Influence of Chronic Phenytoin Administration on the Pharmacokinetics and Pharmacodynamics of Vecuronium

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Background: The duration of action of vecuronium is reduced in patients receiving phenytoin. In this study, the authors examined, simultaneously, the influence of phenytoin on both the pharmacokinetics and the pharmacodynamics of vecuronium.

Methods: This study was approved by the institutional review board of the University of California, San Francisco, and patients gave written informed consent. Twenty-two patients, 11 taking phenytoin and all scheduled to undergo prolonged neurosurgical procedures with general anesthesia, participated in the study. In 12 patients (6 phenytoin, 6 control), vecuronium was infused at 7.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until the first response (T1) of each train-of-four decreased by 50%; in the remaining 10 patients (5 phenytoin, 5 control), 200 $\mu g/kg$ vecuronium was infused over 10 min. Arterial blood samples were drawn at intervals over the next 5–7 h. Plasma concentrations of vecuronium and 3-desacetylvecuronium were measured by capillary gas chromatography. Pharmacokinetic and pharmacodynamic modeling was used to characterize the disposition of vecuronium and patient responses to it in the two groups.

Results: Clearance was typically increased by 138% (95% confidence interval, 93–183%) in patients taking phenytoin. The effect of vecuronium was well described using a sigmoid Emax model. The concentration of vecuronium giving 50% twitch depression was increased 124% (45–202%) in patients taking phenytoin.

Conclusions: Chronic phenytoin therapy reduces the effect of vecuronium by mechanisms that include both increased vecuronium metabolism and reduced sensitivity of the patient to circulating concentrations of vecuronium.

PATIENTS receiving the anticonvulsant phenytoin chronically have a higher dose requirement for neuromuscular-blocking drugs (NMBs) than patients not receiving anticonvulsant therapy.[1-6] Phenytoin induces hepatic enzymes, and it is likely that metabolism and elimination of the muscle relaxant is increased; increased clearance of muscle relaxants has been demon-

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strated after chronic phenytoin use.[6] Phenytoin also has effects that might alter the apparent sensitivity of the patient to circulating muscle relaxants. For example, it has mild blocking action at the neuromuscular junction,[7] which may lead to up-regulation of the acetylcholine receptor.[8] It also might alter the protein binding of muscle relaxants or have effects at presynaptic acetylcholine receptors. The relative contribution of these various possible mechanisms to this interaction is not known.

In our practice, some neurosurgical patients are treated with phenytoin before they arrive for surgery, whereas others never receive an anticonvulsant. Thus, they form a population in which the effects of phenytoin on the pharmacology of vecuronium can be examined and compared with a phenytoin-naive group. Here, we examine three specific effects. We hypothesize that in patients taking phenytoin compared with phenytoin-naive patients, (1) the biodisposition and elimination of vecuronium is altered, (2) the metabolism of vecuronium to 3-desaceylvecuronium is altered, and (3) the patient has altered sensitivity to the neuromuscular-blocking effects of vecuronium.

Materials and Methods

With the approval of the institutional review board (University of California, San Francisco, California) and written, informed patient consent, we studied 22 patients with American Society of Anesthesiologists physical status class II or III who were scheduled to undergo supratentorial craniotomy for tumor resection. None of the patients had focal neurologic deficits. Eleven patients received phenytoin before operation (determined by the presence of seizure activity); the remainder received no anticonvulsants, thus forming two groups that were studied contemporaneously. No other anticonvulsants were administered. Patients were excluded who had intercurrent illness or who were taking other medication expected to influence the action of NMBs; an exception was for those who were given steroids. Nine of the 22 patients received steroids, and these were evenly distributed between the two groups.

Anesthetic Technique

In the operating room, standard vital signs monitoring, according to the guidelines of the American Society of Anesthesiologists, and clinical standards practiced at the Medical Center of the University of California, San Fran-

Table 1. Patient Characteristics and Some Neuromuscular Responses

	Phenytoin	Control
Age, yr	37 (28–54)	36 (26–53)
Weight, kg	74 (47–112)	70 (50–107)
Sex, (M/F)	6/5	5/6
Duration of phenytoin therapy	12 days (3 days–2 yr)	NA
Temperature, °C	35.6 (34.9–36.6)	35.5 (34.6–36.3)
Duration of action, 200 μg/kg, min	47 (33–67)	132 (106–171)

Data are presented as median (range).

