Anaesthesia and amiodarone

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Two recent reports support and one report disputes the existence of dangerous interactions between the new benzofuran antiarrhythmic amiodarone and the anaesthetic state.

We have reviewed our experience with 17 anaesthetics administered to 16 patients taking amiodarone. Haemodynamics and serum amiodarone levels were evaluated where available. Twelve cases involved cardio-pulmonary bypass; of these, three patients died. There were no deaths in the non-cardio-pulmonary bypass group.

The charts of 30 patients with poor left ventricular function, who were not receiving amiodarone but who were undergoing coronary artery bypass surgery, were reviewed to establish a comparison group.

Interactions were manifested in three forms: (1) nodal rhythm and/or complete heart block developed in ten of 15 patients (one patient had a preoperative pacemaker inserted for the sick sinus syndrome), (2) poor cardiac output requiring intra-aortic balloon pump augmentation developed in six of 12 cardio-pulmonary bypass patients, or, (3) a state of alpha adrenergic blockade leading to a low systemic vascular resistance despite alpha agonist therapy developed in two of 16 patients.

We conclude that dangerous, fatal interactions may occur in patients taking amiodarone who undergo general anaesthesia with cardio-pulmonary bypass. Anaesthesia for non-cardiac surgery may be associated with haemodynamically significant bradyarrhythmias. We recommend aggressive invasive monitoring, including pulmonary artery catheterization and consideration of an atrio-ventricular pacemaker in high risk patients.

Key words

ANTIARRHYTHMICS: amiodarone; INTERACTIONS: amiodarone, anaesthetic agents.

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Amiodarone is a new and powerful anti-arrhythmic agent not as yet released for general use in North America. At the Toronto General Hospital more than 300 patients have received amiodarone therapy. Sixteen of these patients have been anaesthetized for 17 surgical procedures, ranging from bronchoscopy to open-heart surgery.

There is presently some dispute in the literature as to the possible existence of detrimental interactions between amiodarone and general anaesthesia, with two cases of severe intra-operative complications already reported^{1,2} and yet a report³ (presently available only in abstract form) suggesting no increased risk of general anaesthesia for patients taking amiodarone. In view of this divergence of conclusions, we reviewed our experience with anaesthetizing patients taking amiodarone.

A spectrum of complications were encountered and in an effort to account for these problems, multiple serum samples were taken to investigate whether the induction of anaesthesia or the institution of cardio-pulmonary bypass (CPB) caused a change in serum amiodarone levels.

Detailed case histories of two patients having severe postoperative complications, felt to be due to the interaction of general anaesthesia and amiodarone therapy are presented, as well as a summary of the remaining fourteen patients (Table I).

As well, we present our recommendations to the anaesthetist encountering a patient taking amiodarone preoperatively.

Methods

This report consists of a retrospective review of our total experience up to the time of preparation of the manuscript in anaesthetizing patients receiving amiodarone. The patients were managed by the anaesthetists(s) administering the anaesthetic and providing postoperative care.

The preoperative function of the left ventricle (LV) was assessed according to the left ventriculogram on cardiac catheterization. A Grade I LV is defined as having an ejection fraction greater than

