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Amiodarone-induced Complications during Coronary Artery Surgery

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The efficacy of amiodarone, an investigational drug, in the medical management of cardiac dysrhythmias and angina pectoris is currently under evaluation. It is a noncompetitive adrenergic blocker[1] which prolongs atrial[2] and ventricular action potential durations,[3] and produces coronary artery vasodilatation.[4] Amiodarone possesses several properties which may present problems to the anesthesiologist, including atropine-resistant bradycardia,[4] myocardial depression,[1] peripheral vasodilatation,[5] and an extremely long (30–45 days) duration of action.[5] We recently encountered most of these problems while anesthetizing a patient taking amiodarone for refractory ventricular tachycardia.

REPORT OF A CASE

A 54-year-old man with coronary artery disease, a left ventricular aneurysm, and medically refractory ventricular tachycardia was scheduled for coronary artery revascularization with endocardial mapping and excision and left ventricular aneurysmectomy.[6] Eight years prior to admission, he underwent an uneventful saphenous vein bypass of the right coronary artery. Nine months prior to admission, he developed progressive angina and ventricular tachycardia refractory to combinations of quinidine and procainamide.

Cardiac catheterization and baseline electrophysiologic studies revealed the inability of standard antiarrhythmic medications alone and in combination to prevent the induction of ventricular tachycardia. After obtaining informed consent, amiodarone therapy was begun and progressively increased. Over a 35-day period, during which the amiodarone was increased to 600 mg/day together with maximally tolerated quinidine, three follow-up electrophysiologic studies demonstrated no suppression of ventricular irritability. Amiodarone was then discontinued and the patient scheduled for surgery three days later. Other medications at the time of surgery included digoxin, 0.25 mg daily, furosemide, 40 mg daily, and isosorbide dinitrate, 20 mg orally every six hours.

Preoperative physical examination revealed a 70-kg man with a heart rate (HR) of 50–55 beats per minute (bpm) and an arterial blood pressure of 120/60 torr. His skin did not have the bluish hue occasionally seen in patients taking amiodarone.[7] The lung fields were clear to auscultation, and a soft holosystolic murmur was present at the cardiac apex with no peripheral edema. The electrocardiogram showed a sinus bradycardia of 50 bpm, an old inferior wall infarction, and an intraventricular conduction delay. Chest roentgenogram and routine laboratory studies, including T_4 and T_3 resin uptake, were normal. Cardiac catheterization demonstrated complete occlusions of the left anterior descending, circumflex and right coronary arteries, a patent right coronary artery graft with prominent retrograde filling of the LAD, a large apical aneurysm and 2+ mitral regurgitation. The left ventricular end-diastolic pressure was 27 torr and the cardiac index was 2.3 l/min. Because of marked left ventricular dyssynergy, no ejection fraction was calculated.

Following the intramuscular administration of morphine sulfate, 4 mg, and scopolamine, 0.3 mg, monitoring was established with the lead V_5 electrocardiogram (ECG), a radial arterial cannula and a thermodilution pulmonary artery (PA) catheter placed via the right internal jugular vein. No ventricular dysrhythmias occurred during PA catheterization. While breathing 100 per cent oxygen, anesthesia was induced with fentanyl, 50 μg/kg.[8] Pancuronium was used to induce paralysis, and ventilation was controlled with an $F_{I_{O_2}}$ of 1.0. Calculated peripheral vascular resistance throughout this period was normal (1350–1580 dyne-sec/cm^5).

