0.2 mg/kg iv in pregnant guinea pigs.[8] Uterine blood flow decreases to 63% of the control value, and requires 5 min to recover fully after epinephrine 10 μg in pregnant ewes.[9] This decrease in uterine blood flow is more striking and prolonged than the effect of epinephrine on the ovine maternal cardiovascular system, for the elevated blood pressure and decreased heart rate return to control values within 1 min of the epinephrine injection. Despite the decreased uterine blood flow, none of the fetuses in either of these studies became distressed.

In contrast, the fetuses of two of our epinephrine group patients developed distress lasting 10–12 min following the administration of epinephrine 15 μg iv. Similarities between our study and previous animal studies[8,9] lead us to suspect that decreased uterine blood flow may have been responsible for this fetal distress. Even though transient decreases in uterine blood flow are well tolerated by normal, healthy fetuses, the response may be different in already stressed fetuses. The difficulty in determining in advance which fetuses may not tolerate a brief period of ischemia is illustrated in our series, for both of the fetuses that developed signs of distress were apparently healthy at the time of drug injection.

Laboring pre-eclamptic patients may have a greater hypertensive response to epinephrine 15 μg iv than normal parturients, for pre-eclamptic patients have exaggerated pressor responses to angiotensin II and norepinephrine.[10] Such vasoconstriction might well endanger the mother as well as the fetus.

In summary, we found that epinephrine 15 μg iv produced a transient tachycardia followed by hypertension and bradycardia in healthy laboring parturients. Fetal distress occurred in two patients following epinephrine 15 μg iv. Our data suggest that, if epinephrine 15 μg is to be an effective test of intravascular injection in laboring patients, then monitoring sophisticated enough to detect a transient 10 beats/min increase in the maximum maternal heart rate is required. However, we question the clinical usefulness of relying on such a subtle and possibly unsafe test dose to detect intravascular catheters and suggest that another marker of intravascular injection should be developed.

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# Resistance to Pancuronium in Patients Receiving Carbamazepine

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Resistance to pancuronium, metocurine, and vecuronium has been demonstrated in patients chronically receiving phenytoin.[1–4] In these patients, resistance was characterized by either an increased hourly requirement of pancuronium or shorter recovery times after an iv bolus dose of pancuronium. To produce a given level of neuromuscular blockade after metocurine, higher plasma metocurine levels were required in patients receiving phenytoin compared to controls. The mechanism of these

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TABLE 1. Times in Minutes to Percent Recovery of Baseline Twitch Height (Mean ± SD)

| | Carbamazepine N = 9 | Control N = 9 | t Test, P< |
|---|---|---|---|
| Age (yr) | 30 ± 11 | 39 ± 12 | NS |
| 25% | 30 ± 5 | 85 ± 30 | 0.001 |
| 50% | 39 ± 5 | 106 ± 29 | 0.0001 |
| 75% | 48 ± 8 | 131 ± 28 | 0.0001 |
| 90% | 57 ± 11 | 149 ± 32 | 0.0001 |
| Recovery index (RI) | 17 ± 10 | 46 ± 19 | 0.002 |

N = 8 for 90% recovery in carbamazepine patients. The study was terminated in one patient after 75% recovery due to technical problems.

phenomena are unclear. When we anesthetized patients receiving carbamazepine, another anticonvulsant, they appeared resistant to pancuronium. We undertook this study to validate this clinical observation.

## METHODS

Subjects for this study were 18 adults, ages 23–50 yr, undergoing craniotomy for tumors, seizure foci, or cerebrovascular surgery. The protocol was approved by the Institutional Review Board of the Cleveland Clinic Foundation, and all patients signed informed consent. The patients were premedicated with diazepam, 10 mg orally, 1 h before surgery. Patients were excluded if renal, hepatic, cardiovascular, pulmonary, or neuromuscular disease was present, or if they received other medications known to alter the action of pancuronium. Group I patients were taking carbamazepine therapy (and no other anticonvulsants) for at least 1 month, while Group II patients received no anticonvulsants. Serum carbamazepine levels drawn the evening prior to surgery were assayed using gas-liquid chromatography. Anesthesia was induced with thiopental, 4–5 mg/kg iv and fentanyl 10–15 μg/kg iv. Pancuronium, 0.1 mg/kg iv, was administered to facilitate endotracheal intubation. Anesthesia was maintained with oxygen 30%, nitrous oxide 70%, and 0.25% end tidal halothane measured by mass spectrometry. Patients were monitored with radial arterial catheters, ECG, mass spectrometry, and esophageal temperature probes. Heating pads and a cascade humidifier were used to maintain temperature above 35° C. The $Pa_{CO_2}$ was maintained by mechanical ventilation at 25–30 mmHg. Oxacillin, 1 g, was given iv to every patient after induction of anesthesia.

TABLE 2. Correlation between Recovery Time (in Minutes) and Daily Carbamazepine Dose (in mg), N = 9

| Level of Recovery (%) | Pearson Correlation (r=) | t Test |
|---|---|---|
| 25 | −0.18 | $P < .64$ (NS) |
| 50 | −0.76 | $P < .02$ |
| 75 | −0.74 | $P < .02$ |
| 90 | −0.72 | $P < .05$ |
| RI | −0.57 | $P < .11$ (NS) |

The ulnar nerve was stimulated indirectly near the wrist using a Grass S-88 stimulator and stimulus isolation unit (SIU). Supramaximal stimuli of 0.15 ms duration were delivered at a rate of 0.1 Hz. The evoked adductor pollicus twitch was quantitated using a Grass FT-10 force-displacement transducer and recorded on a polygraph both before and after administration of pancuronium.

