

## The Neuromuscular Effects of Pancuronium in Burned Children

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Pancuronium bromide (Pm) produces a nondepolarizing type of neuromuscular blockade with cardiovascular stimulating properties.<sup>1,2</sup> The nondepolarizing property is particularly important in the burned population because of the known hyperkalemic response to depolarizing muscle relaxants.<sup>3</sup> The cardiovascular stimulating properties of the drug<sup>1,2</sup> may be desirable in critically ill burned children who often have cardiovascular instability. Prior studies indicate that the dose and plasma concentration requirement of other nondepolarizing neuromuscular blockers is increased following acute thermal injury.<sup>4,5</sup> The neuromuscular effect of Pm have not been documented systematically in the burned patient. In this study, we compared the neuromuscular response to incremental doses of Pm in acutely burned children and age-matched pediatric surgical patients. In addition, we have attempted to characterize the effect of magnitude of burn and the time after burn injury on the dose requirement and on recovery of twitch tension.

## METHODS

The protocol for the study was approved by the Subcommittee on Human Studies and the Committee of Research at our institution. Parental permission was obtained. Nineteen burned children of a mean  $\pm$ SE age of  $10.2 \pm 0.8$  yr (range 3–17 yr), weighing  $37.4 \pm 3.0$  kg (range 12–71 kg) and with a mean body surface area burn  $48.8 \pm 4.4\%$  (range 4–85%), were studied at  $34.2 \pm 7.9$  days after being burned. The 19 burned children were studied 34 times, two patients being studied four times, three patients three times, and another three studied twice during the excision and grafting procedures. The control

group consisted of 19 pediatric surgical patients of a mean age of  $10.3 \pm 1.4$  yr (range 3–17 yr) and weighing  $37.8 \pm 5.3$  kg (range 12–67 kg). Twelve were patients for orthopedic or urologic procedures and seven were for plastic surgical procedures. These seven had burn injury at least 5 yr prior to the study. None of the patients was in renal, hepatic, or cardiac failure assessed by clinical history and physical examination. In the burned patients, clinical signs were confirmed by laboratory and clinical tests such as BUN, creatinine, SGOT, and central venous pressure measurements. Only patients with normal serum electrolytes were included in the study.

Premedication consisted of diazepam 0.1 mg/kg po or rectal methohexital 20–25 mg/kg. Anesthesia was induced with intravenous thiopental (4–8 mg/kg) and maintained with halothane 1–1.5% in nitrous oxide and oxygen. The electrocardiogram, blood pressure, and temperature were monitored. All patients' body temperature was maintained greater than  $36^\circ\text{C}$  during the study period.

Neuromuscular transmission was studied using either an FT03 or FT10 force displacement transducer. The adductor response of thumb to ulnar nerve stimulation was recorded on a Grass polygraph. A Grass S48 stimulator was used to administer supramaximal stimuli of 0.2 ms duration at a rate of 0.15 Hz through a #22 subcutaneous needle electrode. The patient received no other form of stimulus during this period. Following a baseline twitch, incremental doses of Pm (0.01–0.03 mg/kg) were administered until 95–99% twitch depression was obtained. Prior to and 1 min after the administration of total dose, the heart rate and systolic blood pressure were measured and recorded. Administration of the total drug dose was completed in approximately 10 min.

Dose-response data for neuromuscular blockade were plotted on log-probit coordinates. A mean best fit straight line was determined as described by Litchfield and Wilcoxon.<sup>6</sup> The recovery time was measured as the time necessary for spontaneous recovery of the twitch height from 95% twitch depression to 75% depression. Simple and multiple regression analyses were performed to correlate the effect of various clinical variables (burn size, time after burn injury) on both the dose ( $\text{ED}_{95}$ ) and recovery times. Student's *t* test was used to examine differences between groups, and a paired *t* test was applied to evaluate significance within groups (blood pressure

