

Neuromuscular Effects of Mivacurium in 2- to 12-yr-old Children with Burn Injury

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Background: Burned patients are usually resistant to the neuromuscular effects of nondepolarizing relaxants, mostly because of receptor changes. The magnitude of the resistance is related to burn size and time after burn. Mivacurium is a muscle relaxant, degraded by plasma cholinesterase, whose enzyme activity is decreased in burns. The present study tested the hypothesis that burn-induced depressed plasma cholinesterase activity counteracts the receptor-mediated resistance, resulting in a lack of resistance to mivacurium.

Methods: Burned patients (n = 23), aged 2–12 yr, subclassified into burns of 10–30% or > 30% of body surface, were studied at ≤ 6 days and again at 1–12 weeks after burn if possible. Thirteen additional patients served as controls. Neuromuscular variables monitored included onset and recovery following bolus dose, continuous infusion rates required to maintain 95 ± 4% paralysis, and recovery rates following infusion.

Results: The onset times of maximal twitch suppression were not different between burns and controls, but recovery to 25% of baseline twitch height was prolonged in patients with > 30% burn irrespective of time after injury. The continuous infusion rates to maintain twitch suppression at 95 ± 4% were not

different between groups. The recovery indices, including train-of-four to > 75%, 25–75%, or 5–95% in burned patients, were similar or prolonged compared with controls. The prolonged recovery in burned patients was inversely related to plasma cholinesterase activity ($R^2 = 0.86$, $r = -0.93$, $P < 0.001$), and the decreased plasma cholinesterase activity was related to burn size and time after burn.

Conclusions: A normal mivacurium dosage (0.2 mg/kg) effects good relaxation conditions in burned patients, with an onset time similar to that in controls. This finding contrasts with the response seen with other nondepolarizing drugs, higher doses of which are required to effect paralysis. The decreased metabolism of mivacurium, resulting from depressed plasma cholinesterase activity, probably counteracts the receptor-mediated potential for resistance. Because succinylcholine is contraindicated in burned patients, larger doses of nondepolarizing agents are advocated to effect rapid onset of paralysis. This generalization does not hold for mivacurium. (Key words: Pediatrics; plasma cholinesterase; relaxant resistance; succinylcholine, alternative to.)

PATIENTS with thermal burn injury are resistant (or hyposensitive) to nondepolarizing skeletal muscle relaxants such as atracurium,¹⁻³ vecuronium,⁴ pancuronium,⁵ metocurine,⁶ and *d*-tubocurarine.⁷ These subjects, therefore, require greater doses of muscle relaxant than those used for normal subjects to achieve a given degree of neuromuscular paralysis. The magnitude of this resistance is dependent on time after burn and size of burn injury; the resistance is usually seen in patients sustaining greater than 25–30% of total body surface area (TBSA) burn injury, with little or no resistance evident in the first week even after major injury but an increase to a peak resistance about 5 or 6 weeks after injury.^{3,5} Current evidence indicates that the altered response to muscle relaxants can be ascribed primarily to changes in the quality and quantity of acetylcholine receptors after thermal burn injury.⁸

Mivacurium chloride is a short-acting nondepolarizing neuromuscular blocking drug whose pharmacologic activity is terminated primarily by hydrolysis *via* plasma cholinesterases (PCHE). Because of its short duration of action, mivacurium may provide an alternative to succi-

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nylcholine for patients with burn injury in whom the latter is contraindicated. It may also be an alternative to other nondepolarizing drugs, which have been shown to lose potency in this special population. Burn injury, however, results in reduced PCHE activity; the magnitude and time course of this decrease in activity is proportional to the percentage of TBSA injury, with peak effect usually within 1 week.⁹ The phenomena of burn-induced resistance to nondepolarizers and the potential for altered sensitivity to mivacurium (secondary to decreases in PCHE) may produce differential effects upon the depth, duration, or recovery profile of neuromuscular block. For example, in a given patient, there may be a preponderance of one effect over the other, depending on the extent of the burn and the time elapsed since the injury. Consequently, recommended doses of mivacurium could result in either an inadequate neuromuscular block with a shorter than expected duration of action or in profound block with a longer than expected duration of action. Alternatively, these phenomena may offset each other.

Thus, the present study was conducted in 2- to 12-year-old children with varying degrees of thermal burn injury, primarily to examine the neuromuscular effects of mivacurium administered as a bolus dose and by infusion. In addition, this study examined the relationships between neuromuscular pharmacodynamics and a number of variables including time after burn injury, size of burn, and PCHE activity and dibucaine number.

