Neostigmine Produces Bradycardia in a Heart Transplant Patient

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CLAIMS that heart rate in the heart transplant patient is unaffected by neostigmine′–5 have not been verified. Recently, it was demonstrated in cats with autonomic efferent activity to the heart interrupted by propranolol 3 mg/kg intravenous and bilateral vagotomy that neostigmine can still evoke a marked dose-dependent bradycardia.4,5 The mechanism by which this occurs appears to involve direct activation by neostigmine of excitatory cholinergic receptors on cardiac ganglion cells, which results in release of acetylcholine from their terminals and subsequent activation of inhibitory cardiac receptors. The anticholinesterase property of neostigmine did not appear to be responsible for evoking the bradycardia. This then suggests that, in heart transplant patients, neostigmine may be capable of producing bradycardia via a similar mechanism. In this report, we describe a reduction in heart rate following systemic administration of neostigmine to a heart transplant patient. This decrease in heart rate was reversed by atropine.

Informed consent was obtained from patients included in this report. This project was reviewed and approved by the Ethics Committee for human studies at the Royal Victoria Hospital.

Case Report

A 52-yr-old, 82-kg man was admitted for an elective laparoscopic cholecystectomy. He had undergone cardiac transplantation approximately 40 months prior to admission. Medications included cyclo-

sporin 275 mg a.m., 250 mg p.m., imuran 125 mg QD, prednisone 2.5 mg QD, nifedipine 10 mg BID, furosemide 40 mg QD, and niasin 750 mg TD. The patient had a preoperative heart rate of 100 beats/min and blood pressure of 110/80 mmHg. Physical examination was unremarkable except for the presence of jaundice. Laboratory investigation demonstrated the following: Na 143, K 4.0, Cl 106, HCO3 27, BUN 12.1, Cr 115, glucose 5.7, total bilirubin 68.4, alkaline phosphatase 544, ALT 107, AST 61, LDH 155, cholesterol 6.8, HGB 119, WBC 4.64, platelets 293, PT 9.9/10.2, and PTT 25/29. A 12-lead ECG recording revealed a normal sinus rhythm at 80 beats/min.

General anesthesia consisted of thiopental 400 mg, fentanyl 200 µg, vecuronium 9 mg, enflurane 0.5–1.5%, and ventilation with a nitrous oxide–oxygen mixture with FIO2 of 0.3.

Monitoring included an automated blood pressure cuff, ECG (lead II), pulse oximetry, capnography, and a nerve stimulator. A second ECG was recorded using a cardiocapnometer (Portex, Wilmington, MA) inserted into the esophagus at a depth that produced a large biphasic p wave.

The effect of neostigmine on heart rate was studied after surgery was completed. At this time, the heart rate, taken as control, was 95 beats/min (fig. 1A). Neostigmine 0.04 mg/kg intravenous was administered without a muscarinic antagonist. Heart rate gradually decreased over the next 4–5 min to a nadir of 75 beats/min (fig. 1B). After administration of 1.2 mg atropine intravenous, heart rate returned to control value within approximately 90 s (fig. 1C).

Discussion

This demonstration that neostigmine evoked a reduction in heart rate in a patient who had undergone cardiac transplantation differs from the widely held belief that anticholinesterases are without cardiac effect in this type of patient.′–5 However, we are unaware of any clinical study that has actually tested the effect of neostigmine on heart rate in patients who have undergone cardiac transplantation. Stemple et al.6 reported the lack of effect of a bolus dose of 0.1 mg/kg of edrophonium followed by an infusion of the same drug at 0.14 mg·kg−1·min−1 on the sinus rhythm of the donor heart in a cardiac transplant patient, while noting a reduction in p wave rate of the recipient's remnant atrium. Similarly, edrophonium has been shown to produce only a very weak bradycardic response in cats with interrupted cardiac efferent activity.4,5 The observations described in this case report are entirely consistent with the finding, in cats, that neostigmine can cause bradycardia even when autonomic input to

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the heart is interrupted.\textsuperscript{4,5} By analogy from experiments in cats, it is indicated in the current report that neostigmine induces bradycardia \textit{via} direct activation of cholinergic receptors on cardiac ganglion cells, causing release of acetylcholine from their terminals and activation of inhibitory cardiac muscarinic receptors. This hypothesis is supported by the observation, in the current report, that the neostigmine-induced bradycardia was reversed by atropine. It should be noted that, in the study of the mechanism of the neostigmine-induced bradycardia in the cat, the decrease in heart rate produced by neostigmine was also reversed by atropine, a muscarinic M1 and M2 antagonist, and by pancuronium, an inhibitory muscarinic M2 antagonist.\textsuperscript{4,5} In the current study, care was taken to avoid the administration of any muscarinic antagonists before neostigmine.

