Temperature-dependent Pharmacokinetics and Pharmacodynamics of Vecuronium

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Background: The authors evaluated the influence of temperature on the pharmacokinetics and pharmacodynamics of vecuronium because mild core hypothermia doubles its duration of action.

This article is featured in “This Month in Anesthesiology.” Please see this issue of Anesthesiology, page 5A.

Methods: Anesthesia was induced with alfentanil and propofol and maintained with nitrous oxide and isoflurane in 12 healthy volunteers. Train-of-four stimuli were applied to the ulnar nerve, and the mechanical response of the adductor pollicis was measured. Volunteers were actively cooled or warmed until their distal esophageal temperatures were in one of four ranges: <35.0°C, 35.0–35.9°C, 36.0–36.9°C, and ≥37.0°C. With temperature stabilized, vecuronium was infused at 5 μg·kg⁻¹·min⁻¹ until the first response of each train-of-four had decreased by 70%. Arterial blood (for vecuronium analysis) was sampled at intervals until the first response recovered to at least 90% of its prevecuronium level. Vecuronium, 20 μg·kg⁻¹·min⁻¹, was then infused for 10 min, and arterial blood was sampled at intervals for up to 7 h. Population-based nonlinear mixed-effects modeling was used to examine the effect of physical characteristics and core temperature on vecuronium pharmacokinetics and pharmacodynamics.

Results: Decreasing core temperature over 38.0–34.0°C decreases the plasma clearance of vecuronium (11.3% per °C), decreases the rate constant for drug equilibration between plasma and effect site (0.023 min⁻¹ per °C), and increases the slope of the concentration–response relationship (0.43 per °C).

Conclusions: Our results show that reduced clearance and rate of effect site equilibration explain the increased duration of action of vecuronium with reducing core temperature. Tissue sensitivity to vecuronium is not influenced by core temperature. (Key words: Gender; hypothermia; mixed-effects modeling; muscle relaxants.)

MILD hypothermia doubles the duration of vecuronium-induced neuromuscular block,1 an effect that could have a pharmacokinetic or a pharmacodynamic basis.2,5 Results from an earlier study found that the pharmacodynamics (concentration–effect relationship) of vecuronium were not altered by mild hypothermia, suggesting but not demonstrating that the interaction of mild hypothermia and vecuronium-induced block has a pharmacokinetic basis.4 The dose of vecuronium used in the study by Heier et al.1 (30 μg/kg) was chosen to optimize pharmacodynamic estimations, and because it was small, plasma concentrations of vecuronium were not detectable for a sufficiently long period of time to allow for pharmacokinetic analysis. In addition, previous investigations were further limited in that subjects were com-
pared at two discrete temperature states, normothermic (> 36.5°C) or hypothermic (approximately 34.5°C).1,4
The aim of the present study was to investigate core temperature as the continuous variable that it is, rather
than as a dichotomous variable. Hence, we expanded on
our previous investigations by studying subjects over a
range of temperatures from mild hyperthermia to mild
hypothermia and used a nonlinear mixed-effects model
to obtain a more complete picture of the effect of tem-
perature on both the pharmacodynamics and pharmaco-
kinetics of vecuronium. In addition, because the prin-
cipal metabolite of vecuronium, 3-desacetylvecuronium,
has potent neuromuscular blocking effects,5 the neu-
romuscular block after vecuronium administration is a sum
of the effect of the parent drug and the metabolite.
Therefore, we estimated the pharmacokinetics of this
metabolite to take its effect into account.

Materials and Methods

With the approval of our local institutional review
board and written informed consent from subjects, we
studied six male and six female volunteers (American
Society of Anesthesiologists physical class I, weight
44–90 kg, age 21–32 yr).

Anesthetic Technique

Subjects emptied their bladder, and before anesthesia
was induced, standard monitoring of vital signs was
instituted according to the guidelines of the American
Society of Anesthesiologists and clinical standards prac-
ticed at the Medical Center of the University of Califor-
nia, San Francisco. Lactated Ringer’s solution was in-
fused via an 18-gauge intravenous catheter inserted in
the subject’s arm.

