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Prolonged Effect of Succinylcholine after Neostigmine and Pyridostigmine Administration in Patients with Renal Failure

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We report two cases of prolonged succinylcholine neuromuscular blockade in patients with renal failure, each of which occurred when the drug was administered several hours after the end of a kidney transplantation. We feel these prolonged blockades can be explained by altered anticholinesterase kinetics, although lower than normal pseudocholinesterase levels also have contributed. That prolonged blockade has not been reported previously in this circumstance is explained by the rare occurrence of a combination of events; the patient with renal failure who has received an anticholinesterase and is administered succinylcholine several hours later. Based on our experience and review of the pertinent literature, when these three conditions are present, prolonged succinylcholine blockade probably is the rule rather than the exception.

REPORTS OF TWO CASES

Case 1

A 30-year-old, 70-kg woman with chronic renal failure was anesthetized with halothane and nitrous oxide for a kidney transplantation. The patient had been undergoing peritoneal dialysis three times a week. Intravenous medications administered during the five-hour transplant procedure included 300 mg thiopental, 21 mg *d*-tubocurarine, 40 mg furosemide, 40 mg methylprednisolone, 12.5 g mannitol, and 50 mg diphenhydramine. At the end of the procedure, 1 mg atropine and 2.5 mg neostigmine, iv, successfully antagonized the *d*-tubocurarine neuromuscular blockade. The trachea was extubated and the patient then was taken to the recovery room in satisfactory condition, although she remained anuric.

Two hours after the end of surgery, the patient returned to the operating room because of continued bleeding at the surgical site and persistent anuria. Halothane and nitrous oxide anesthesia were again used, but this time endotracheal intubation was facilitated by the iv administration of 100 mg succinylcholine. One hour later, at the end of the procedure, tetanic stimulation produced marked fade and a phase II neuromuscular block was diagnosed. Ventilation was controlled in the recovery room until full muscular strength returned two hours later.

Serum pseudocholinesterase activity, measured immediately postoperatively was 3.1 IU (normal, 4.3–10.9), and dibucaine and fluoride numbers were both within the normal range.

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Case 2 occurred at the University of California, San Francisco during Dr. Bishop's residency training.

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Case 2

A 37-year-old, 68-kg man with chronic renal failure was anesthetized with halothane for a kidney transplantation. The patient underwent dialysis on the day prior to surgery.

Anesthesia was induced with 250 mg thiopental and 40 mg *d*-tubocurarine were administered iv by constant infusion during the four-hour operation. Forty milligrams furosemide and 12.5 g mannitol, iv, also were given. At the end of the procedure, 2 mg atropine and 24 mg pyridostigmine, iv, successfully reversed the *d*-tubocurarine neuromuscular blockade. In the recovery room, the patient received 12 mg morphine and 30 mg prednisolone, iv.

Six hours after the end of the procedure, the patient was returned to the operating room for removal of the transplanted kidney because of hyperacute rejection. Three milligrams *d*-tubocurarine were given and anesthesia was induced with 150 mg thiopental, iv. One hundred milligrams succinylcholine; iv, facilitated endotracheal intubation, and anesthesia was maintained with 50% nitrous oxide and intermittent halothane at inspired concentrations of less than 0.5%. The patient demonstrated no significant response to train-of-four or tetanic stimulation for the first 30 min, but over the following 30 min the train-of-four twitches returned in full and the trachea was extubated. The serum pseudocholinesterase activity was not measured.

Discussion

Recognized causes of prolonged paralysis after administration of succinylcholine include markedly decreased or absent serum pseudocholinesterase, phase II blockade from high doses of the drug, and administration of the drug in the presence of a cholinesterase inhibitor.

A decreased pseudocholinesterase activity of apparently normal phenotype was found in patient 1. While not measured in patient 2, there is a strong likelihood the level was low since McArdle[1] noted the mean levels of the enzyme in patients with renal failure to be 45% of normal, and Simon *et al.*[2] found the levels to be more than two standard deviations below the mean in 60% of such patients. However, clinically significant prolongations of a succinylcholine neuromuscular blockade due to low pseudocholinesterase levels alone usually occur only with the very low levels of the enzyme produced by genetic abnormalities. In 39 patients who were heterozygotes for atypical cholinesterase and thus had levels approximately one-half of normal, recovery to 90% twitch height was prolonged by only five minutes.[3] Foldes examined 11 patients with severe liver disease and a mean enzyme level of 27% of normal and found a prolongation of apnea time from 3.0 to 8.6 minutes.[4] Thus, the low enzyme levels seen in patients with uremia are probably contributory but do not alone account for the prolonged paralysis in these two cases.

A probably more significant factor in the prolonged blockade in our patients was the antecedent administration of a cholinesterase inhibitor at the end of surgery two and six hours prior to the subsequent administration of succinylcholine. The durations of neostigmine and pyridostigmine inhibition of pseudocholinesterase remain controversial.[5–8] Sunew and Hicks[7] found a 35-min duration of action of 1 mg/kg of succinylcholine given immediately following neostigmine, while Stoelting[9] reported a three-hour duration of action of succinylcholine given one hour after pyridostigmine. Miller and Savarese state that a 100-mg dose of succinylcholine will induce a neuromuscular blockade which will last up to 60 minutes when given soon after the administration of neostigmine.[10] In contrast, in both our patients, several hours had passed between the administration of the cholinesterase inhibitor and the administration of the succinylcholine. A possible explanation is the alteration in the pharmacokinetics of both drugs in patients with renal failure and their prolonged durations of action.[11] Cronnelly *et al.* found the elimination half-life of neostigmine to be extended from 80 minutes to 181 minutes in anephric patients,[12] while the elimination half-life of pyridostigmine was 379 minutes in patients with renal failure.[13] Thus, patients with renal failure who receive an anticholinesterase remain at risk for prolonged action of succinylcholine for a much longer time than do normal patients.

Other causes for the prolonged blockade seem less likely. While both patients received furosemide, which has been reported to prolong *d*-tubocurarine blockade in patients with renal failure, the extent of the prolongation in our patients far exceeds the usual duration of blockade associated with this drug.[14] Variant enzyme phenotypes which yield normal results with usual *in vitro* assays but having low *in vivo* activity have been reported but are statistically unlikely.[15] A predominant phase II blockade based on dose alone generally does not occur after a 100-mg dose of succinylcholine as used in these patients.

Our patient's prolonged blockade following succinylcholine most likely resulted from the persistence of previously administered cholinesterase inhibitors. The moderately reduced enzyme levels associated with renal failure activity also may have contributed to the blockade. Patients with renal failure requiring muscle relaxation are at greater risk than normals for prolonged succinylcholine blockade if they have recently undergone anticholinesterase-induced reversal of neuromuscular blockade.

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