

## Temperature-dependent Pharmacokinetics and Pharmacodynamics of Vecuronium

James E. Caldwell, M.B.Ch.B.,\* Tom Heier, Ph.D.,† Peter M. C. Wright, M.D.,‡ Sean Lin, M.D.,§  
Gerald McCarthy, M.D.,|| Janos Szenohradszky, M.D.,# Manohar L. Sharma, Ph.D.,\*\* Jeremy P. Hing, M.Sc.,††  
Marc Schroeder, M.D.,§ Daniel I. Sessler, M.D.‡‡

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

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\* Professor of Anesthesia, University of California-San Francisco.

† Assistant Professor of Anesthesia, University of California-San Francisco. Current position: Consultant Anesthetist, Ullevaal University, Oslo, Norway.

‡ Senior Lecturer, University of Newcastle-upon-Tyne, Newcastle-upon-Tyne, United Kingdom.

§ Research Associate, University of California-San Francisco.

|| Assistant Professor of Anesthesia, University of California-San Francisco. Current position: Consultant Anesthetist, The Queens University of Belfast, Belfast, United Kingdom.

# Assistant Professor of Anesthesia, University of California-San Francisco. Current position: Assistant Professor of Anesthesia, University of Southern California, Los Angeles, California.

\*\* Research Chemist, University of California-San Francisco.

†† Research Associate, University of Newcastle-upon-Tyne, Newcastle-upon-Tyne, United Kingdom.

‡‡ Professor of Anesthesia, University of California-San Francisco; Professor, Ludwig Boltzmann Institute for Clinical Anesthesia and Intensive Care, Vienna, Austria; Director, Outcomes Research™, and Vice Chair, Department of Anesthesia and General Intensive Care, University of Vienna, Vienna, Austria.

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Address reprint requests to Dr. Caldwell: Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA 94143-0648. Address electronic mail to: [caldwell@anesthesia.ucsf.edu](mailto:caldwell@anesthesia.ucsf.edu). On the world wide web: [www.outcomes.ucsf.edu](http://www.outcomes.ucsf.edu)

**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<sup>-1</sup> · min<sup>-1</sup> 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<sup>-1</sup> · min<sup>-1</sup>, 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<sup>-1</sup> 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,<sup>1</sup> an effect that could have a pharmacokinetic or a pharmacodynamic basis.<sup>2,3</sup> 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.<sup>4</sup> The dose of vecuronium used in the study by Heier *et al.*<sup>4</sup> (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 ( $> 36.5^{\circ}\text{C}$ ) or hypothermic (approximately  $34.5^{\circ}\text{C}$ ).<sup>1,4</sup> 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 temperature on both the pharmacodynamics and pharmacokinetics of vecuronium. In addition, because the principal metabolite of vecuronium, 3-desacetylvecuronium, has potent neuromuscular blocking effects,<sup>5</sup> the neuromuscular 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 practiced at the Medical Center of the University of California, San Francisco. Lactated Ringer's solution was infused *via* an 18-gauge intravenous catheter inserted in the subject's arm.

All drugs were administered through this catheter. Anesthesia was induced with  $30\ \mu\text{g}/\text{kg}$  alfentanil and  $3\ \text{mg}/\text{kg}$  propofol. Tracheal intubation was then performed 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*

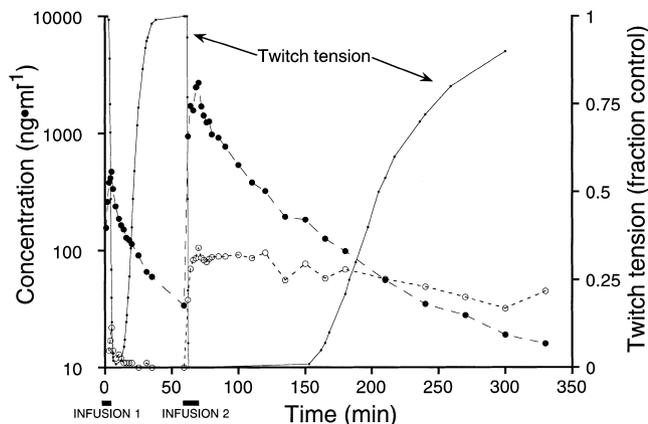
Core body temperature was measured by a thermocouple placed in the distal esophagus (Mon-a-Therm; Mallinckrodt, Anesthesia Products Inc., St. Louis, MO). Three volunteers were randomly assigned to be studied in each of four core temperature ranges:  $\geq 37.0^{\circ}\text{C}$ ,  $36.0$ – $36.9^{\circ}\text{C}$ ,  $35.0$ – $35.9^{\circ}\text{C}$ , and  $< 35.0^{\circ}\text{C}$ . Core temperature was manipulated by a combination of forced-air warming (Bair Hugger; Augustine Medical Inc., Minneapolis, MN) and surface cooling. The target temperature, once achieved and stabilized, was maintained within  $\pm 0.1^{\circ}\text{C}$  throughout the remainder of the study.

