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# *Resistance to Metocurine-induced Neuromuscular Blockade in Patients Receiving Phenytoin*

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**Recent reports have described resistance to pancuronium-induced neuromuscular blockade in patients chronically receiving anticonvulsants. This study examines the pharmacokinetics and pharmacodynamics of metocurine (MTC) in 12 patients undergoing craniotomy—six on chronic phenytoin therapy and six comparable controls. Each patient received MTC 0.2 mg/kg during the induction of general anesthesia. Quantification of plasma MTC concentration was performed by radioimmunoassay, while the response to MTC was evaluated by evoked compound electromyography (ECEMG). Patients in the phenytoin group were resistant to this dosage of MTC, as demonstrated by their response (83 ± 16% compared with 98 ± 2% depression of ECEMG in control patients, $P < 0.05$) and by recovery index, defined as the time required for recovery from 25 to 75% of the control ECEMG (53 ± 22 min compared with 125 ± 54 min in control patients, $P < 0.01$). Similarly, the total duration of neuromuscular blockade, measured to recovery to 90% of control ECEMG, was significantly shorter in the phenytoin group (122 ± 25 min compared with 269 ± 64 min in the control group, $P < 0.01$). Plasma concentration–time curves were fit to biexponential equations for both groups. These were used to generate two-compartment models. Neither the model parameters nor the plasma concentrations of MTC at any time in the study were significantly different for the two groups. The pharmacodynamic analysis, however, showed that patients on phenytoin require a higher plasma concentration of MTC (0.415 ± 0.095 μg/ml compared with 0.249 ± 0.066 μg/ml in control patients at 50% ECEMG, $P < 0.01$) to effect a given level of neuromuscular blockade. This resistance could be demonstrated at all levels of neuromuscular blockade (20–80% depression of ECEMG). On the basis of this study, it can be concluded that resistance to metocurine in patients chronically being treated with phenytoin does exist as a result of some, yet undefined, pharmacodynamic alteration in this patient group. (Key words: Interactions (drug): metocurine; phenytoin. Neuromuscular relaxants: metocurine. Pharmacokinetics: metocurine. Pharmacodynamics: metocurine.)**

THE RELATIONSHIP between an administered dose of a nondepolarizing neuromuscular blocker such as metocurine and the resultant degree of neuromuscular blockade is known to be modified by a multiplicity of factors. These include age, acid–base status, temperature, pathologic derangements (burns, upper and lower motoneuron disease, *etc.*), and concurrent drug therapy. Drug interactions described to date generally have involved the potentiation of neuromuscular blockade, most notably by antibiotics. In regard to the interaction of nondepolarizing muscle relaxants with anticonvulsant drugs, initial studies by Gandhi *et al.*,[1] using both an *in vitro* nerve muscle preparation and an intact animal model, have shown that a nondepolarizing neuromuscular blockade induced with *d*-tubocurarine is enhanced by a wide variety of anticonvulsant drugs, including phenytoin, trimethadione, phenobarbital, and ethusuximide. These studies involved the acute administration of anticonvulsants at a dosage sufficient to cause blockade of neuromuscular transmission, even without the simultaneous administration of *d*-tubocurarine.

In light of these studies, it might be expected that at therapeutic plasma levels of anticonvulsant drugs, patients might exhibit greater sensitivity to nondepolarizing neuromuscular agents. Two recent reports have demonstrated that this is not the case. In fact, patients receiving anticonvulsant therapy before surgery seem to be resistant to the nondepolarizers. Messick *et al.*[2] have reported that the duration of neuromuscular blockade induced by pancuronium 0.1 mg/kg, measured from time of injection to reappearance of the third twitch in response to a train-of-four, was shorter in patients taking anticonvulsants preoperatively than in comparable patients. Chen *et al.*[3] examined the requirement for pancuronium during craniotomies in patients receiving phenytoin for at least 7 days preoperatively. An initial dose of pancuronium 0.1–0.15 mg/kg was followed by additional boluses of 25% of the initial dose whenever there was reappearance of two twitches in response to a train-of-four applied every 15 min. Patients being treated with phenytoin therapy required approximately 80% more pancuronium than control patients in order to maintain a stable level of neuromuscular blockade.