Methods

Patients and Study Protocol

This study was approved by the Subcommittee on Human Studies, Committee on Research of the Massachusetts General Hospital, in Boston, Massachusetts. Written informed consent was obtained from a parent or guardian of all burned and control patients included in this study. Twenty-three burned and 13 control pediatric patients aged 2-12 yr, with American Society of Anesthesiologists physical status I, II, or III, undergoing surgery were enrolled. The burned patients were classified according to burn size as having 10-30% or > 30% TBSA burn. Each of these groups was divided into subgroups according to time of burn injury: ≤ 6 days or 1-12 weeks after burn injury. Every attempt was made to re-enroll each patient who was studied ≤ 6 days after burn injury for a subsequent study at 1 to 12 weeks after the burn injury. Thus, participants who were in the 10-30% or >

30% burn group were studied again, if possible, 1-12 weeks after burn. A control group of 13 patients was also studied. The number of studies performed, therefore, exceeded the number of patients. The control group patients were studied only once. Thus, the five subgroups in this study, depending on TBSA burn sustained and the time of surgery after thermal injury, were as follows: patients with 10-30% TBSA burn undergoing surgery ≤ 6 days after burn injury ($n = 8$); patients with 10-30% TBSA burn undergoing surgery 1-12 weeks after burn injury ($n = 9$); patients with > 30% TBSA burn undergoing surgery ≤ 6 days after burn injury ($n = 9$); patients with > 30% TBSA burn undergoing surgery 1-12 weeks after burn injury ($n = 13$); and patients with a history of thermal burn injury ≥ 3 yr before enrollment in this study ($n = 8$) or no history of thermal burn injury ($n = 5$; total control group = 13). Thus, a total of 52 studies were performed in the five groups.

Two subjects with 10-30% burns and four with > 30% burns were not studied initially at ≤ 6 days after burn; one subject with 10-30% burn studied early did not participate in the second study at 1-12 weeks. Patients who were obese (> 30% of ideal body weight) or had clinically significant pulmonary, renal, hepatic, psychiatric, neurologic, neuromuscular, or cardiovascular disease were excluded from study. Also excluded were those receiving medications known to influence neuromuscular transmission, although such medications, *e.g.*, aminoglycosides, could be administered immediately after full recovery from mivacurium-induced neuromuscular block. Patients with clinically significant abnormalities in hematology and clinical chemistry tests (creatinine, alkaline phosphatase, and alanine aminotransferase) were also excluded. Venous blood was sampled to determine PCHE activity and dibucaine number at the time of the study.

Anesthesia

Preoperative medication consisted of appropriate doses of one or more of the following: midazolam, lorazepam, diazepam, morphine, and methohexital, administered orally, intravenously, or rectally. Monitoring consisted of electrocardiography, noninvasive blood pressure measurement (except in those patients who had an indwelling arterial cannula), pulse oximetry, and measurement of end-tidal pressure of carbon dioxide and temperature, continuously. Anesthesia was induced with thiopental (2.5-5.0 mg/kg intravenous) or halothane 0.5-3% end-tidal concentration in oxygen by mask. In infants with no venous access, halothane was always the

anesthetic of choice for induction (< 5 min) until a vein was cannulated. Anesthesia was maintained with halothane (0.5–1.5% end-tidal), nitrous oxide, and oxygen. Occasionally, intravenous bolus doses of propofol or thiopental were administered along with opioid agents (fentanyl/morphine) as anesthetic supplements. Ventilation was controlled to maintain normocapnia.

Neuromuscular Pharmacodynamics

After induction of anesthesia, the ulnar nerve was stimulated with a Grass S48 stimulator (Grass Instruments, Quincy, MA) through 25-gauge needles inserted to a forearm immobilized on a padded board. Some burned patients did have burns of the hands and arms, but this did not affect our ability to perform the study. The thumb was linked to a Grass FT03 force transducer, and the evoked twitch tension of the adductor pollicis was recorded as twitch height on a Grass strip-chart recorder. Single square-wave stimuli of a 0.2-ms duration were administered at 0.15 Hz. Initially, tetanic stimuli were applied for 30–60 s for maximal recruitment of all neuromuscular synapses. Baseline (control) twitch height was then obtained from a stable recording for at least 3–5 min prior to administration of a bolus dose of mivacurium. Toward the anticipated end of the surgical procedure, the mivacurium infusion was terminated. After this point, when recovery of twitch response was apparent, the stimulation mode was changed to supra-maximal train-of-four stimuli (0.2-ms square waves) administered at 2 Hz. Maximal recovery of twitch height (end-control) was ascertained by recording for approximately 3 min beyond attainment of 95% recovery of first twitch or $\geq 75\%$ of the train-of-four ratio (ratio of fourth to first twitch, $T_4:T_1$).