The hemodynamic status was entirely stable other than a bradycardia of 35–40 bpm immediately prior to sternotomy. This sinus bradycardia was associated with decreases in arterial BP from 120/70 to 100/50 torr, and in cardiac output from 4.0 to 2.5 l/min without ECG evidence of myocardial ischemia. The bradycardia was unresponsive to either incremental doses of atropine to 1.5 mg or to isoproterenol injected in boluses of 4 and 8 μg. Ventricular pacing was established without difficulty and no further hemodynamic disturbances occurred during the prebypass period. Normothermic cardiopulmonary bypass (CPB) was utilized during epicardial and endocardial mapping,[6] and hypothermic (25° C) CPB with potassium cardioplegia was instituted prior to left ventricular aneurysmectomy and coronary artery revascularization. Calculated pump flow during CPB (2.21·min^{-1}·m^{-2} body surface area) was adequate to maintain arterial pressure between 60 to 70 torr. Aortic cross-clamp time was 96 min. The proximal vein grafts and an intra-aortic balloon pump (IABP) were placed while the patient was rewarmed to 37° C. Following completion of the proximal anastomoses, Pa_{O_2} was 425 torr ($F_{I_{O_2}}$ = 1.0), Pa_{CO_2} 35 torr, and pH 7.40. Serum potassium was 4.8 mEq/l, sodium 139 mEq/l, ionized calcium 2.2 mEq/l, and hemoglobin 8 g/dl. Calculated peripheral vascular resistance (PVR) was low (600 dyne-sec/cm^5) and the patient was in complete heart block with a ventricular rate of 40 bpm. The heart block was unresponsive to atropine, calcium chloride, isoproterenol, and sodium bicarbonate (given with the intention of lowering the potassium concentration in the myocardial extracellular fluid). Sequential atrioventricular (A-V) pacing was initiated. Similarly, the low PVR was unresponsive to simultaneous infusions of

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epinephrine (8 μg/min), norepinephrine (16 μg/min), and metaraminol (200 μg/min), even when supplemented with 1-mg boluses of phenylephrine. Moreover, despite the inotropic infusions, calcium chloride, and IABP, the heart remained sluggish, and the patient could not be weaned from CPB. Urine output remained nearly 2 $ml \cdot kg^{-1} \cdot hr^{-1}$ despite the vasconstrictor therapy.

Over the next 60 min, the PVR increased to 1200 dyne-sec/cm^5 and his heart began to beat more vigorously without change in infusion rates. CPB was finally discontinued 95 min after the initial attempt. The post-CPB period was remarkably stable. The PVR stabilized at 1200 dyne-sec/cm^5, allowing for the gradual discontinuation of norepinephrine, metaraminol, and phenylephrine. The heart block did not resolve, and A-V sequential pacing was continued. Epinephrine was required for inotropic support for the remainder of the operation. The patient left the operating room with the heart being paced at 80 bpm, the IABP assisting at 1:1, and epinephrine infusing at 24 μg/min. C.O. was 2.5 l/min, and urine output was still approximately 2 $ml \cdot kg^{-1} \cdot hr^{-1}$.

The postoperative course was not complicated by any hemodynamic or electrophysiologic deterioration. Again, despite an epinephrine infusion at rates as high as 30 μg/min during the first 48 hours, the PVR remained normal, extremities remained warm, and urine output exceeded 100 ml/h. Epinephrine infusion and cardiac pacing were discontinued on the fifth postoperative day, and the IABP was discontinued two days later. The patient continued to do well, taking only quinidine sulfate, 200 mg, four times daily, for occasional premature ventricular contractions. He had no recurrence of ventricular tachycardia, and was discharged from the hospital 20 days following surgery.

Discussion

Amiodarone, first introduced in 1967 as an antianginal compound, was subsequently found to be an effective antiarrythmic agent.[10] Amiodarone produces a noncompetitive adrenergic blockade[1] resulting in arteriolar and venous dilatation,[5] decreased myocardial contractility,[1] and decreased HR.[5] Canine studies demonstrated a 23 per cent decrease in HR with amiodarone, despite prior maximum vagal and adrenergic blockade.[1,4,11] Amiodarone partially antagonized the hypertension, tachycardia, and positive inotropy caused by injection of adrenergic agents,[1] yet failed to completely abolish epinephrine's positive inotropy as did propranolol.[4,12] Amiodarone did not alter myocardial catecholamine content, but does antagonize the hypertension and tachycardia produced by glucagon.[4] Since glucagon and catecholamines both stimulate adenyl cyclase induced elevations of intracellular cyclic adenosine monophos- (cAMP),[13,14] amiodarone may interfere with adenyl cyclase activation.[15] This mechanism is supported by finding an amiodarone-induced increase in ventricular fibrillation threshold with a decrease in myocardial cAMP production.[16]