TABLE 1 Case summaries

Amiodarone dosage, duration, indication		Preoperative cardiac status	Anaesthetic technique (total doses)	Operation, complications, postoperative status, outcome
Case 1 62 yr M	800 mg/day 5 days/week for 1 month Ventricular tachycardia Last dose 24 hr pre-op	Grade III LV CAD EKG = sinus rhythm, 1° heart block	Fentanyl 72 µg·kg ⁻¹ Diazepam 0.12 mg·kg ⁻¹	CABG × 2 vessels. Post-op: CO = 6.1, SVR = 681 on dopamine 10 µg·kg ⁻¹ ·min ⁻¹ and levaterenol 2 µg·kg ⁻¹ ; A-V paced for CHB SURVIVED
Case 2 59 yr M	400 mg/day 5 days/week for 3 years Ventricular tachycardia Last dose 48 hr pre-op	Grade II LV Mitral regurgitation Tricuspid regurgitation EKG = atrial fibrillation	Fentanyl 67 µg·kg ⁻¹ Diazepam 0.03 mg·kg ⁻¹	Mitral and tricuspid valve replacements. Post-op: CO = 4.0, SVR = 720 on dopamine 110 µg·kg ⁻¹ ·min ⁻¹ and epinephrine 40 µg·min ⁻¹ ; A-V paced for CHB IABPA DECEASED
Case 3 63 yr M	400 mg/day 7 days/week for 3 weeks Ventricular tachycardia Last dose 60 hr pre-op	Grade IV LV CAD EKG = sinus rhythm, LBBB	Fentanyl 68 µg·kg ⁻¹ Diazepam 0.03 mg·kg ⁻¹	CABG × 3 vessels. Post-op: CO = 6.2, SVR = 5.82 on dopamine 25 µg·kg ⁻¹ ·min ⁻¹ ; A-V paced for CHB IABPA DECEASED
Case 4 51 yr M	600 mg/day 5 days/week for 4 months Ventricular tachycardia and fibrillation Last dose 12 hr pre-op	Grade IV LV CAD EKG = sinus rhythm, 1° heart block	Fentanyl 50 µg·kg ⁻¹ Diazepam 0.22 mg·kg ⁻¹ Enflurane 0–0.5%	CABG × 4 vessels. Dopamine 8 µg·kg ⁻¹ ·min ⁻¹ to wean from CPB IABPA SURVIVED
Case 5 59 yr F	600 mg/day 7 days/week for 2 weeks Paroxysmal atrial tachycardia & fibrillation Last dose 24 hr pre-op	Pulmonary hypertension Hypertrophic subaortic stenosis Mitral regurgitation 100 mm Hg aortic gradient EKG = sinus rhythm, LBBB	Fentanyl 77 µg·kg ⁻¹ Diazepam 0.04 mg·kg ⁻¹	Subendocardial myectomy. Unable to wean from CPB despite dopamine, isoproterenol, phenylephrine and levaterenol re-perfused on femoral-femoral CPB for 107 minutes then weaned from CPB on isoproterenol 3 µg·min ⁻¹ ; A-V paced for CHB IABPA SURVIVED
Case 6 55 yr F	800 mg/day 7 days/week for 3 months Ventricular tachycardia Last dose 12 hr pre-op	Left ventricular aneurysm Mitral regurgitation CAD EKG = sinus rhythm, LAHB	Fentanyl 4 µg·kg ⁻¹ Pantopon 0.7 mg·kg ⁻¹ Diazepam 0.3 mg·kg ⁻¹	Left ventricular aneurysmectomy. Phenylephrine 400 µg for intraoperative hypotension. Post-op: dopamine 12–15 µg·kg ⁻¹ ·min ⁻¹ ; Persistent nodal rhythm IABPA SURVIVED

TABLE 1 (Continued)

	Anaesthetic dosage, duration, indication	Preoperative cardiac status	Anaesthetic technique (total doses)	Operation, complications, postoperative status, outcome
Case 7 48 yr F	800 mg/day 7 days/week for 2 weeks Atrial fibrillation Last dose 12 hr pre-op	Mitral regurgitation Tricuspid regurgitation Aortic stenosis/regurgitation EKG = atrial fibrillation	Fentanyl 73 $\mu\text{g}\cdot\text{kg}^{-1}$ Diazepam 0.35 $\text{mg}\cdot\text{kg}^{-1}$ Isoflurane 0–0.5%	Mitral and aortic valve replacements, tricuspid annuloplasty. Post CPB vasodilatation and heat loss to 31.8°C causing cardiac arrest. Re-warmed on CPB. Required dopamine, epinephrine and sodium nitroprusside to be weaned from CPB. A–V paced for CHB IABPA DECEASED
Case 8 54 yr M	400 mg/day 7 days/week for 26 months Ventricular tachycardia Last dose 24 hr pre-op	Mitral regurgitation Aortic stenosis/regurgitation EKG = sinus rhythm, LAHB	Fentanyl 45 $\mu\text{g}\cdot\text{kg}^{-1}$ Diazepam 0.14 $\text{mg}\cdot\text{kg}^{-1}$	Mitral and aortic valve replacements. Intra-op atropine resistant nodal bradycardia. Post-op: CO = 6.7, SVR = 600 on dopamine 4–5 $\mu\text{g}\cdot\text{kg}^{-1}\text{min}^{-1}$ SURVIVED
Case 9 55 yr M	600 mg/day 7 days/week for 2 months Ventricular tachycardia Last dose 4 days pre-op	Grade IV LV Left ventricular aneurysm CAD EKG = sinus rhythm	Fentanyl 82 $\mu\text{g}\cdot\text{kg}^{-1}$ Diazepam 0.44 $\text{mg}\cdot\text{kg}^{-1}$	CABG $\times$ 4 vessels, endocardial mapping and left ventricular aneurysmectomy. Intra-op phenylephrine for hypotension. A–V paced for CHB. SURVIVED
Case 10 60 yr F	400 mg/day 5 days/week for 4 months Atrial fibrillation Last dose 12 hr pre-op	EKG = sinus rhythm, LAHB	Fentanyl 91 $\mu\text{g}\cdot\text{kg}^{-1}$ Diazepam 0.09 $\text{mg}\cdot\text{kg}^{-1}$ Morphine 0.2 $\text{mg}\cdot\text{kg}^{-1}$ Isoflurane 0–1.0%	Aorto-bifemoral graft. Post-op: atropine resistant nodal bradycardia, requiring dopamine and isoproterenol infusions for 48 hrs, then spontaneous reversion to sinus rhythm. SURVIVED
Case 11 66 yr M	600 mg/day 5 days/week for 5 months Ventricular premature beats Last dose 24 hr pre-op for (a) and (b)	Grade I LV EKG = sinus rhythm, LAHB	(a) Fentanyl 1.2 $\mu\text{g}\cdot\text{kg}^{-1}$ Thiopentone 5 $\text{mg}\cdot\text{kg}^{-1}$ Isoflurane 0.25–0.5% N ₂ O 50% (b) Fentanyl 1.5 $\mu\text{g}\cdot\text{kg}^{-1}$ Diazepam 0.06 $\text{mg}\cdot\text{kg}^{-1}$ Isoflurane 0.25–0.5% N ₂ O 50%	(a) Flexible bronchoscopy During (a) and (b) recurrent hypotension with nodal rhythm, normal response to 50–100 μg intravenous boluses of phenylephrine. SURVIVED (b) Pulmonary lobectomy

