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Resistance to Succinylcholine in Myasthenia Gravis: A Dose-response Study

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Patients with myasthenia gravis have been described as being resistant to succinylcholine,[1] while others have found that the normal tracheal intubating dose of succinylcholine provides adequate relaxation.[2,3] The purpose of this study was to establish dose-response relationships for succinylcholine in patients with and without myasthenia gravis.

MATERIALS AND METHODS

Ten normal and five myasthenia gravis patients gave their written informed consent to participate in this institutionally approved study. The ten normal patients were ASA physical status 1 or 2, free from medications or conditions known to affect neuromuscular transmission, and scheduled to undergo gynecologic or orthopedic surgical procedures. The five myasthenic patients were scheduled to undergo thymectomy as a surgical treatment for their myasthenia gravis. A brief description of each myasthenic patient follows, together with their clinical classification according to the system described by Osserman and Genkins.[4]

Case 1. A 26-yr-old, 48-kg woman with an 8-month history of moderate generalized weakness of the arms and legs, and dysphagia (myasthenia gravis class IIB). She was taking pyridostigmine (Mestinon®) 60 mg q.i.d. She was otherwise healthy.

Case 2. A 51-yr-old, 96-kg man with a 6-month history of generalized myasthenia. He had been treated with pyridostigmine and plasmapheresis, but had steadily deteriorated and 5 months prior to admission spent 1 month being ventilated in a respiratory care unit. (class III). A diagnosis of malignant thymoma was made and he was treated with prednisone 100 mg QD and six courses of chemotherapy (bleomycin and cis-platinum). At the time of his surgery he was receiving only prednisone 100 mg, q.o.d., 20 mg q.o.d.

Case 3. A 36-yr-old, 87-kg man with a 10-month history of ocular and moderate generalized myasthenia (class IIB). He was treated with pyridostigmine 180 mg q. 3 h with improvement of his ocular symptoms but not the weakness in his limbs.

Case 4. A 37-yr-old, 80-kg man with a 3-month history of dysarthria, dysphagia, and generalized limb weakness (class IIA). A computerized tomography scan showed a mediastinal mass that was diagnosed as a thymoma. He was receiving pyridostigmine in a total daily dosage of 270 mg.

Case 5. A 27-yr-old, 65-kg woman with a 2-yr history of ocular myasthenia and a 4-month history of mild generalized myasthenia gravis (class IIA) particularly affecting the facial muscles. She was being treated with pyridostigmine 90 mg q.3 h.

In all of the myasthenic patients, the diagnosis had been confirmed by electrophysiologic (EMG) and/or pharmacologic (Tensilon) testing.[3] On the day of surgery, all patients were premedicated 60–90 min preoperatively with oral diazepam, 5–10 mg. In addition, myasthenia gravis case 2 received hydrocortisone 100 mg im, and case 3 received pyridostigmine 3 mg im. The other four myasthenic patients received no pyridostigmine on the day of surgery.

Upon arrival in the operating room, routine monitoring was established with a non-invasive blood pressure monitor (Dinamap®), EKG, and pulse oximeter. The surface electrodes used for neuromuscular transmission monitoring by integrated electromyography (Datex 221 Neuromuscular Transmission Monitor, Puritan Bennett, Wilmington, MA) were placed over the ulnar nerve at the wrist and the skin overlying the hypothenar muscles of the hand. Anesthesia was induced with thiamylal, 3–5 mg/kg, iv, and maintained with N_2O 66% in oxygen; supplemental doses of thiamylal, 0.5–1.0 mg/kg, and fentanyl, 1–2 μg/kg, iv, were given as required. Ventilation was assisted to maintain end-tidal CO_2 within the normal range