### *Neuromuscular Function Monitoring*

To measure neuromuscular responses, supramaximal stimuli ( $200\ \mu\text{s}$  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 resulting evoked mechanical responses of the adductor pollicis were measured with a calibrated force transducer (Myotrace; Life-Tech Inc., Houston, TX) and amplified (DC Signal Conditioner; Gould Electronics, Valley View, OH). 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 parameter determination for both pharmacodynamics and pharmacokinetics. Pharmacodynamic parameters are best determined with a small, subparalyzing dose of muscle relaxant. To achieve this, vecuronium was infused at a rate of  $5\ \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  until the T1 response decreased by 70% of control, at which point the infusion was stopped. Arterial samples were obtained 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



**Fig. 1.** Flow of the study in one subject (volunteer no. 1) whose core temperature was 34.3°C. Vecuronium plasma concentrations are represented by the filled circles and dashed line, whereas those of the metabolite 3-desacetylvecuronium are represented by open circles and dashed line. The solid line indicates twitch tension of the adductor pollicis (as a fraction of prevecuronium control).

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.<sup>6</sup> 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 ( $\text{Cl}_{\text{dist}}$ ), and volumes of the central (V1) and peripheral (V2) compartments. Structural models with three compartments had additional parameters: slow distributional Cl ( $\text{Cl}_{\text{slow}}$ ) 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<sup>7</sup>) were fit to the vecuronium plasma concentration data using a model-building approach<sup>8</sup> 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:

$$\text{Cl} = \text{Cl}_{\text{typical}} \cdot \exp(\eta)$$

where  $Cl$  is the value for an individual,  $Cl_{\text{typical}}$  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  $Cl$ , intercompartmental  $Cl$  ( $Cl_{\text{dist}}$ ),  $V1$ , 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) vecuro-

nium 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  $Cl$  for 3-desacetylvecuronium could not be estimated; in turn, all distribution volumes and  $Cl$  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  $Cl$  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  $k_{eo}$  (the rate constant for equilibration of vecuronium between plasma and effect site),  $C_{50}$  (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%<sup>5</sup>; 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 =  $1,269 - 31 \cdot \text{core temperature [}^\circ\text{C]};$   $r^2 = 0.58;$   $P < 0.005$ ), thus confirming our earlier result that hypothermia increases the duration of action of vecuronium.<sup>1</sup> 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 re-