NA = not applicable.

cisco, were instituted. Anesthesia was induced with 5–10 μg/kg fentanyl and 1–2 mg/kg sodium thiopental; 1.5 mg/kg succinylcholine was then administered, and the patients' tracheas were intubated. Anesthesia was maintained with 60–70% nitrous oxide in oxygen, and 0.2–0.5% end-tidal concentration isoflurane. Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide at 25–30 mmHg. After induction of anesthesia, a 20-gauge catheter was inserted into each patient's radial artery at the wrist.

Neuromuscular Function Monitoring

To measure neuromuscular transmission, supramaximal stimuli (0.2 ms in duration) in a train-of-four sequence at 2 Hz were applied every 12 s, *via* surface electrodes, to the ulnar nerve at the wrist (Digistim II; Neuro Technology Inc., Houston, TX). The resulting evoked mechanical responses of the adductor pollicis (preload 200–300 g) 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 computer (LabView; National Instruments, Austin, TX). When the effect of succinylcholine had dissipated and the adductor pollicis twitch tension had not changed for 15 min, the T1 response was determined and used as the control to which all subsequent T1 responses were compared. Vecuronium was then administered.

Drug Administration, Sampling, and Assay

Twelve patients (six phenytoin, six control) received a small dose of vecuronium to give data suitable for the determination of neuromuscular junction sensitivity. In these patients, vecuronium was infused at 7.5 μg · kg^{-1} · min^{-1} until T1 had decreased to less than 50% of control; the infusion was then discontinued. Twitch tension was monitored as described above until T1 was more than 90%. Arterial blood samples were obtained immediately before vecuronium administration and at 1,

2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45, 50, 55, and 60 min thereafter or until T1 recovered to greater than 90% of control (whichever occurred sooner). Ten patients (five phenytoin, five control) received a larger dose of vecuronium to give data more suitable for the determination of vecuronium disposition. In these patients, 200 μg/kg vecuronium was infused over 10 min, and arterial blood samples were drawn at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, 240, 300, and 360 min after the start of the infusion. In these patients, urine was collected before vecuronium administration and hourly for 6 h after drug administration.

Blood samples were immediately heparinized, placed in ice, and centrifuged. They were acidified within 1 h and stored at −30°C. Urine was acidified and stored at −30°C. Plasma concentrations of vecuronium and 3-desacetylvecuronium in plasma and urine were measured by a capillary gas chromatograph with nitrogen-sensitive detection. This assay is sensitive to 5 ng/ml for vecuronium and 3-desacetylvecuronium and is linear over the range 5–5,000 ng/ml, with a coefficient of variation of 15% or less.[9]

Pharmacokinetic–Pharmacodynamic Analysis

The analysis was performed in four phases; all used NONMEM (Globomax, Hanover, MD) version 5 running on a SUN Ultra Enterprise (Sun Microsystems, Santa Clara, CA) computer. The first three phases involved vecuronium pharmacokinetics and used plasma concentration data from all 22 patients. In the first phase, a population model of vecuronium was determined using a model-building approach (*i.e.*, we first fit a simple model and then added additional parameters to the model as justified). In the second phase, the previously determined vecuronium kinetics were fixed, and renal clearance as a proportion of total clearance was determined. In the third phase, a population model of 3-desacetylvecuronium was built, again using a model-building approach. During each of these three phases, we tested additional model parameters, each in an attempt to explain variation in drug disposition by modeling it as a function of chronic phenytoin therapy. We also attempted to add additional parameters that modeled variation as a function of age, sex, weight, duration of phenytoin treatment, and concurrent steroid medication.

