiding complete block. The infusion was continued until maximum effect was reached and a stable response was observed for 45 s on the neuromuscular transmission monitor.

Individual TCI data (weight, target Cp and duration of TCI) were used to calculate theoretical Cp values with all pharmacokinetic sets. To do this, Stanpump was used in the simulation mode, based on the individual TCI data of the patients. This resulted in four predicted Cp versus time curves for each patient. These values were used to calculate the predicted effect versus time curves (see below).

Neuromuscular transmission was evaluated using the acceleromyographic method (TOF-Guard, Organon, Oss, The Netherlands). The i.v. infusion as well as the non-invasive arterial pressure cuff were placed on the contralateral arm to the TOF-Guard. Arterial pressure was not recorded during the rocuronium TCI (7–9 min). Stimulation electrodes were placed over the ulnar nerve close to the wrist at the radial side of the flexor carpi ulnaris muscle, and the acceleration transducer was placed on the thumb, perpendicular to the movement. An arm board (TOF-Guard Arm Board, Organon, Oss, The Netherlands) was used to stabilize the position of the hand and to assure free movement of the thumb. Tetanic stimulation (50 Hz) was applied for 5 s in order to shorten the stabilization time.$^7$

After calibration to obtain supramaximal nerve stimulation, stimulation was maintained until a stable response was observed. Supramaximal stimuli with a duration of 0.2 ms in a train-of-four (TOF) mode at 2 Hz every 15 s were used. Peripheral skin temperature was monitored continuously by means of a thermistor placed on the thenar eminence. Peripheral skin temperature was kept at 32–35°C by wrapping the forearm in foil. After stopping the infusion, spontaneous recovery of neuromuscular transmission was observed until a TOF ratio (T4/T1) of 0.9$^8$ was reached.

### Analysis of pharmacokinetic and pharmacodynamic data

The height of the first twitch was measured every 15 s, and these measurements constituted the effect versus time curve. From these values, the area under the observed effect versus time curve (AUC$_{OE}$) was calculated using the linear trapezoidal rule,$^9$ from the following formula:

$$AUC_{OE}^{m} = \sum_{i=1}^{n} \frac{\% block_{i} + \% block_{i+1}}{2} \times \Delta t$$

The time from starting the TCI to the T4/T1 reaching 0.9,$^8$ was used to derive the AUC$_{OE}$.
The Stanpump automatically generated an output file, which allowed analysis of predicted plasma concentrations. The theoretical Cp of rocuronium was calculated every 10 s and these values were used to calculate a theoretical effect-site concentration based on the pharmacokinetic-link model described by Sheiner and colleagues. A sigmoid $E_{\text{max}}$ model (Hill equation) was used to calculate predicted effect (PE):

$$PE = E_{\text{max}} \times \frac{Ce^\gamma}{EC_{50}^\gamma + Ce^\gamma}$$

where $E_{\text{max}}$ is the maximum effect; $\gamma$ is a measure of the slope and sigmoidicity of the effect versus concentration curve; and $EC_{50}$ the steady-state plasma rocuronium concentration corresponding to 50% neuromuscular block. The following values were taken from Plaud and colleagues: $\gamma=4.79$; $EC_{50}=0.823 \ \mu g \ \text{ml}^{-1}$; and the rate constant $k_{e0}=0.168 \ \text{min}^{-1}$. $E_{\text{max}}$ is 100%.

The area under the predicted effect curve (AUCPE) was estimated with the linear trapezoidal rule, using the following formula:

$$AUC_{PE} = \sum_{i=1}^{n} \frac{PE_i + PE_{i+1}}{2} \times \Delta t$$

AUCPE was calculated during the same time interval as AUCOE: from the start of the TCI to recovery of the T4/T1 ratio to 0.9.

An example from one patient to illustrate the AUC analysis is given in Figure 1. A graphical representation of the four calculated predicted effect curves together with the observed effect versus time curve are shown. The dosing rate of rocuronium with the four pharmacokinetic models is also included.

The effect of altered pharmacokinetic-link and altered pharmacodynamic parameters on predicted effect results was studied by increasing and decreasing the $k_{e0}$, $EC_{50}$ and $\gamma$ values by 10%. These calculations were done for all predicted effect results. This approach allowed us to study the differences between measured and predicted values of neuromuscular block produced by rocuronium when four pharmacokinetic models were randomly used to administer the drug. The differences between AUCPE and AUCOE were used to study the pharmacokinetic–pharmacodynamic relationship.

**Statistical analysis**

A randomization list was created before the start of the study and used to assign the patients to one of the four TCI models. Results are reported as mean (range). The null hypothesis, that AUCPE and AUCOE were equal, was tested with a Student’s paired t-test. ANOVA was used to detect differences between the models after control for normal distribution. Subsequent comparison was done with the Scheffé test. Statview 4.5 (Abacus Concepts Inc., Berkeley, CA, USA) was used for statistical analysis. $P<0.05$ was considered statistically significant.