The first part of the study consisted of an initial intravenous bolus dose of 0.20 mg/kg of mivacurium administered approximately 5 min after attaining stable anesthesia and stable recording of neuromuscular transmission as described previously. With few exceptions, intubation generally proceeded 2–8 min after administration of the initial dose of mivacurium, when maximal twitch suppression was reached. The recovery of twitch to 25% of baseline (control) twitch height was monitored. The second part of the study consisted of continuous infusion of mivacurium. Following recovery of twitch from the bolus dose to 25% of baseline twitch height, additional mivacurium bolus doses were administered, followed by a continuous infusion to maintain neuromuscular suppression at approximately $95 \pm 4\%$ ($5 \pm 4\%$ twitch height). Continuous infusion rate was initiated at

$20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and generally adjusted every 3 min, if necessary, in increments or decrements of $1\text{--}2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to maintain adequate neuromuscular block within the range of $95 \pm 4\%$.

The following variables were determined for each patient if possible following the bolus doses of mivacurium: maximum twitch suppression, onset (time from completion of mivacurium injection to maximum twitch suppression), and clinically effective duration (time from completion of injection of the initial dose to 25% twitch recovery) of neuromuscular block. Recovery parameters were also noted following termination of continuous infusion, the time to 5%, 25%, 75%, and 95% recovery of twitch relative to end-control, time to $T_4:T_1 \geq 75\%$, and average infusion rates for each patient who received a continuous infusion of mivacurium for a minimum of 30 min.

Data Analysis

The analysis was stratified to study the effect of age, burn size, and the time after burn on various clinical end points (pharmacodynamics, PCHE, and so forth). Because of the repeated-measures structure of the data, there is presumably a positive correlation between the observations obtained from the two surgeries of the same patient. To account for the correlation structure, mixed-effect regression models with compound symmetry correlation structure were used to compare differences between groups. Age and PCHE activity were included as covariates in all models. Unless otherwise specified, $P < 0.005$ was considered statistically significant to correct for the inflation of type I error with multiple testing (Bonferroni correction). All values indicated in the tables are mean \pm SD.

Results

Efficacy data were excluded from all analyses if intravenous doses of gentamicin were administered within 2 h before the initial 0.20-mg/kg bolus dose of mivacurium (two patients) or shortly after administration of the initial dose of mivacurium (one subject), or if the time of administration was unrecorded (one subject). Two other patients who received intravenous gentamicin shortly after initiation of continuous infusion of mivacurium had their infusion-related pharmacodynamic data excluded from all analyses. One male patient aged 11 yr designated American Society of Anesthesiologists physical status IV was inadvertently enrolled, and therefore all data from

Table 1. Patient Demographics

Burn Size (% TBSA)	Time of Study after Burn Injury	Age, yr (no. of patients)	Weight (kg)	Gender (male/female)	ASA Physical Status (I/II/III)	Ethnic Origin (white/black/other)
10–30	≤ 6 days	6.7 ± 3.9 (7)	26.7 ± 18.6	2/5	2/3/2	7/0/0
10–30	1–12 weeks	7.8 ± 3.9 (9)	30.7 ± 18.6	2/7	5/4/0	9/0/0
> 30	≤ 6 days	5.0 ± 3.4* (8)	18.0 ± 5.8*	4/4	0/2/6	6/0/2
> 30	1–12 weeks	4.5 ± 3.0* (11)	17.8 ± 4.8*	5/6	2/3/6	8/0/3
Control	—	7.5 ± 3.0 (13)	28.7 ± 12.9	7/6	11/2/0	7/1/5

Age and weight data are mean ± SD.

TBSA = total body surface area.