All drugs were administered through this catheter.
Anesthesia was induced with 30 μg/kg alfentanil and 3
mg/kg propofol. Tracheal intubation was then per-
formed without the use of neuromuscular blocking
drugs. Anesthesia was maintained with nitrous oxide,
60–70% in oxygen, and isoflurane, 0.7–0.9% end-tidal
concentration. Mechanical ventilation was adjusted to
maintain end-tidal carbon dioxide at 30–35 mmHg. After
induction of anesthesia, a 20-gauge catheter was inserted
in each subject’s radial artery at the wrist. The subjects
were maintained with anesthesia for the duration of the
study.

Temperature Manipulation

Core body temperature was measured by a thermocou-
ple placed in the distal esophagus (Mon-a-Therm;
Mallinckrodt, Anesthesia Products Inc., St. Louis, MO).
Three volunteers were randomly assigned to be studied
in each of four core temperature ranges: ≥ 37.0°C,
36.0–36.9°C, 35.0–35.9°C, and < 35.0°C. Core temper-
ature was manipulated by a combination of forced-air
warming (Bair Hugger; Augustine Medical Inc., Minne-
apolis, MN) and surface cooling. The target temperature,
once achieved and stabilized, was maintained within ±
0.1°C throughout the remainder of the study.

Neuromuscular Function Monitoring

To measure neuromuscular responses, supramaximal
stimuli (200 μs duration) in a train-of-four sequence at 2
Hz were applied every 12 s to the ulnar nerve at the wrist
via surface electrodes (Digistim II; Neuro Technology
Inc., Houston, TX). The twitch tension of the first train-of-four response (T1) and the ratio of the
fourth to the first response (train-of-four ratio) were
digitized, displayed, and recorded on a Macintosh IICi
computer (Lab View; National Instruments Inc., Austin,
TX). When the target temperature was achieved and
both it and the adductor pollicis’ twitch tension had
been stable for 15 min, the T1 response was determined
and used as the control to which all subsequent T1
responses were compared. At this time (approximately
2 h after induction of anesthesia and commencement of
isoflurane), vecuronium was administered.

Drug Administration, Sampling, and Assay

We administered vecuronium twice to optimize pa-
rameter determination for both pharmacodynamics and
pharmacokinetics. Pharmacodynamic parameters are
best determined with a small, subparalyzing dose of
muscle relaxant. To achieve this, vecuronium was in-
fused at a rate of 5 μg · kg⁻¹ · min⁻¹ until the T1
response decreased by 70% of control, at which point
the infusion was stopped. Arterial samples were ob-
tained immediately before vecuronium administration
and at 1, 2, 3, 4, 5, 8, 10, 12, 14, 16, 18, 20, 25, 30, 35,
40, 45, 50, 55, and 60 min thereafter, or until the T1
response had recovered to > 90% of control (whichever
occurred first). The dose of vecuronium administered
for the pharmacodynamic study was too small to permit

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detection of drug in the plasma for a sufficient time to precisely determine pharmacokinetics. Consequently, we administered a second infusion with a larger dose of vecuronium at a rate of 20 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) for 10 min. Arterial blood samples were drawn at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 30, 40, 50, 60, 75, 90, 120, 150, 180, 240, and 300 min after the start of the second infusion. The flow of the study for a representative volunteer is illustrated in figure 1. Blood samples were heparinized, iced, and centrifuged within 1 h, and the plasma was stored at \(-30^\circ\text{C}\) until analysis.

When the subjects emerged from anesthesia, their urine (the total for the entire study period) was collected, and a final blood sample was obtained. Urine was acidified and stored at \(-30^\circ\text{C}\). Plasma and urine concentrations of vecuronium, 3-desacetylvecuronium, 17-desacetylvecuronium, and 3,17-bisdesacetylvecuronium in plasma and urine were measured by capillary gas chromatography with nitrogen-sensitive detection. This assay is sensitive to 5 ng/ml for vecuronium, 3-desacetylvecuronium, 17-desacetylvecuronium, and 3,17-bisdesacetylvecuronium and linear over 5–5,000 ng/ml, with a coefficient of variation \(\leq 15\%\) at a vecuronium concentration of 10 ng/ml.

