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The Effect of Phenytoin on the Magnitude and Duration of Neuromuscular Block Following Atracurium or Vecuronium

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Patients chronically receiving anticonvulsants have been reported to be resistant to the long-acting competitive neuromuscular blockers. This study examines the effects of atracurium and vecuronium on 100 neurosurgical patients; 50 receiving chronic phenytoin therapy (group I) and 50 controls (group II). During O_2/N_2O/halothane anesthesia, five patients in each group were given a bolus of vecuronium 0.1 mg/kg, and a different five patients in each group were given atracurium 0.5 mg/kg, to produce neuromuscular blockade in excess of 95%. The time to maximum blockade and the recovery from atracurium was unaffected by phenytoin therapy. Recovery from vercuronium was enhanced in the phenytoin group, as demonstrated by the recovery index, defined as the time required for recovery from 25–75% of the control neuromuscular response (7.9 ± 2.2 min compared with 17.8 ± 5.1 min in controls, $P < 0.005$). Similarly, the total duration of neuromuscular blockade, defined as recovery to 90% of control response, was significantly shorter in the phenytoin group (31.9 ± 6.0 min compared with 69.7 ± 12.9 min in controls, $P < 0.001$). The remaining 40 patients from each group were given a preselected dose of either vecuronium (0.02–0.06 mg/kg) or atracurium (0.10–0.25 mg/kg) during anesthesia with O_2/N_2O/fentanyl, to generate dose-response curves for the relaxants. Using analysis of covariance, the slopes and elevations for atracurium were found to be essentially identical in the two groups; as were the calculated ED_{50} and ED_{95}. Patients receiving chronic phenytoin therapy were resistant to vecuronium-induced neuromuscular blockade. With vecuronium, the dose-response curves for the two groups were parallel; the curve for phenytoin patients was shifted to the right. A larger dose of vecuronium is required in phenytoin-treated patients to provide a given level of neuromuscular blockade. For example, the ED_{50} was 0.042 mg/kg in the phenytoin group, compared to 0.028 mg/kg in the control group. This study demonstrates that, although vecuronium is affected by phenytoin in an interaction similar to that previously reported with the long-acting neuromuscular relaxants, atracurium is not similarly affected. (Key words: Interaction (drug): atracurium; phenytoin; vecuronium. Neuromuscular relaxants: atracurium; vecuronium. Pharmacodynamics: Atracurium; vecuronium. Pharmacology, drug interactions: atracurium; phenytoin; vecuronium.)

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INITIAL STUDIES BY Ghandi *et al.*,[1] utilizing both an *in vitro* nerve muscle preparation and an intact animal model, have shown that nondepolarizing neuromuscular blockade induced with d-tubocurarine is enhanced by the acute administration of large doses of a wide variety of anticonvulsant drugs, including phenytoin, trimethadione, phenobarbital, and ethosuximide. In the clinical setting, however, patients receiving chronic phenytoin therapy have been demonstrated to be resistant to the neuromuscular blocking effects of the long-acting competitive relaxants. Ornstein *et al.*[2] found that patients receiving chronic phenytoin therapy require a 64–80% greater plasma metocurine concentration than control patients to achieve equal levels of neuromuscular blockade. Inasmuch as no pharmacokinetic differences for metocurine could be demonstrated between the two groups, it was concluded that this resistance was a pharmacodynamic phenomenon confirmed by a rightward shift of the plasma log concentration *versus* response curve. Through the use of various dose-response paradigms, patients chronically receiving phenytoin have also been shown to be resistant to pancuronium,[3–5] and, possibly, d-tubocuraine.[5] Recently, Roth *et al.*[6] have demonstrated a similar drug interaction between carbamazepime and pancuronium.

In light of these studies, it is reasonable to expect that, at therapeutic plasma levels of anticonvulsant drugs, patients might exhibit similar resistance to the newer intermediate duration neuromuscular blockers: atracurium and vecuronium. Through the generation of dose-response curves and the quantification of recovery from bolus doses of atracurium and vecuronium, this study was undertaken to determine whether chronic exposure to phenytoin attenuates the neuromuscular blocking effects of these relaxants.