* $P < 0.05$ compared with 10–30% burn and controls.

this subject were excluded. Thus, more than 23 burned patients and 13 controls were enrolled, but only patients whose neuromuscular pharmacodynamics were usable were included in the results (52 studies). On average, patients with > 30% TBSA burns were younger and therefore of lower body weight than those who sustained 10–30% TBSA or those enrolled in the control group (table 1). Otherwise, the study populations were generally comparable.

At the preset dose of 0.20 mg/kg mivacurium, patients on the average experienced complete or deep neuromuscular block (> 95%; table 2). The onset of maximum effect of mivacurium did not differ between groups. The duration of action of a 0.20-mg/kg dose of mivacurium from injection to 25% recovery of control twitch height, for patients with small (10–30%) TBSA burns, was comparable to that seen in the control group. In contrast, the recovery to 25% in the patients with > 30% burns was nearly double that seen in controls and in patients with smaller burns, irrespective of time of study after injury (table 2).

The average duration of continuous infusion varied considerably among the groups, ranging from 40.0 to

80.0 min (table 3). There was wide variability in the infusion rates of mivacurium. The mean infusion rates in patients with burns were similar to those for the control group regardless of time of study after injury (≤ 6 days vs. 1–12 weeks; table 3). It is noteworthy that the patients with > 30% burns were significantly younger than the reference group, and therefore the former group would have been expected to have a higher infusion rate. After termination of infusion, the times to recovery to $T_4:T_1 > 75\%$ for those patients with 10–30% or > 30% TBSA burns were similar or greater than that of the control group. This trend for a prolonged recovery time was almost always observed for all recovery variables in patients with > 30% burns. Patients with > 30% TBSA burns and studied ≤ 6 days after the burn injury showed the slowest rate of recovery compared with controls and patients in the other comparator groups.

The dibucaine number and cholinesterase levels, measures of qualitative and quantitative changes in PCHE activity, are indicated in table 4. There were no differences in dibucaine number, confirming that the prolongation of recovery did not result from a qualitative change. In contrast, the PCHE activity was significantly

Table 2. Mivacurium Pharmacodynamics after 0.20 mg/kg Bolus Dose

Burn Size (% TBSA)	Time of Study after Burn Injury	Maximum Suppression (%)	Time (min) to:	
			Maximum Suppression	25% T_1 Recovery
10–30	≤ 6 days	98 ± 2 (7)	3 ± 1 (7)	12 ± 4 (7)
10–30	1–12 weeks	99 ± 1 (9)	3 ± 1 (9)	14 ± 5 (8)
> 30	≤ 6 days	97 ± 7 (7)	2 ± 1 (7)	22 ± 7*† (6)
> 30	1–12 weeks	96 ± 14 (11)	2 ± 1 (11)	20 ± 10†‡ (9)
Control	—	95 ± 10 (13)	3 ± 1 (13)	13 ± 4 (11)

Data are mean ± SD; number of patients are in parentheses.

TBSA = total body surface area.

* $P < 0.005$ compared with 10–30% burn groups.

† $P < 0.05$ compared with control group.

‡ $P < 0.05$ compared with 10–30% burn groups.

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Table 3. Mivacurium Pharmacodynamics during and after Continuous Infusion

Burn Size (% TBSA)	Time of Study after Burn Injury	Twitch Height at the End of Infusion (%)	Duration of Infusion (min)	Mean Infusion Rate ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	Recovery Indices (min), Time to:		
					T ₄ : T ₁ \geq 75%	5–95%	25–75%
10–30	\leq 6 days	3 \pm 1 (6)	80 \pm 27 (7)	13 \pm 8 (6)	23 \pm 17 (6)	13 \pm 5 (4)	9 \pm 8 (6)
10–30	1–12 weeks	5 \pm 6 (7)	43 \pm 36 (8)	16 \pm 8 (3)	18 \pm 6 (6)	12 \pm 5 (7)	6 \pm 2 (8)
> 30	\leq 6 days	3 \pm 3 (7)	69 \pm 30 (7)	10 \pm 3 (4)	33 \pm 21* (2)	24 \pm 10†‡ (3)	16 \pm 11†‡§ (6)
> 30	1–12 weeks	3 \pm 2 (8)	40 \pm 17§ (9)	8 \pm 2 (6)	26 \pm 10 (8)	17 \pm 6*† (7)	8 \pm 2 (9)
Control	—	5 \pm 3 (13)	68 \pm 28 (13)	9 \pm 4 (13)	14 \pm 5 (12)	11 \pm 6 (7)	5 \pm 3 (13)

Data are mean \pm SD; number of subjects in parentheses.