**Duration of Action of Vecuronium**

To determine if the previously observed phenomenon of hypothermia–prolonged duration of action of vecuronium was present in this study, we measured the time from the beginning of administration of the second dose of vecuronium until T1 had recovered to 25%. We used linear regression to examine the relationship of core temperature to this measure of duration.

**Pharmacokinetic/Pharmacodynamic Analysis**

The analysis was conducted in four phases. In phase 1, a population-based pharmacokinetic model of vecuronium was determined using a model-building approach. Initially, two- and three-compartment models were compared to determine which was more appropriate. The parameters for structural models with two compartments were plasma clearance (Cl), distributional Cl (Cl\text{dist}), and volumes of the central (V1) and peripheral (V2) compartments. Structural models with three compartments had additional parameters: slow distributional Cl (Cl\text{slow}) and volume of a deep peripheral compartment (V3). The volume of distribution at steady state was the sum of V1 and V2 for two-compartment models and the sum of V1, V2, and V3 for models with three compartments.

A nonlinear mixed-effects modeling (NONMEM) post hoc step was used to generate the parameters for individual subjects. The resultant individual descriptions of vecuronium concentration in plasma was used as the input for phases 2 and 3. In phase 2, a model describing renal Cl as a proportion of total Cl was fit to the urinary amounts of vecuronium. In phase 3, a population model of 3-desacetylvecuronium was built. During each of these three phases we tested additional parameters, attempting to explain interindividual variability as a function of temperature. NONMEM’s post hoc step was used to generate the 3-desacetylvecuronium parameters for individual subjects. Finally, the combined individual descriptions of vecuronium and metabolite concentration in plasma were used as the input for phase 4, in which models of vecuronium effect were evaluated and the relationship of pharmacodynamic parameter values and temperature was determined using linear regression.

**Vecuronium Pharmacokinetics**

Mixed-effects population models (NONMEM) were fit to the vecuronium plasma concentration data using a model-building approach to estimate typical values (population means) for the pharmacokinetic and pharmacodynamic parameters, SEs of these estimates, and interindividual variability. Interindividual variability was generated through the use of \(\eta\) terms, e.g., Cl was modeled as:

\[
\text{Cl} = \text{Cl}_{\text{typical}} \cdot \exp(\eta)
\]
TEMPERATURE AND VECURONIUM PHARMACOLOGY

where CI is the value for an individual, CI\text{typical} is the typical value for the population, and \eta is a normally distributed random variable with mean zero. Both the basic model and the interindividual variability can also be wholly or partially modeled as functions of physiologic covariates, the aim being to reduce the magnitude of residual interindividual variability.

Improvements in three criteria were used to determine if additional parameters should be incorporated into the model. These criteria were goodness of fit (−2 log likelihood), precision for all parameters, and visual assessment. We first compared models with two or three compartments, then we evaluated models with parameters that were weight-normalized or not weight-normalized. Finally, we tested additional parameters that permitted linear variation with temperature of the parameters plasma CI, intercompartmental CI (Cldist), V1, or volume of distribution at steady state.

Vecuronium Renal Clearance

The cumulative fraction of vecuronium eliminated via the kidneys \(f_{\text{renal}}\) was modeled using the following assumptions: (1) values for the plasma pharmacokinetics of vecuronium were fixed to the post hoc values determined in the analyses previously described (i.e., fitting of the model to urinary excretion of vecuronium was not permitted to influence the quality of the fit to the plasma concentrations of vecuronium); (2) vecuronium was eliminated only from the central compartment; and (3) the fraction of vecuronium eliminated by the kidneys versus other routes did not vary with the concentration of vecuronium. Predictions from a model describing a constant urinary fraction of vecuronium elimination were fit to the amount of vecuronium observed in the urine. Plots of individual \(f_{\text{renal}}\) against gender indicated that \(f_{\text{renal}}\) varied according to gender, and a parameter added to the model to account for this significantly improved the fit. There was no indication that temperature influenced \(f_{\text{renal}}\) and a parameter added to the model permitting this fraction to vary with temperature did not improve the fit.