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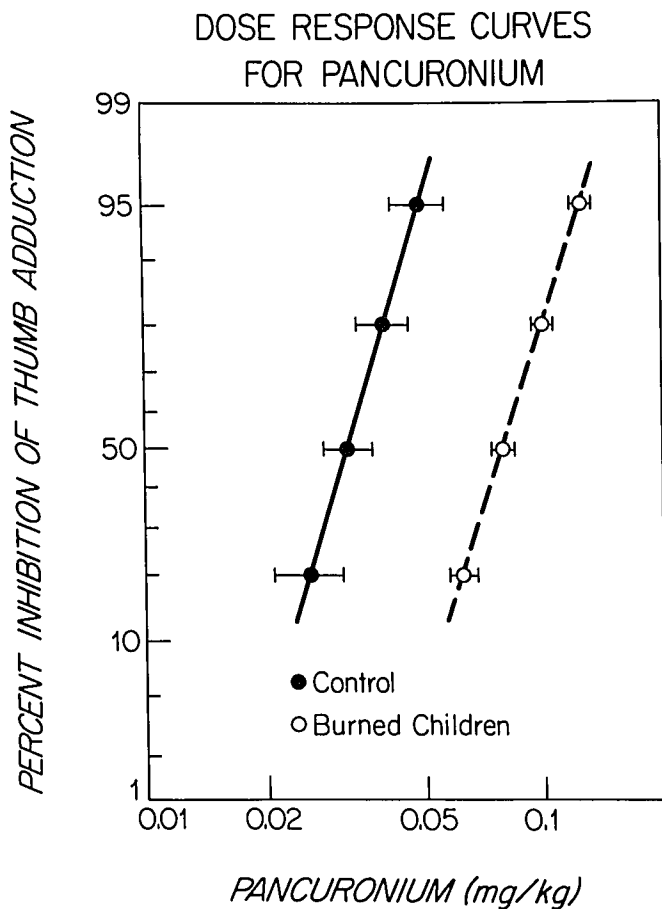


FIG. 1. The dose response curves of Pm in burned and control children anesthetized with halothane. Note in burned patients the significant ( $P < 0.005$ ) 2.5-fold shift to the right in the dose-response curve.

and heart rate). Results were considered statistically significant when  $P < 0.05$ .

### RESULTS

There was no significant difference in the dose response curves of the nonburned children and the children who were burned 5 yr prior to the study. Hence, these two groups of patients were grouped together as the control group. The dose response curves of acutely burned and control children are shown in figure 1. The mean  $\pm$  SE  $ED_{50}$  and  $ED_{95}$  were  $0.08 \pm 0.006$  and  $0.13 \pm 0.01$  mg/kg, respectively, for burned children, compared with  $0.031 \pm 0.02$  and  $0.054 \pm 0.02$  mg/kg respectively in control children. The differences in these values between the two groups were highly significant ( $P < 0.005$ ).

There was a significant correlation between log dose ( $ED_{95}$ ) and the magnitude of burn ( $r = 0.83$ ,  $r^2 = 0.69$ ;  $P < 0.001$ ), but no correlation between the log dose and the time after burn injury ( $r = 0.29$ ) (fig. 2). The rela-

tionship between dose and burn size was described by the equation,  $\log ED_{95} = 0.00641 - 1.256$ . A multiple regression combining the time after burn and burn size did not significantly ( $P > 0.05$ ) improve the prediction of the dose. When the patients who were studied more than once were examined individually, there was a tendency for dose to increase or remain the same up to the first four weeks after burn injury and then gradually decrease with time. The statistical significance of this could not be tested because of paucity of observations.

Recovery of twitch height from 5 to 25% of control was significantly ( $P > 0.005$ ) slower in burned children ( $24.5 \pm 2.6$  min) compared with control children ( $16.1 \pm 1.1$  min). The recovery time in the burned subjects did not correlate with the dose ( $r = 0.33$ ), time after burn ( $r = 0.31$ ) or size of the burn ( $r = 0.29$ ). At the end of the anesthetic, neuromuscular blockade in all patients was antagonized adequately with atropine (0.02 mg/kg) and neostigmine (0.06 mg/kg) as determined by the return of twitch tension and train-of-four to control level.

