Dose-response Relationship for Succinylcholine in a Patient with Genetically Determined Low Plasma Cholinesterase Activity

CHARLES E. SMITH, M.D., F.R.C.P.(C),* GERAINT LEWIS, M.D., F.R.C.P.(C),*
FRANCOIS DONATI, M.D., PH.D., F.R.C.P.(C),* DAVID R. BEVAN, M.B., M.R.C.P., F.F.A.R.C.S.†

The duration of neuromuscular blockade following succinylcholine may be prolonged in patients with known pseudocholinesterase deficiency and/or atypical variants of this enzyme.[1-3] As little as 0.04-0.06 mg/kg of succinylcholine may be required to achieve 90% block in patients with low plasma cholinesterase activity.[4] However, dose-response relationships have not been reported in these individuals, and no comparisons of potency have been made with normal patients. This case report describes a cumulative technique used to construct dose-response curves and to determine the potency of succinylcholine in an individual with a heterozygous atypical variety of plasma cholinesterase not involving the normal gene. These data were compared with those obtained in normal individuals.

CASE REPORT

A 35-yr-old, 57-kg, 170-cm woman was admitted with a history of diffuse, crampy abdominal pain and constipation. Four years prior to the present admission, she underwent peritoneal laparoscopy that revealed extensive endometriosis. A succinylcholine infusion was employed. Following this procedure, the patient experienced prolonged apnea (1 h) and required mechanical ventilation postoperatively. A tentative diagnosis of atypical plasma cholinesterase was made, although no biochemical studies were performed. Conservative management of her endometriosis failed to bring about any significant improvement, and total abdominal hysterectomy with bilateral salpingo oopherectomy was performed 3 yr later. Muscle relaxation was achieved with d-tubocurarine, and there were no postoperative complications. There was extensive large bowel involvement at this time. Her symptoms continued to persist and 2 months prior to the present admission, fiberoptic colonoscopy to 40 cm revealed stenosis of the sigmoid colon. She was therefore scheduled for elective resection of her sigmoid colon. She smoked ten cigarettes per day for many years, and was taking conjugated estrogens daily. Aside from one episode of bronchitis 6 months prior to admission, there were no other medical problems or history of anesthetic complications. Physical examination was unremarkable

* Assistant Professor of Anesthesia.
† Professor of Anesthesia and Chairman.

except for the scars of her previous surgery and mild diffuse abdominal tenderness. Routine hemogram and serum electrolytes were normal.

Because of her history of abnormal response to succinylcholine, quantitative neuromuscular monitoring was planned during the procedure, and the patient gave informed consent to receive succinylcholine. Premedication was with morphine 7.5 mg and glycopyrrolate 0.2 mg im. Upon entry to the operating room, an automatic blood pressure cuff and electrocardiograph were applied. Blood was drawn for plasma cholinesterase studies just prior to insertion of the intravenous infusion. Anesthesia was induced with thiopental 300 mg and fentanyl 100 μg iv, and maintained with nitrous oxide 66% in oxygen. Ventilation was assisted using bag and mask to maintain end-tidal CO_2 tension at 30-35 mmHg (mass spectrometer). The hand and forearm were immobilized in a splint. The ulnar nerve was stimulated supramaximally at the elbow using train-of-four impulses (duration 0.2 ms, frequency 2 Hz) delivered every 12 s. The force of contraction of the adductor pollicis was measured and recorded. After muscle twitch height reached a stable level, cumulative doses of succinylcholine (initial dose = 2 mg or 0.035 mg/kg, subsequent doses = 1 mg or 0.017 mg/kg) were administered until 95% first twitch (T1) depression relative to control was attained. Each dose increment was given only after the effect from the previous dose had reached a stable response defined as three equal consecutive first twitches.

The first dose produced a 16% depression of T1 within 1.3 min. The next two incremental doses produced an 89% and 98% T1 depression respectively. The total dose given was 4 mg (0.070 mg/kg) with maximum block occurring at 5.3 min from the initial dose. The trachea was then intubated, and isoflurane was introduced (end-tidal concentration 0.9-1.4% as measured by a mass spectrometer). Spontaneous recovery to a T1 of 10% relative to control occurred at 7.4 min following the initial dose of succinylcholine. By 10.8 min, T1 had recovered to 90% of control value with a recovery index (25-75% recovery of T1) of 1.9 min. During recovery from succinylcholine block, the fourth twitch was nearly as high as T1, indicating no phase II block. Vecuronium was then administered, and the operative procedure allowed to commence. Surgery was uneventful, and the patient made a good recovery. There were no anesthetic or surgical complications. Results from the plasma cholinesterase analysis were: total activity 19.9 units/1 (normal 43-69), dibucaine number 42 (normal 78-85), fluoride number 40 (normal 57-64), and chloride number 39 (normal 11-20). This was suggestive of the genotype E1ᵃE1ᶠ, a heterozygous atypical variety not involving the normal gene E1ᵘ.[3]