TABLE I (Continued)

<i>Anaesthetic dosage, duration, indication</i>	<i>Preoperative cardiac status</i>	<i>Anaesthetic technique (total doses)</i>	<i>Operation, complications, postoperative status, outcome</i>
<i>Case 12</i> 60 yr M 300 mg/day 7 days/week for 3 months Ventricular premature beats Last dose 24 hr pre-op	Grade III-IV LV Mitral stenosis/regurgitation CAD EKG = atrial fibrillation	Fentanyl 68 $\mu\text{g}\cdot\text{kg}^{-1}$ Diazepam 0.1 $\text{mg}\cdot\text{kg}^{-1}$ Isoflurane 0-0.5%	Mitral valve replacement. Intra-op: atropine-resistant sinus bradycardia. Required dopamine 15 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to wean from CPB. SURVIVED
<i>Case 13</i> 74 yr M 400 mg/day 7 days/week for 2 months Ventricular tachycardia Last dose 24 h pre-op	Grade IV LV Left ventricular aneurysm CAD EKG = sinus rhythm	Fentanyl 68 $\mu\text{g}\cdot\text{kg}^{-1}$ Halothane 0-0.25%	Trans-urethral resection of prostate. Intra-op: scattered nodal premature beats. SURVIVED
<i>Case 14</i> 54 yr M 400 mg/day 7 days/week for 3 months Ventricular tachycardia Last dose 12 hr pre-op	Left ventricular aneurysm CAD EKG = sinus rhythm	Fentanyl 81 $\mu\text{g}\cdot\text{kg}^{-1}$ Diazepam 0.6 $\text{mg}\cdot\text{kg}^{-1}$	CABG $\times$ 3 vessels, endocardial mapping and left ventricular aneurysmectomy. Post-op dopamine 2-3 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for oliguria. SURVIVED
<i>Case 15</i> 70 yr M 800 mg/day 7 days/week for 4 months Ventricular tachycardia Last dose 5 days pre-op	Grade IV LV Previous CABG Permanent pacemaker for sick sinus syndrome EKG = A-V pacemaker	Fentanyl 60 $\mu\text{g}\cdot\text{kg}^{-1}$	Abdominal aortic aneurysmectomy (infra-renal) and cholecystectomy. No complications. SURVIVED
<i>Case 16</i> 43 yr F 400 mg/day 5 days/week for 1 month Last dose 12 hr pre-op	Grade II LV Mitral regurgitation CAD EKG = sinus rhythm	Fentanyl 6 $\mu\text{g}\cdot\text{kg}^{-1}$ Morphine 1.3 $\text{mg}\cdot\text{kg}^{-1}$ Diazepam 0.3 $\text{mg}\cdot\text{kg}^{-1}$ Enflurane 0-0.5%	Left ventricular aneurysmectomy. No complications. SURVIVED

ABBREVIATIONS.