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as measured by a mass spectrometer. Potent inhaled anesthetics were not used during the study period. Supramaximal train-of-four stimulation (2 Hz) was applied to the ulnar nerve at 10-s intervals and the integrated EMG response of the hypothenar muscles was continuously recorded. When the response appeared to be stable, the monitor was recalibrated to read a control value of 100% for the first response in the train-of-four. After stabilization of the response, patients received succinylcholine, 0.15 mg/kg, iv followed by incremental bolus doses of 0.1–0.2 mg/kg together with an infusion of succinylcholine, the rate of which was adjusted to replace eliminated drug.[5] Incremental doses were administered and the infusion rate increased when two consecutive equal first responses (T1/control) were observed in the continuously monitored EMG trains-of-four. For each patient, linear regressions (least squares) were obtained between the logarithm of the cumulative dose of succinylcholine and the logit transformation of neuromuscular blockade as measured by percentage decrease in T1/control. A regression line was calculated for each patient, from which the ED_{50}, ED_{90}, and ED_{95} were derived. From the equations to the individual patient regression lines, mean dose-response curves were constructed for the group of ten normal patients and the group of five myasthenic patients. The mean dose-response curves were compared for slope, intercept, and ED_{50}, ED_{90}, and ED_{95} values using a Student's t test for unpaired data. Results are expressed as means together with 95% confidence limits for the ED values. A P value of less than 0.05 was considered significant.

Results

No complications were associated with the administration of succinylcholine in either group and the tracheas of all patients were successfully intubated when T1/control was 0–10%. The dose-response curves are shown in figures 1 and 2 and the ED_{50}, ED_{90}, and ED_{95} values are shown in table 1. The dose-response curve for the myasthenics was to the right of that for the normal patients. There were significant differences between the groups in the slopes ($P < 0.01$) and intercepts ($P < 0.001$) of the mean dose-response curves. Similarly, there were significant differences between the groups in the ED_{50}, ED_{90}, and ED_{95} values for succinylcholine. Immediately following completion of the dose-response studies, none of the normal patients but four of the five myasthenic patients developed fade in the train-of-four response.

Discussion

Using a cumulative dose plus infusion technique to construct dose-response curves, we have demonstrated

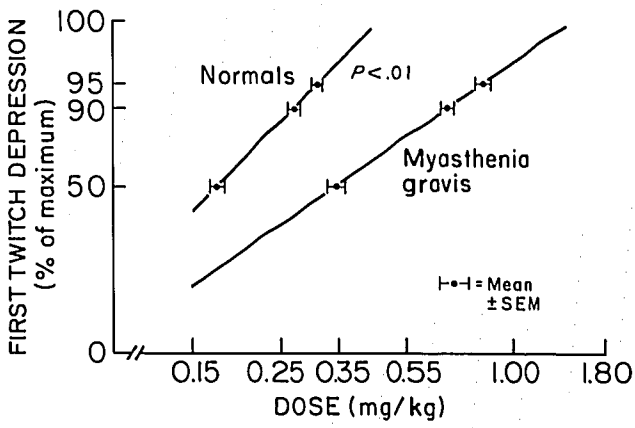

FIG. 1. Mean succinylcholine dose-response curves in normal (n = 10) and myasthenic (n = 5) patients. Horizontal axis shows succinylcholine cumulative dose (log scale). Vertical axis shows response (logit transformation). Normal patients—equation: logit response = 5.61 ($\log_{10}$ dose) + 4.17. Myasthenia gravis patients—equation: logit response = 3.64 ($\log_{10}$ dose) + 1.73.

that myasthenic patients are resistant to succinylcholine. The ED_{50} was twice the normal value and the ED_{95} 2.6 times normal.