3-Desacetylvecuronium Pharmacokinetics

Pharmacokinetic characteristics of 3-desacetylvecuronium were modeled using the following assumptions: (1) values for the pharmacokinetics of vecuronium were fixed to the values determined in the analyses previously described (i.e., fitting of the model to 3-desacetylvecuronium concentrations was not permitted to influence the quality of the fit to the vecuronium values); (2) vecuronium was converted to 3-desacetylvecuronium in vecuronium’s central compartment and was unidirectional; (3) 3-desacetylvecuronium was eliminated unidirectionally from its central compartment; (4) 3-desacetylvecuronium distributed to only a single compartment or to the central and one peripheral compartment; and (5) the administered drug contained no 3-desacetylvecuronium.

Because urinary recovery of the administered dose of vecuronium as either vecuronium or 3-desacetylvecuronium was not complete, the fraction of the administered dose of vecuronium converted to 3-desacetylvecuronium \(f_{\text{metabolized}}\) could not be estimated. As a result, volume of distribution and CI for 3-desacetylvecuronium could not be estimated; in turn, all distribution volumes and CI for 3-desacetylvecuronium were normalized by \(f_{\text{metabolized}}\). The shape of the plasma concentration-versus-time curve for 3-desacetylvecuronium was well described; therefore, we were able to accurately estimate values for the half-lives of 3-desacetylvecuronium.

Population-based mixed-effects models were fit to the 3-desacetylvecuronium plasma concentration data using a model-building approach similar to that used for vecuronium pharmacokinetics. We modeled using one or two compartments and models with parameters that were weight-normalized or not weight-normalized. Next, guided by visual plots, we evaluated models that permitted CI and volumes to differ with covariates. When all justified additional effects had been added to the model, the necessity for each was tested by removing it from the model. Model building was conducted using either NONMEM’s first-order or first-order conditional estimates search method.

Pharmacodynamic Modeling

Finally, we fit vecuronium effect (using data from both infusions) to sigmoid E-max effect compartment models. The parameters for these models were \(k_{\text{eo}}\) (the rate constant for equilibration of vecuronium between plasma and effect site), \(C_{\text{eq}}\) (the steady-state plasma concentration producing 50% decrease in muscle twitch tension), and \(\gamma\) (the power function of the sigmoid E-max model). A two-stage approach was taken, i.e., models were fit to each individual’s data, and then the parameters thus determined were regressed against temperature to seek temperature-related effects. The following assumptions were made: (1) values for the plasma pharmacokinetics of vecuronium and 3-desacetylvecuronium were fixed to the post hoc values determined in the analyses previously described (i.e., fitting of the model to vecuronium effect was not permitted to influence the
quality of the fit to the plasma concentrations of vecuronium or its metabolite); (2) the potency of 3-desacetylvecuronium relative to vecuronium is 84%5; and (3) the values of $k_{eo}$ and $\gamma$ for 3-desacetylvecuronium and vecuronium are the same.

Simulations
In previous experiments, it has been observed that core hypothermia prolongs the duration of action of vecuronium. To confirm that our analysis of the effects of temperature on the pharmacokinetics/pharmacodynamics of vecuronium would predict an increased duration of action, we conducted additional steps. After determining the optimal pharmacokinetic/pharmacodynamic model, we simulated the time course of 0.1 mg/kg vecuronium at different core temperatures.