**Results**

We studied 72 patients, 26 were male and 46 female. Mean age was 38 (20–64) yr, weight was 75 (48–102) kg, height 173 (152–197) cm. Mean dose of rocuronium administered was 0.308 (0.213–0.390) mg kg$^{-1}$. Duration of rocuronium administration was 536 (296–755) s. Maximum neuromus-
circular block was 72 (38–97)%. Mean duration to T4/T1: 0.9 was 2018 (1050–3430) s. The mean AUCOE curve was 25.1 (SD 11.9)% block×h.

The results of the comparison between AUCPE and AUCOE are given in Table 2. AUCPE differed significantly from AUCOE in the Szenohradszky and the Alvarez-Gomez models, both for the reference link-pharmacodynamic values and during simulations based on altered link-pharmacodynamic variables. There were no statistically significant differences with the Wiera or the Cooper models between AUCPE and AUCOE except for EC50±10% (Wierda), and EC50±10% (Cooper).

The difference between AUCPE and AUCOE (AUCPE–AUCOE) was significantly larger in the Szenohradszky model when compared with the other pharmacokinetic models. This difference remained when the link or pharmacodynamic parameters were modified. A decrease of EC50 to 741 μg ml−1 caused AUCPE–AUCOE to increase significantly in the Szenohradszky model.

The smallest AUCPE–AUCOE difference was found with the Wiera pharmacokinetic model. The results with the Cooper model were comparable with Wiera, both for reference link-pharmacodynamic and for altered link-pharmacodynamic variables. The AUCPE–AUCOE difference with the Alvarez-Gomez model was larger than with the Wiera model although not statistically significant. The difference with the Cooper results was statistically significant. The Alvarez-Gomez results differed significantly from all other models when the γ parameter was increased by 10%.

### Discussion

This study describes a method for selecting a pharmacokinetic data set from the literature that is most appropriate to rocuronium TCI in a study population, without taking blood samples. It was demonstrated that comparison of AUCOE and AUCPE data differed between the four pharmacokinetic models, and that it was possible to select the most appropriate model. Furthermore, it was demonstrated that altering the arbitrary pharmacodynamic parameters did not influence the general conclusions.

A pharmacodynamic evaluation method has been described by Hochhaus and Derendorf12 as a tool for drug use optimization. These authors studied effect and side-effect versus drug concentration curves and used AUC analysis to define the dose with the optimal effect/side-effect relationship. We compared pharmacokinetic sets in a similar way by calculating AUCPE and AUCOE. Different administration profiles (based on different pharmacokinetic data) were studied, while Hochhaus and Derendorf studied different dosages and different intervals.

The significant difference between AUCPE and AUCOE in two of the models (Szenohradszky and Alvarez-Gomez) indicated that the method used could identify the pharmacokinetic parameters that did not agree well with the pharmacodynamic characteristics of our patients. The pharmacokinetic data of the Szenohradszky model corresponded least with the pharmacodynamic results of our patients and may therefore reflect other population characteristics. This is probably because Szenohradszky studied healthy patients as well as patients with renal insufficiency, in a population approach. Their pharmacokinetic parameters may therefore be less accurate for use in healthy patients.

Throughout the analysis, both with reference and with altered link-pharmacodynamic values, the Wiera and the Cooper results were similar, with a slightly smaller AUCPE–AUCOE difference for the Wiera results. We therefore concluded that the Wiera model combined with the reference link-pharmacodynamic values could be used for rocuronium TCI in our patients.

AUCPE calculations were based on theoretical Cp values, calculated by Stanpump and transformed to predicted effect values by means of the Sheiner model. In 1979, Sheiner and colleagues10 developed a pharmacokinetic–pharmacodynamic model where an effect compartment is linked to a central (plasma) compartment by a first-order process. The temporal relationship between these two compartments is described by a rate constant (ke0), while the relation between the ‘effect-site concentration’ and the observed clinical

### Table 2

Comparison of AUCPE and AUCOE within each model (t-test) and between models (ANOVA). Values are mean difference (range). Units are % block×h. Reference link-pharmacodynamic parameters: k0,e=0.168; EC50=823 μg litre−1; γ=4.79. *P<0.05 (t-test); ¹P<0.05 vs all other models; ²P<0.05 vs Cooper.