Electrophysiologic effects include prolongation of sinus node recovery time,[17] atrial action potential duration,[2] and intra-atrial conduction time.[6] The A-V nodal refractory period[6] and ventricular action potential duration are also prolonged.[3] This is manifested as bradycardia and Q-T interval prolongation[10] and results in effective control of both supraventricular[10,18,19] and ventricular[20] tachyarrhythmias. Amiodarone's antianginal effects are mediated by increased coronary blood flow with decreased coronary vascular resistance[4] and diminished myocardial oxygen consumption through decrease HR,[1] depressed myocardial contractility,[1] decreased PVR[5] and decreased left ventricular end-diastolic pressure through venous and arteriolar dilatation.[5]

Amiodarone, an iodinated benzofuran derivative, is effective both orally and parenterally and distributes widely throughout the body.[4] It is structurally similar to thyroxine[4] and can produce both hypo-[21] and hyperthyroidism,[22] corneal microdeposits,[6] and a melanodermatitis related to crystal deposition resulting in a bluish skin discoloration.[23] Notably, an elimination half-life of 30 days results in persistent pharmacologic effects for as long as 45 days after drug discontinuation.[24]

Although refractory bradycardia, A-V block, and abnormally low PVR may be seen in patients undergoing coronary artery surgery, the complications we observed were due to amiodarone, but increasing experience is required before the drug can be implicated with certainty. The presternotomy bradycardia was unresponsive to a fairly large dose of atropine. The sluggish contractility and low PVR prior to discontinuation of CPB were responsive only to large doses of alpha- and beta-agonists. Moreover, the A-V node was completely unresponsive to therapy with atropine, calcium, and beta-agonists, and required A-V sequential pacing. Large doses of epinephrine (30 μg/min) were required for 48 hours postoperatively. That this dose of epinephrine, usually associated with marked alpha- as well as beta-adrenergic stimulation, failed to produce systemic hypertension, elevated PVR, oliguria, or cardiac dysrhythmias even after spontaneous restoration of A-V conduction and return of normal sinus rhythm, suggests the presence of a long-acting peripheral vasodilator and myocardial depressant. Kryzhanovskii suggested that amiodarone may potentiate the negative inotropic and chronotropic effects of anesthetic agents in dogs.[25] Limited experience precludes our drawing any conclusions for humans. Our patient was anesthetized with high-dose fentanyl and oxygen, a technique associated with minimal alterations in cardiovascular dynamics.[8]

The intent of this report is not to create another propranolol,[26] or reserpine[27] scare. Rather, we present this case to alert anesthesiologists to the problems we encountered. Any patient who had received

amiodarone within the preceding 45 days may be at risk of developing atropine-resistant bradycardia, as well as decreased peripheral resistance and diminished contractility. Regardless of the anesthetic technique used, there may be a need for unusually high doses of inotropic agents with little effect on HR or PVR.