CAD = coronary artery disease, LBBB = left bundle branch block, LAHB = left anterior hemi-block, CO = cardiac output in litres/minute, SVR = systemic vascular resistance in $\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$, IABPA = intra-aortic balloon pump augmentation, CABG = coronary artery by-pass graft, CHB = complete heart block.
See text for left ventricular grading classification.

60 per cent, a Grade II LV between 40 and 60 per cent, a Grade III LV between 20 and 40 per cent and a Grade IV LV less than 20 per cent.

Quoted cardiac outputs are the average of at least three measurements by ice water thermodilution technique via an indwelling Swan-Ganz catheter.*

Serum amiodarone levels were assayed by reverse phase high performance liquid chromatography (Appendix I).

To establish a control group, we reviewed the charts of 30 randomly selected patients who underwent a CABG of three or more vessels in 1983 whose preoperative LV function was assessed as Grade III or IV.

Student's paired *t* testing was used to define statistical significance of changes in serum amiodarone levels, and Chi-squared testing was used to define statistical significance of complications (low SVR/high cardiac output state, necessity for intra-aortic balloon pump augmentation (IABPA), and bradyarrhythmias). We accepted a $p < 0.05$ as indicating statistical significance.

Results

Seventeen anaesthetics were administered to the 16 patients taking amiodarone. The operations ranged from bronchoscopy to complicated cardiac surgery. Complications developed in disproportionate frequency to what we noted in the patients not on amiodarone therapy and who had poor left ventricular function preoperatively (Table II).

The amiodarone group consisted of five female and 11 male patients, aged 43 to 74 years. The control group consisted of six female and 24 male patients, aged 43 to 71 years. A state of normal to high cardiac output (CO) and low systemic vascular resistance (SVR) despite alpha adrenergic therapy similar to that described previously¹ developed in 13 per cent (2/16) of amiodarone patients compared with 0/30 controls ($p < 0.05$). Fifty per cent (6/12) of amiodarone patients undergoing cardiac surgery required IABPA to be weaned from CPB compared with seven per cent (2/30) of controls ($p < 0.05$). The indication for IABPA was failure to wean from CPB despite an adequate trial of intra-vascular volume expansion, inotropic support and afterload

TABLE II Incidence of complications

Complication	Incidence	
	Amiodarone patients	Control patients
Low SVR	2/16*	0/30
High cardiac output		
Intra-aortic balloon pump augmentation	6/12*	2/30
Slow nodal rhythm, complete heart block, or pacemaker dependency	10/15*	5/30
Atropine resistant sinus bradycardia	1/15	0/30

* $p < 0.05$.

reduction, as judged by the anaesthetist administering the anaesthetic.

A slow nodal rhythm, complete heart block (CHB), or a pacemaker dependent state developed intra-operatively or in the early postoperative period in 66 per cent (10/15) of amiodarone patients, compared with 17 per cent (5/30) of controls ($p < 0.05$). One amiodarone patient had a permanent pacemaker implanted preoperatively for the sick sinus syndrome. Only one of our amiodarone patients developed atropine resistant sinus bradycardia, as described in the rabbit, guinea pig and dog models,⁴ compared with none of the controls ($p > 0.05$).

Mortality was 19 per cent (3/16) for the amiodarone patients (all in the open-heart surgery patients) compared with zero in the control group ($p < 0.05$).

Amiodarone serum levels were available for eight patients (Table III). Student's paired *t* testing failed to reveal any significant differences between the pre-induction and the post-induction serum amiodarone levels ($p > 0.05$), nor between the pre-induction and postoperative serum levels ($p > 0.05$), nor between the level prior to termination of CPB and the level post-termination of CPB ($p > 0.05$). However, there was a significant decrease in serum amiodarone levels within 15 minutes after the onset of CPB as compared to the pre-induction serum amiodarone levels ($p < 0.05$).

Case Histories

Case 1

A 62-year-old male with coronary artery disease (CAD) and medically refractory ventricular tachy-

*Edwards Laboratories, Cardiac Output Computer, #9520A.