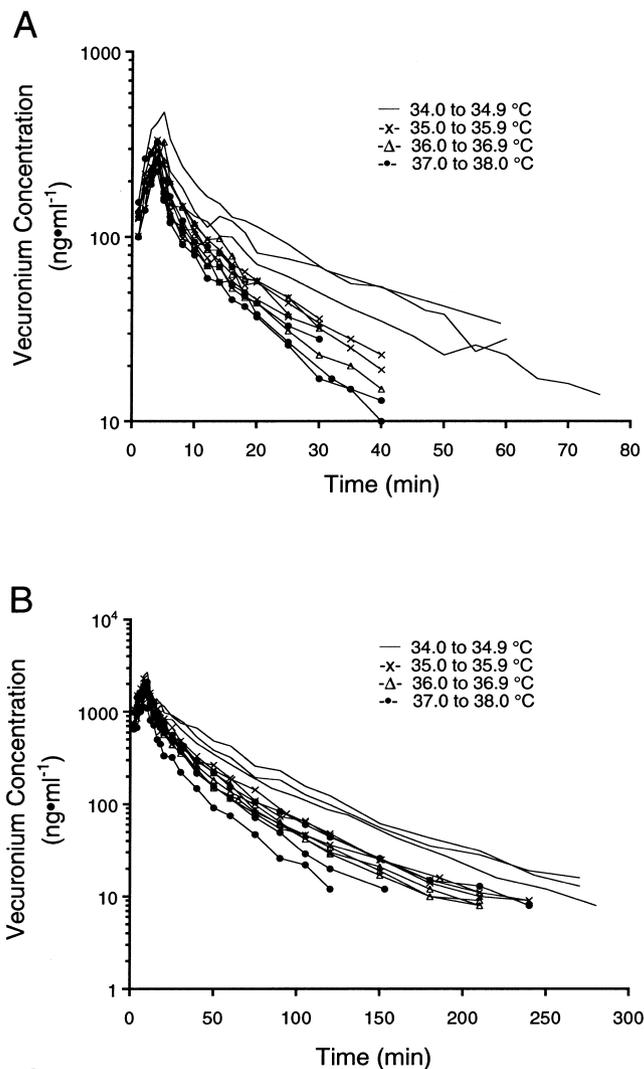


Fig. 2. Vecuronium plasma concentration versus time for all subjects. The symbols separate the four different ranges of core temperature at which the subjects were studied. (A) Concentrations after the initial (low-dose) infusion; (B) concentrations after the second infusion (total dose, 0.2 mg/kg).

covery 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

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

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

V1 = volume of central compartment.

compartments, was not weight-normalized, and allowed V1 and V2 to increase with temperature and Cl and Cl<sub>dist</sub> to differ between genders. The relationship of predicted *versus* observed 3-desacetylvecuronium 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:  $k_{eo}$  ( $\text{min}^{-1}$ ) =

$$-0.639 + 0.023 \cdot \text{temperature} \quad (r^2 = 0.443 \text{ and } P < 0.05); \text{ and } \gamma \text{ (unitless)} = 20.755 - 0.439 \cdot \text{temperature} \quad (r^2 = 0.383 \text{ and } P < 0.05).$$

#### 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).

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

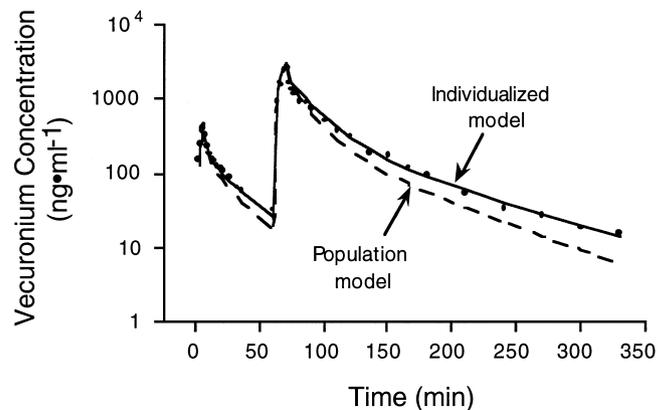
	Typical Value	95% Confidence Interval	Coefficient of Variation (%)
Clearance ( $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	4.21	3.34–5.07	20
Distributional	11.8	9.3–14.3	9
Slow distributional	1.63	1.16–2.09	9
Volume (ml/kg)			
Central compartment (ml/kg)	39.8	35.8–43.8	11
Second compartment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

\* 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.

#### Discussion

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



**Fig. 3. Representative subject (volunteer no. 1) showing the fit of the model prediction to the vecuronium plasma concentrations. The dashed line shows the prediction according to the parameters of the “typical” individual. The solid line is the prediction of the individualized *post hoc* fit, which takes the individual variability factors ( $\eta$ ) into account.**