References

1. Charlier R: Cardiac actions in the dog of a new antagonist of adrenergic excitation which does not produce competitive blockade of adrenoceptors. Br J Pharmacol 39:674–688, 1970
2. Vaughan-Williams E: The development of new antidysrhythmic drugs. Schweiz Med Wochenschr 103:262–275, 1973
3. Singh B, Vaughan-Williams E: The effect of amiodarone, a new antianginal drug, on cardiac muscle. Br J Pharmacol 39:657–667, 1970
4. Charlier R, Deltour G, Baudine A, et al: Pharmacology of amiodarone an antianginal drug with a new biological profile. Arzneim Forsch 18:1408–1417, 1968
5. Cote P, Bourassa M, Delaye J, et al: Effects of amiodarone on cardiac and coronary hemodynamics and on myocardial metabolism in patients with coronary artery disease. Circulation 59:1165–1172, 1979
6. Horowitz L, Harken A, Kastor J, et al: Ventricular resection guided by epicardial and endocardial mapping for treatment of recurrent ventricular tachycardia. N Engl J Med 302:589–593, 1980
7. Rosenbaum M, Chiale P, Halpern M, et al: Clinical efficacy of amiodarone as an antiarrhythmic agent. Am J Cardiol 38:934–944, 1978
8. Stanley T, Webster L. Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl–diazepam–oxygen anesthesia in man. Anesth Analg (Cleve) 57:421–426, 1978
9. Vastesaeger M, Gillot P, Rasson G. Etude clinique d'une nouvelle medication anti-angoreuse. Acta Cardiol (Brux) 22:483–500, 1967
10. Olsson SB, Brorson L, Varnawskas E: Class 3 antiarrhythmic action in man, observations from monophasic action potential recordings and amiodarone treatment. Br Heart J 35:1255–1259, 1973
11. Charlier R, Baudine A, Chaillet F: Recherches dans la serie des benzofurannes. XXXII. Mode d'action de l'amiodarone sur le systeme cardiovasculaire. Arch Int Physiol Biochim 75:787–808, 1967
12. Charlier R, Delaunois G, Bautheir J: Opposite effects of amiodarone and beta-blocking agents on cardiac function under adrenergic stimulation. Arzneim Forsch 22:545–552, 1972
13. Levey G, Epstein S: Activation of adenyl cyclase by glucagon in cat and human heart. Circ Res 24:151–156, 1969
14. Sutherland EW, Rall TW, Menon T: Adenyl cyclase. I. Distribution, preparation, and properties. J Biol Chem 237: 1220–1227, 1962
15. Polster P, Broekhuysen J: The adrenergic antagonism of amiodarone. Biochem Pharmacol 25:431–434, 1976
16. Lubbe W, McFadyen M, Muller C, et al: Protective action of amiodarone against ventricular fibrillation in the isolated perfused rat heart, Am J Cardiol 43:533–540, 1979
17. Taboul P, Attallah G, Gressard A, et al: Effects of amiodarone on sinus node in man. Br Heart J 42:573–578, 1979
18. Brown A, Primhak R, Newton P: Use of amiodarone in bradycardiatachycardia syndrome. Br Heart J 40:1149–1152, 1978
19. Rosenbaum M, Chiale P, Ryba D, et al: Control of tachyarrhythmias associated with Wolff-Parkinson-White Syndrome by amiodarone hydrochloride. Am J Cardiol 34:215–223, 1974
20. Wheeler P, Puritz R, Ingram D, et al: Amiodarone in the treatment of refractory supraventricular and ventricular arrhythmias. Postgrad Med J 55:1–9, 1979
21. Barrillon A, Himbert J: Amiodarone et Thyroide. Nouv Presse Med 33:1498–1499, 1971
22. Savoie J, Massin J, Thomopoulos R, et al: Iodine-induced thyrotoxicosis in apparently normal thyroid glands. J Clin Endocrinol Metab 41:685–687, 1975
23. Geerts ML: Amiodarone pigmentation—an electron microscopic study. Arch Belg Dermatol 23:339–351, 1971
24. Singh B, Collett J, Chew C: New perspectives in the pharmacologic therapy of cardiac arrhythmias. Prog Cardiovasc Dis 22:243–301, 1980
25. Kryzhanovskii S: Vliianie Kordarona na Krovoobrashchenie v Usloviiakh Obshechei Anestezii i Svobodnogo Povedeniia. Farmakol Toksikol 41:309–314, 1978
26. Viljoen JF, Estafanous FG, Kellner GA: Propranolol and cardiac surgery. J Thorac Cardiovasc Surg 64:826–830, 1972
27. Ominsky AJ, Wollman H: Hazards of general anesthesia in reserpinized patients. Anesthesiology 30:443–446, 1969