Impaired Myocardial Conduction in Patients Receiving Diltiazem Therapy during Enflurane Anesthesia


Drug interactions continue to be a potential cause of anesthetic-related morbidity and mortality, particularly when they involve the cardiovascular system. The potential for adverse effects on myocardial conduction in patients who are anesthetized with inhaled anesthetics while taking calcium channel blockers has been addressed previously.1 In animals, both groups of drugs depress SA node function2,3 and prolong atrioventricular conduction.2,4 There have been no clinical reports, however, of adverse effects on myocardial conduction in patients taking calcium channel blockers while undergoing anesthesia with inhaled anesthetics. This report describes two cases in which atrioventricular conduction and sinus node automaticity were altered in patients receiving diltiazem while undergoing enflurane anesthesia. The first patient demonstrated impaired atrioventricular and sinus node function prior to anesthesia. Enflurane further impaired atrioventricular nodal conduction, and this effect was readily reversible both by discontinuing the anesthetic and by initiating surgical stimulation. The second patient demonstrated severe sinus bradycardia progressing to asystole following administration of enflurane.

REPORT OF CASE 1

A 69-yr-old man with a history of angina and shortness of breath on exertion was scheduled for mitral valve replacement and aorta-coronary vein bypass grafting. He had angiographic evidence of stenosis of the left anterior descending and right coronary arteries, and moderate mitral regurgitation. His ejection fraction was 55%, and the ventricular wall motion was normal. Preoperative medications included diltiazem 120 mg t.i.d., atenolol 50 mg o.d., and hydrochlorothiazide 50 mg q.d. The admission electrocardiogram (ECG) revealed a sinus bradycardia of 47 bpm, PR interval of 0.24 s, and QRS of 0.07-s duration. The usual morning dose of diltiazem and atenolol were given to the patient, who was then given lorazepam 2 mg and meperidine 75 mg im 1 h preoperatively. During preparation for anesthesia and surgery, ECG leads were applied, two peripheral intravenous lines were inserted, and the radial artery was cannulated. Arterial blood pressure (BP) was 120/70 mmHg and the heart rate (HR) was 35 bpm. The ECG showed sinus bradycardia. A pacing thermoludition balloon-tipped pulmonary artery catheter was inserted via the right internal jugular vein, and the pulmonary capillary wedge pressure (PCWP) was 20 mmHg. Attrial and ventricular pacing was achieved with a diastolic threshold between 5–10 mamps. The pacing rate was increased by 5 bpm every 10 beats until Wenckebach periodicity occurred (i.e., the heart rate at which heart block of the Mobitz type I, first occurred) (fig. 1). This happened at 90 bpm (BP during this maneuver was 140/70 mmHg). Atrial pacing was then set at 50 bpm and the BP stabilized at 120/60 mmHg. Anesthesia was induced with fentanyl 25 μg/kg iv, lorazepam 2 mg iv, and neuromuscular blockade was achieved with pancuronium 0.15 mg/kg iv. Three minutes later, the...
trachea was intubated uneventfully. Five minutes later, Wenckebach periodicity was again elicited and occurred at 90 bpm. At this time, the $\text{PaCO}_2$ was 38 mmHg and the serum potassium 3.6 mEq/L. A heart rate of 50 bpm was maintained, and enflurane, 1% inspired concentration, was given for 10 min. The Wenckebach interval was determined during enflurane anesthesia and occurred at a heart rate of 55 bpm. The patient was again paced at 50 bpm and enflurane was discontinued. Ten minutes following discontinuation of enflurane, Wenckebach periodicity occurred at 90 bpm.

Enflurane, 1%, was again administered, and Wenckebach periodicity occurred at 60 bpm. Two minutes after skin incision, with an inspired concentration of enflurane 0.5%, Wenckebach periodicity was elicited at 90 bpm. Throughout the anesthetic, systolic blood pressure remained between 105–120 mmHg, the pulmonary artery diastolic pressure 9–12 mmHg, and the cardiac output 5.0–5.7 L/min.

On termination of cardiopulmonary bypass, atrio-ventricular sequential pacing was utilized and the surgical procedure completed uneventfully. The patient had an uncomplicated postoperative course. Diltiazem was replaced by nifedipine postoperatively, and the patient was discharged from the hospital with a normal sinus rhythm and a PR interval of 0.28 s.

**REPORT OF CASE 2**

A 72-yr-old woman presented with primary hyperparathyroidism refractory to medical treatment and was scheduled for parathyroidectomy. Serum calcium was 12.3 mg/dL. Three weeks prior to this admission, during a routine preoperative investigation in preparation for coronary transplantation, serum calcium was 13.9 mg/dL, and the diagnosis of hyperparathyroidism was made. Past medical history revealed myocardial infarction 4 months prior to this admission, hypertension for 10 yr, and diabetes mellitus type II for 10 yr. Medications at the time of admission included diltiazem 90 mg q.i.d., isosorbide dinitrate 30 mg q.i.d., and lente insulin 10 units q.i.d. Preoperative ECG showed complete left bundle branch block (LBBB), with accompanying ST-segment and T wave changes, heart rate 65 bpm sinus rhythm, PR interval was 0.18 s, and QRS interval was 0.12 s. Graded exercise test showed poor exercise tolerance, no chest pain, additional 1 mm ST segment elevation in leads V₁ and V₂, and 1 mm ST depression with T wave inversion in V₃₅₆.