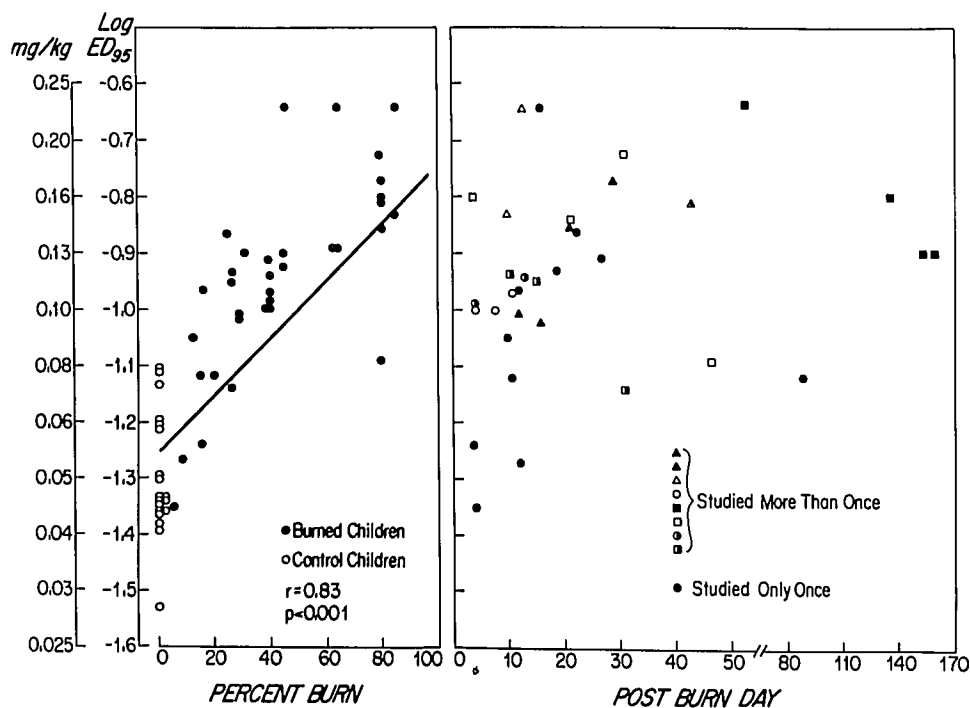
The mean  $\pm$  SE, blood pressure, and heart rate prior to the administration of Pm was  $90 \pm 5.0$  mmHg and  $97 \pm 5.0$  beats/min in the control patients and  $98 \pm 4.0$  mmHg and  $112 \pm 4.0$  beats/min in burned children. Following the last incremental dose of Pm, there was a significant increase in both the heart rate ( $9.7 \pm 3.6\%$ ) and blood pressure ( $5.8 \pm 2.6\%$ ) in the acutely burned children ( $P < 0.025$ ). In the control group, there was no significant change in the blood pressure ( $-3.9 \pm 5.6\%$ ), but there was a significant increase in the heart rate ( $7.4 \pm 4.8\%$ ). The changes in cardiovascular indices were not significantly different between groups.

### DISCUSSION

This study demonstrates that the mean dose requirement of Pm during halothane anesthesia is increased 2.5-fold in children during the acute phase of burn injury compared with control children. The magnitude of the shift in dose response curve was correlated positively to the magnitude of the burn injury, with a correlation coefficient of 0.83 or  $r^2 = 0.69$ . The latter indicates that only 68% of the variation in the dose can be explained by burn size. Chronic immobilization<sup>7</sup> reduced acetylcholinesterase activity<sup>8</sup> and other unknown factors may contribute additionally to the altered dose requirement.

The plasma protein binding of metocurine and *d*-tubocurarine increase from the normal 30–50% to 50–70% in the burned patient.<sup>9</sup> Unlike the above drugs, the plasma binding of Pm is only about 10%.<sup>10</sup> When a drug is bound to such a small extent, even large increases in plasma binding may not induce significant changes in pharmacodynamic effect.<sup>10,11</sup> The findings of increased require-

FIG. 2. The correlation between log dose of 95% twitch depression and magnitude of burn. Note the good correlation between dose and magnitude of burn. The regression line was described by the equation  $\log ED_{95} = 0.00641\% \text{ burn} - 1.256$ . Patients studied more than once have been identified in the right panel in which dose vs. post burn day is plotted.



