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Serum Cholinesterase Activity Following Pancuronium and Antagonism with Neostigmine or Pyridostigmine

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We observed a patient who had prolonged neuromuscular blockade (more than three hours) following succinylcholine (SCh) when pyridostigmine had been administered an hour earlier to reverse pancuronium-induced paralysis.[1] The patient had responded normally to SCh before pancuronium and pyridostigmine. Both pancuronium[2,3] and anticholinesterase drugs[4] have been reported to inhibit serum cholinesterase (pseudocholinesterase) activity. Conceivably, such inhibition could have contributed to the prolonged SCh paralysis observed in our patient. Since the extent and duration of the reduction of serum cholinesterase activity after administration of anticholinesterase drugs, as used by anesthesiologists to antagonize competitive neuromuscular blockade, had not been established, we measured serum cholinesterase activity following pancuronium administration and reversal with either neostigmine or pyridostigmine.

METHODS

Eighteen adult patients without known hepatic or renal disease, undergoing elective operations requiring neuromuscular blockade, were studied. Preanesthetic medication was with morphine (8–12 mg) and scopolamine (0.4 mg). Anesthetic induction was with thiamylal, 4 mg/kg, plus pancuronium, 0.1 mg/kg, to facilitate tracheal intubation. Ventilation was mechanically controlled and anesthesia maintained with 60 per cent nitrous oxide and fentanyl. Additional pancuronium, 0.01 to 0.02 mg/kg, was administered as indicated by tetanic response to ulnar-nerve stimu-

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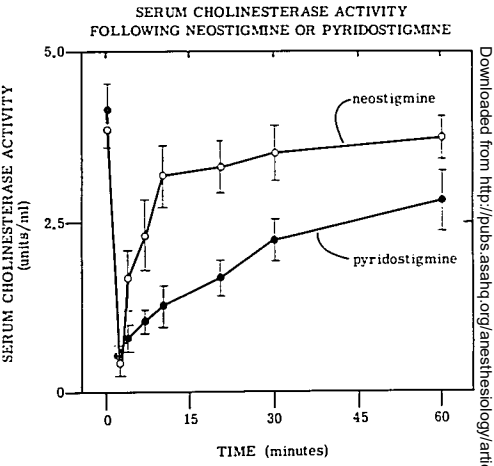

FIG. 1. Mean ± SE. Cholinesterase activity was significantly reduced ($P < 0.05$) for 5 minutes after neostigmine and for at least 120 minutes (enzymatic activity 3.0 units/ml at 120 minutes) following pyridostigmine. Following the one-minute measurement, enzymatic activity was significantly more decreased ($P < 0.05$) after pyridostigmine than after neostigmine.

lation. Reversal of neuromuscular blockade was accomplished by the rapid intravenous administration of neostigmine (0.04 mg/kg) or pyridostigmine (0.225 mg/kg) plus atropine (0.02 mg/kg) in the same syringe. A sustained response to tetanic stimulation was present in every patient within 10 minutes. Extubation was possible 10 to 20 minutes after pancuronium reversal.

Peripheral venous blood samples for measurement of serum cholinesterase activity[3] were obtained before induction of anesthesia but after preanesthetic medication (awake samples) from all patients and then intermittently for 10 minutes following pancuronium administration from seven of the patients. Blood samples were again obtained before pancuronium reversal and for 60 minutes after neostigmine (nine patients) and for 120 minutes after pyridostigmine (nine patients). Serum cholinesterase activity was also determined following pyridostigmine reversal of pancuronium-induced neuromuscular blockade in two patients with alcoholic hepatic disease and in two additional patients without known hepatic disease receiving only atropine, 0.02 mg/kg, iv. Dibucaine numbers were also measured in the awake samples of all patients.

All determinations were performed by Bio-Science Laboratories (7600 Tyrone Avenue, Van Nuys, California, 91405). Data were analyzed using Student's t test, and $P < 0.05$ was considered significant.

RESULTS

Serum cholinesterase activity did not change significantly in the first 10 minutes following pancuronium administration (table 1). Furthermore, awake enzymatic activity (3.9 ± 0.2 units/ml, mean ± SE) was not significantly different from the values obtained just before pancuronium reversal (3.7 ± 0.3 units/ml).

Serum cholinesterase activity was reduced 88 and 85 per cent one minute after neostigmine (2.8 ± 0.3 mg) and one minute after pyridostigmine (14.6 ± 1.1 mg), respectively (fig. 1). Enzymatic activity had returned to nearly 50 per cent of the control value 3 minutes after neostigmine, and was no longer significantly reduced after 10 minutes. In contrast, enzymatic activity remained significantly reduced 120 minutes after pyridostigmine. Furthermore, activity was significantly more reduced after pyridostigmine than after neostigmine at all times, for at least an hour after the one-minute measurement.