This study was undertaken to further our knowledge regarding the interaction of nondepolarizing muscle relaxants with anticonvulsants used in the perioperative period. An attempt was made to determine whether chronic exposure to phenytoin attenuated the neuromuscular blocking effect of metocurine, as might be predicted from the aforementioned studies with pancuronium. If such a drug interaction could be demon-

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strated, a pharmacologic mechanism would be sought. By measuring the plasma metocurine concentration *versus* time, the pharmacokinetics of metocurine in this group of patients could be compared with a similar control group. In addition, through the use of evoked compound electromyography (ECEMG), pharmacodynamic differences between the two groups could be examined.

## 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 for craniotomies for excision of tumors or arteriovenous malformations, were assigned to one of two groups. Group 1 consisted of six patients who had received phenytoin for at least 7 days, with therapeutic plasma drug levels (10–20 μg/ml) verified before surgery. Group 2 consisted of six patients of comparable age and weight (table 1) who were not being treated with phenytoin. Patients taking other anticonvulsants were excluded from both groups of this study, as were patients with known neuromuscular pathology and patients scheduled for deliberately induced hypotension. Patients were generally premedicated with oral diazepam 10 mg and intramuscular glycopyrrolate 0.2 mg. Anesthesia was induced with thiopental 4–6 mg/kg, followed by moderate hyperventilation with nitrous oxide 50% and halothane 1–1.5% inspired in oxygen for approximately 10 min, at which time, metocurine 0.2 mg/kg was given. When suitable relaxation was appreciated, lidocaine 1 mg/kg was administered intravenously and the trachea was intubated. Patients were ventilated to a stable end tidal $CO_2$ tension of 20–28 mmHg with nitrous oxide 60% and halothane 0.7%–1.0% inspired, in oxygen. Esophageal temperatures were maintained above 34.8° C with the aid of heating blankets. All patients received dexamethasone 10 mg and oxacillin 2 g intravenously just after the induction of general anesthesia.

The ulnar nerve was stimulated through thin-needle electrodes at the wrist with 0.15 ms duration supramaximal stimuli delivered at 0.1 Hz from a Grass® model S-8 stimulator used in conjunction with a Grass® stimulus isolation unit. The evoked responses were quantitatively assessed from recordings of the ECEMG of the thumb adductor.[4] Responses were compared with baseline recordings made just before administration of metocurine. Plasma metocurine concentration was determined by radioimmunoassay[5] from samples drawn, from a preoperatively placed radial artery catheter, at 1, 3, 5, 10, 15, 25, 35, 45, and 60 min after injection and at 30-min intervals for an additional 3 h. Additional samples were taken during the recovery of the ECEMG, at approximately 15-min intervals, to facilitate pharmacodynamic analysis.

TABLE 1. Response to Metocurine 0.2 mg/kg with and without Chronic Phenytoin Therapy (Mean ± SD)

| | Group 1 Phenytoin (n = 6) | Group 2 control (n = 6) | P< |
|---|---|---|---|
| Age (yr) | 35 ± 10 | 38 ± 13 | 0.70 (NS) |
| Weight (kg) | 69 ± 17 | 78 ± 13 | 0.40 (NS) |
| Maximum block (%) | 83 ± 16 | 98 ± 2 | 0.05 |
| Time to 50% Recovery (min) | 61 ± 26 | 156 ± 67 | 0.05 |
| Time to 90% Recovery (min) | 122 ± 25 | 269 ± 64 | 0.01 |
| Recovery index (min) | 53 ± 22 | 125 ± 54 | 0.05 |