In the final phase, the previously determined models of vecuronium and 3-desacetylvecuronium were used as a basis to determine models of the effect of vecuronium. We assumed that the potency of 3-desacetylvecuronium relative to vecuronium is 84%.[10] The model used had the following parameters: effect site equilibration, effect site concentration giving 50% effect, and the slope of the concentration–effect relation. A two-stage approach was taken (*i.e.*, each patient was modeled separately), and

Table 2. Models Tested for the Pharmacokinetics of Vecuronium and Influence of Phenytoin Administration on Those Pharmacokinetics

Model No.	No. of Compartments	No. of ETAs	No. of Phenytoin Factors	No. of EPSs	Issue Tested	Objective Function
1	2	4	0	2	Base model	3422.398
2	3	4	0	2	No. of compartments	3175.200
3	3	3	0	2	Number of variability factors (best result of several possibilities)	3185.995
4	*3*	*4*	*1*	*2*	*Phenytoin administration influences clearance*	*3056.132*
5	3	4	1	2	Phenytoin administration influences V_{ss}	3175.197
6	3	4	1	2	Phenytoin administration influences intercompartment clearance	3164.375
7	3	4	2	2	Phenytoin influences two parameters (best result of several possibilities)	3056.132
8	3	4	1	2	Sex affects pharmacokinetic parameters (best result of several)	3056.460
9	3	4	1	1	Error model	3298.017

The optimal model (No. 4) is shown in italics.

EPS = parameter modeling for within individual measurement error; ETA = parameter modeling between individual variation in the model structure; V_{ss} = central volume of distribution at study state.

data for each patient were modeled independently. The influence of chronic phenytoin therapy was examined by comparing the pharmacodynamic parameters between the phenytoin patients and the control patients using the Student *t* test. Further details of the analyses are given in the appendix.

Results

The patients in the two groups had similar physical characteristics and similar sex distribution (table 1). The duration of action of the large dose of vecuronium was reduced in the patients taking phenytoin (table 1).

The plasma concentration profile for vecuronium was better described by a three-compartment model compared with a two-compartment model; of the six parameters defining this model, only clearance varied systematically with chronic phenytoin therapy. The model-building process for vecuronium pharmacokinetics and the parameters of the final model are given in tables 2 and 3. Each individual's plasma concentration profile was well described by the individualized models. The vecuronium plasma concentration profiles are given in figure 1, and examples of model fits are given in figure 2.

Urine collection was completed in eight patients (four phenytoin, four controls); the proportion of vecuronium elimination (f_{renal}) recovered in the urine ranged from 6.33 to 12.6% of the administered dose. The typical values for f_{renal} were 6.96% (range, 6.33–7.57%) in the patients receiving phenytoin and 12.2% (range, 12.0–12.6%) in the controls. A model parameter describing f_{renal} to be different between phenytoin patients and controls was justified.

A model of 3-desacetylvecuronium disposition was successfully built, and the individualized models described each individual's plasma profile well. However, the proportion of vecuronium converted to 3-desacetylvecuronium might have been influenced by phenytoin. Consequently, we cannot interpret the model for 3-desacetylvecuronium with respect to the influence of phenytoin on its disposition, and the model is not presented here. Further details are given in the appendix.

Based on the individualized models of vecuronium and 3-desacetylvecuronium concentrations, we determined 22 individual models of the effect of vecuronium. We summarized the parameters in table 4 and provided some example model fits in figure 3. The concentration of vecuronium required to produce 50% block was 213

Table 3. Pharmacokinetic Parameters of the Model Determined for Vecuronium and Influence of Phenytoin Therapy on Each Parameter (where Justified)

	Typical Value	95% CI	CV, %	Effect of Phenytoin, % Change (95% CI)
Clearance, ml · kg^{-1} · min^{-1}	3.37	2.66–4.08	38	138 (93–183)*
Intercompartment clearance 1 to 2, ml · kg^{-1} · min^{-1}	7.5	5.99–9.00	37	
Intercompartment clearance 1 to 3, ml · kg^{-1} · min^{-1}	1.08	0.81–1.34	37	
Volume 1, ml/kg	34.1	28.6–39.6	29	
Volume 2, ml/kg	41.3	36.1–46.5	23	
Volume 3, ml/kg	45.7	37.6–53.8	32	

* The clearance in patients taking phenytoin was 3.37 + (1.38 × 3.37) = 8.02 ml · kg^{-1} · min^{-1}. All other parameters were unchanged with phenytoin.

