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The Dose-effect Relationship of Metocurine: The Integrated Electromyogram of the First Dorsal Interosseous Muscle and the Mechanomyogram of the Adductor Pollicis Compared

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The evoked response to indirect muscle stimulation as measured electromyographically in general correlates closely with isometric recordings of mechanical tension. Certain authors have found excellent agreement between the evoked mechanomyographic (MMG) response of the adductor pollicis and the thenar electromyogram (EMG).^{1,2} Although there are no published data comparing the evoked EMG response of the first dorsal interosseous muscle to the adductor pollicis MMG, Alif† found these two parameters to give essentially identical information. Not all investigators, however, have been able to achieve these results. Other published work indicates that, during recovery from nondepolarizing neuromuscular blockade, EMG and MMG estimates of single twitch depression and train-of-four fade can be quite different.³⁻⁵ There is also evidence that the hypothenar muscles are more resistant to the effects of nondepolarizing blocking drugs than is the adductor pollicis.⁶ This may, in part, explain the discrepancies between the evoked EMG and MMG responses found by Kopman³ and Weber and Muravchick.⁴ Harper *et al.*,⁵ however, used the same muscle groups when comparing the EMG to the MMG, and still found that these two techniques often gave different information. In view of these discrepancies, the accuracy and reliability of the integrated EMG as a research tool is still open to some question.

As part of a pilot study for another investigation, we found that, when using the evoked EMG response of the first dorsal interosseous (DI) muscle, we could not reproduce the results most commonly quoted for the potency of metocurine.⁷ To determine whether this difference was the result of our methodology, or represented a real variation in the potency of metocurine, in a separate group of patients we repeated an investiga-

tion of the potency of metocurine while simultaneously measuring both the evoked EMG of the 1st DI and the MMG of the adductor pollicis (AP).

MATERIALS AND METHODS

Thirty-eight adult ASA I-II patients (ages 18-65 yr) undergoing elective surgical procedures, for whom the administration of a muscle relaxant was indicated by the proposed surgery, were included in the study. All patients were free from neuromuscular disease and were within 15% of ideal body weight. The protocol was approved by our hospital's Human Subject Review Committee. Anesthesia was induced with thiamylal sodium iv and maintained with inhalation of nitrous oxide plus iv narcotics as needed.

Group 1 (EMG only, n = 18). The indirectly evoked integrated compound action potential of the first dorsal interosseous muscle to supramaximal stimulation of the ulnar nerve was measured and recorded using a Datex™ 221 NMT monitor. Supramaximal nerve stimulation was achieved using the nerve stimulator incorporated into the Datex™ unit (pulse width 100 μ s, constant current, 0-70 ma range). The test hand was immobilized, but no resting tension was applied to the thumb. Stimulating and recording electrodes were 3M infant Red Dot™ electrodes. After anesthesia was induced and before any muscle relaxants were administered, control twitch height and train-of-four (T4/T1) fade ratio were established. Train-of-four stimulation was given every 20 s during the period of observation, and single twitch depression (height of first twitch in a train/control twitch) (T1/Tc) and train-of-four fade were continuously recorded.

A cumulative dose-response curve was determined by incremental administration of metocurine 0.05 mg/kg until a neuromuscular block of at least 90% was reached. The first dose usually was 0.05 mg/kg, but, in five patients, it was 0.1 mg/kg. Incremental doses (0.05 mg/kg) were given when the evoked T1/Tc ratio was stable ($\pm 1\%$) for three consecutive trains. At least three incremental doses were administered to each patient.

Group 2 (EMG vs. MMG, n = 20). Protocol in this group was identical to that in group 1, except that simultaneous measurement of the evoked isometric mechanical response of the ipsilateral adductor pollicis

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TABLE 1. Log-probit Analysis of Dose-response Relationships for Metocurine

	EMG Only (No Preload)*	Simultaneously Evoked†	
		EMG	MMG
(n) Patients	18	20	20
(n) Observations	62	64	64
Slope ± (SE)	5.062 ± 0.26	4.493 ± 0.34	4.084 ± 0.31
Intercept ± (SE)	5.085 ± 0.25	4.337 ± 0.30	3.960 ± 0.27
Sy,x	0.430	0.468	0.424
r	0.929	0.861	0.862
Estimated Potency (from pooled data)			
ED50 (mg/kg)	0.099	0.108	0.107
ED95 (mg/kg)	0.209‡	0.252§	0.271§
Mean Values of individual patients (±SE)			
ED50 (mg/kg)	0.100 ± .004	0.111 ± .006	0.112 ± .006
ED95 (mg/kg)	0.201 ± .006‡	0.237 ± .009§	0.253 ± .010§

* Group 1.
† Group 2.