TABLE III Serum amiodarone levels ($\text{mg}\cdot\text{L}^{-1}$)

Case	Prior to induction	Post-induction	Prior to CPB onset	Post CPB onset	Prior to CPB cessation	Post CPB cessation	Post-op
2	1.3	—	—	—	—	—	—
7	0.9	0.7	0.5	†	†	†	0.3
8	1.9	0.8	—	0.1	0.6	0.7	—
9	0.9	1.2	0.9	0.4	—	0.3	0.8
12	0.6	0.5	0.9	0.5	0.7	0.6	1.0
13	0.6	0.3	—	Not a CPB case		—	0.4
14	1.0	1.0	0.8	0.5	0.4	0.5	0.9
15	0.4	0.1	—	Not a CPB case		—	—

— = data not available.

† = serum level undetectable.

cardia presented for aorto-coronary bypass surgery. He had suffered an inferior wall myocardial infarction five years prior to admission, and since that time ventricular premature beats had been documented. He had a three-year history of short bursts of ventricular tachycardia which were well tolerated. Following failure of conventional medical therapy to control his ventricular ectopy, he was started on amiodarone 800 mg p.o. daily, five days per week, commencing one month prior to surgery.

Routine laboratory studies, including liver function tests and serum electrolytes were within normal limits. Cardiac catheterization revealed a Grade II LV and two vessel CAD. No aneurysm was seen. The preoperative electrocardiogram revealed normal sinus rhythm, first degree heart block and changes consistent with an old inferior wall myocardial infarction.

Preoperative medications were digoxin 0.125 mg p.o. daily, dipyridamole 50 mg p.o. three times daily, procainamide 375 mg three times daily, potassium chloride 16 mEq p.o. twice daily, triamterene 50 mg p.o. twice daily, hydrochlorothiazide 25 mg p.o. twice daily, isosorbide dinitrate 60 mg p.o. four times daily, amiodarone 800 mg p.o. daily five days per week, and oral warfarin with the dose adjusted according to prothrombin time. The patient's amiodarone was continued until 24 hours prior to surgery.

The patient was pre-medicated with diazepam 10 mg orally, morphine 15 mg intramuscularly and perphenazine 5 mg intramuscularly. Anaesthesia consisted of high dose fentanyl with diazepam supplementation. Pancuronium was administered for muscle paralysis and ventilation controlled ($\text{FiO}_2 = 1.0$). A total of $72 \mu\text{g}\cdot\text{kg}^{-1}$ fentanyl and

$0.12 \text{ mg}\cdot\text{kg}^{-1}$ diazepam was administered intravenously. Time on CPB was 90 minutes and aortic cross clamp time was 11 minutes. Two vessel CABG surgery was performed. The course prior to institution of CPB was complicated only by a brief episode of supraventricular tachycardia of 120 beats per minute associated with a drop in systolic blood pressure from 120 mmHg to 80 mmHg. This responded to the administration of edrophonium 10 mg intravenously.

The patient required atrio-ventricular (A-V) sequential pacing for complete heart block, plus epinephrine and dopamine infusions to allow weaning from CPB. For the first four postoperative days, despite both alpha and beta agonist therapy, there was a persistently low SVR. At one time, while receiving dopamine $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and levartelenol $2 \mu\text{g}\cdot\text{min}^{-1}$ infusions, the patient had a CO of $6.1 \text{ L}\cdot\text{min}^{-1}$ and an SVR of $681 \text{ dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$. This state slowly resolved over the ensuing 48 hours, and the patient was extubated on the fifth postoperative day and weaned from all pharmacologic support by the seventh postoperative day. There was no evidence of a perioperative myocardial infarction as judged by serial electrocardiograms. The patient was discharged home on the nineteenth postoperative day.

Case 2

A 59-year-old male with no known history of rheumatic fever presented for mitral and tricuspid valve replacements. In January 1972 he had undergone a mitral valve replacement for mixed mitral stenosis and mitral regurgitation. Pathologically the valve was myxomatous and prolapsed. In 1979 he suffered two episodes of syncope and was found to

have complex ventricular premature beats and ventricular tachycardia. After failure of conventional therapy he was started on amiodarone 200 mg p.o. twice daily, five days per week.

In November 1982 the patient was admitted for mitral and tricuspid valve replacements due to progressive dyspnoea. Routine laboratory studies, including liver function tests and serum electrolytes were within normal limits. The preoperative creatinine clearance was $22 \text{ ml} \cdot \text{min}^{-1}$, radio-immune T_3 uptake was 37 per cent, thyroxine level $120 \text{ nmol} \cdot \text{L}^{-1}$ and serum amiodarone level $1.3 \text{ mg} \cdot \text{L}^{-1}$. Preoperatively he had an ejection fraction of 68 per cent (gated nuclear angiogram). Cardiac catheterization showed a Grade II LV, biatrial enlargement, normal coronary arteries with a small arterial-venous fistula from the acute marginal artery to the right ventricle. A moderate mitral peri-prosthetic leak and free tricuspid regurgitation were demonstrated. The preoperative electrocardiogram revealed atrial fibrillation, with a ventricular rate of 60 beats per minute, and was otherwise normal. Chest radiography showed biatrial enlargement and normal pulmonary vasculature.