Results
Unless otherwise stated, the values for a given pharmacokinetic or pharmacodynamic variable are calculated at 37°C. The range of temperatures studied were 34.3–38.0°C, and the median temperatures in each group were 34.3°C, 35.4°C, 36.6°C, and 37.7°C. The plasma concentrations of vecuronium for all subjects are shown in figure 2. Decreasing core temperature correlated with an increasing duration of action of the second infusion of vecuronium (duration in minutes $= 1.269 – 31 \cdot$ core temperature [°C]; $r^2 = 0.58; P < 0.005$), thus confirming our earlier result that hypothermia increases the duration of action of vecuronium.1 Individual results for duration of action are not presented because the dosing paradigm (low-dose infusion followed by high-dose infusion) is not a standard method of administering vecuronium.

**Vecuronium Pharmacokinetics**
The results of the model-building process are summarized in table 1. The optimal model (table 2) had three compartments and volumes and CI were weight normalized. In addition, CI decreased by 11.3% per °C decrease in temperature, and CI and V1 were 22.5% larger and 22% smaller, respectively, in men compared with women. The fit of a representative subject is illustrated in figure 3, and the relationship of predicted versus observed vecuronium concentrations for the population fit is shown in figure 4.

A complete urine collection was not obtained for two subjects, and their results were not analyzed. Urine recovery of vecuronium ranged from 4.3–15.6%. Plots of individual $f_{renal}$ against gender indicated that $f_{renal}$ varied according to gender, and a parameter added to the model to account for this significantly improved the fit. Temperature did not influence $f_{renal}$. The typical value for $f_{renal}$ in the 10 volunteers was 6.6% in men and 10.8% in women.

**3-Desacetylvecuronium Pharmacokinetics**
The results of the model-building process are summarized in table 3. The optimal model (table 4) had two...
compartments, was not weight-normalized, and allowed V1 and V2 to increase with temperature and Cl and Cl$_{\text{dist}}$ to differ between genders. The relationship of predicted versus observed 3-desacytyleveronium concentrations for the population fit is shown in figure 4.

**Pharmacodynamic Modeling**

Each individual’s $k_{eo}$, $C_{50}$, and $\gamma$ and the regression for each is shown in figure 5. Regression of individual values for vecuronium against temperature indicated that $k_{eo}$ and $\gamma$ were influenced by temperature, and $C_{50}$ was not. The regression equations for the two variables influenced by temperature are as follows: $k_{eo}$ (min$^{-1}$) = $-0.639 + 0.023 \cdot \text{temperature}$ ($r^2 = 0.443$ and $P < 0.05$); and $\gamma$ (unitless) = $20.755 - 0.439 \cdot \text{temperature}$ ($r^2 = 0.383$ and $P < 0.05$).

**Simulations**

Simulations predict an increasing duration of action of vecuronium as core temperature decreases (fig. 6). The simulation also indicates that the effect of temperature is larger as temperature decreases. For example, after a dose of 0.1 mg/kg, decreasing core temperature from 37°C to 36°C increases clinical duration 15% (from 41 to 47 min), but from 35°C to 34°C it increases clinical duration 22% (from 55 to 67 min; fig. 6).

**Discussion**

One of our principal findings was that mild hypothermia decreased vecuronium Cl. The liver and kidney are

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Table 1. Summary of Models Tested for the Pharmacokinetics of Vecuronium and the Influence of Temperature on Those Pharmacokinetics

<table>
<thead>
<tr>
<th>Model No.</th>
<th>Compartments</th>
<th>Weight-Normalized</th>
<th>Issue Tested</th>
<th>Objective Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>No</td>
<td>Weight normalization, number of compartments</td>
<td>4071.323</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Yes</td>
<td>Weight normalization, number of compartments</td>
<td>4007.340</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>No</td>
<td>Weight normalization, number of compartments</td>
<td>3705.268</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Yes</td>
<td>Weight normalization, number of compartments</td>
<td>3624.268</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>Yes</td>
<td>Temperature on clearance</td>
<td>3602.100</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>Yes</td>
<td>Model 5 plus gender on clearance</td>
<td>3573.122</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>Yes</td>
<td>Model 6 plus gender on V1</td>
<td>3560.455</td>
</tr>
</tbody>
</table>

V1 = volume of central compartment.