‡ Different from Group 2, $P < 0.005$.
§ Different from each other, $P < 0.05$.

muscle was also recorded. Thumb preload was adjusted to between 250–350 grams, and twitch tension was measured with either a Grass FT-10 linear force transducer or with a Medar Adductor Pollicis Monitor®. In addition, in each patient, six to ten simultaneous EMG and MMG T1/Tc determinations were recorded at different levels of paralysis so that the correlation of these two parameters could be analyzed.

At the end of surgery, any residual paralysis was antagonized with neostigmine to an MMG T4/T1 ratio of at least 0.70. Simultaneous responses were examined in pairs by linear regression (least squares) analysis. Only individuals in whom both the MMG and EMG T1/Tc ratio returned to 1.0 ± 0.1 were included in the study.

The observed values for dosage and twitch depression in both groups were analysed by linear regression after the data had first undergone log-probit transformation. ED50 and ED95 values (pooled data) for each group was derived from the calculated lines of regression (table 1). The projected ED50 and ED95 values were then compared by repeated measures hierarchical multiple regression.

The ED50 and ED95 for metocurine (EMG in group 1, both EMG and MMG in group 2) were also calculated by averaging the values for these parameters as determined by log-probit regression analysis of each individual patient. These mean values were then compared by one-way analysis of variance, and the Scheffé test for multiple comparisons. The simultaneously evoked EMG and MMG responses in group 2 were also compared using a paired Student's *t* Test. Observed differences were considered significant when $P = < 0.05$.

RESULTS

As can be seen in figure 1, the line of regression representing the relationship between the MMG and

EMG T1/Tc ratio ($y = 0.947x + 0.038$) is quite close to the line of identity ($y = x$). The maximum predicted difference between the two parameters is less than 4% of control over the entire range of evoked responses. As a result, the simultaneously recorded evoked responses of the adductor pollicis MMG and the first dorsal interosseous EMG give very similar, but not identical, values for the potency of metocurine (table 1). In group 2, the MMG derived estimate for the ED95 (0.25–0.27 mg/kg) is higher than the evoked EMG value by about 7%. While the discrepancy in the estimated potency of metocurine that these two methods produce is quite

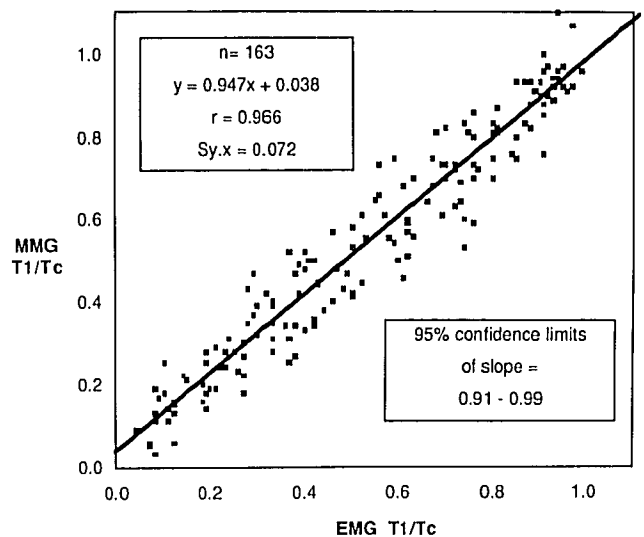


FIG. 1. Evoked mechanical twitch height of the adductor pollicis (MMG) versus 1st dorsal interosseous electromyogram (EMG). Note the very close correlation of these two parameters. For any given EMG value, the predicted MMG response will agree within <4% of control twitch height.

small, it does just reach statistical significance ($P < 0.04$). It is doubtful, however, if these differences are of any clinical importance.

Depending on the method of calculation (see Methods and Discussion), the EMG determined ED95 of metocurine in group 2 is between 0.24–0.25 mg/kg. This is significantly greater ($P < 0.005$) than the value of 0.20–0.21 mg/kg which was found in group 1 (no resting tension applied to thumb).

DISCUSSION

Although differences have frequently been noted between indirectly evoked electromyographic and mechanical responses,³⁻⁶ in this study we found very close agreement between the T1/Tc ratio of the adductor pollicis MMG and the 1st dorsal interosseous EMG. As noted in figure 1, the line of regression relating response of the EMG to the MMG is very similar to the line of identity. As a result, the ED50 and ED95 values for metocurine in group 2 as calculated from EMG versus MMG data were within about 7% of each other. These results were 15–30% higher than those obtained in group 1 where no preload was applied to the thumb ($P = <0.005$). Several years ago, Donlon *et al.*⁸ demonstrated that raising resting tension on the thumb from 50 to 100–200 grams increased evoked mechanical twitch tension by approximately 15–20%. Although Donlon *et al.* were unable to discern differences in the cumulative dose-response curves for gallamine as a function of the resting thumb tension, they nevertheless suggested: "If comparisons of potency are to be made, it is suggested that resting tension be adjusted to approximately 200 g so as to minimize the effect of spurious variations in resting tension." Since the only difference in methodology in this study between groups 1 and 2 was the absence of preload in group 1, it appears that resting tension may, in fact, also effect the evoked compound action potential. However, it is possible that the "increased sensitivity" demonstrated in group 1 may reflect nothing more than a technical problem in recording the evoked action potential. In group 2, because the thumb was abducted under tension, the distance between recording electrode and muscle may have been reduced, resulting in a larger EMG signal. Whatever the cause, electromyographic studies of drug potency that do not take this action into account may overestimate drug potency by a significant amount. This phenomenon clearly needs to be investigated further.