No premedication was ordered, but diltiazem, isosorbide dinitrate, and insulin were given before anesthesia and surgery. Because of the presence of LBBB and the history of a recent myocardial infarction, a pacing balloon-tipped thermodilution catheter was inserted prior to surgery. Arterial blood pressure before induction was 150/80 mmHg and HR 80 bpm sinus rhythm. Anesthesia was induced with thiopental 200 mg iv, neuromuscular blockade achieved with vecuronium 0.08 mg/kg iv, and the trachea was intubated following enflurane administration. Anesthesia was then maintained with enflurane 1.5%. The heart rate decreased to 25 bpm, and atrial pacing was commenced at a rate of 60 bpm.

Enflurane was continued at 1% inspired concentration. Following skin incision, the pacemaker was discontinued. The patient was asystolic and pacing was reinstituted. Several unsuccessful attempts were made to discontinue pacing, with asystole occurring each time.

Calcium chloride, 10 mg/kg, was given in divided doses. Despite this, this patient remained asystolic when pacing was discontinued. The pulmonary capillary wedge pressure was maintained between 9–14 mmHg, and the systolic blood pressure maintained between 110–130 mmHg throughout the case. Following surgery, the heart was paced at a rate of 60 bpm. Thirty minutes following discontinuation of anesthesia, the patient returned to normal sinus rhythm and pacing was not required. Postoperative recovery was uneventful, and the patient was discharged 3 days following surgery.

**DISCUSSION**

These cases demonstrate an additive depressive effect on atrioventricular nodal conduction and sinus node function when enflurane is administered to patients receiving diltiazem therapy.

Diltiazem is a calcium channel blocker, and, as such, it inhibits calcium-dependent membrane depolarization. In the sinoatrial and atrioventricular nodes, depolarization is primarily due to a calcium-dependent slow inward current; and, thus, diltiazem can inhibit the sinus pacemaker and AV conduction. Diltiazem in humans prolongs the AH (atrial-His) interval by up to 25%, slows AV node conduction, and increases Wenckebach cycle length. Beta-adrenergic blockers in general and atenolol specifically prolong AV conduction, probably by inhibiting the enhancement of AV conduction caused by catecholamines. Enflurane also alters the normal calcium flux in myocaridial cells, as shown by depression of the slow action potentials in myocardial conducting tissue. In canine models, enflurane prolongs AV conduction time.

In the first patient, a prolonged P-R interval and the appearance of Wenckebach periodicity at a normal heart rate suggest impaired atrioventricular conduction, possibly related to preoperative medication with diltiazem and atenolol. With the addition of enflurane, the Wenckebach phenomenon occurred at even lower heart rates, suggesting further impairment of atrioventricular conduction.

Wenckebach periodicity does not normally occur at heart rates below 130 bpm, but is affected by vagal and sympathetic tone. The fact that the Wenckebach periodicity occurred at higher heart rates after incision is probably due to sympathetic stimulation, which facilitates conduction through the AV node. This also suggests that the beta-adrenergic blockade produced by atenolol may have been incomplete.

An additive depressive effect on AV nodal conduction of a combination of diltiazem and enflurane, probably mediated by their effect on slow calcium channels in the presence of beta-adrenergic blockade, seems the most likely cause for the changes observed.

Sinus node function during surgery could not be as-
sessed because spontaneous heart rate was not compatible with hemodynamic stability.

The second case illustrates the additive depressive effects of diltiazem and enflurane on sinus node function; again, probably, mediated via effects on the slow calcium channels. In experimental studies, diltiazem slows the rate of spontaneous depolarization of the SA node, and, with increasing dosage, sinus arrest can occur. In clinical studies, such severe degree of SA node depression is not seen, but a decrease in heart rate is common.

Enflurane causes a direct slowing in the spontaneous rate of discharge of the SA node which partly involves the slow calcium channels, but is not solely due to this mechanism, since its effects are only incompletely reversed by calcium.

The additive effect mediated via slow calcium channels would be a reasonable explanation for the effects seen. In this case, the additive effect was not counteracted by the stimulation of surgery, and sinus node function did not occur until after the enflurane was discontinued at the end of surgery. The fact that sinus arrest occurred despite a high serum calcium concentration following a bolus of calcium chloride is in agreement with the experimental data that the depressant effect seen with enflurane is not competitive, and that calcium does not completely reverse the block.

In summary, these two cases suggest that enflurane may precipitate life-threatening dysrhythmias in patients taking diltiazem, due to an additive depressive effect on myocardial conduction, particularly involving the SA node and AV conduction systems. Whether similar clinical problems exist with the other inhaled anesthetics or other calcium channel blockers remains to be documented.

REFERENCES