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Table 2. Pharmacokinetic Parameters of the Model Determined for Vecuronium and the Influence of Core Temperature on Each Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical Value</th>
<th>95% Confidence Interval</th>
<th>Coefficient of Variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (ml·kg$^{-1}$·min$^{-1}$)</td>
<td>4.21</td>
<td>3.34–5.07</td>
<td>20</td>
</tr>
<tr>
<td>Distributional</td>
<td>11.8</td>
<td>9.3–14.3</td>
<td>9</td>
</tr>
<tr>
<td>Slow distributional</td>
<td>1.63</td>
<td>1.16–2.09</td>
<td>9</td>
</tr>
<tr>
<td>Volume (ml/kg)</td>
<td>39.8</td>
<td>35.8–43.8</td>
<td>11</td>
</tr>
<tr>
<td>Central compartment (ml/kg)</td>
<td>67.3</td>
<td>57.2–77.4</td>
<td>20</td>
</tr>
<tr>
<td>Second compartment (ml/kg)</td>
<td>94.2</td>
<td>72.6–115</td>
<td>20</td>
</tr>
<tr>
<td>Third compartment (ml/kg)</td>
<td>22.5</td>
<td>10.1–36.0</td>
<td>—</td>
</tr>
<tr>
<td>Gender (% change males vs. females)</td>
<td>−22.0</td>
<td>−11 to −32</td>
<td>—</td>
</tr>
<tr>
<td>On clearance†</td>
<td>11.3</td>
<td>8.3–14.0</td>
<td>—</td>
</tr>
<tr>
<td>On volume of central compartment†</td>
<td>10.1–36.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Temperature on clearance (% change per °C)†</td>
<td>8.3–14.0</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

* Where justified; where gender values differ, the primary value in the table is for women.
† The 95% confidence interval for these effects was calculated using likelihood ratio testing.
the main organs of elimination for vecuronium, and there may be temperature-related effects on vecuronium elimination by these organs. Vecuronium is eliminated via the liver by a carrier-mediated active transport process, which is temperature-dependent and may be inhibited by hypothermia. Rocuronium is a structural relative of vecuronium, and its Cl also decreases with hypothermia. Like vecuronium, it is eliminated primarily in the liver by carrier-mediated active transport systems. Thus, temperature-mediated effects on hepatic elimination is a potential mechanism for the hypothermia-related decrease in vecuronium Cl that we observed.

Liver blood flow (in cats) does not change with mild hypothermia. This observation and the extraction ratio of vecuronium (0.7 in rats) suggest that the effects of hypothermia on vecuronium Cl are not mediated by changes in liver blood flow.

The fractional renal Cl of vecuronium was unchanged by temperature, which means that the absolute renal Cl decreased with hypothermia. This is consistent with the decreased renal blood flow and glomerular filtration rate that occurs with hypothermia.

Gender influenced both the Cl and V1 of vecuronium. The Cl for vecuronium was less in women than in men. We have no direct evidence as to the mechanism for this gender-related difference in Cl, but gender-related differences in the activity of hepatic enzyme systems is well established. However, we have no direct evidence for the effect of these putative mechanisms and cannot speculate in detail on their influence.

Our finding of decreased Cl in women conflicts with results from the study by Xue et al., who found no gender-related difference in Cl. Investigators in that study used an assay that did not differentiate vecuronium from its principal metabolite, 3-desacetylvecuronium. Thus, the value they measured for "vecuronium" concentration was composed of an indeterminate sum of vecuronium and 3-desacetylvecuronium concentrations, and would therefore give erroneous values for vecuronium Cl. Because they further assumed that there were no gender-related differences in metabolite kinetics, any error would be similar for men and women. However, our data indicate that there are gender-related differences in the Cl of the 3-desacetyl metabolite.