There have been several previous reports of "resistance" to succinylcholine in myasthenic patients. Initially, it was inferred from the work of Churchill-Davidson and Richardson[6] who studied the EMG responses in the hypothenar muscles to ulnar nerve stimulation in 16 controls and 11 myasthenic patients before and following the administration of decamethonium. They reported that the uninvolved muscles in myasthenic patients were relatively resistant to the effects of decamethonium. Resistance was particularly marked in those patients in whom the only clinical evidence of myasthenia gravis was ptosis and diplopia.[6]

Ginsberg and Varejes[7] described a patient with severe generalized myasthenia gravis, who showed resistance to two bolus doses (25 mg and 100 mg) of succinylcholine and a subsequently administered succinylcholine infusion. Graham and Grant[8] described a patient in whom vocal cord relaxation could not be achieved using 450 mg of succinylcholine; severe generalized myasthenia gravis was diagnosed in this patient 1 week later. In this case report, however, there were no objective measurements of neuromuscular transmission.[8] Baraka *et al.*[9] reported that, whereas succinylcholine 20 mg completely abolished the twitch response to stimulation at 0.25 Hz in normal patients, it failed to do so in a patient with ocular myasthenia, again suggesting resistance in the non-involved muscles. Stanski *et al.*[10] used an isolated arm technique to demonstrate relative resistance to succinylcholine in a patient with myasthenia gravis and atypical cholinesterase.

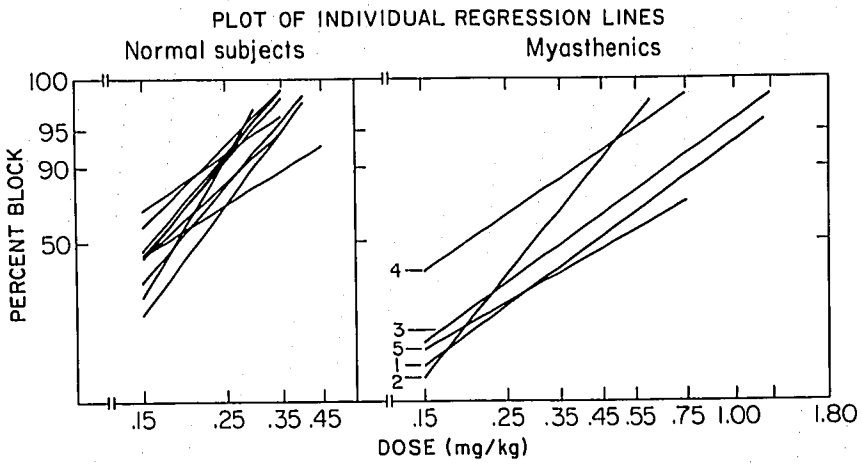

FIG. 2. Individual dose-response regression lines for succinylcholine. *Left panel.* Normal patients. *Right panel.* Myasthenic patients, numbered according to the description of each case in the Materials and Methods section.

Clinically, however, the use of succinylcholine in patients with myasthenia gravis has been generally without incident, with normal doses producing adequate relaxation for endotracheal intubation. Foldes, McNall, and Nagashima[11,12] suggested a single 0.4–0.6 mg/kg dose to facilitate endotracheal intubation in myasthenic patients, while others[2] have found the "usual intubating dose" (dose not specified) to be adequate. Wainwright and Brodrick[13] studied the mechanomyographic (MMG) responses to succinylcholine 0.5 and 1.0 mg/kg in ten myasthenic patients. In the five who received 0.5 mg/kg, three were considered resistant (defined in this study as no reduction of T1 from control levels), because two failed to develop any block and a third patient only developed a 65% reduction in T1/control. Resistance was not encountered at the 1.0-mg/kg dose, although quantified responses were not reported in this study.[13] The responses to succinylcholine and decamethonium have been quantified *in vitro* in nerve-muscle preparations from rats with experimental autoimmune myasthenia gravis.[14] Such affected muscle showed resistance to both depolarizing blockers.