Methods

This study was approved by the Institutional Review Board of the Columbia University, College of Physicians and Surgeons. Informed consent was obtained from all patients who participated in this study. Patients with normal cardiac, hepatic, and renal function, scheduled to undergo neurosurgical procedures, were assigned to one of two groups. Group I consisted of 50 patients who had received phenytoin for at least 7 days, with therapeutic plasma drug levels (10–20 mcg/ml, by

TABLE 1. Demographic Data: Phenytoin and Control Groups (Mean ± SD)

	Group I: Phenytoin (n = 50)	Group 2: Control (n = 50)
Age (yr)	39 ± 13	42 ± 14
Weight (kg)	70 ± 15	72 ± 14
Male/female	26/24	25/25

No significant differences between groups.

radioimmunoassay) verified prior to surgery. Group II consisted of 50 patients of comparable age and weight (table 1) who were not receiving anticonvulsant therapy. All patients were within 30% of ideal weight. Patients taking other anticonvulsants or drugs thought to affect the neuromuscular junction were excluded from both groups of this study, as were patients with known neuromuscular pathology and patients scheduled for deliberately induced hypotension. The need for premedication was left to the discretion of the anesthesiologist assigned to the patient. Drugs permitted included oral valium and intramuscular morphine, robinul, hydroxyzine, and secobarbital.

The study was completed in two phases. In the first phase, the recovery from a dose of either vecuronium 0.1 mg/kg or atracurium 0.5 mg/kg during O_2/N_2O/halothane anesthesia was evaluated in five patients for each drug, in each of the two groups. After administration of thiopental 4–6 mg/kg, patients were moderately hyperventilated with N_2O 50% and halothane 1–1.5% inspired, in O_2 for approximately 10 min. At this time, the preselected muscle relaxant was administered intravenously. When suitable relaxation was attained, lidocaine 1–1.5 mg/kg was administered iv, and the trachea was intubated. Maintenance consisted of N_2O 60% and halothane 0.5–1.0% in O_2 inspired, by IPPV to maintain $EtCO_2$ at 20–28 mmHg. Esophageal temperature was maintained above 34.8° C with the aid of heating blankets. The response to ulnar nerve stimulation with 0.15 ms supramaximal pulses at 0.1 Hz from a Grass model S–88 stimulator, used in conjunction with a Grass stimulus isolation unit, was quantitatively evaluated by either a Grass model FT-10 force adduction transducer (three control and two phenytoin patients receiving vecuronium), or by evoked compound electyromyography (ECEMG)[7] of the thenar muscles. Although, during halothane anesthesia, neuromuscular response as measured by mechanical twitch tension tends to be slightly greater than that measured by ECEMG, the slopes of the regression lines are near unity for both vecuronium (0.92)[8] and atracurium (1.0).[9] In all cases, neuromuscular response had stabilized within the 10-min period prior to the administration of the atracurium or vecuronium. The time required for neuromuscular blockade to become first noticeable (onset), the time to maximum neuromuscular blockade, as well as the times to recovery to 10, 25, 50, 75, and 90% of baseline response were noted for all patients. The recovery index (RI) was calculated as the time required to recover from 25–75% of baseline response. Comparisons were made between the phenytoin and control patients for each of the two neuromuscular blockers studied using the two-tailed *t* test for unpaired data. The threshold for statistical significance was $P < 0.05$.