Preoperative medications included spironolactone 25 mg p.o. three times daily, warfarin 2.5 mg p.o. daily, furosemide 80 mg p.o. three times daily, digoxin 0.125 mg p.o. daily, captopril 25 mg p.o. three times daily and 37.5 mg p.o. at bed-time, and amiodarone 200 mg p.o. twice daily, five days per week. The amiodarone was discontinued 48 hours preoperatively.

The patient was premedicated with morphine 8 mg and perphenazine 2.5 mg intramuscularly. Anaesthesia consisted of high dose fentanyl with diazepam supplementation. Pancuronium was administered for muscle paralysis and ventilation controlled ($\text{FiO}_2 = 1.0$). A total of $67 \mu\text{g} \cdot \text{kg}^{-1}$ fentanyl and $0.03 \text{ mg} \cdot \text{kg}^{-1}$ diazepam was administered intravenously. Prior to institution of CPB, two 100 μg boluses of intravenous phenylephrine were administered to treat a decrease in systolic pressure from 120 mmHg to 100 mmHg, associated with atrial cannulation, with an appropriate response. Time on CPB was 125 minutes and aortic cross clamp time was 75 minutes. Mitral and tricuspid valve replacements were performed.

The patient required 3 gm calcium chloride, dopamine $40 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and epinephrine $20 \mu\text{g} \cdot \text{min}^{-1}$ infusions, A-V sequential pacing and IABPA at one-to-one augmentation to allow

weaning from CPB. With one-to-one IABPA and infusions of dopamine $110 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and epinephrine $40 \mu\text{g} \cdot \text{min}^{-1}$, the patient had a CO of $4 \text{ L} \cdot \text{min}^{-1}$ and an SVR of $720 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$. The postoperative amiodarone level was $0.7 \text{ mg} \cdot \text{L}^{-1}$.

There was no change in CO nor SVR when the dopamine infusion was decreased to $45 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, when several 1 mg boluses of intravenous phenylephrine were administered nor when a 200 μg bolus of intravenous levarterenol was administered. The patient was awake, followed commands, anuric and had a metabolic acidosis. His skin and extremities were warm and pink. Blood pressure was 60/30 mmHg with one-to-one IABPA and infusions of dopamine $30 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, phenylephrine $30 \mu\text{g} \cdot \text{min}^{-1}$, levarterenol $20 \mu\text{g} \cdot \text{min}^{-1}$ and epinephrine $7 \mu\text{g} \cdot \text{min}^{-1}$. Sudden progressive hypotension developed and the patient expired on the first postoperative day.

Discussion

Amiodarone was first introduced in 1967 as an antianginal medication⁵ and then found to be a class III anti-arrhythmic.⁶ Although amiodarone has been shown to be effective for a variety of ventricular and supra-ventricular tachyarrhythmias,⁷⁻¹¹ its major role is in the treatment of refractory ventricular tachycardia and fibrillation.

Amiodarone is an iodinated benzofuran derivative (2 butyl, 3-(4 diethyl-aminoethoxy; 3-5 diiodo-benzoyl) benzofuran hydrochloride) structurally similar to triiodo-thyronine.^{12,13} In animals⁴ and in man¹⁴ it has been shown to cause lengthening of the action potential duration in atrial and ventricular muscle with a slightly depressing effect on the maximal rate of depolarization. Amiodarone increases the spontaneous sinus cycle length, the atrium-His-bundle interval, the intra-atrial conduction time, the A-V nodal refractory period, and the ventricular effective refractory period.¹⁵ As well, it increases the sinus node recovery time¹⁶ and the atrial action potential duration,¹⁷ which is manifested as sinus bradycardia with Q-T interval prolongation,¹⁴ suppressing both supraventricular and ventricular tachyarrhythmias.