We also found temperature-related differences in the pharmacodynamics of vecuronium. The $k_{eo}$ decreased (0.023 min$^{-1}$ per °C) with lower temperature, suggesting slightly delayed equilibration of drug between the circulation and the neuromuscular junction during hypothermia. This effect has potential clinical significance. Because of the slower movement of drug between the circulation and the neuromuscular junction during hypothermia, the onset of vecuronium will be significantly delayed, and its recovery may be minimally prolonged.

The sensitivity of the neuromuscular junction to the effect of vecuronium, as measured by the $C_{50}$, was unchanged by temperature, consistent with results from an earlier study. A potential problem with the design of that earlier study was that it took no account of the influence of 3-desacetylvecuronium, the principal me-
Table 3: Models Tested for the Pharmacokinetics of 3-Desacetylvecuronium and the Influence of Temperature on those Pharmacokinetics

<table>
<thead>
<tr>
<th>Model No.</th>
<th>Weight-Normalized</th>
<th>Issue Tested</th>
<th>Objective Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>Weight normalization</td>
<td>2095.892</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Weight normalization</td>
<td>2142.769</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>Model 1 plus gender on clearance</td>
<td>2081.910</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>Model 3 plus gender on intercompartmental clearance</td>
<td>2071.483</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>Model 3 plus temperature on V1</td>
<td>2052.009</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>Model 4 plus temperature on V2</td>
<td>2042.162</td>
</tr>
</tbody>
</table>

V1 = volume of central compartment; V2 = volume of peripheral compartment.

Table 4: Pharmacokinetic Parameters of the Model Determined for 3-Desacetylvecuronium and the Influence of Core Temperature on Each Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical Value</th>
<th>95% Confidence Interval</th>
<th>Coefficient of Variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (l/min)</td>
<td>0.638</td>
<td>.210 to 1.06</td>
<td>59</td>
</tr>
<tr>
<td>Distribution†</td>
<td>12.8</td>
<td>-.2 to 26.8</td>
<td>81</td>
</tr>
<tr>
<td>Volume (l)</td>
<td>6.470</td>
<td>2.55 to 10.3</td>
<td>70</td>
</tr>
<tr>
<td>Central compartment</td>
<td>191</td>
<td>91.2 to 290</td>
<td>57</td>
</tr>
<tr>
<td>Second compartment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (% change males vs. females)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On clearance</td>
<td>-49</td>
<td>-84 to -13</td>
<td>—</td>
</tr>
<tr>
<td>On distributional clearance</td>
<td>-71</td>
<td>-9 to -132</td>
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</tr>
<tr>
<td>Temperature (% change per °C)</td>
<td></td>
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</tr>
<tr>
<td>On volume of central compartment</td>
<td>15.5</td>
<td>5.02 to 25.9</td>
<td>—</td>
</tr>
<tr>
<td>On volume of peripheral compartment†</td>
<td>21</td>
<td>-4.8 to 48</td>
<td>—</td>
</tr>
</tbody>
</table>

* Where justified; all parameters are normalized to $f_{\text{metabolized}}$ (i.e., they are presented as if all vecuronium were converted to 3-desacetylvecuronium; if only half is converted the parameters will be half this magnitude). Where gender values differ, the primary value in the table is for women.
† The 95% confidence interval for this effect calculated using the standard error includes the value 0, but the true 95% confidence interval is likely to be asymmetrical; therefore, we included it in the model because the parameter is statistically justified.

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Tabolite of vecuronium and a potent neuromuscular blocking drug in its own right. Therefore, it is conceivable that although the plasma concentration of vecuronium at 50% block was not different at hypothermia and normothermia, the concentration of the metabolite may have been. Consequently, the conclusion from the previous study that hypothermia did not alter the sensitivity of the neuromuscular junction to nondepolarizing neuromuscular block could have been incorrect. Because in this study we measured plasma concentrations of 3-desacetylvecuronium and factored the effect of this compound into our analysis, we can be confident in the conclusion that the sensitivity of the neuromuscular junction to nondepolarizing block (as measured by the $C_{50}$ of vecuronium) does not change over the range of temperatures we studied.