TBSA = total body surface area.

* $P < 0.05$ compared with control group.

† $P < 0.05$ compared with 10–30% burn and controls.

‡ $P < 0.005$ compared with control group.

§ $P < 0.05$ compared with 1–12 weeks of same burn size.

decreased in burn groups. The magnitude of the decrease in the latter groups was related to burn size and time after burn, with the most change in patients with > 30% TBSA burn at 1–12 weeks and the least change in those with 10–30% burn at \leq 6 days. A regression plot of recovery time *versus* PCHE level indicated a significant negative correlation ($R^2 = 0.86$, $r = -0.93$) between the two for all patients at 1–12 weeks after burn. This relationship was not observed in burned patients at \leq 6 days after injury.

Discussion

Resistance to nondepolarizing relaxants is best demonstrated by plasma concentration–effect data showing that a higher concentration of relaxant is required for a given effect. Alternatively, resistance can be demonstrated as inadequate paralysis for a normal dose, prolonged onset of effect, faster recovery, or more frequent doses.^{1–7} The principal finding in this study is that pediatric burned patients have a neuromuscular response to mivacurium similar to concurrent controls, judged by

time of onset of effect, the maximal paralysis achieved with a given bolus dose, and the rates of infusions. All these features suggest a lack of resistance to mivacurium. Some burned patients, however, differed from controls in having a prolonged recovery time following bolus and infusions. Our study, therefore, is consistent with a previous study in nine adult patients with 40–60% TBSA burn, in which a prolonged recovery from mivacurium-induced paralysis also was observed.¹⁰ The effect of burn size and time after burn and the correlation of recovery or infusion rates to cholinesterase activity, however, were not reported in that adult study. This observation of effective paralysis with a normal dose or infusion rate, therefore, contrasts with previous observations with other neuromuscular relaxants in which resistance was confirmed by a higher dose or plasma concentration requirement, faster recovery, or more frequent doses.^{1–7}

In the present study in children aged 2–12 yr, a bolus dose of 0.2 mg/kg of mivacurium administered intravenously caused equipotent maximal effect in all burn groups, irrespective of time after burn or magnitude of burn, and the responses were similar to controls studied

Table 4. Mean Plasma Cholinesterase Activity and Dibucaine Number

Burn Size (% TBSA)	Time of Study after Burn Injury	Mean Dibucaine Number (%)	Mean Plasma Cholinesterase Activity (IU/ml)
10–30	\leq 6 days	73.7 \pm 8.6 (7)	3.1 \pm 1.5* (7)
10–30	1–12 weeks	77.2 \pm 12.5 (9)	3.0 \pm 1.3* (9)
> 30	\leq 6 days	69.9 \pm 13.6 (8)	2.3 \pm 2.2* (8)
> 30	1–12 weeks	71.8 \pm 11.0 (8)	1.3 \pm 0.8† (11)
Control	—	76.5 \pm 8.5 (12)	5.4 \pm 1.4 (13)

Data are mean \pm SD; number of subjects in parentheses.

* $P < 0.05$ compared with controls.

† $P < 0.005$ compared with controls.

concurrently. The results observed in our controls (and burned patients) are, therefore, consistent with previous studies performed in healthy children during halothane anesthesia.^{11,12} The time to recovery of twitch to 25% of baseline height following the bolus was similar between the 10–30% burn group and controls but prolonged in children with > 30% burn. The finding of comparable maximal twitch inhibition and recovery to 25% of baseline in patients with 10–30% and controls is consistent with previous studies showing that patients with less than 25–30% burn do not demonstrate resistance to nondepolarizers.⁸ In contrast, if burns exceeded this magnitude, previous studies with other nondepolarizing relaxants demonstrated resistance. In the present study, however, patients with > 30% TBSA burn demonstrated twitch suppression similar to other burn groups and controls. The recovery time was, however, prolonged compared with other groups. The findings in this study are therefore unexpected, because patients with > 30% TBSA burn at 1–12 weeks after burn demonstrate a higher dose or concentration requirement to nondepolarizers, and the twitch recovery is also quicker.^{1–8}

Requirement for nondepolarizing agents administered by continuous infusion has not been reported previously in burned patients. Thus, the infusion requirements of mivacurium in this study cannot be compared with previous studies of other nondepolarizing relaxants. In the contemporary controls of the present study, infusion rates necessary to maintain twitch inhibition at a given level were similar to those observed previously in normal children undergoing routine elective surgery.^{11,13} Even in patients with major burns, the infusion rates were similar to those of the control group, despite the age being younger in the major injury (> 30% burn) group. In normal subjects the younger the age group, the higher the infusion or dose requirement or the faster the recovery rates.¹⁴ The recovery profiles of burned patients after termination of continuous infusion regimens were either similar or prolonged compared with controls irrespective of burn size or time after burn. Thus, these results on recovery following infusion are consistent with the results of the bolus-dose studies on the same patients.