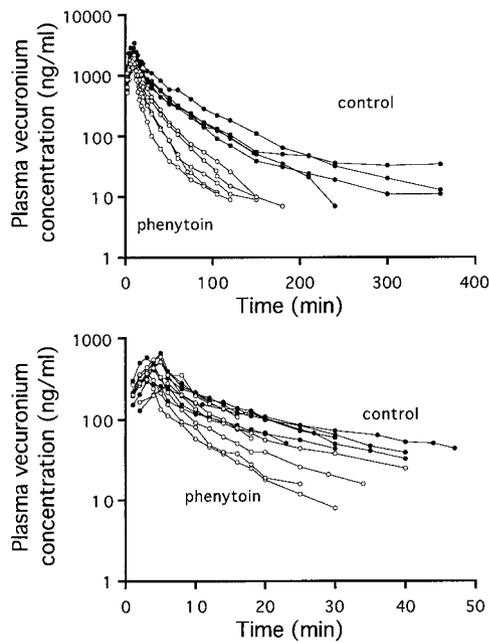CI = confidence interval; CV = coefficient of variation.

Fig. 1. Plasma vecuronium concentration profiles for the 22 patients studied. Data from the 10 patients who received a large fixed dose of vecuronium (*top*) and the 12 patients who received the smaller dose (*bottom*) are shown.

Table 4. Pharmacodynamic Parameters in the Control Patients and Those Who Received Phenytoin

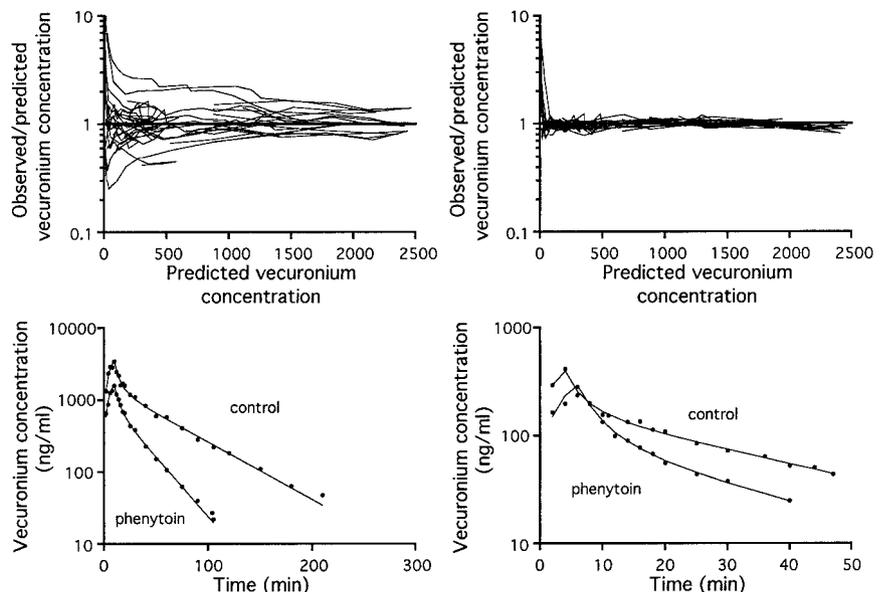|	Phenytoin	Control
k_{e0}, min^{-1}	0.177 (0.11)	0.165 (0.05)
C_{50}, ng/ml*	213 (109)	95 (46)
γ	5.6 (1.1)	4.6 (1.4)

Data are presented as mean (SD).

* $P = 0.005$.

C_{50} = effect site concentration giving 50% effect; γ = slope of the concentration–effect relation; k_{e0} = effect site equilibration.

(109) ng/ml (mean and SD) after phenytoin and 95 (46) ng/ml in control patients ($P < 0.05$; fig. 4). The rate constant of equilibration for the biophase and the sigmoidicity of the concentration–response curve were similar in the phenytoin and control patients. An analysis confined to the patients who received the low dose of vecuronium yielded similar results.