Amiodarone acts as an effective anti-anginal medication by increasing coronary blood flow^{13,18} and reducing cardiac work, myocardial oxygen consumption, heart rate¹³ and coronary and systemic vascular resistances.^{13,18}

Although early reports state that amiodarone

does not have significant negative inotropic effects in the normal or failing myocardium,¹⁹ and an increase in cardiac index has been noted,^{18,20,21} a recent canine study suggests that amiodarone is a primary myocardial depressant.² Amiodarone has anti-adrenergic effects,¹³ felt to be a non-competitive blockade of both alpha and beta adrenergic receptors.^{20,21} The elimination half-life is 30 days, and the pharmacologic effects last more than 45 days after discontinuation of therapy.¹²

In the non-anaesthetized patient the adrenergic blockade of amiodarone is of minimal importance, being manifested mainly as an atropine resistant sinus bradycardia⁴ or as hypotension due to vasodilation. The hypotension is dose-related and only of significance with intravenous administration of the drug.^{18,22} From our experience it is clear that following the administration of a general anaesthetic these adrenergic blocking effects may become unmasked, sometimes leading to grave consequences.

The complications we observed were generally of three types: (i) sinus node slowing or cardiac conduction defects leading to CHB, often with a nodal escape rhythm whose rate would not increase with the administration of atropine, or a pacemaker dependent state, (ii) low cardiac output requiring IABPA, or (iii) a state of partial to complete alpha adrenergic blockade causing a low SVR, usually with a normal or increased CO, while receiving moderate to very high doses of alpha adrenergic agonists.

We chose as a control group patients with poor LV function (Grade III or IV) who underwent three or more vessel CABG, since these patients tend to have a more prolonged and complicated postoperative course than patients undergoing a similar operation who have better preoperative LV function. The patients taking amiodarone preoperatively did significantly worse ($p < 0.05$) than the control group with regards to incidence of low SVR/high CO state, need for IABPA to wean from CPB, postoperative bradyarrhythmias and mortality. We were unable to demonstrate a significant difference in incidence of developing an atropine resistant sinus bradycardia between the amiodarone group and the control group, possibly due to the infrequency of this complication and the small patient groups.

Two cases of an amiodarone-anaesthesia interaction have been previously reported,^{1,2} but a recent

abstract suggests that there is no increased risk of decompensation with anaesthesia in the presence of amiodarone therapy.³ Our observations clearly dispute this. Of the reported cases, one case required massive doses of alpha and beta agonists to obtain a modest response.¹ Similarly, our Case 2 showed severe non-competitive alpha blockade, with a normal CO and a low SVR which remained unaltered despite potent alpha agonist therapy. In spite of the large doses of vasoconstrictors, the patient had warm skin and extremities and was awake and following commands, even with a blood pressure of 60/30 mmHg. Clearly not all patients require such massive doses of adrenergic agonists. As demonstrated by Case 1, a partial alpha agonist resistant state may also exist, whereby a subnormal response to agonist therapy is present.

Complications occurred over a wide range of pre-anaesthetic dosage, duration of therapy and serum amiodarone levels. Others have also found poor correlation between amiodarone levels and clinical effect.²³ We could not demonstrate any significant change in serum level with the induction of anaesthesia, however, there was a significant drop in serum amiodarone level with the institution of CPB, which we attribute to dilution by the priming solution. Postoperatively the serum level rose back towards the pre-induction value, which is in keeping with the normal diuresis seen following CPB.

The development of nodal bradycardia and/or CHB in our patients who underwent non-cardiac surgery, such as pulmonary lobectomy and abdominal aortic aneurysmectomy points to an interaction between the anaesthetic agents used and amiodarone, rather than due to surgery involving the heart. Most patients tolerated non-cardiac surgery, with all of the deaths being in the sub-group who underwent CPB.

Why some patients manifest primarily an alpha agonist resistant state, whereas others manifest a beta agonist resistant state, or a mixed picture, remains a mystery. It is clear that when an anaesthetist encounters a patient taking amiodarone one should be prepared for either extreme. Invasive monitoring and an A-V sequential pacemaker should be considered preoperatively. We recommend that all patients undergoing open-heart surgery with CPB have temporary epicardial pacemaker wires inserted at the time of surgery for postoperative management. The anaesthetist should

be prepared to administer potent inotropes and alpha adrenergic agonists in concentrations far in excess of those ordinarily required. The choice of anaesthetic technique will be dictated by the response of CO and SVR measurements.

These patients can be extremely preload dependent for maintenance of an adequate CO to maintain a sufficient blood pressure in the face of a low SVR. While large amounts of fluid may be required to maintain the intravascular volume, pulmonary oedema is easily precipitated when the critical volume is exceeded. The Swan-Ganz catheter allows repeated measurements of left ventricular filling pressures and CO, as well as allowing calculation of the SVR.