In contrast to the earlier study, we found a temperature-related change in the slope of the concentration–response curve ($\gamma$), which decreased with greater temperature. This is probably a result of the different designs of the two studies. In the earlier study, four two groups of five subjects were compared at widely differing temperatures (34.4°C and 36.8°C). Because of the small number of subjects, that study may have lacked the statistical power to identify a difference. The effect of temperature on $\gamma$ was shown in the present study, because subjects were studied over a range of temperatures and the statistical analysis was more powerful.

With decreasing temperature, $\gamma$ increased, thus making the slope of the dose–response curve steeper. As a result of the temperature-related change in $\gamma$, initial recovery of neuromuscular function after a full paralyzing dose of vecuronium will occur at lower plasma concentrations in colder patients (i.e., it will be delayed). However, as recovery progresses and T1 becomes greater than 50% of control, colder patients will have a smaller degree of block for the same plasma concentration of vecuronium, i.e., they are less sensitive to residual concentrations of vecuronium. However, these pharmacodynamic factors cannot be examined in isolation from the pharmacokinetic effects of temperature, precluding predictions of effect based on only one factor. Consequently, we simulated the effect of hypothermia on vecuronium-induced neuromuscular block based on all our data.

The simulations (fig. 6) showed that the duration of action of vecuronium was significantly prolonged by hypothermia. These results are consistent with those of an earlier study that showed that the duration of action of vecuronium was doubled by 2°C core hypothermia. The magnitude of the effect predicted by our simulations is less than that observed in the earlier study. However, there are many differences in the experimental condi-
As a consequence, the difference in magnitude of effect is not surprising. However, it is clear from both studies that a small decrease in core temperature, on the order of 2°C, significantly prolongs the duration of vecuronium block.

We studied only vecuronium, but a similar prolongation of action occurs with other muscle relaxants during mild hypothermia. Such an effect has also been shown for rocuronium, a drug with similar biodisposition to vecuronium, and for atracurium, a drug with very different elimination processes.

We have used a complex model-building analysis to examine many aspects of the pharmacokinetics and pharmacodynamics of vecuronium and its 3-desacetyl metabolite. This approach may make interpretation of our analysis difficult for those not facile in the use of such techniques. However, we believe that our approach is justified. This method permits us to account for otherwise unexplained variability and to explain it as attributable to other factors, such as gender, thus increasing our ability to detect changes associated with the variable of interest: core temperature. Any other approach would have involved performing studies with a greater number of subjects. Because we conducted the study with human volunteers, we believed it incumbent to maximize the amount of information obtained from a

Fig. 5. Plot from two-stage analysis of individual values for the pharmacodynamic variables against core temperature: $k_{eq}$ = rate constant for equilibration of vecuronium between the plasma and the neuromuscular junction; $C_{50}$ = plasma concentration of vecuronium producing 50% neuromuscular block; $\gamma$ = function representing the steepness of the dose–response relationship. Regression line is not shown for $C_{50}$ because there was no significant relationship between this variable and core temperature.

Fig. 6. Simulations using the optimal pharmacokinetic/pharmacodynamic model to predict the duration of action of a 0.1-mg/kg bolus dose of vecuronium at different core temperatures. Duration is time from drug injection to 25% recovery of the prevecuronium twitch tension. The simulations assume a 75-kg male patient. Differing weight and gender would vary the results.
limited number of subjects. The complexity of the analysis and the final model reflects the interaction of physiologic factors that influence the pharmacokinetics and pharmacodynamics of vecuronium.

In summary, we demonstrated that both mild hypothermia and gender have significant effects on the pharmacokinetics/pharmacodynamics of vecuronium. The primary implications of our results is that core hypothermia increases duration of vecuronium-induced neuromuscular block by both pharmacokinetic and pharmacodynamic mechanisms.

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References


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