Pharmacodynamically, resistance or sensitivity to a drug is defined in terms of altered dose-response relationships and differences in effective dose. Response curves to single doses of succinylcholine are readily constructed for normal patients. To use such a technique to construct curves for patients with myasthenia gravis would be difficult, however, because of the small number available for study. Cumulative dose-response curves are inappropriate for succinylcholine because much of the drug is metabolized during the study period. Smith *et al.*[5] recently demonstrated that the dose-response curves constructed using a cumulative dose technique *combined* with an infusion (CDI) of succinylcholine to replace metabolized drug are very close to those obtained by single dose studies. This CDI technique is particularly useful for the study of responses in uncommon conditions such as myasthenia gravis. In their study, Smith *et al.*[5] used the MMG to monitor responses to succinylcholine in normal patients. They found an ED_{50} and ED_{90} of 0.17 and 0.26 mg/kg, respectively, by the CDI technique. These values are essentially identical to the values of 0.17 and 0.27 mg/kg that we found using an integrated EMG monitor.

It has been shown that 95% depression of T1/control is required for good tracheal intubating conditions and succinylcholine is usually the drug of choice, because the onset time is short.[15] The doses in common clinical use (1.0–1.5 mg/kg) represent three to five times the ED_{95} in normals and 1.25–2.0 times the ED_{95} in myasthenic patients. Adequate intubating conditions should, therefore, be achieved using these doses in myasthenic patients, although the onset of block may be slower. Higher doses of succinylcholine may, however, be required for a rapid sequence tracheal intubation of a patient with myasthenia gravis.

The patient (case 3) who received pyridostigmine preoperatively also demonstrated resistance as evidenced by increases in ED_{50} and ED_{95} (fig. 2). Although not measured in this study, the duration of action of succinylcholine would be expected to be prolonged due to inhibition of hydrolysis by pseudocholinesterase.[11]

TABLE 1. Mean Effective Doses of Succinylcholine in Normal and Myasthenic Patients

	Normals (n = 10)	Myasthenics (n = 5)
ED_{50} (mg/kg) (95% confidence limits)	0.17 (0.15–0.20)	0.33 (0.22–0.54)
ED_{90} (mg/kg) (95% confidence limits)	0.27 (0.23–0.31)	0.66 (0.38–1.14)
ED_{95} (mg/kg) (95% confidence limits)	0.31 (0.27–0.37)	0.82 (0.45–1.48)

Following completion of the dose-response studies, anesthesia was maintained with isoflurane and it was, therefore, not possible to adequately study recovery from succinylcholine. This is because myasthenic patients are sensitive to the neuromuscular depressant effects of the potent inhaled anesthetics, which cause decreases in T1/control and T4/T1 ratios, at reduced dosages.[3] ¶

In summary, we have shown that myasthenic patients are resistant to succinylcholine and that the ED_{50} and ED_{95} in these patients is 2.0 and 2.6 times normal, respectively. Because the doses in common clinical use (1.0–1.5 mg/kg) represent three to five times the ED_{95} in normals, adequate intubating conditions should be achieved in myasthenic patients using these doses. If a rapid sequence tracheal intubation is required, however, our results suggest that a succinylcholine dose of at least 1.5–2.0 mg/kg may be needed to produce rapid onset of excellent intubating conditions. The mechanism whereby patients with myasthenia gravis are resistant to succinylcholine is unknown, although the decreased number of acetylcholine receptors at the motor end plate may serve as a possible explanation.[16]

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A Blinded Study Using Nalbuphine for Prevention of Pruritus Induced by Epidural Fentanyl

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Epidural fentanyl is frequently used and has been found effective for treatment of postsurgical and labor pain.[1] Pruritus, although seemingly trivial, is a common side effect occurring in 13–63% of patients.[2,3] Methods of detection of pruritus have a great bearing on its reported incidence,[1] and in our experience most patients admit to some degree of pruritus after effective pain relief from a variety of epidural narcotics.

Treatment of pruritus after intrathecal opiates has generally involved use of antihistamines or naloxone. Antihistamines have been largely ineffective and are reported to cause sedation.[1] Naloxone may reverse analgesia and because of its short duration of action has generally re-

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