Calculation of an effect compartment rate constant using recovery indices obtained with an isolated arm technique

C. A. SHANKS, M. J. AVRAM, T. C. KREJCIE AND T. K. HENTHORN

Summary
We have examined the implications of the theoretical single pharmacokinetic compartment associated with blocker-induced paralysis, in relation to the isolated arm technique. It is assumed that the blocker concentration–effect relationship can be characterized by a sigmoid curve, which incorporates an exponent, s. After tourniquet release, the concentration gradient between the effect compartment and plasma should be large, and elimination related to the rate constant, $k_{eo}$. The major measurement of spontaneous recovery with the isolated arm is the time interval between 75 % and 25 % twitch depression, T25–T75. The general equation relating these three variables is developed:

$$k_{eo}/(s \times (T25-T75))$$

Insertion of published values for T25–T75 with isolated arm studies into this equation gave estimates for an intrinsic $k_{eo}$ for atracurium, vecuronium, rocuronium and pancuronium. (Br. J. Anaesth. 1995; 75: 109–112)

Key words

Methods
When the concentration–effect relationship in the effect compartment is postulated to be a sigmoid curve, this can take the general form

$$\text{fractional effect} = \frac{EC}{EC_{50} + EC}$$

where the fractional effect is determined by any concentration (EC) in terms of the midpoint of the curve (that concentration related 50 % effect, $EC_{50}$) and the Hill exponent ($s$). Derivations for the effect compartment concentrations associated with 25 % and 75 % effects ($EC_{25}$ and $EC_{75}$, respectively) are:

$$25\%/100\% = \frac{1}{4} = \frac{EC_{25}}{EC_{50} + EC_{75}}$$

$$75\%/100\% = \frac{3}{4} = \frac{EC_{75}}{EC_{50} + EC_{75}}$$

Solving equations (2) and (3) to eliminate $EC_{50}$ by forming a ratio gives:

$$EC_{75}/EC_{25} = 9$$

which, with log transforming becomes:

$$\ln \left( \frac{EC_{75}}{EC_{25}} \right) = \ln (9)/s$$

Concentrations in a one-compartment model, for any time interval ($t$) from time zero, may be characterized by the general equation:

$$C(t) = C_{(0)}e^{-kt}$$

where $k$ = elimination rate constant and $C_{(0)}$ is the initial concentration at time zero.
The isolated arm technique assumes negligible plasma blocker concentrations enabling the dynamic model to be characterized as a single effect compartment. The monoexponential equation, made specific for the effect compartment rate constant, \( k_{eo} \), and for concentrations over the time interval, T25–T75, becomes:

\[
EC_{25} = EC_{75}e^{-k_{eo}(T25-T75)}
\]

which, with rearrangement and inversion, becomes:

\[
EC_{75}/EC_{25} = e^{k_{eo}*(T25-T75)}
\]

Log transform and combination with equation (5) gives:

\[
\ln(9)/s = k_{eo}*(T25 - T75)
\]

and thus

\[
k_{eo} = 2.2/(s*(T25 - T75))
\]

giving a general equation for the relationship between T25–T75, the Hill exponent and the intrinsic rate:

\[
t_{1/2} = k_{eo}*(T25 - T75)
\]

**Results**

As a special case, when the concentration EC75 is double that of EC25, then:

\[
EC_{75}/EC_{25} = 2
\]

It follows from equations (4) and (11) that

\[
(EC_{75}/EC_{25})^{s} = 2^{s} = 9
\]

giving a value of

\[
s = 3.17
\]

Combining equations (8) and (11), with log transforms the special case gives:

\[
\ln(2)/s = k_{eo}*(T25 - T75)
\]

and

\[
T25-T75 = 0.693/k_{eo} = T_{1/2}k_{eo}
\]

Thus, if the EC75/EC25 ratio = 2, the recovery index obtained with an isolated arm technique gives a value for an intrinsic half-life for the effect compartment, with quantification of the \( T_{1/2}k_{eo} \).

A recent article comparing atracurium and vecuronium in the isolated arms of the same subjects reported that the mean recovery index for vecuronium was significantly shorter (7.9 min) than that for atracurium (10.6 min) [2]. A similar study gave recovery indices for rocuronium (9.32 min) and pancuronium (12.5 min) [3]. Table 1 shows the relationships between selected EC75/EC25 ratios and the Hill exponent. It also gives values for the intrinsic \( k_{eo} \), estimated from equation (10) and the recovery indices for these four blockers [2, 3].