The time to 25, 50, 75, and 90% recovery of baseline twitch height was recorded and the recovery index (RI) calculated as the time difference between 75 and 25% recovery. Comparisons of the recovery times between the two groups were made using an unpaired *t* test. Correlations between carbamazepine dosages and blood levels the evening before surgery and time to recovery were compared by Pearson's correlation coefficient. Differences between the groups were considered statistically significant for $P < 0.05$.

## RESULTS

There was no significant difference in age between the control group and those receiving carbamazepine (table 1). The patients receiving carbamazepine recovered significantly faster from a pancuronium neuromuscular blockade than controls, with recovery times approximately 65% shorter than control at each level of recovery. The recovery index, the time difference between 25 and 75% recovery, was also significantly shorter for patients receiving carbamazepine (17 ± 10 min *vs.* 46 ± 19 min, $P < 0.002$).

The correlation between daily carbamazepine dose and time to recovery to 90, 75, 50, and 25% of baseline twitch height was examined for each patient using the Pearson's correlation coefficient (table 2). There was a significant ($P < 0.05$) inverse correlation between carbamazepine daily dose and times to 50, 75, and 90% recovery of baseline twitch height (fig. 1). No correlation was found between plasma carbamazepine levels and recovery times (table 3).

## DISCUSSION

This study confirms faster recovery from a pancuronium-induced neuromuscular blockade in patients receiving chronic carbamazepine therapy. This faster recovery from neuromuscular blockade in patients chronically receiving this anticonvulsant is similar to that after another anticonvulsant, phenytoin. Carbamazepine, an iminostilbene, is structurally related to the tricyclic antidepressants.[5] It is indicated for the treatment of seizures of focal origin (partial seizures) and major generalized (grand mal) seizures.[6] Phenytoin, used in the treatment of all types of epilepsy, is structurally unrelated to carbamazepine. Recovery times in our patients were approximately 30% shorter than those reported for patients on chronic phenytoin therapy.[3] This difference may not be significant,

however; we found a recovery index of 17 ± 10 min for carbamazepine-pancuronium *versus* 29 ± 5 min reported by Ornstein *et al.*[3] for phenytoin-pancuronium.

It is not clear why these structurally unrelated anticonvulsants are associated with similar degrees of accelerated recovery after pancuronium neuromuscular blockade. In patients receiving phenytoin who were resistant to metocurine, there was no difference in the pharmacokinetics of metocurine compared to control patients.[2] However, at all levels of neuromuscular blockade, the plasma concentrations of metocurine required to produce the same degree of blockade were 64–80% greater for phenytoin patients.[2] This indicated a pharmacodynamic, rather than a pharmacokinetic, explanation for the resistance to metocurine.

In an *in vitro* frog motor end plate system, carbamazepine decreased neurotransmitter release and diminished post-junctional sensitivity to acetylcholine.[7] While this does not explain the present findings, perhaps pancuronium and carbamazepine and other anticonvulsants compete for the same site(s) at the neuromuscular junction. The findings of greater resistance to pancuronium at higher doses of carbamazepine lend some support to such a concept. Further study is necessary to test the validity of this hypothesis.

In our study, no correlation was found between recovery times and carbamazepine serum concentrations. This lack of correlation may be related to several different factors. It was possible to measure serum anticonvulsant levels in only six of nine patients. All six had blood samples drawn the evening prior to surgery, and then received their daily morning dose of carbamazepine approximately 1 h before surgery. Therefore, the serum levels reported may not have accurately reflected the concentrations during the intraoperative period. In addition, the relationship between dose and serum concentration for carbamazepine is not strong, perhaps related to individual variation in drug disposition and metabolism.[8] Finally, the concentration of drug at the motor end plate or other site of interaction with muscle relaxants may not correlate with serum concentration. In our study, there was a correlation between dose of carbamazepine and recovery times, which gives some credence to these explanations for error in sampling time or sample origin (blood) as reasons for the lack of correlation of serum concentrations and recovery times.

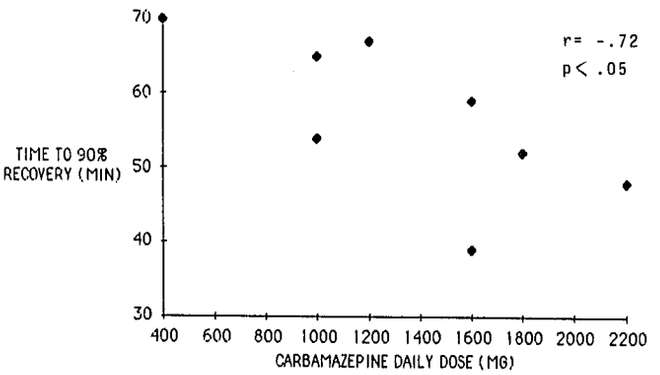


FIG. 1. Correlation between time to 90% recovery and carbamazepine daily dose. N = 8. In one patient, the study was terminated prior to the time of 90% recovery due to technical problems.

TABLE 3. Correlation between Recovery Time (in Minutes) and Carbamazepine Serum Concentration (μg/ml)

| Level of Recovery (%) | Pearson Correlation (r=) | *t* Test, *P*< |
|---|---|---|
| 25% | .44 | .38 (NS) |
| 50% | .59 | .22 (NS) |
| 75% | .51 | .30 (NS) |
| 90% | .45 | .37 (NS) |
| RI | .23 | .65 (NS) |

In conclusion, we found resistance to neuromuscular blockade after pancuronium in patients receiving carbamazepine. The mechanism of this interaction does not appear to be pharmacokinetic, but pharmacodynamic; its exact mechanism remains to be elucidated. Patients receiving carbamazepine (and perhaps all anticonvulsants) should be closely monitored as a more rapid neuromuscular recovery after pancuronium is expected to occur.

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