Discussion

Patients taking anticonvulsant drugs often respond less to NMBs than expected. The magnitude of this effect can be considerable, and consequently, the interaction is important. Drug interactions such as this may have a pharmacokinetic and/or a pharmacodynamic basis,[11,12] and in the case of this particular interaction, there are feasible mechanisms for either. In this study, we examine the specific interaction between phenytoin and vecuronium. We show that, in patients taking phenytoin chronically compared with other patients, the clearance of vecuronium is increased more than twofold and that the concentration of vecuronium needed to produce 50% neuromuscular block is also increased more than twofold. The interaction between muscle relaxants and anticonvulsants has been explored in many previous studies, and it is already quite well understood; this study adds to our knowledge by quantifying the relative contributions of the kinetic and dynamic components of the interaction with a high degree of precision.

The patients included in this study had been taking phenytoin for periods of time varying from 3 days to several years. All but one had received phenytoin for more than 1 week. The effects of acute phenytoin administration are to augment neuromuscular block (the contrary effect to that seen with chronic treatment).[13,14] We recruited patients with varying duration of treatment with the intention of elucidating the time course of this

Fig. 2. Predicted *versus* observed vecuronium plasma concentrations. *Top* panels show observed/predicted vecuronium concentrations based on the typical value model (*left*) and the individualized models (*right*). *Bottom* panels show the fit of the model to the data for a typical control and phenytoin patient for the large dose (*left*) and the small dose (*right*).
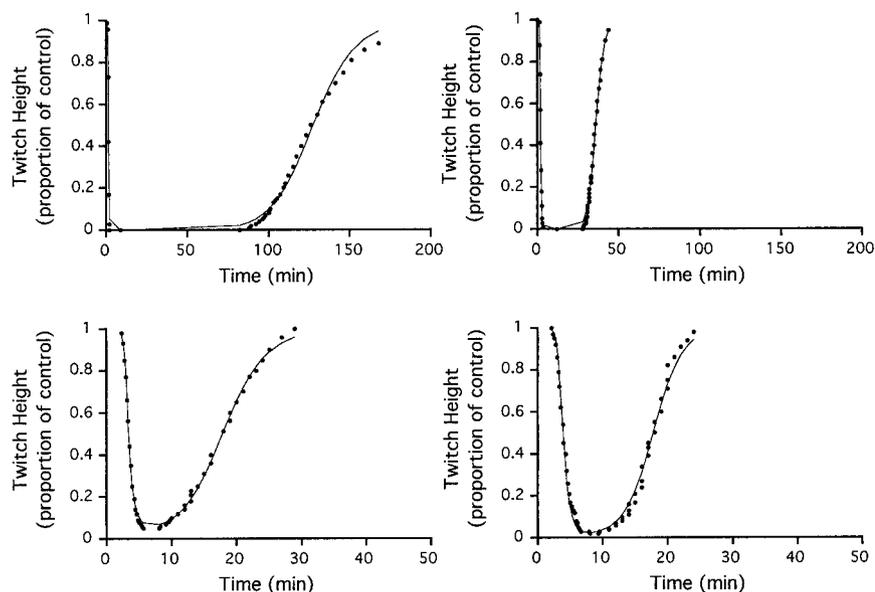
Fig. 3. Four typical effect-*versus*-time profiles. The *top panels* are from patients who received a larger dose (*top left*: control patients; *top right*: patients taking phenytoin). The *bottom panels* are from patients who received a small dose (*bottom left*: control patients; *bottom right*: patients taking phenytoin). *Lines* = model predictions; *points* = observed data.