The remaining 40 patients from each group were entered in the second phase of the study, the purpose of which was to generate dose-response curves for vecuronium and atracurium in the two patient groups. Anesthesia was induced with thiopental 3–5 mg/kg and maintained during the study with N_2O 60% inspired in oxygen. Patients were ventilated by mask to maintain mild hypocarbia. Supplementary doses of thiopental 1 mg/kg and/or fentanyl 0.001 mg/kg were given as necessary for increasing blood pressure or heart rate. The ulnar nerve was stimulated at the wrist with 0.15 ms supramaximal pulses from a Grass S–88 stimulator with a stimulus isolation unit at a rate of 0.1 Hz. The response was measured with an FT-10 force displacement transducer. After stabilization of the neuromuscular response for a minimum of 5 min, when the response to ulnar nerve stimulation became constant for at least 30 s, patients received either one of four preselected doses of atracurium (0.1, 0.15, 0.2, or 0.25 mg/kg for both phenytoin and control groups), or one of four preselected doses of vecuronium (0.03, 0.04, 0.05, or 0.06 mg/kg for phenytoin patients, group I; 0.02, 0.03, 0.04, or 0.05 mg/kg for control patients, group II). The neuromuscular response was recorded until maximum blockade was noted, at which time, if necessary, a supplementary dose of muscle relaxant was given to facilitate intubation. The onset time (first depression of twitch below control), the time to maximum response, and the maximum response for each patient were noted. Comparisons between groups were made by Student's *t* test. The response to the various doses of each relaxant was analyzed as log dose *versus* probit response. This transformation is linear in the range from 1–99% effect. The data were fitted by means of linear least square regression. The dose response curves thus generated were compared between groups by analysis of covariance. Differences between groups were considered significant if $P < 0.05$.

Results

The response to an intubating dose of vecuronium 0.1 mg/kg or atracurium 0.5 mg/kg is shown in table

2. All patients responded to the neuromuscular blocker with at least a 95% depression in baseline twitch or ECEMG. For both agents studied, there were no statistically significant differences between phenytoin and control groups in the time required to attain the maximum response. Although the patients who received atracurium proved to be uneffected by prior phenytoin therapy, the phenytoin patients receiving vecuronium had a markedly accelerated recovery from neuromuscular blockade compared to controls. The atracurium study yielded a recovery index, and recovery times to 10, 25, 50, 75, and 90% of baseline which were virtually identical in the two groups. With vecuronium, however, the phenytoin group recovered in less then half the time required by the control group.

The dose-response relationships generated in the second phase of this study are shown in table 3. Again, there were no differences between groups for either relaxants in terms of the onset time or the time to maximum block. As shown in figure 1, the dose-response curves for atracurium appear to coincide for the two groups. Analysis of covariance confirms this, with no significant differences between the two lines in slope or elevation. In contrast, phenytoin therapy is associated with a rightward shift of the vecuronium dose-response curve (fig. 2). Although the slopes are not significantly different, the elevation of the dose-response curve for the phenytoin group lies significantly to the right of the control group ($P < 0.001$). As a result, the calculated ED_{50}, ED_{90}, ED_{95} is significantly higher in the phenytoin group (table 4).

TABLE 2. Times to Maximum Neuromuscular Blockade and Recovery of Baseline Neuromuscular Response in Minutes (Mean ± SD)

	Group 1: Phenytoin	Group 2: Control	$P <$
Atracurium 0.5 mg/kg	n = 5	n = 5	
Onset (min)	1.2 ± 0.3	1.2 ± 0.2	NS
Maximum block (%)	4.2 ± 1.4	5.0 ± 1.6	NS
10% Recovery (min)	38 ± 8	35 ± 6	NS
25% Recovery (min)	45 ± 9	41 ± 8	NS
50% Recovery (min)	51 ± 9	47 ± 9	NS
75% Recovery (min)	56 ± 9	54 ± 9	NS
90% Recovery (min)	62 ± 8	60 ± 9	NS
Recovery index (min)*	12 ± 2	13 ± 2	NS
Vecuronium 0.1 mg/kg	n = 5	n = 5	
Onset (min)	1.1 ± 0.6	1.0 ± 0.3	NS
Maximum block (%)	4.3 ± 0.7	3.8 ± 0.8	NS
10% Recovery (min)	16 ± 4	35 ± 5	0.001
25% Recovery (min)	19 ± 4	42 ± 8	0.001
50% Recovery (min)	23 ± 5	51 ± 10	0.001
75% Recovery (min)	27 ± 6	60 ± 12	0.001
90% Recovery (min)	32 ± 6	70 ± 13	0.001
Recovery index (min)*	8 ± 2	18 ± 5	0.005

* Recovery index = time to recover from 25–75% recovery.