Pharmacokinetic parameters were obtained by fitting the observed concentration *versus* time data to sums of two and three exponentials, through the use of weighted nonlinear regression provided by the BMDP package.[6] A weighting function of $1/X_i^2$ was used. These polyexponential functions correspond respectively to two- and three-compartment mamillary models with elimination solely from the central compartment. The ultimate model selected was determined by F ratio test comparisons of the weighted mean square errors from the two- and three-compartment models.[7] Initial volume of distribution ($V_i$), total volume of distribution ($V_{D_{area}}$), distribution half-life ($T_{1/2}\alpha$), elimination half-life ($T_{1/2}\beta$), plasma clearance ($Cl_p$), and the intercompartmental rate constants were derived from the coefficients and time constants of the polyexponential equations.[8]

Pharmacodynamic data were analyzed by linear regression of the extrapolated log plasma metocurine concentrations at 80, 70, 60, 50, 40, 30, and 20% depression of the control ECEMG *versus* response curve. This corresponds to the linear portion of the Hill equation. The complete sigmoid Hill equation was not used because of a paucity of data points above 70% neuromuscular blockade in the phenytoin group. In addition, the various dose–response characteristics for both groups were determined. These include the time required to return to 50 and 90% of the baseline ECEMG, and the recovery index (RI), defined as the time interval between 25 and 75% recovery of neuromuscular blockade.

All data are given as mean ± standard deviation. Results between groups were compared by the two-tailed unpaired *t* test. The pharmacodynamic regression

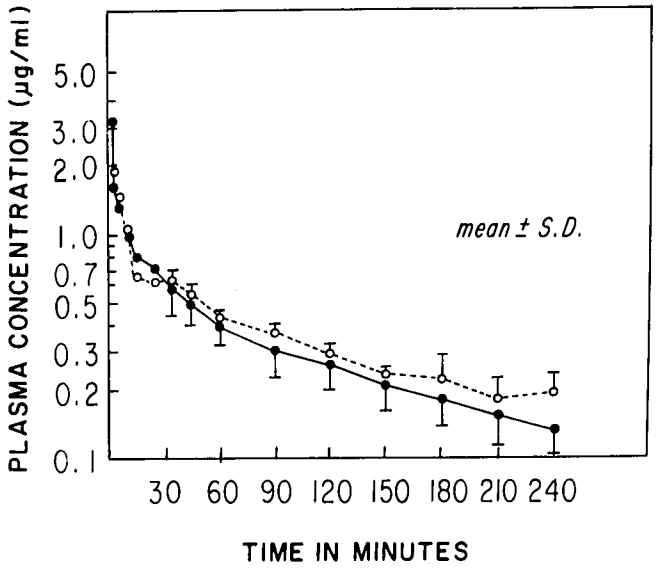


FIG. 1. Semilogarithmic plot of plasma concentration decay curve for patients on chronic phenytoin therapy (● —— ●) and controls (O - - - O) after a single dose of metocurine 0.2 mg/kg. Mean ± SD, n = 6 in both groups. Results not significantly different.

lines were compared by analysis of covariance. The threshold for statistical significance accepted was $P < 0.05$.

## Results

As shown in table 1, patients on chronic phenytoin therapy have an altered response to metocurine. The bolus administration of 0.2 mg/kg was sufficient to effect essentially complete (98 ± 2%) neuromuscular blockade in each of the control patients. However, in two of the patients treated with phenytoin, this dose did not completely block neuromuscular transmission. The