biphasic response. We are not aware of any previous studies that examined this time course, although a period of 1 week has been suggested for the chronic effects to occur.[15] Within the range of 3 days to several years that we studied, we did not find any statistically justified evidence for treatment duration having an influence. There were some indications that the resistance to vecuronium seen in patients taking phenytoin was not as evident when the exposure to phenytoin was for very short periods. In figure 4, patients taking phenytoin for less than 10 days all appear in the lower 50% of the range of effect site concentrations giving 50% effect observed in the phenytoin patients. Therefore, it is conceivable that if we had only studied patients taking phenytoin for longer periods, the resistance to vecuronium might have been even more pronounced. Another potentially confounding issue was the coadministration of steroids in a proportion of patients (9 of the 22). These were distributed in proportion between the two groups, and so we
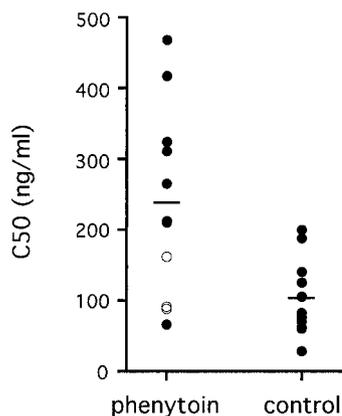
are confident that any effect of steroid treatment on the response to vecuronium did not influence our findings.

Both steroidal and benzylisoquinoline (NMBs) have been observed to have a reduced effect in patients taking anticonvulsant drugs. For steroidal NMBs, this interaction has been observed with phenytoin,[2,4,6,15-20] carbamazepine,[17,19-24] and other anticonvulsant drugs.[25] For the benzylisoquinoline NMBs, evidence is less clear; some studies report an effect,[3,26,27] and others do not.[2,4,18,28,29] These differences might be explained by the typical metabolism of these drugs. For steroidal NMBs, liver metabolism is an important route of drug elimination.[30] Many anticonvulsant drugs are potent inducers of liver enzymes. Therefore, a possible explanation for the reduced effect of steroid NMBs is that they are eliminated more rapidly because of liver enzyme induction. More rapid elimination of the NMB has been demonstrated for vecuronium (discussed further below), pancuronium,[18] and rocuronium[6] in patients taking phenytoin. In contrast, benzylisoquinoline NMBs are typically not dependent on liver metabolism or excretion. However, patients taking anticonvulsant drugs are resistant to their effects. Therefore, we must consider other mechanisms for the interaction.

Acute phenytoin treatment produces neuromuscular block[31] and enhances the action of nondepolarizing NMDs.[13,14] A wide range of anticonvulsant drugs have similar effects.[32] These observations provide a further putative mechanism for the resistance to NMB action with chronic anticonvulsant administration. The weak neuromuscular-blocking properties of anticonvulsant drugs results in postjunctional acetylcholine receptor up-regulation.[8,33,34] Thus, the enhancement of the action of nondepolarizing NMDs that occurs with acute administration of phenytoin gives way to resistance. Other possible explanations for resistance to vecuro-

Fig. 4. Individual effect site concentrations giving 50% effect (C_{50} values) for all 22 patients. Phenytoin values (*left*) and control values (*right*) are shown. *Open circles* = data for patients taking phenytoin for 10 days or less.

nium that do not involve changes in the disposition of vecuronium include changes in the protein binding of vecuronium or a presynaptic effect of phenytoin. For example, phenytoin increases α1-acid glycoprotein concentrations, which might alter the free fraction of the NMB. However, a study that examined this proposal concluded that altered protein binding does not cause resistance to vecuronium.[16] The study presented here indicates that one of these nondispositional mechanisms of resistance is important and may potentially be of equal magnitude to that of increased elimination, even in the case of steroid-based NMBs. We found that, in patients receiving chronic phenytoin therapy, the clearance of vecuronium was increased more than twofold, and the steady state circulating concentration needed to produce 50% block was also increased more than twofold. The nature of our study is such that we cannot distinguish between the different putative mechanisms for this altered patient sensitivity; decreased end organ sensitivity and increased protein binding of vecuronium are the most likely candidates.