Discussion

This study demonstrates that patients treated chronically with phenytoin are resistant to the effects of vecuronium in much the same way as has been demonstrated for metocurine,[2] pancuronium[3-5] and, possibly, d-tubocurarine.[5] The results of the first phase of this study, evaluating the recovery from a paralyzing dose of vecuronium could be explained by either a pharmacoki-

TABLE 3. Neuromuscular Effects for Atracurium and Vecuronium (Mean ± SD)

	Group 1: Phenytoin			Group II: Control		
Dose (mg/kg)	Onset (Min)	Max Time (Min)	Max Block (Percent)	Onset (Min)	Max Time (Min)	Max Block (Percent)
Atracurium						
0.10	2.1 ± 0.7	6.3 ± 0.2	24 ± 27	2.2 ± 0.7	6.5 ± 0.2	14 ± 9
0.15	1.9 ± 1.1	6.5 ± 1.8	45 ± 17	1.8 ± 0.7	5.7 ± 0.9	33 ± 37
0.20	1.4 ± 0.5	6.8 ± 0.8	56 ± 22	1.4 ± 0.3	7.9 ± 1.5	68 ± 9
0.25	1.2 ± 0.8	6.9 ± 1.2	87 ± 14	1.2 ± 0.3	6.4 ± 0.8	89 ± 4
Vecuronium						
0.02				1.6 ± 0.7	6.0 ± 0.7	16 ± 3
0.03	1.4 ± 0.7	5.6 ± 0.8	10 ± 3*	1.5 ± 0.5	5.9 ± 0.9	58 ± 22
0.04	1.5 ± 0.4	5.1 ± 1.0	44 ± 17*	1.3 ± 0.3	6.1 ± 1.1	85 ± 10
0.05	1.4 ± 0.3	5.8 ± 0.9	74 ± 18†	0.9 ± 0.3	6.6 ± 1.7	95 ± 3
0.06	1.3 ± 0.3	6.1 ± 0.8	79 ± 15			

* Significantly different from control group, $P < 0.002$. † Significantly different from control group, $P < 0.05$.

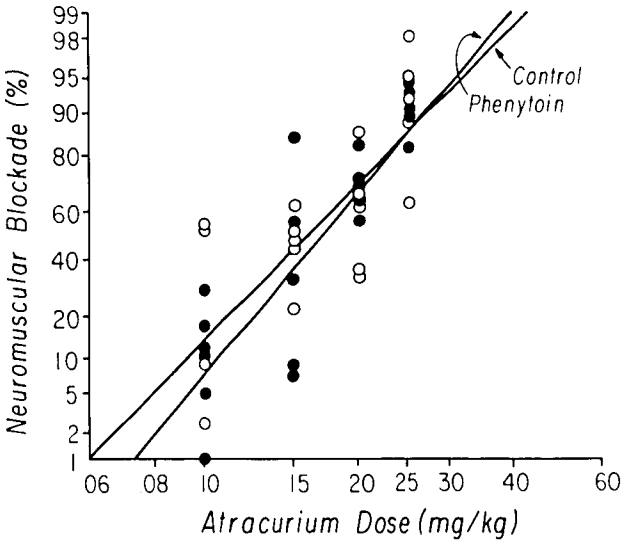

FIG. 1. Dose-response curves for atracurium for patients receiving chronic phenytoin therapy (open circles) and for controls (solid circles). N = 20 in both groups. Results not significantly different.

netic or pharmacodynamic mechanism. Conversely, the dose-response data from the second phase of this study imply a pharmacodynamic alteration or, possibly, a change in initial volume of distribution, V_d. Although there is no intuitive reason to suspect on increased V_d in phenytoin-treated patients, in the absence of blood relaxant levels, one cannot exclude a pharmacokinetic explanation for these findings. There remains the possibil-