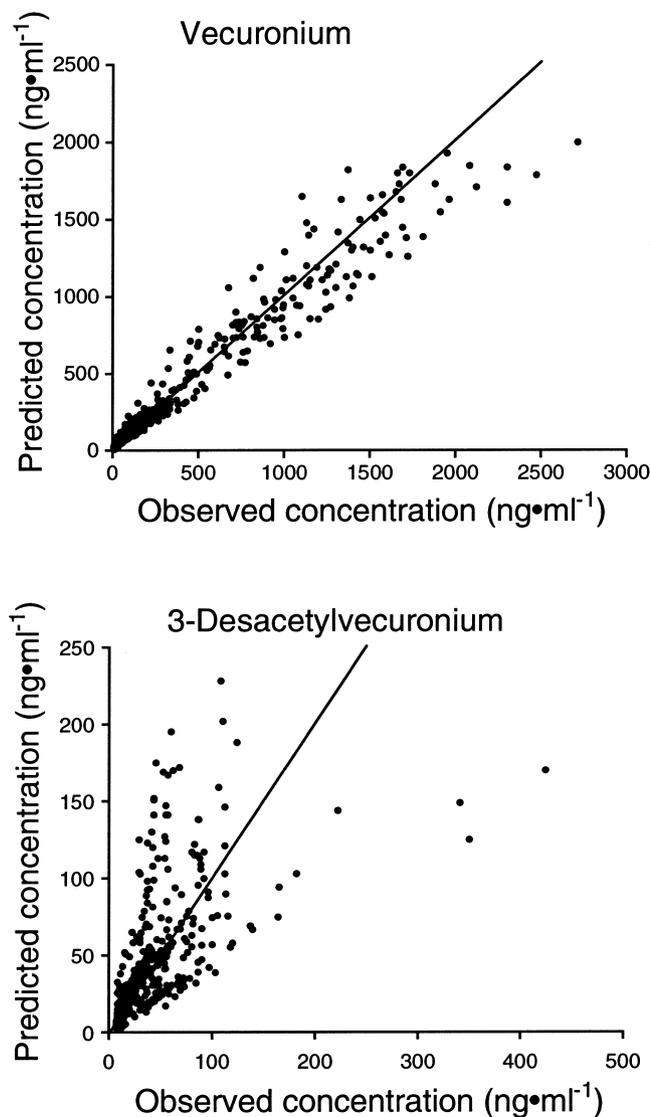


Fig. 4. Plots (with line of identity) from the nonlinear mixed-effects modeling population model of the observed *versus* predicted plasma concentrations of vecuronium and its metabolite, 3-desacetylvecuronium.

the main organs of elimination for vecuronium,<sup>9,10</sup> 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,<sup>11,12</sup> which is temperature-dependent and may be inhibited by hypothermia.<sup>11-13</sup> Rocuronium is a structural relative of vecuronium, and its CI also decreases with hypothermia.<sup>14</sup> Like vecuronium, it is eliminated primarily in the liver<sup>15,16</sup> by carrier-mediated active transport systems.<sup>17</sup> Thus, temperature-mediated effects on hepatic elimination is a potential mechanism for the

hypothermia-related decrease in vecuronium CI that we observed.

Liver blood flow (in cats) does not change with mild hypothermia.<sup>18</sup> This observation and the extraction ratio of vecuronium (0.7 in rats)<sup>19</sup> suggest that the effects of hypothermia on vecuronium CI are not mediated by changes in liver blood flow.

The fractional renal CI of vecuronium was unchanged by temperature, which means that the absolute renal CI decreased with hypothermia. This is consistent with the decreased renal blood flow and glomerular filtration rate that occurs with hypothermia.<sup>20,21</sup>

Gender influenced both the CI and V1 of vecuronium. The CI for vecuronium was less in women than in men. We have no direct evidence as to the mechanism for this gender-related difference in CI, but gender-related differences in the activity of hepatic enzyme systems is well established.<sup>22,23</sup> 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 CI in women conflicts with results from the study by Xue *et al.*,<sup>24</sup> who found no gender-related difference in CI. 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 CI. 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 CI of the 3-desacetyl metabolite.

We also found temperature-related differences in the pharmacodynamics of vecuronium. The  $k_{eo}$  decreased ( $0.023 \text{ min}^{-1} \text{ per } ^\circ\text{C}$ ) 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.<sup>4</sup> 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-

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**Table 3. Models Tested for the Pharmacokinetics of 3-Desacetylvecuronium and the Influence of Temperature on those Pharmacokinetics**

Model No.	Weight-Normalized	Issue Tested	Objective Function
1	No	Weight normalization	2095.892
2	Yes	Weight normalization	2142.769
3	No	Model 1 plus gender on clearance	2081.910
4	No	Model 3 plus gender on intercompartmental clearance	2071.483
5	No	Model 3 plus temperature on V1	2052.009
6	No	Model 4 plus temperature on V2	2042.162

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

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,<sup>4</sup> 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.<sup>1</sup> 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-

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

	Typical Value	95% Confidence Interval	Coefficient of Variation (%)
Clearance (l/min)	0.638	.210 to 1.06	59
Distributional†	12.8	-1.2 to 26.8	81
Volume (l)			
Central compartment	6.470	2.55 to 10.3	70
Second compartment	191	91.2 to 290	57
Gender (% change males vs. females)			
On clearance	-49	-84 to -13	—
On distributional clearance	-71	-9 to -132	—
Temperature (% change per °C)			
On volume of central compartment	15.5	5.02 to 25.9	—
On volume of peripheral compartment†	21	-4.8 to 48	—

\* 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.