TABLE 2. Pharmacokinetic Characteristics of Metocurine with and without Chronic Phenytoin Therapy (mean ± SD)

| | Group 1 Phenytoin | Group 2 Control | P< |
|---|---|---|---|
| $T_{1/2}\alpha$ (min) | 8.2 ± 5.0 | 4.8 ± 2.5 | 0.20 (NS) |
| $T_{1/2}\beta$ (min) | 141 ± 63 | 160 ± 19 | 0.50 (NS) |
| $Cl_p$ (ml·kg$^{-1}$·min$^{-1}$) | 1.82 ± 0.40 | 1.40 ± 0.30 | 0.20 (NS) |
| $V_i$ (ml/kg) | 102 ± 41 | 74 ± 38 | 0.30 (NS) |
| $V_{D_{area}}$ (ml/kg) | 355 ± 116 | 341 ± 62 | 0.80 (NS) |
| $k_{10}$ (l/min) | 0.022 ± 0.013 | 0.028 ± 0.021 | 0.60 (NS) |
| $k_{12}$ (l/min) | 0.061 ± 0.071 | 0.154 ± 0.147 | 0.20 (NS) |
| $k_{21}$ (l/min) | 0.031 ± 0.013 | 0.033 ± 0.008 | 0.80 (NS) |

$T_{1/2}\alpha$ = distribution half-life; $T_{1/2}\beta$ = elimination half-life; $Cl_p$ = plasma clearance; $V_i$ = initial volume of distribution; $V_{D_{area}}$ = total apparent volume of distribution; $k_{12}$, $k_{21}$ = intercompartmental rate constants; $k_{10}$ = elimination rate constant. n = 6 in each group.

TABLE 3. Plasma Concentrations of Metocurine with and without Chronic Phenytoin Therapy at Various Levels of Neuromuscular Blockade (mean ± SD)

| Neuromuscular Blockade | Concentration (μg/ml) | | |
|---|---|---|---|
| | Group 1 Phenytoin | Group 2 Control | P< |
| 80% | * | 0.344 ± 0.046 | * |
| 70% | 0.567 ± 0.202 | 0.315 ± 0.042 | 0.05 |
| 60% | 0.486 ± 0.136 | 0.283 ± 0.046 | 0.01 |
| 50% | 0.415 ± 0.095 | 0.249 ± 0.066 | 0.01 |
| 40% | 0.370 ± 0.089 | 0.226 ± 0.067 | 0.01 |
| 30% | 0.342 ± 0.080 | 0.201 ± 0.061 | 0.01 |
| 20% | 0.303 ± 0.076 | 0.180 ± 0.056 | 0.01 |

* Note: No entry for 80% in Group 1 because two of these patients did not achieve this level of neuromuscular blockade. n = 6 in each group.

ECEMG in the phenytoin group was depressed to 83 ± 16% of control. The elapsed time from injection to recovery of 50% ECEMG was significantly shorter in patients taking phenytoin (61 ± 26 min *vs.* 156 ± 67 min). Resistance of this same magnitude is seen upon examining the differences in recovery time to 90% of baseline ECEMG (122 ± 25 min *vs.* 269 ± 64 min). The recovery index (RI), defined as the time required to progress from 25 to 75% recovery from neuromuscular blockade was significantly shorter in the phenytoin group (53 ± 22 min *vs.* 125 ± 54 min). Of note, RI could only be defined for four of the phenytoin patients because of a failure of the administered dose to effect complete paralysis in the remaining two patients.

In the pharmacokinetic analysis, a two-compartmental model was found to be most suitable. Attempts to fit the data to the sum of three exponentials (corresponding to a three-compartment model) resulted most frequently in either a statistically insignificant improvement in weighted mean square error, the generation of two exponentials with similar time constants, or an exponential with a time constant that was too small to be acceptable on the basis of the sampling frequency. The average relationship between the plasma concentration of metocurine and time was $C(t) = 1.87e^{-0.125t} + 0.53e^{-0.0055t}$ for the phenytoin group, and $C(t) = 3.36e^{-0.209t} + 0.54e^{-0.0044t}$ for the control group. The concentration *versus* time data are shown in figure 1, with the pharmacokinetic model parameters listed in table 2. At no time on the plasma metocurine decay curve was there a statistically significant difference in concentration between the two groups. As a result, the two groups were not different in terms of any of the pharmacokinetic parameters listed.

