Increased d-Tubocurarine Requirement Following Major Thermal Injury


Depression of the indirectly evoked twitch in response to a given dose of muscle relaxant varies depending on the species, the type of relaxant used, and the pathophysiologic state of the motor unit. Increased sensitivity to the effects of nondepolarizing muscle relaxants such as d-tubocurarine (dTc) is known and is well documented for patients with myasthenia gravis. An increased requirement for nondepolarizing muscle relaxants is a much rarer phenomenon, and has been observed clinically in patients with hepatic disease. Our clinical experience with burned patients indicates that these individuals demonstrate a marked resistance to the neuromuscular blocking effects of dTc, to an extent not seen in any other pathologic state. Herein we report the neuromuscular responses to the intravenous administration of dTc in five burned patients who needed anesthesia and operation for excision and grafting of burned wound.

METHODS

The clinical summary and the immediate preoperative laboratory values of the five patients are listed in Table 1. Monovalent serum electrolytes were within normal limits. All patients received as premedication morphine, 0.2 mg/kg, im, about one to two hours before induction of anesthesia. In addition, four patients received atropine, 0.5 mg, while one received

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<th>Table 1. Clinical Data and Preoperative Laboratory Values</th>
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<td>Patient 1</td>
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<td>Age</td>
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<td>Weight</td>
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<td>Total protein (6.0–8.4 g/dl*)</td>
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<td>Albumin (52–68 per cent*)</td>
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<td>α1 globulin (4.2–7.2 per cent*)</td>
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<td>α2 globulin (6.8–12 per cent*)</td>
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<td>β globulin (9.3–15 per cent*)</td>
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<td>γ globulin (13–23 per cent*)</td>
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<td>Serum calcium (8.5–10.5 mg/dl*)</td>
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* Normal values for our clinical laboratory.
FIG. 1. A highly significant linear correlation ($r = 0.72, P < 0.001$) was found between serum $d$Tc concentration ($y$) and percentage recovery of twitch ($x$). The equation for the regression line is given by $y = 3.44 - 0.022x$. The regression for normal patients previously described by Matteo et al. is at the bottom of the graph. The 95 per cent confidence bands for the mean serum concentrations for normal subjects and burned patients are shown by the shaded areas. There is no overlap of the bands.

diazepam, 15 mg, orally, at the same time as the morphine. Anesthesia was induced in one patient with incremental intravenous doses of ketamine, 3.0 mg/kg; the others received sodium thiopental, 3–5 mg/kg. Anesthesia was maintained with nitrous oxide–oxygen and narcotic drugs, four patients receiving morphine, while the other received fentanyl. Supplemental doses of morphine or fentanyl were intermittently administered when clinically indicated.

Following induction of anesthesia, the patient's hand and forearm were immobilized in a special arm board. The thumb was connected to a Grass® FT-10 force-displacement transducer. Supramaximal square-wave pulses of 0.2 msec duration at a frequency of 0.15 Hz were applied to the ulnar nerve at the wrist or elbow through subcutaneous 22-gauge steel needle electrodes. The stimuli were generated by a Grass S88 stimulator via an isolation unit (S1U5). Evoked twitch tension of thumb adduction was recorded continuously on a Grass Model 7 polygraph. When a stable baseline twitch tension recording had been present for 10 to 15 min, $d$Tc was given in incremental doses approximately every 3 min until 50 to 98 per cent twitch depression had been attained. Following termination of administration of $d$Tc, blood samples were drawn at intervals from a separate venous catheter for measurement of serum $d$Tc concentrations. The serum was separated within two hours of sampling, frozen, and later analyzed by the radioimmunoassay technique described by Horowitz and Spector. The twitch tension at the time of sampling was noted. Supplemental doses of $d$Tc were not administered intraoperatively subsequent to the initial post-induction doses.

A least-squares regression of serum $d$Tc level versus percentage recovery of twitch was constructed. Twitch recovery of more than 99 per cent was not included in the regression of serum $d$Tc level versus twitch recovery. Critical values for sample correlation coefficient, $r$, as test of significance were obtained from the table of Pearson and Hartley. Dose–response data for neuromuscular blockade were plotted on log–probit coordinates. A mean best-fit straight line was determined by probit regression. Parallelism of the mean dose–response curve for burned subjects to that previously obtained for normal subjects under similar conditions was determined by the method of Litchfield and Wilcoxon. Differences were considered significant when $P < 0.05$.