Could the observed effect of neostigmine in this patient be a consequence of reinnervation of the heart following cardiac transplantation? It appears that, in humans, after cardiac transplantation, the majority of studies refute sympathetic and parasympathetic efferent reinnervation of the heart.\textsuperscript{7–12} However, afferent reinnervation may occur.\textsuperscript{13} Although cardiac reinnervation in this particular patient cannot be ruled out, we have observed that the administration of 0.05 mg/kg of neostigmine immediately after heart transplantation produces an 8–15% (\overline{X} = 10.8\% \pm 3\% SD) reduction in heart rate that is reversed by 1.2 mg of atropine (n = 4). We have also observed a reduction in heart rate produced by neostigmine when administered to two other patients who had undergone heart transplantation approximately 1 yr previously (reduction in heart rate was 7% and 14%, respectively). Whether the somewhat larger reduction in heart rate evoked by neostigmine described in this case report is a consequence of cardiac reinnervation, or of prolonged denervation,\textsuperscript{14,15} cannot presently be answered. In any event, it demonstrates that changes in heart rate associated with neostigmine might be anticipated in patients who have undergone cardiac transplantation. Coadministration of a suitable muscarinic antagonist may prevent any such changes.

References

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Anaphylactic Reaction to Topical Bovine Thrombin

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THE use of topical bovine thrombin (TBT) alone or in conjunction with cryoprecipitated fibrinogen is common for facilitation of intraoperative hemostasis for a variety of surgical procedures.1-4 Topical bovine thrombin may be applied directly, or in conjunction with surgical sponges or gelatin sponges, to bleeding capillaries or small venules, and acts specifically by clotting fibrinogen in the blood. The speed with which a clot forms is dependent on the concentration of the solution used and the serum level of fibrinogen. Topical bovine thrombin is a protein substance with a high antigenic potential that may lead to the development of antithrombin antibodies and, although relatively rare, anaphylactoid reactions to TBT may, therefore, occur on reexposure to the drug.4-6 The severity of this or any other anaphylactic reaction may be mediated by the concomitant administration of β-adrenergic antagonists, with these agents not only impairing the efficacy of epinephrine in treating the condition, but also altering the threshold for pronounced anaphylaxis.7

In this report, we describe a patient in whom anaphylaxis occurred immediately after the application of TBT, and whose initial therapy was hampered by the prior administration of a β-adrenergic antagonist.

Case Report

A 51-yr-old man with a history of lumbar stenosis was admitted for treatment of decompressive lumbar laminectomy and spinal fusion. The patient's past surgical history was remarkable for uncomplicated cervical spine fusion 5 yr before admission, and a lumbar decompression 2 yr before admission. The patient's past medical history was otherwise unremarkable. He denied prior transfusion therapy. He denied tobacco or alcohol abuse and the only medication he was taking was aspirin. His allergy history was remarkable for sulfa-induced skin rashes. He denied other manifestations, such as urticaria, stridor, bronchospasm, or shock. His physical examination was remarkable only for a positive straight leg raise sign bilaterally. Preoperative laboratory values were within normal limits, with the exception of a cholesterol of 228 mg/dL and an alkaline phosphatase of 133 U/L (normal 35-110 U/L). Chest x-ray and electrocardiogram were also within normal limits.

The patient received no preoperative medication the morning of surgery. Before the induction of anesthesia, two 16-g peripheral intravenous lines and a 20-g radial arterial catheter were inserted under local anesthesia with lidocaine 1% subcutaneously. A total of 3 mg of midazolam was titrated intravenously for preoperative sedation. Cefazolin, 2 g in 100 mL of 0.9% normal saline, was infused over 20 min for surgical prophylaxis. Routine monitors were placed and the patient breathed oxygen. Anesthetic induction with thiopental, sufentanil, and vecuronium ensued and was followed by uncomplicated tracheal intubation. Electrodes were placed at the posterior tibial nerves and the scalp for somatosensory evoked potential monitoring (SEEP). The patient was then placed in the prone position using an Andrew's frame. The patient's vital signs remained stable while he received 70% nitrous oxide and a sufentanil infusion of 0.3

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