The factors potentially contributing to the resistance to nondepolarizing neuromuscular blockers include altered pharmacokinetics resulting from enhanced renal elimination and loss of drug through burn wound¹⁵; increased protein binding, especially to α_1 -acid glycoprotein fraction¹⁶; and acetylcholine receptor changes.¹⁷ The possibility exists of the presence of one or more of

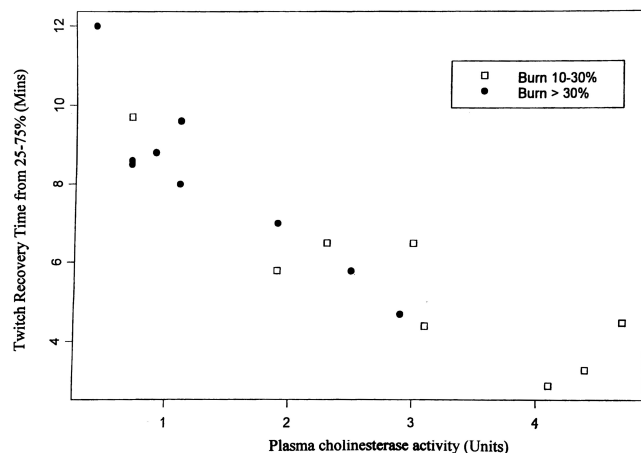


Fig. 1. Relationship of pseudocholinesterase levels to twitch recovery index (25–75%). There was an inverse relationship between the two variables. Patients included are those with 10–30% and \geq 30% body surface area burns at 1–12 weeks after injury. The correlation coefficient was -0.96 ; $P < 0.001$.

these factors in our burned patients, which would contribute to resistance. Mivacurium, like succinylcholine, is metabolized by PCHE. Previous studies have documented the importance of this enzyme in the offset of mivacurium-induced paralysis, even in phenotypically normal patients.^{14,18} Consistent with previous reports in burned patients,⁹ our results confirm an effect of burn size and time after burn on PCHE activity. The most profound depression of PCHE was observed in patients with > 30% burn at 1–12 weeks after burn explaining the prolonged recovery from mivacurium; the least depression was in patients with 10–30% burn at \leq 6 days after burn. Regression analyses of PCHE activity with recovery times indicated a strongly inverse correlation for the period 1–12 weeks after burn for both burn sizes (fig. 1). The inverse relationship between PCHE and recovery suggests that depressed metabolic degradation of mivacurium was more dominant than the factors that induce resistance.

The high dosage requirement for most nondepolarizing relaxants after burns could potentially cause adverse cardiovascular effects, especially if high dosages are necessary for rapid onset of effect. Even if high dosages are used, for example $2 \times ED_{95}$ dose of pancuronium-metocurine used in combination, the onset for maximal effect exceeds 3 min.¹⁹ The serious drawback of underdosing, to avoid cardiovascular side effects, is prolonged onset of effect or inadequate paralysis. This becomes a life-threatening problem if rapid intubation is indicated or in the presence of laryngospasm. Laryngospasm in a burned patient results in a faster desaturation of the

oxygen tension in blood because of the hypermetabolic state and poor lung function.²⁰ The use of succinylcholine in these situations is unwise because of the potential for hyperkalemic cardiac arrest.¹⁷ Mivacurium, in contrast, can be administered in normal doses to effect paralysis with possibly minimal cardiovascular effects. Furthermore, our study documents that the onset of maximal paralysis with mivacurium can be achieved at approximately 2 min in patients with major burns even at 1–12 weeks, when resistance could be expected (table 2). Partial relief of laryngospasm could possibly be achieved at a time earlier than this. Thus, in contrast with other nondepolarizing agents, mivacurium, administered at normally recommended doses, may be a reasonable and efficacious alternative to other nondepolarizing relaxants.

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