TABLE 1. Serum Cholinesterase Activities (Units/ml, Normal 3–8) before and after Pancuronium (0.1 mg/kg) Administration to Seven Patients

	Units/ml Awake	Units/ml after Pancuronium				Pancuronium (mg)	Patients Ages (Years)
		1 Min	3 Min	5 Min	10 Min		
Mean	3.9	4.0	3.9	3.6	3.8	6.9	45
SE	0.2	0.3	0.2	0.4	0.4	.6	6
P vs. awake		NS	NS	NS	NS		

NS = not significant.

TABLE 2. Serum Cholinesterase Activities (Units/ml, Normal 3–8) before and after Pyridostigmine (0.225 mg/kg) and Atropine (0.02 mg/kg) in Patients with Alcoholic Hepatic Disease

	Units/ml Awake	Units/ml after Pyridostigmine-Atropine								Weight (kg)	Age (Years) Sex
		1 Min	3 Min	5 Min	10 Min	20 Min	30 Min	60 Min	120 Min		
Patient 1	2.1	0.3	0.6	0.7	1.0	1.2	1.4	1.7	2.1	80	64, M
Patient 2	2.2	0.3	0.6	0.8	0.9	1.4	1.6	1.6	2.5	50	69, F

TABLE 3. Serum Cholinesterase Activities (Units/ml, Normal 3–8) before and after Atropine (0.02 mg/kg)

	Units/ml Awake	Units/ml after Atropine				Weight (kg)	Age (Years) Sex
		1 Min	3 Min	5 Min	10 Min		
Patient 1	3.8	3.8	3.9	4.0	3.6	52	50, F
Patient 2	3.9	3.7	3.7	3.6	3.6	60	24, F

The two patients with alcoholic hepatic disease had abnormally low serum cholinesterase activities (less than 3 units/ml) before induction of anesthesia, but the magnitude of enzymatic inhibition after pyridostigmine was similar to that observed in patients without hepatic disease (table 2).

Atropine, 0.02 mg/kg, iv, did not alter enzymatic activity (table 3).

All patients had dibucaine numbers consistent with typical cholinesterase enzyme.

DISCUSSION

These data demonstrate that neostigmine and pyridostigmine, as used to reverse competitive neuromuscular blockade, reduce serum cholinesterase activity within a minute of administration in healthy patients or in patients who have hepatic disease. Normal dibucaine numbers confirmed the presence of typical cholinesterase enzyme in all patients. Despite equipotent doses of pyridostigmine and neostigmine (about 5:1),[6] the depression of cholinesterase activity was significantly longer-lasting and greater after pyridostigmine. For example, enzymatic activity was significantly decreased from control values two hours after pyridostigmine, but had returned to near control measurements 10 minutes after neostigmine. Furthermore, after one minute, depression of serum cholinesterase activity was always greater after pyridostigmine than after neostigmine. The longer duration of pyridostigmine effect agrees with the longer action of pyridostigmine on true cholinesterase, as previously reported by Miller *et al.*[7]

Drugs not classified as anticholinesterases may also inhibit serum cholinesterase activity.[2] Stovner *et al.*[2] reported that 0.1 mg/kg pancuronium reduced enzymatic activity 60 to 80 per cent for 3 minutes. Bennett *et al.*[3] also found decreased enzymatic activity in seven of ten patients 2 minutes following pancuronium, 0.2 mg/kg. In contrast, enzymatic activity was not significantly reduced following pancuronium (0.1 mg/kg)

administration to our patients. The reasons for these differences are not apparent.

Atropine may inhibit serum cholinesterase activity.[7] Nevertheless, atropine, 0.02 mg/kg, iv, did not alter enzymatic activity in the two patients we studied, suggesting that the observed reduction in serum cholinesterase activity following the combined administration of atropine with neostigmine or pyridostigmine was due entirely to the anticholinesterase drugs. Likewise, the unchanged enzymatic activity just before pancuronium reversal, compared with the awake measurements, confirms that anesthetic drugs do not influence enzymatic activity.