A dose-response curve was constructed in this patient by plotting the logit transformation of T1 depression relative to control at the adductor pollicis as a function of the logarithm of the dose using the method of least-squares analysis.[5] This dose-response curve was compared with that obtained in 18 normal individuals studied in our department using a single dose technique during thiopental-nitrous-oxide anesthesia (fig. 1).[6] The patient was found to be five times more sensitive to succinylcholine than normal individuals. The regression lines appeared parallel (slope = 8.01 atypical plasma cholinesterase, 5.79 normals). The potency estimates derived from the regressions from patients with normal or atypical plasma cholinesterase are compared in table

1. Approximately one-fifth as much succinylcholine was required as in normal individuals.

DISCUSSION

This case report confirms previous reports of the increased sensitivity of individuals with abnormal plasma cholinesterase to succinylcholine.[4,7–10] This is presumably because an unusually high fraction of the drug is available at the neuromuscular junction, and the atypical plasma cholinesterase hydrolyzes succinylcholine at a much slower rate.[3] The potency estimates obtained in this patient are similar to those obtained by Cass et al.[11] in an individual homozygous for atypical plasma cholinesterase (table 1). They administered four single doses (0.05–0.1 mg/kg) of succinylcholine on separate occasions for electroconvulsive therapy during thiopental-nitrous oxide anaesthesia. The potency estimates obtained in the present study are less than those reported by Lee-Son et al.[12] in a patient homozygous for atypical plasma cholinesterase during thiopentone anaesthesia (table 1). However, their cumulative dose technique may have underestimated potency due to the large number of doses required to produce 90% depression (approximately six to seven doses) which may have allowed for some degree of redistribution or metabolism. Also, they employed linear rather than probit or logit transformation of neuromuscular response, which may bias their results, particularly if many points are in the asymptotes of the curve, where the response to neuromuscular blocking agents may not be linear. Our potency estimates are larger than those derived from the data obtained by Hickey et al.[4] in a patient with the homozygous atypical gene during methohexital anesthesia (table 1). The difference may be due to the diminished plasma cholinesterase activity in their patient.

The patient in the present study was taking estrogens, which decrease plasma cholinesterase activity by approximately 20% in patients with normal plasma cholinesterase.[3,13] The effect of estrogens on the atypical enzyme is unknown, but it appears unlikely that estrogens played a major role in the increased sensitivity of our patient to succinylcholine.

Dose-response curves obtained with a cumulative dose technique are extremely useful in evaluating potency of neuromuscular blocking agents. This technique allows the study of a muscle relaxant's effects at a variety of dosage levels in the same patient, thus permitting the construction of a dose-response relationship in a single patient.[14] The major limitation of the cumulative dose-response technique is the requirement that redistribution and elimination be negligible during the period of cumulative dose administration. For the long-acting muscle relaxants d-tubocurarine and pancuronium, this assumption holds true,[15] and the potency of the intermediate-acting relax-
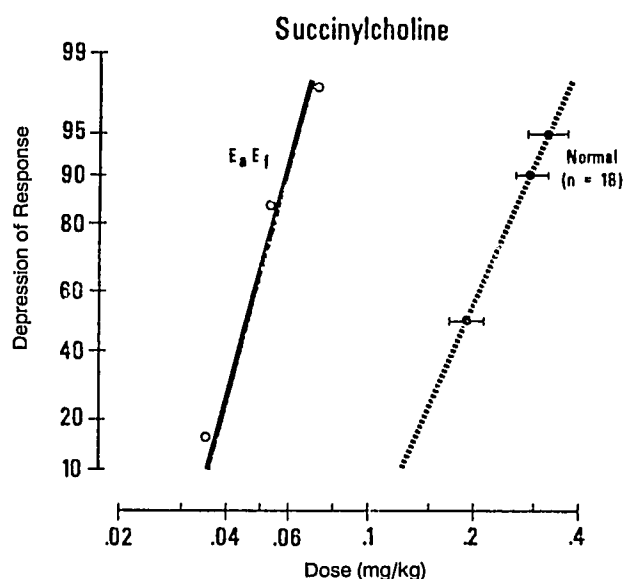

FIG. 1. Dose-response relationships for succinylcholine using a single dose (18 normal patients),[6] or cumulative dose technique (single patient with atypical plasma cholinesterase). The logit transformation of first twitch depression is plotted against the logarithm of the dose. The lines were obtained by linear regression. Error bars represent SEM.

ants vecuronium and atracurium (as evaluated by the single dose and cumulative dose techniques) did not differ by more than 16%.[16] Since the patient in this study received all dose increments within a relatively short period of time (time to maximum twitch depression was 5.3 min.), the potency estimates are probably within 15% of the true values. This is supported by the fact that when a cumulative dose of 0.08 $mg \cdot kg^{-1}$ was given over 15 min to the patient in Cass et al.'s study,[11] 95% twitch depression was achieved which is similar to that predicted by the logit transformation of their single dose results.