**Discussion**

Kinetic–dynamic modelling with a sigmoid curve to define the concentration–effect relationship (equation (1)) assumes that concentrations in the effect compartment are identical during both onset and offset of neuromuscular block. As the concentration–effect relationship is independent of time, curves inherent in equations (1)–(5) resemble those which might be realized with laboratory organ-bath studies. In patient-based studies, the non-linear relationship between plasma concentrations and effect is obvious, particularly during onset of paralysis. The time domain is added by a link model, here using an effect compartment rate constant, \( k_{eo} \), reported in reciprocal minutes (table 1). Classically, its derivation minimizes the hysteresis in the effect compartment, a curve depicted when onset and offset plasma concentrations are plotted against the concomitantly observed paralysis. The intrinsic \( k_{eo} \), calculated in table 1, uses T25–T75 values obtained in isolated arm studies [2, 3]. These assume that the small dose of blocker administered in an isolated arm study does not result in adequate plasma concentrations to affect the gradient between the neuromuscular junction and plasma. Separate simulations with kinetic–dynamic models of systemic administration of blockers confirmed that concentration gradients in the effect compartment would not be altered materially by the entry of the blocker into the body with release of the tourniquet.

In the isolated arm study comparing atracurium and vecuronium, it was proposed that the different recovery times (T25–T75) reflect different affinities with biophase binding sites [2]. Our calculations are consistent with this concept, and indicate that the value of T25–T75 with the isolated arm technique is proportional to the elimination half-life of the effect compartment, \( T_{1/2}k_{eo} \) (equation (10)), enabling quantification of removal of blocker from the biophase. As a general rule, the rate-limiting step in spontaneous recovery from blocker-induced paralysis must be the rate of decrease in plasma concentrations, the concurrent “context-sensitive” plasma half-life [6]. From systemic studies it seems extraordinarily rare for the plasma half-life to be less than the intrinsic \( T_{1/2}k_{eo} \). This exception might be true for the trans-

<table>
<thead>
<tr>
<th>EC75/EC25 ratio</th>
<th>Exponent s*</th>
<th>Atracurium</th>
<th>Vecuronium</th>
<th>Rocuronium</th>
<th>Pancuronium</th>
</tr>
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<tr>
<td>1.4</td>
<td>6.5</td>
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<td>0.04</td>
<td>0.04</td>
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</tr>
<tr>
<td>2.4</td>
<td>2.5</td>
<td>0.08</td>
<td>0.11</td>
<td>0.09</td>
<td>0.17</td>
</tr>
</tbody>
</table>

* Calculated from equation (5)
Effect compartment with the isolated arm

<table>
<thead>
<tr>
<th>Pharmacokinetic model*</th>
<th>$k_{eo}$ (min$^{-1}$)</th>
<th>Exponent</th>
<th>EC$<em>{75}$/EC$</em>{25}$ (from equation (5))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td></td>
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<tr>
<td>Non-compartmental [11]</td>
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<td>6.1</td>
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</tr>
<tr>
<td>Two-compartment [12]</td>
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<td>4.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Two-compartment [13]</td>
<td>0.10</td>
<td>4.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Non-compartmental [14]</td>
<td>0.12</td>
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<td>1.8</td>
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<tr>
<td>Vecuronium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three-compartment [15]</td>
<td>0.10</td>
<td>5.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Three-compartment [16]</td>
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<td>5.8</td>
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<tr>
<td>Two- and three-compartment [17]</td>
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<td>5.3</td>
<td>1.5</td>
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<td>1.8</td>
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<tr>
<td>Three-compartment [18]</td>
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<tr>
<td>Three-compartment [20]</td>
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</table>


trans and cis-trans isomers of mivacurium, assuming the cis-cis isomer to have insignificant action. In studies with i.v. administration of mivacurium, the trans-trans and cis-trans isomers were reported to have a plasma half-life of approximately 2 min [7], yet the T25$–$T75 for the parent mixture was between 6 and 10 min [7–9]. Equation (15) suggests that the $T_{25}$/$T_{75}$ for the parent mixture was between 0.03–0.11 min

0.09 min$^{-1}$ shown in table 2 is for a traditional back-extrapolated non-compartment model, but inclusion of data with an initial time delay reduced this (to 0.06 min$^{-1}$). Table 1 gives calculated values for $k_{eo}$ that are in the lower range of those in the literature (table 2). The largest difference between the tables is for the long-acting blocker pancuronium. This difference emphasizes the predominant influence of the context-sensitive half-life over the $T_{25}$ of the effect compartment, where the value in table 1 reflects the lack of pharmacokinetic influence, the relative purity of the effect compartment with the isolated arm technique, in the derivation of the “intrinsic” value for the rate constant.

References

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