<table>
<thead>
<tr>
<th>Model</th>
<th>Szenohradszky (n=72)</th>
<th>Alvarez-Gomez (n=72)</th>
<th>Wierda (n=72)</th>
<th>Cooper (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCPE–AUCOE</td>
<td>15.1±² (±15.2/47.7)</td>
<td>5.0³ (±29.9/41.3)</td>
<td>0.6 (±34.5/38.9)</td>
<td>-2.2 (±36.4/35.4)</td>
</tr>
<tr>
<td>(reference link-pharmacodynamic)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AUCPE–AUCOE (k0,e-10%)</td>
<td>15.1±² (±16.1/48.3)</td>
<td>3.6³ (±31.3/41.0)</td>
<td>-0.3 (±35.8/38.5)</td>
<td>-3.2 (±37.6/34.9)</td>
</tr>
<tr>
<td>AUCPE–AUCOE (k0,e+10%)</td>
<td>17.0³ (±13.3/49.7)</td>
<td>6.3³ (±28.5/42.5)</td>
<td>1.8 (±33.4/40.1)</td>
<td>-1.1 (±35.4/36.4)</td>
</tr>
<tr>
<td>AUCPE–AUCOE (γ-10%)</td>
<td>15.5±² (±14.7/48.1)</td>
<td>5.2³ (±29.1/41.2)</td>
<td>0.9 (±33.8/38.8)</td>
<td>-1.9 (±35.7/35.4)</td>
</tr>
<tr>
<td>AUCPE–AUCOE (γ+10%)</td>
<td>16.9³ (±14.3/49.9)</td>
<td>5.6³ (±30.4/42.4)</td>
<td>0.8 (±35.1/39.7)</td>
<td>-2.2 (±36.9/35.9)</td>
</tr>
<tr>
<td>AUCPE–AUCOE (EC50-10%)</td>
<td>19.8³ (±9.1/51.5)</td>
<td>9.3³ (±25.6/45.6)</td>
<td>4.9³ (±31.5/43.4)</td>
<td>1.6 (±34.0/39.7)</td>
</tr>
<tr>
<td>AUCPE–AUCOE (EC50+10%)</td>
<td>12.1³ (±19.9/46.0)</td>
<td>1.3³ (±33.3/37.8)</td>
<td>-3.1 (±37.1/35.0)</td>
<td>-5.5³ (±37.8/31.7)</td>
</tr>
</tbody>
</table>
Validation of pharmacokinetic models by analysis of pharmacodynamic data

In conclusion, AUC analysis of predicted and measured effect data allowed us to evaluate four pharmacokinetic models for rocuronium TCI. It was possible to decide which model predicted best the pharmacodynamic characteristics of our patient population.

Acknowledgement
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Effect is described by a sigmoidal $E_{\max}$ model (Hill equation: $y, EC_{50}$). This Sheiner model has been transformed mathematically by different investigators into equations that include only pharmacodynamic data (infusion rate to maintain 50% effect, $k_{e0}$ and $y$). They were able to estimate these pharmacodynamic data by fitting these equations to the measured effect data. In this study, we used published pharmacokinetic–pharmacodynamic link and pharmacodynamic data, and combined them with the predicted $C_p$ data to study pharmacokinetic parameters. We tried to validate pharmacokinetic models without taking blood samples based on measured effect data. The assumption we made was that published link-pharmacodynamic data could be combined with different models. Gentry and colleagues and Wakeling and colleagues demonstrated that a particular value for $k_{e0}$ and $EC_{50}$ can only be used with the pharmacokinetic model to which they are referenced. In the present study, ±10% changes in the reference pharmacodynamic values did not lead to other statistically significant differences. This may support our assumption.

In the method we used, a flaw may have been introduced by inaccuracies in pharmacokinetic, link or pharmacodynamic values. The possibility also exists that inaccuracies may have been obscured by counterbalancing inaccuracies. Therefore we included a parallel analysis based on 10% changes in link and pharmacodynamic variables. This allowed us to evaluate if the combination of the pharmacokinetic models with altered pharmacokinetic–pharmacodynamic link or pharmacodynamic data caused changes in the predicted effect parameters when compared with the reference pharmacokinetic–pharmacodynamic link or pharmacodynamic data from the literature. Modification of $k_{e0}$ and $y$ by 10% apparently did not change $AUC_{PE}$. Increasing or decreasing $EC_{50}$ by 10% resulted in a significantly different $AUC_{PE}$. From our results, we conclude that $EC_{50}$ is the most important parameter in this respect. Our general results and conclusion, however, were similar with all calculation conditions.

Measurement of neuromuscular transmission in this study complied with the Good Clinical Research Practice Guidelines on pharmacodynamic studies published by Viby-Mogensen and colleagues in 1996. These allow the use of acceleromyography in phase IV studies and of a TOF stimulation pattern. It is, however, difficult to extrapolate these results to mechanomyographic measurements since the limits of agreement between mechanomyography and acceleromyography are wide (>10%), and the recovery profiles differ.

This study illustrates how a non-invasive and inexpensive methodology helps to evaluate the accuracy of a pharmacokinetic model taken from another population. It can be used without taking blood samples, provided drug effect can be measured. Whether this methodology can be extrapolated to other drugs or to other effect measurement techniques has to be studied.

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