Many published studies of the interaction between NMBs and anticonvulsant drugs are limited to clinical observations and are not designed to address the mechanism for the interaction. Of those studies that examine potential mechanisms, many are designed to examine pharmacokinetics but not to reconcile any pharmacokinetic findings to clinical observations of drug effects *via* the concentration–effect relation (pharmacodynamics). One study that does examine both the kinetic and dynamic components of the interaction between phenytoin and vecuronium was published recently by Soriano *et al.*[20] Our results are consistent with those of Soriano *et al.* in that both studies demonstrate greatly increased vecuronium clearance. However, the effect data in the study of Soriano *et al.* were insufficient to permit the vecuronium plasma concentration data to be reconciled with the time course of effect. Hence, the authors were not able to quantify the pharmacodynamic component of the interaction. In the same study, Soriano *et al.* also looked at the interaction of carbamazepine with vecuronium, a question also examined by Alloul *et al.*[21] Each of these studies also attempted to quantify the pharmacodynamic component of the interaction. In each case, data limitations restricted the characterization of the pharmacodynamics of vecuronium. The study presented here was designed to address both pharmacokinetics and pharmacodynamics and to quantify the relative contributions of these two components. We examine whether chronic phenytoin therapy alters the disposition of vecuronium and whether any altered disposition can account for changes in the time course of effect of vecuronium. The altered disposition of vecuronium alone could not account for its altered time course, and we concluded that the sensitivity of the patient to vecuronium was altered. We quantified this dynamic component of the interaction as being of equal magnitude with the kinetic component.

We confirm that the biodisposition of vecuronium is altered in patients taking phenytoin. This alteration is limited to a change in the elimination rate of vecuronium. We modeled the plasma concentration profile of vecuronium as a three-compartment model that varied between individuals. With the small number of individuals studied and the number of parameters needed to specify a three-compartment model (six), we might have had difficulty in demonstrating convincingly a systematic difference between the treatment groups. The covariation in parameters might have confounded our ability to demonstrate parameter differences between subgroups.[35] We addressed this problem by analyzing our data using mixed-effects modeling.[36] With mixed-effects modeling, all data from all individuals are modeled together, and covariation between model parameters is accounted for. Using this technique, we found that only clearance of vecuronium was altered between our two treatment groups. No other changes in biodisposition were supported by our data. We assume that this increased clearance of vecuronium occurs as a consequence of inducted liver enzymes. A consistent finding was that, as expected, the fraction of clearance of vecuronium that appeared in the urine was reduced in the patients taking phenytoin by a similar proportion, suggesting that the renal elimination remained unchanged.

We also determined a population model of the disposition of 3-desacetylvecuronium for the purpose of describing the observed concentrations of 3-desacetylvecuronium before undertaking pharmacodynamic modeling. Because this model cannot be interpreted meaningfully, we do not present it here (see appendix). Concentrations of 3-desacetylvecuronium were small in both groups.

Finally, we reconciled the plasma concentrations of vecuronium and 3-desacetylvecuronium with the observed effect using effect compartment modeling assuming a sigmoid Emax relation between the concentration of drug at the site of effect and the resultant effect. In this case, each individual's model was considered independently. We found that the circulating concentration of vecuronium giving 50% twitch depression was much more variable in the patients taking phenytoin compared with control patients, and typically, it was more than twofold greater. We repeated this analysis, considering only those patients who had received a limited dose of vecuronium. This analysis yielded similar results. These findings are consistent with the work of Ornstein *et al.*,[26] who showed that during recovery from metocurine (another NMB), the plasma concentration associated with 50% twitch depression was increased in patients taking phenytoin.

The resistance to NMBs in patients taking anticonvulsant drugs chronically has been recognized for several years. The evidence is stronger for drugs with liver-based

metabolism but is also present for drugs that are eliminated independently of liver function. Increased elimination of NMBs that are dependent on liver metabolism has also been demonstrated previously.[6,18,21] This study adds to that understanding by showing that, at least with phenytoin, there is resistance to the effect of vecuronium and that this mechanism is of equal importance. NMB dose requirements are increased in patients taking phenytoin, and this effect may be greater for steroid-based NMBs than others. With continued administration, the dose of vecuronium needed to maintain a given degree of block is increased fourfold to fivefold in patients taking phenytoin compared with controls.