In the only published study of the potency of metocurine in adults using currently accepted methodology, Savarese *et al.*⁷ found the ED95 of this drug to be 0.28

mg/kg. The only two other investigations of metocurine employing log-probit regression analysis during balanced anesthesia^{9,10} are flawed by using rapid stimulation rates (0.20–0.25 Hz).¹¹ The results of the present study are summarized in table 1. Depending on the method of calculation, the ED95 of metocurine as estimated from the evoked MMG was between 0.25 and 0.27 mg/kg and the corresponding EMG potency was from 0.24–0.25 mg/kg.

While the differences between our results and those of Savarese *et al.* are minor, it should be noted that the experimental design of the two studies was quite different. Although it has been shown that the single bolus technique (employed by Savarese) can give identical results to the cumulative dose method when long-acting neuromuscular blockers are the drugs under investigation,¹² the single dose method does have one practical weakness. When predetermined doses of drug are administered, it is inevitable that some patients will show 100% twitch depression. While these individuals may not be discarded from a study, they nevertheless generate data that are difficult to utilize, and can potentially be quite misleading. For example, if a single bolus of 0.3 mg/kg of metocurine abolishes all evoked response in an individual, it then becomes unclear if the patient is exactly 100% paralyzed, or if, perhaps, the dose administered actually represents as much as two to three times the ED95. Several related problems also arise. How does one plot a response of >100% on a dose-response curve? Is it proper to average a response of 90% and a response of 100% and conclude that the mean of these two values is 95%?

In the study of Savarese *et al.*, there were a total of 55 patients (observations). However, only 22 of their subjects received less than 0.3 mg/kg. Hence, an unspecified but large proportion of their recorded responses resulted in 100% twitch depression. The authors "solved" this problem by averaging the results at each dosage level. For example, 0.4 mg/kg produced 92–100% twitch depression with a mean value of 98.8%. While plotting values calculated in this manner is a perfectly reasonable method when the total range of responses is between 1 and 99%, when a large percentage of evoked responses exceed this range, the wisdom of this approach must be questioned. Certainly, at the higher end of the dose-response curve, this method would tend to underestimate potency. These problems can be almost completely avoided if the cumulative bolus method is used to determine the dose-response curve. If, for example, a small initial dose produces a greater than anticipated effect, it is possible to reduce the second dose to avoid total twitch suppression. Therefore, although the present study (group 2) contains only 20 patients, the total number of useful obser-

vations probably exceeds those in the paper of Savarese *et al.*

When performing a cumulative bolus dose-response study, potency may be calculated in several ways. First, all data from every patient can be pooled and linear regression analysis performed on the total number of observations. An alternative method, if two or more doses per patient are administered, is to perform regression analysis on the data from each subject and to average the calculated individual ED50 and ED95 values. These two methods produce similar, but not identical, estimates of potency, even when the number of observations in all patients is the same. Since it is unclear to this investigator that one method clearly has greater validity than the other, both estimates of potency are included in table 1.

In summary, the evoked adductor pollicis MMG and the 1st dorsal interosseous EMG may be used essentially interchangeably in determining the depth of nondepolarizing neuromuscular blockade. The calculated ED95 of metocurine as measured by the MMG is between 0.25 and 0.27 mg/kg. Calculating the ED95 of metocurine from the EMG will result in a very slight (approximately 7%) overestimation of its potency.

This study also suggests that, without a preload applied to the muscle under investigation, the EMG may significantly overestimate the sensitivity to nondepolarizing neuromuscular blocking drugs. This possibility needs further substantiation, especially if EMG studies are to be used in evaluating future generations of nondepolarizing blocking drugs.

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Pediatric Orthotopic Liver Transplantation: Multifactorial Predictions of Blood Loss

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Orthotopic liver transplantation is an established method of therapy for pediatric patients with end-stage

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liver disease. Because of the magnitude of the operation, blood loss can be substantial. Blood for this procedure must be available on a 3-4-h notice.

Retrospective investigations have quantified intraoperative blood loss for pediatric patients. In two previous reports, blood usage during liver transplantation in pediatric patients ranged from 2 to 59 units,¹ and averaged 3.9 blood volumes.² No study, though, has attempted to identify factors that might predict blood loss as well as survival in children. Such data might indicate roughly how many units the blood bank should have prepared for each patient, as well as the extent of venous access and monitoring that should be prepared before a case. We have collected clinical and laboratory information, as well as intraoperative blood loss data, to