The recovery of neuromuscular function after 98% neuromuscular block was rapid in our patient (recovery index 1.9 min, time to 90% recovery = 10.8 min.) This

TABLE 1. Potency Estimates Derived from Dose-Response Curves Using the Logit Transformation of Neuromuscular Blockade as a Function of the Logarithm of the Dose in Patients with Abnormal and Normal Plasma Cholinesterase

ED50	ED90	ED95	Slope	Author
Abnormal				
0.043	0.057	0.062	8.01	Present report
0.039	0.060	0.070	5.01	Cass et al.[11]
0.032	0.039	0.042	10.20	Hickey et al.[13]
Normal				
0.190	0.270	0.310	5.79	Smith et al.[6]

ED = effective dose (mg/kg) to produce a percent neuromuscular block.

recovery index is similar to that reported by Viby-Mogenson in three patients heterozygous for both the fluoride resistant and the atypical gene, $E1^fE1^a$ (3 min).[1] Although prolonged respiratory muscle insufficiency following succinylcholine is relatively rare, this unexpected occurrence may lead to serious complications in patients with unknown hypersensitivity to the drug.[7] The cumulative dose-response technique was not only able to document an abnormal response to succinylcholine in this patient, it was also able to quantify the increased potency of the drug. The present case report and review of the literature suggests that succinylcholine is four to seven times as potent in patients with genetically determined low plasma cholinesterase compared with normal individuals.

REFERENCES

1. Viby-Mogensen J: Succinylcholine neuromuscular blockade in subjects heterozygous for abnormal plasma cholinesterase. ANESTHESIOLOGY 55:231–235, 1981

2. Viby-Mogensen J: Succinylcholine neuromuscular blockade in subjects homozygous for atypical plasma cholinesterase. ANESTHESIOLOGY 55:429–434, 1981

3. Whittaker M: Plasma cholinesterase variants and the anesthetist. Anaesthesia 35:174–197, 1980

4. Hickey DR, O'Connor JP, Donati F: Comparison of atracurium and succinylcholine for electroconvulsive therapy in a patient with atypical plasma cholinesterase. Can J Anaesth 34:280–283, 1987

5. Norman J: Drug-receptor reactions. Br J Anaesth 51:595–601, 1979

6. Smith CE, Donati F, Bevan DR: Dose-response curves for succinylcholine: Single *versus* cumulative techniques. ANESTHESIOLOGY 67:A358, 1987

7. Viby-Mogensen J, Hanel HK: A Danish cholinesterase research unit. Acta Anaesthesiol Scand 12:405–412, 1977

8. Kalow W, Gunn D: The relation between dose of succinylcholine and duration of apnea in man. J Pharmacol Exp 120:203–214, 1957

9. Viby-Mogensen J, Hanel HK: Prolonged apnea after suxamethonium. An analysis of the first 225 cases reported to the Danish Cholinesterase Research Unit. Acta Anaesthesiol Scand 22:371–380, 1978

10. Foldes FF, Foldes VM, Smith JC, Zsigmond EK: The relation between plasma cholinesterase and prolonged apnea caused by succinylcholine. ANESTHESIOLOGY 24:208–216, 1963

11. Cass NM, Doolan LA, Gutteridge GA: Repeated administration of suxamethonium in a patient with atypical cholinesterase. Anaesth Intensive Care 10:25–28, 1982

12. Lee-Son S, Pilon RN, Nahor A, Waud BE: Use of succinylcholine in presence of atypical cholinesterase. ANESTHESIOLOGY 43:493–496, 1975

13. Robertson GS: Serum protein and cholinesterase changes in association with contraceptive pills. Lancet 1:232–235, 1967

14. Laycock JRD, Smith CE, Donati F, Bevan DR: Sensitivity of the adductor pollicis and diaphragm muscles to atracurium in a hemiplegic patient. ANESTHESIOLOGY 67:851–853, 1987

15. Donlon JV, Savarese JJ, Ali HH, Teplik RS: Human dose response curves for neuromuscular blocking drugs: A comparison of two methods of construction and analysis. ANESTHESIOLOGY 53:161–166, 1980

16. Smith CE, Donati F, Bevan DR: A new technique to determine cumulative dose-response curves of vecuronium and atracurium. Can J Anaesth 34:S76, 1987