RESULTS

The mean serum concentrations for 50 and 95 per cent twitch depression were 2.3 and 3.5 $\mu$g/ml, respectively, in our patients, compared with approximate concentrations of 0.4 and 0.7 $\mu$g/ml in normal subjects, reported by Matteo et al. (fig. 1). Burned patients needed approximately five times higher concentrations to attain a given percentage of twitch depression. The twitch inhibition in burned patients correlated
significantly with intravenous dose of \( d'Tc \) (fig. 2). When compared with the normal curve previously reported, there was a rightward shift by a factor of three in the dose–response curve for burned patients. The mean \( ED_{95} \) and \( ED_{90} \) for burned patients were 0.78 and 1.8 mg/kg, respectively, compared with 0.26 and 0.51 mg/kg for normal subjects. All patients in our study had larger than normal doses of \( d'Tc \), but none had complete abolition of the twitch response to the high doses administered. The dose–response curves for normal and burned patients did not deviate significantly from parallelism. Just prior to the administration of atropine, 10–20 \( \mu g/kg \), and neostigmine, 25–40 \( \mu g/kg \), serum \( d'Tc \) concentrations in the five patients were 0.82, 1.54, 1.30, 0.99, and 2.52 \( \mu g/ml \), which corresponded to twitch recovery percentages of 100, 50, 95, 100, and 80 per cent, respectively. These \( d'Tc \) concentrations would give 100 per cent twitch depression in normal subjects. As evidenced by train-of-four measurements, residual neuromuscular blockade in all five patients was antagonized to train-of-four values of 75 per cent or more within 15 min. None showed any evidence of recurarization in the postoperative period.

**Discussion**

An increased requirement for nondepolarizing neuromuscular blocking drugs has been observed previously in patients with hepatic disease, and increased binding of \( d'Tc \) to the globulin fraction was suggested as the cause. Subsequent but more precise studies of the binding of \( d'Tc \) to plasma protein fractions did not reveal any significant difference between healthy normal patients and those with hepatic disease. Furthermore, in contradistinction to patients with hepatic disease, burned patients did not show consistent increases in either total or \( \gamma \) globulins. The only finding common to all our patients was a decrease in albumin with an increase in \( \alpha \) globulins, which are by far the most common alterations in plasma proteins occurring after tissue injury and inflammation (the acute-phase plasma protein response). \( \alpha \)-acid glycoprotein, a component of \( \alpha \) globulin, is an acute-phase reactant, reported to cause increased binding of cationic drugs following inflammation-induced changes in its concentration. \( d'Tc \) is a cationic drug, and the \( \alpha \) globulins were increased in our patients, but the importance of disease-induced changes in plasma protein to our findings is presently unclear.

Duvaldestin et al. studied the pharmacokinetics of pancuronium in patients with hepatic cirrhosis. They concluded that the initial increased dose of pancuronium necessary to achieve effective muscle relaxation is due to an increase in the distribution volume of pancuronium in these patients. This was a possibility in our patients, in view of the massive resuscitation fluid requirement, edema, and the hemodynamic adjustment to burn trauma. However, this does not explain our finding of uncomplicated reversal of the block by neostigmine, 20–40 \( \mu g/kg \), at \( d'Tc \) concentrations that would give 100 per cent twitch depression in normal subjects. Previous studies have demonstrated the leaking of drugs such as gentamicin through burn wounds, and increased urinary excretion of tobramycin. Therefore, higher than normal doses of these drugs were necessary to achieve therapeutic blood levels. Sequestration, leaking, or increased urinary excretion of \( d'Tc \) would have been a plausible explanation for the increased \( d'Tc \) requirement had serum levels been normal or low, despite our high intravenous doses.

Monovalent serum electrolyte values were within acceptable limits in our patients, but hypocalcemia was present (table 1). Following major thermal injury of more than 25 per cent of body surface area, patients have persistent depression of both ionized and total calcium and are hypermagnesemic. The clinical
importance of hypocalcemia, particularly its interaction with neuromuscular blockers, is unclear. However, on the basis of laboratory data delineating the roles of calcium and magnesium in the release of acetylcholine at the nerve terminal, one would anticipate a diminished quanta18 of release of acetylcholine per nerve impulse in the presence of hypocalcemia and hypermagnesemia. This would not only enhance clinical block produced by a competitive receptor blocker but would also make reversal more difficult. Our results are contrary to these expectations.

Physicochemical changes at the neuromuscular junction and muscle membrane have been shown to occur following denervation and trauma. Similar changes, though not documented for burns, have been implicated as the cause of succinylcholine-induced hyperkalemia. A change such as an increase in the number of acetylcholine receptors in muscle, altered sensitivity of the muscle membrane, or altered neuromuscular receptor affinity may be present following thermal injury to skin. Such changes, if present, might explain the phenomenon of post-burn succinylcholine-induced hyperkalemia, as well as an increased $d$Tc requirement. These possibilities require further study.

Nondepolarizing muscle relaxants such as $d$-tubocurarine have been the drugs of choice to induce skeletal muscle relaxation in burned patients. This is because of the known hyperkalemic response in such patients following the use of succinylcholine. We have demonstrated that following burns of more than 25 percent of body surface area both the total dose of $d$Tc administered intravenously and the serum concentration necessary to attain a given twitch depression are greatly increased, compared with values for healthy normal patients. The recovery of neuromuscular blockade seen at serum concentrations which would give 100 percent twitch depression in normal subjects indicates that neither increased urinary excretion nor increased loss of $d$Tc through burn wounds caused these changes. Although this study was not specifically directed to elucidate the etiology of the increased $d$Tc requirement, we have speculated on the possible etiologic mechanisms. The pathophysiology of neuromuscular transmission and pharmacokinetics of $d$Tc following thermal injury require further study.

References