In view of the long pharmacologic half-life of amiodarone, it is not surprising that cessation of drug therapy up to 60 hours preoperatively did not seem to protect from the risk of serious complications, and it is not practical to withhold the drug for a prolonged period of time if it is effective in controlling life-threatening dysrhythmias. Both amiodarone and its major metabolite desmethyl-amiodarone are measurable in plasma for at least nine months after cessation of amiodarone therapy.²⁴

We are unable to prove a definite cause and effect relationship between amiodarone therapy and the complications which we found; however, complications and mortality were significantly more frequent in patients taking amiodarone than in our control group of patients in whom one would expect a high incidence of complications and death.

Since amiodarone is a non-competitive alpha receptor antagonist^{20,21} there may be a role for non-alpha receptor mediated vasoconstrictive agents, such as angiotensin II, as therapy for the high CO, low SVR state seen in our patients; however, at the time of preparation of the manuscript this drug was not available for general use in Canada.

It is not our intention to dissuade cardiologists from prescribing amiodarone, as it may be a life-saving anti-arrhythmic agent, nor do we suggest that an anaesthetist refuse to anaesthetize a patient taking the drug; but we do wish to alert our colleagues to the possible complications and to help to clarify the dispute which seems to be developing in the literature as to the incidence, severity, and even as to existence of detrimental interactions between general anaesthesia and amiodarone therapy.

Appendix I

Serum amiodarone assays were performed by a method of high performance liquid chromatography developed at Toronto General Hospital. Blood samples were collected from the antecubital vein preoperatively and from the arterial line intraoperatively and postoperatively for measurement of amiodarone levels.

Each 0.5 ml serum sample was acidified with 1.0 ml acetate buffer ($0.2 \text{ mol} \cdot \text{L}^{-1}$, $\text{pH} = 3.8$) containing internal standard, benzoethiophene (Labaz, Brussels). Then the acidified serum sample was extracted with 5 ml hexane which was evaporated to dryness with the residual being dissolved in 100 μl methanol. 20 μl of the methanol sample were eluted with 80 methanol:10 water:10 dibutylamine ($0.1 \text{ mol} \cdot \text{L}^{-1}$) at $1.6 \text{ ml} \cdot \text{min}^{-1}$ through a high pressure liquid chromatograph with a u-bondpak C-18 column (Waters Scientific, Toronto, Ontario). Detection was at 254 nm. Amiodarone standards and controls were treated similarly to the serum samples.

For a pooled serum with a mean amiodarone level of $2.42 \text{ mg} \cdot \text{L}^{-1}$, the coefficient of variation ranged from 3.3 to 8.8 per cent over the study period.

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Résumé

Deux rapports récents supportent alors qu'un autre refute l'existence d'interactions dangereuses entre le nouvel antiarrhythmique benzofuran (amiodarone) et l'anesthésie générale.

On a revu notre expérience avec dix sept anesthésies administrées à 16 patients recevant l'amiodarone. L'état hémodynamique et le taux d'amiodarone sérique ont été évalué lorsque disponible. Une circulation extracorporelle a été utilisée chez douze patients, trois de ceux-là sont morts. Aucun décès n'est survenu chez les patients n'ayant pas subi de circulation extracorporelle.

Les interactions médicamenteuses se sont manifestées sous trois formes: 1) rythme nodal et/ou bloc AV complet chez dix des quinze patients (un patient avait déjà dans la période pré-opératoire un pacemaker installé pour un syndrome d'une maladie du sinus); 2) un débit cardiaque bas nécessitant un ballon intra-aortique chez six des douze patients qui ont subi une circulation extra-corporelle; ou, 3) un état de blocage adrénergique alpha démontré par une résistance vasculaire systémique diminuée malgré l'administration de médicament alpha agoniste chez deux des seize patients.

On conclut que des interactions dangereuses et parfois fatales peuvent survenir chez des patients recevant l'amiodarone et devant subir sous anesthésie générale une circulation extracorporelle. L'anesthésie pour chirurgie non cardiaque peut être associée avec des bradyarrhythmies hémodynamiquement significative. On recommande une surveillance hémodynamique agressive et invasive incluant l'insertion d'un cathéter dans l'artère pulmonaire et la considération d'un pacemaker atrio-ventriculaire chez les patients à risque.