Appendix: Pharmacokinetic–Pharmacodynamic Analysis

The analysis was performed in four phases. In the first, a population pharmacokinetic model of vecuronium was determined using a model-building approach. This model was fixed, and the resultant individual descriptions of the concentration of vecuronium in plasma were used as the input for phases 2 and 3. In phase 2, a model describing renal clearance as a proportion of total clearance was fit to the urinary concentrations of vecuronium. In phase 3, a population model of 3-desacetylvecuronium was built. During each of these three phases, we tested additional parameters in an attempt to explain variation in structural parameters by modeling variation as a function of phenytoin treatment. Finally, the model of 3-desacetylvecuronium was fixed, and the combined descriptions of vecuronium and metabolite concentration in plasma were used as the input for phase 4. In phase 4, 22 individual models of the effect of vecuronium were determined, and their parameter values were compared between phenytoin patients and control patients with use of the Student *t* test.

Phase 1 Vecuronium Kinetics

Mixed-effects population models were fit to the vecuronium plasma concentration data. A model-building approach was used, and improvements in three criteria were used to determine whether additional parameters could be incorporated into the model. These criteria were goodness of fit (−2 log likelihood) evaluated against a chi-square distribution, determinable precision for all parameters, and visual acceptability. We first tested models with two and three compartments; when these indicated that three compartments were justified, we subsequently used only three-compartment models. We then tested models with two, three, or four parameters modeled for within individual measurement error (these are interindividual variation factors). Next, guided by visual plots, we evaluated models that permitted structural parameters (*i.e.*, clearances and volumes) to differ with covariates. We concentrated our search on age, weight, sex, and the duration of phenytoin administration. When all justified additional effects had been added to the model, the necessity for each was tested by removing it from the model.

Modeled interindividual variation was justified for clearance, intercompartmental clearance, central volume of distribution, and central volume of distribution at steady state. Clearance (but no other parameter) varied between phenytoin and control, being 138% greater in patients taking phenytoin. No other covariate effects were found.

Renal Clearance of Vecuronium

In the eight patients in whom urine collection was complete, the cumulative fraction of vecuronium eliminated *via* the kidneys (f$_{renal}$) 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 described above (*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.
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 the elimination of vecuronium were fit to the amount of vecuronium observed in the urine. Plots of individual f$_{renal}$ against phenytoin administration indicated that f$_{renal}$ varied according to phenytoin administration, and a parameter was added to the model to account for this, significantly improving the fit.

In the eight patients from whom urine was collected, urinary recovery of vecuronium ranged from 6.33 to 12.6%. The typical values for f$_{renal}$ were 6.96% (range, 6.33–7.57%) in the four patients receiving phenytoin and 12.2% (range, 12.0–12.6%) in the four controls.

3-Desacetylvecuronium Kinetics

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 described above (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. Conversion of vecuronium to 3-desacetylvecuronium occurred in the central compartment of vecuronium and was unidirectional.
3. 3-Desacetylvecuronium was eliminated unidirectionally from its central compartment.
4. 3-Desacetylvecuronium distributed to only a single compartment or to central and peripheral compartments.
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 cannot be estimated. Hence, absolute pharmacokinetic parameters cannot be determined, and the pharmacokinetic model for 3-desacetylvecuronium is not meaningfully interpretable. We modeled 3-desacetylvecuronium only to provide a description of its concentration–time curve as a basis for pharmacodynamic modeling. 3-Desacetylvecuronium models are not presented here.

Pharmacodynamic Modeling

Finally, we fit sigmoid Emax effect compartment models to the effect of vecuronium. A two-stage approach was taken (*i.e.*, models were fit to each individual's data and the parameters thus determined were compared between phenytoin and control using the Student *t* test). 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 described above (*i.e.*, fitting of the model to the effect of vecuronium 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%.[10]
3. The 3-desacetylvecuronium dose–response curve has a similar sigmoidicity to that of vecuronium, and it equilibrates into the effect compartment at the same rate.

The rate constant of equilibration and the sigmoidicity of the concentration–response curve were similar in the control and phenytoin patients. However, the concentration of vecuronium required to pro-

duce 50% block was greater in the phenytoin patients compared with controls. An analysis confined to the patients who received the low dose of vecuronium yielded similar results.

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