A pertinent question is whether reduced serum cholinesterase activity following neostigmine or pyridostigmine would prolong paralysis from subsequently administered SCh. Thesleff *et al.*[8] reported that the duration of action of SCh after 0.2 mg/kg was nearly doubled when SCh was administered 10 minutes after 0.03 mg/kg neostigmine, but not after 0.01 or 0.02 mg/kg neostigmine. These investigators did not determine serum cholinesterase activity, but in our study enzymatic activity 10 minutes after anticholinesterase drugs was reduced 21 per cent by neostigmine and 69 per cent by pyridostigmine. Wang and Ross[10] reported seven hours of apnea following 1 mg/kg SCh in a patient in whom an 80 per cent decrease in enzymatic activity had been produced by cytotoxic drugs. However, Foldes *et al.*[11] found that prolonged apnea (more than an hour) was unlikely even with fourfold reductions in enzymatic activity. Nevertheless, knowing that neostigmine and pyridostigmine may reduce serum cholinesterase activity emphasizes the need to reduce the SCh dose should this drug become necessary following the earlier administration of anticholinesterase drugs used to antagonize competitive neuromuscular blockers. Since longer-lasting and greater enzymatic inhibition occurred after pyridostigmine, one should be particularly cautious when this drug precedes SCh. Indeed, we observed prolonged SCh paralysis when pyridostigmine had been administered one hour earlier.[1]

Finally, factors other than serum cholinesterase inhibition may be responsible for anticholinesterase prolongation of SCh neuromuscular blockade. For example, neostigmine has been reported to prolong SCh paralysis in patients who have atypical serum cholinesterase enzyme.[12] Since enzymatic activity plays little role in the responses of these patients to SCh, it was speculated that neostigmine acted by mechanisms other than enzymatic inhibition, possibly in the endplate region.[13]

In summary, serum cholinesterase activity was not altered in the first 10 minutes after administration of pancuronium (6.9 ± 0.6 mg, mean ± SE), but was reduced 88 and 85 per cent from the control levels one minute after neostigmine (2.8 ± 0.3 mg) or pyridostigmine (14.6 ± 1.1 mg) plus atropine. Enzymatic activity was no longer significantly reduced ($P > 0.05$) 10 minutes after neostigmine, but remained significantly decreased for 120 minutes after pyridostigmine. Furthermore, enzymatic activity was significantly more decreased after pyridostigmine than after neostigmine at all times after the one-minute measurement. Atropine alone (0.02 mg/kg) did not alter enzymatic activity (two patients).

One should consider the likelihood of reduced serum cholinesterase activity following neostigmine and pyridostigmine when succinylcholine is administered to patients who have recently received these anticholinesterase drugs to antagonize competitive neuromuscular blockade.

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Helium–Oxygen in Treatment of Upper Airway Obstruction

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The therapeutic use of helium–oxygen for treatment of upper airway obstruction is dependent upon the low density of helium.[1–4] A helium–oxygen mixture may be indicated when the obstruction is unresponsive to conventional techniques or in cases of obstructive pulmonary disease in which respiratory fatigue is marked.[2,3]

REPORT OF A CASE

A 49-year-old black woman received a right pneumonectomy for bronchogenic squamous-cell carcinoma. Three weeks later she was readmitted with marked dyspnea and inspiratory stridor.

Bronchoscopy was performed the next day with anesthesia standby. No premedication was given. Two milliliters of 4 per cent lidocaine were administered transtracheally and the vocal cords sprayed. Diazepam, 5 mg, iv, was given for sedation, and bronchoscopy was performed in 15 min. A marked narrowing of the left mainstem bronchus (estimated 4 mm diameter) just distal to the carina was visualized. The narrowing was the result of extrinsic compression of the left mainstem bronchus. Following withdrawal of the bronchoscope, the patient experienced increasing difficulty in breathing, and she became unconscious during the ensuing 10 min. Attempts to ventilate her with an anesthetic mask and 100 per cent oxygen were unsuccessful. The trachea was intubated without difficulty and without the use of any drug. An attempt was made to ventilate her with a Bennett MA-1 ventilator with 100 per cent oxygen. Ventilation became progressively more difficult, and tidal volumes became unmeasurable before the maximum inspiratory pressure limit of the ventilator was reached.

Analysis of arterial blood drawn at this time revealed Pa_{O_2} 190 torr, Pa_{CO_2} more than 100 torr, and *p*H 7.01. Sodium bicarbonate, 90 mEq, iv, was administered to treat the severe acidosis. Meanwhile, a tank of helium was summoned to the scene. A helium–oxygen (3.5–1.5 l) mixture, $FI_{O_2} = 0.3$, was delivered by the Bennett MA-1 ventilator through the medication chamber to the patient.

In a matter of a few breaths, ventilation showed a dramatic improvement, with measurable tidal volumes as much as 175 ml, minute volume about 4,900 ml, with a peak inspiratory pressure of 56 cm H_2O. After 45 minutes Pa_{O_2} was 89 torr, Pa_{CO_2} 56 torr, *p*H 7.41. The patient had regained consciousness.

To substantiate our clinical impression, the following laboratory study simulating the pulmonary abnormality in the patient was performed.

METHOD

The tracheas of six unpremedicated mongrel dogs weighing 20–30 kg were intubated following thiopental, 12–15 mg/kg, iv, and the dogs were anesthetized with halothane in oxygen.

A central arterial line was inserted via a femoral artery for pressure and blood-gas

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