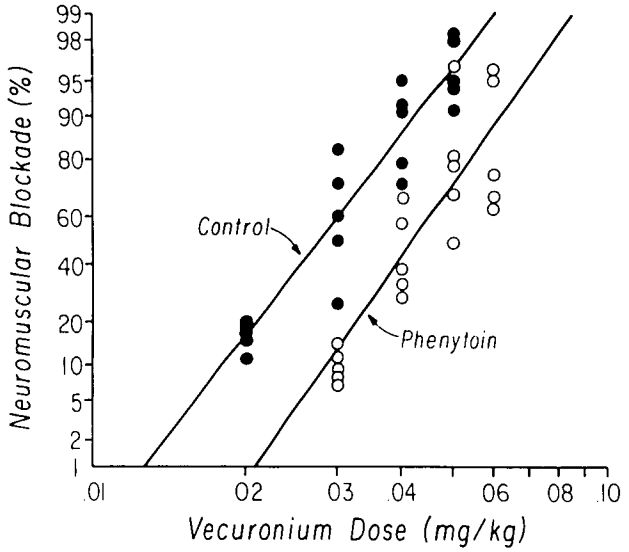

FIG. 2. Dose-response curves for vecuronium for patients receiving chronic phenytoin therapy (open circles) and for controls (solid circles). N = 20 in both groups. Significantly different elevations between groups, $P < 0.001$ by analysis of covariance. Slopes not significantly different.

TABLE 4. Derived Parameters from Log—Probit Dose-Response Data

	Atracurium		Vecuronium	
	Group I: Phenytoin	Group II: Control	Group I: Phenytoin	Group II: Control
Slope	2.44	2.62	3.39	3.02
Correlation	0.76	0.85	0.87	0.94
ED_{50} (mg/kg)	0.16	0.17	0.042*	0.028
ED_{90} (mg/kg)	0.27	0.27	0.062*	0.042
ED_{95} (mg/kg)	0.32	0.31	0.069*	0.048

* Significantly different from control ($P < 0.001$).

ity that either altered protein binding or metabolism could have led to decreased vecuronium levels in patients receiving phenytoin. It appears more likely, however, that the resistance seen with vecuronium is due to a pharmacodynamic change similar to that reported with metocurine.[2]

Multiple possible mechanisms have been proposed for the observed resistance to neuromuscular blockers seen with phenytoin.[4] These include: 1) increased metabolism *via* enzyme induction, 2) decreased sensitivity at the receptor sites, 3) an increase in receptor number, or 4) increased end-plate anticholinesterase activity.

Phenytoin is known to have a variety of effects at the neuromuscular junction.[10,11] These effects are generally prejunctional in nature. For this reason, a brief review of the prejunctional properties of neuromuscular relaxants follows. Originally d-tubocurarine (dTC) was thought to block neuromuscular transmission solely by the antagonism of acetylcholine at the post-junctional receptor. In 1964, however, Standaert[12] described a prejunctional effect of dTC in cats, whereby the post tetanic repetitive activity at motor nerve terminals normally seen following high frequency stimulation was abolished by very small doses of dTC (10 mcg/kg intraarterially). This dose does not appreciably affect the twitch response to indirect stimulation of muscle. Looking at changes in end-plate potentials during high frequency stimulation, pre-junctional effects have also been described for pancuronium and metocurine, and verified for dTC.[13] The progressive diminution of end-plate potential that is seen is felt to be due to interference with acetylcholine release. Most recently, Baker *et al.*[14] demonstrated that small subparalytic doses of vecuronium (1–5 mcg/kg) suppress post-tetanic repetition and post-tetanic potentiation in cats. In even smaller doses (0.5 mcg/kg), vecuronium was found to actually evoke repetitive discharges at the nerve terminal, acting as a partial agonist at motor nerve endings. The presence of these consequences of competitive neuromuscular blockade in humans was verified by Stanec and Baker.[15] Notably, the aforementioned presynaptic phenomema, that are antagonized by neuro-

muscular blockers, occur with stimulus frequencies within the range of normal physiologic function.[16]

Raines and Standaert[11] have described pre-junctional effects for phenytoin in cats which are virtually identical to those previously reported for nondepolarizing relaxants. In anticonvulsant doses, phentoin suppresses post-tetanic repetition in nerve terminals with a resultant decrease in post-tetanic potentiation of muscle. They also reported variable direct effect on muscle, whereby 57% of cats studied showed an increase in twitch tension in response to direct muscle stimulation. Yaari *et al.*,[11] using an isolated frog sartorius nerve muscle preparation, found that phenytoin causes a reduction in end-plate potential. They determined that this was due to a presynaptic inhibitory action on the amount of acetylcholine quanta released by a nerve impulse.