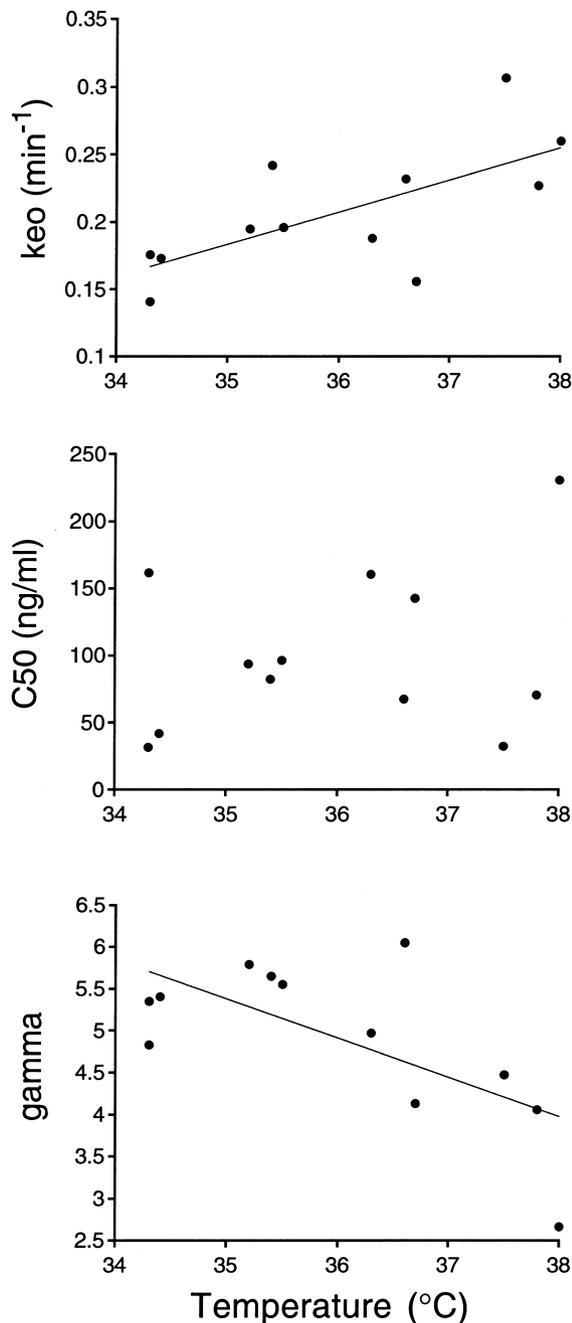


Fig. 5. Plot from two-stage analysis of individual values for the pharmacodynamic variables against core temperature:  $k_{eo}$  = rate constant for equilibration of vecuronium between the plasma and the neuromuscular junction;  $C_{50}$  = plasma concentration of vecuronium producing 50% neuromuscular 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.

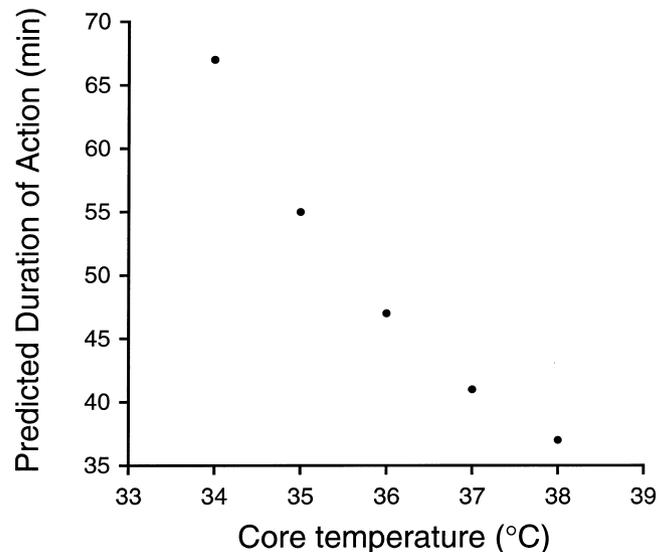


Fig. 6. Simulations using the optimal pharmacokinetic/pharmacodynamic model to predict the duration of action of a 0.1-mg/kg bolus dose of vecuronium at different core temperatures. Duration is time from drug injection to 25% recovery of the prevecuronium twitch tension. The simulations assume a 75-kg male patient. Differing weight and gender would vary the results.

tions of the two studies. 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,<sup>14</sup> a drug with similar biodisposition to vecuronium,<sup>15,16</sup> and for atracurium,<sup>25</sup> a drug with very different elimination processes.<sup>26</sup>

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 (e.g., 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

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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