Analysis of the pharmacodynamic parameters, however, revealed differences that were statistically signifi-

cant, and of sufficient magnitude to account for the different response in the two groups. At all levels of neuromuscular blockade, the plasma concentrations required to yield the same levels of blockade were between 64 and 80% greater in the phenytoin group, as shown in table 3. For example, the mean plasma concentration at 50% block (C50%) was 0.415 μg/ml in the phenytoin group and 0.249 μg/ml in the control group. The relationships between log plasma metocurine concentration and response, in the range of 20–80% depression of the control ECEMG, may be expressed by a straight line for both groups of patients. Analysis of covariance reveals a significant difference between the elevations (intercept) of the two lines ($P < 0.01$), with no significant difference in slopes.

## Discussion

This study demonstrates that patients who have been chronically treated with phenytoin are resistant to the effects of metocurine in much the same way as others[2,3] have demonstrated for pancuronium. These previous reports, however, were semiquantitative in nature; in both, the response to pancuronium was measured strictly by visual interpretation of an infrequently applied train-of-four. With a more rigorous quantitative evaluation of the pharmacokinetics and pharmacodynamics, an attempt can be made to suggest a mechanism for this altered response to nondepolarizing muscle relaxants.

Because of time constraints, the pharmacodynamic profiles in this study were not obtained at true steady state with multiple constant infusions. Instead, plasma samples used to derive the pharmacodynamic parameters were drawn during the recovery from neuromuscular blockade, at times that were at least four distribution half-lives past the administration of metocurine. This corresponds to the pseudoequilibrium phase, wherein the lag between plasma and tissue drug concentration is minimized.[9]

In studies with pancuronium, Chen *et al.*[3] proposed three possible mechanisms for the resistance seen with phenytoin: 1) decreased sensitivity at the receptor sites; 2) increased metabolism via enzyme induction; or 3) an increase in receptor number. Their results, which showed an 80% increase in pancuronium dose requirement in patients on phenytoin correlate well with the 64–80% increase in plasma concentration requirement for metocurine reported here. Inasmuch as no pharmacokinetic differences for metocurine could be demonstrated, it is clear that increased metabolism or elimination cannot be cited as the mechanism for resistance to metocurine. This is logical in light of metocurine's almost complete reliance on renal elimination. A generalization, though, cannot be made to pancuronium and other nondepolarizers, especially when one considers the increased metabolism of steroids shown in patients taking phenytoin.[10]

Although, with the information derived from this study, it cannot be said with certainty whether decreased sensitivity at the receptor site or an increase in receptor number is the true mechanism, one can be assured that the resistance to metocurine is a pharmacodynamic phenomenon that is reminiscent of the altered response seen with motoneuron dysfunction.[11] In both cases, the log concentration *versus* response curve is shifted to the right.

Of interest, Norris *et al.*,[12] demonstrated a biphasic action of phenytoin on the neuromuscular junction in rats. At high doses (10–20 mg/kg), phenytoin was shown to cause antagonism of decamethonium induced neuromuscular blockade. Larger doses of phenytoin (greater than 20 mg/kg), however, potentiated decamethonium blockade. Similarly, if neuromuscular blockade first was produced with a moderate dose of phenytoin, the block could be antagonized by edrophonium. At higher phenytoin doses, edrophonium administration led to potentiation of neuromuscular blockade. The authors postulated that although moderately large doses of phenytoin lead to competitive blockade at neuromuscular junction, the blockade caused by larger doses of phenytoin result from either end-plate depolarization or anticholinesterase activity. A similar mechanism can be proposed for the current study. It is possible that chronic phenytoin therapy increases end-plate anticholinesterase activity in much the same way as large dose acute phenytoin therapy. This could result in a higher concentration of acetylcholine at the neuromuscular junction, consistent with the observation that the log-concentration *versus* response curve was shifted to the right in the phenytoin group.

In summary, this study demonstrates that resistance to metocurine, similar to that seen with pancuronium, exists in patients on chronic phenytoin therapy, as a result of some, yet undefined, pharmacodynamic alteration in this patient group.

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