It is conceivable that the maintainance of a therapeutic level of phenytoin over a period of time simulates a state of chronic chemical denervation. The similarity between the pre-junctional effects of phenytoin and those of the nondepolarizing muscle relaxants studied to date, suggests that chronic phenytoin therapy might lead to prolonged antagonism of acetylcholine at prejunctional receptors. Inasmuch as continuous exposure to acetylcholine leads to a state of desensitization,[17] continuous antagonism of acetylcholine could, conversely, result in a state of hypersensitivity. This has already been demonstrated in cases of disuse atrophy[18] and motoneuron dysfunction[19]; clinical situations associated with resistance to nondepolarizing muscle relaxants. Bender *et al.*[20] studied denervated rats and, also, muscle tissue from patients with denervating diseases. They found that this clinical state leads to the spread of acetylcholine receptors beyond the neuromuscular endplate. This group also verified the presence of prejunctional acetylcholine receptors in normal tissue. A study by Matteo and Diaz,[21] involving the continuous use of dTC for 72 h in cats, provides some evidence for a chemical denervation effect following chronic antagonism of acetylcholine. At the end of the dTC infusion, the cats were shown to be markedly resistant to dTC. On the basis of these studies, it is hypothesized that chronic phenytoin use antagonizes acetylcholine at the pre-junctional receptor, causing an increase in number or an increase in sensitivity of this receptor, thus leading to resistance to long-acting nondepolarizers and vecuronium.

The results of this study for vecuronium were not unexpected, in light of previous studies involving the long-acting relaxants. The lack of a drug interaction between phenytoin and atracurium is perplexing, however. At this time, it is difficult to explain this result. Although it was felt that atracurium might have a smaller prejunctional effect, Otagiri and Sokoll have recently demonstrated nerve terminal inhibitory properties with atracurium.[22]

One factor yet to be studied is the possibility of a pharmacokinetic alteration for atracurium in the presence of phenytoin therapy, which might completely negate the expected pharmacodynamic resistance. This is possible when one considers the unique metabolism by which atracurium is eliminated from the plasma. The difficulty in extrapolating from pharmacokinetic studies of other neuromuscular blockers to atracurium is alluded to by data from Fisher and Rosen,[23] who demonstrated the uniqueness of atracurium in that it is the only nondepolarizing relaxant with no cumulative properties after repeated doses, regardless of the initial dose studied. In addition, recovery times following varying single doses of relaxants were dose-dependent for pancuronium and vecuronium, but not for atracurium. The authors postulated that these differences were attributable to the recovery from atracurium which occurs essentially in its entirety within the elimination phase, while recovery from the other two relaxants occurs to some extent in the distribution phase. With the exception of atracurium, elimination of relaxants from the blood is primarily a result of clearance of unchanged drug by the liver and the kidneys. Atracurium, on the other hand, is metabolized by the processes of Hofmann elimination and ester hydrolysis. Approximately 60% of the administered dose of atracurium, however, is now thought to be eliminated by some other mechanism, either excretion or metabolism.[24] Inasmuch as phenytoin is known to have a metabolic pathway involving a saturable enzyme,[25] the metabolism of phenytoin may, in some way, compete with the metabolism of atracurium, thus enhancing the effect of atracurium in patients chronically receiving phenytoin. This pharmacokinetically mediated sensitivity, in conjunction with the expected pharmacodynamically mediated resistance, could explain the uniformity of atracurium effect, despite the presence of phenytoin therapy.

In conclusion, of all the nondepolarizing muscle relaxants currently available, only atracurium has been shown to have the same effect whether or not the patient is receiving chronic phenytoin therapy. Vecuronium, when used during concurrent phenytoin therapy, has both a decreased effect and a shorter duration of action.

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