ment with a drug bound very little to plasma protein confirms the results of previous studies that altered binding<sup>9</sup> and altered pharmacokinetics<sup>12</sup> cannot explain all of the augmented dose requirement. As elucidated by Sheiner *et al.*<sup>13</sup> and reiterated by Holley,<sup>14</sup> changes in blood flow that cause prolonged equilibration time between drug in plasma and the site of action can also cause an artifactual shift to the right in the dose response curve. Such a pharmacokinetic factor may play a role. However, a change such as an increase in acetylcholine receptor also must be present at the neuromuscular junction to explain both the hyperkalemia with succinylcholine and the relative resistance to nondepolarizing muscle relaxants seen in burned patients.

The good correlation between dose and the size of the burn is consistent with our previous study with metocurine in children.<sup>5</sup> The metocurine study differs, however, from the present study in that there was a poor but significant correlation ( $r = 0.44$ ) between dose and time after burn. The mean ( $\pm$ SE) time of study after burn was  $25 \pm 5.1$  days for metocurine, while it was  $34.2 \pm 7.9$  days for Pm. In the latter study, when the patients who were studied multiple times were individually examined, there was a trend for the dose to increase or stay the same the first 4 weeks after burn, after which there was a gradual decrease in the dose (fig. 2). The confounding early and late effects of burn on the dose may have contributed to the lack of correlation between dose and time after burn in the present study, which was carried out for a longer period after burn.

In the metocurine and Pm studies the magnitude of burn ( $41.8 \pm 9.2$  vs.  $48.8 \pm 4.4\%$ ), the ages ( $10.4 \pm 0.95$  vs.  $10.2 \pm 0.8$  yr), and the shift in the dose-response curves (2.5 fold) were comparable. Despite the higher metocurine dose administered to burned patients, the recovery time of twitch was not different from control children.<sup>5</sup> In contradistinction there was prolongation of the Pm recovery time, which was not correlated to dose ( $r = 0.33$ ), time after injury ( $r = 0.31$ ), or to burn size. Thus the prolonged recovery time is not due to any of the above clinical variables including the dose administered. It is tempting to speculate that the differences might be related to the dissimilar metabolic clearances of the two drugs. Unlike metocurine, about 15–40% of Pm is metabolized by the liver<sup>15</sup> and burn injury itself, and the concomitant administration of multiple drugs has been shown to depress drug metabolism.<sup>16</sup> The prolonged recovery time of Pm possibly may be related to depressed metabolism by the liver.

The lack of significant increase in blood pressure in this study in control children compared with previous studies in children<sup>1,2</sup> probably is related to the slower rate of administration of Pm (bolus vs. incremental doses) and the smaller dose administered. Although the previous studies with *d*-tubocurarine<sup>4</sup> and metocurine<sup>5</sup> in burned patients did not document the hemodynamic responses, the larger doses required in these patients can result in some hemodynamic instability.<sup>15</sup> The present study demonstrates some cardiovascular stimulating properties following the large dose administration of Pm. This feature

may be especially useful in certain situations, particularly in children where there is a need for bolus administration of a large dose for rapid onset of neuromuscular paralysis.

In conclusion, we have demonstrated that Pm is a useful neuromuscular blocking drug in burned children and that the dose-response curve is shifted 2.5-fold to the right and that the dose requirement correlates with the degree of burn injury. The high doses administered also resulted in modest increases in heart rate and blood pressure and a prolonged recovery time.

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## Comparison of Continuous Infusion Fentanyl or Ketamine *versus* Thiopental—Determining the Mean Effective Serum Concentrations for Outpatient Surgery

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Recent studies of outpatients undergoing minor surgical procedures indicate that the use of continuous in-

fusion fentanyl or ketamine significantly decreases the drug dosage and recovery time when compared with the traditional intermittent bolus technique.<sup>1</sup> The present study was designed to compare the intraoperative and postoperative effects of the intravenous anesthetics fentanyl and ketamine with thiopental when each drug was administered by continuous infusion in combination with nitrous oxide during midtrimester abortions. Serum samples were obtained during the maintenance infusions in order to determine their therapeutic concentration ranges in the presence of nitrous oxide.

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