Clinical Reports

Ventricular tachycardia precipitated by sodium iothalamate (Conray 420) injection during prenylamine treatment: a predictable adverse drug interaction

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Summary: A case of ventricular tachycardia occurring after intravenous injection of sodium iothalamate (Conray 420) into a patient taking prenylamine is described. Both of these drugs may cause prolongation of the corrected QT interval and the mechanisms of this potentially fatal drug interaction are discussed.

Introduction

Prenylamine is an antianginal drug which depletes catecholamine stores in adrenergic nerve endings. It frequently prolongs the corrected QT interval (QTc; Oakley et al., 1980), and this is sometimes extreme. Extreme prolongation of the QTc predisposes to serious ventricular arrhythmias and there have been several reports of ventricular tachycardia associated with prenylamine treatment (Bens et al., 1973; Kriker & Curry, 1976; Puritz et al., 1977; Riccioni et al., 1980; Freestone et al., 1981; Meanock & Noble, 1981; Grenadier et al., 1982; Tamari et al., 1982). This tachycardia often has the peculiar configuration termed torsade de pointes. To avoid this the manufacturer's data sheet warns that other drugs which also prolong the QTc, for example quinidine or procainamide, should not be prescribed simultaneously and that hypokalaemia must be avoided as this also tends to prolong the QTc interval.

Bolus injection of sodium iothalamate can cause substantial prolongation of the QTc interval and may constitute a considerable hazard to patients taking prenylamine, and possibly other drugs which also prolong the QTc interval. An episode of a life threatening ventricular tachycardia occurring immediately after injection of sodium iothalamate contrast medium in a patient taking prenylamine is reported.

Case report

A 72 year old man was admitted with a 6 d history of urinary retention and overflow incontinence. Angina had been diagnosed 9 y before and he had taken prenylamine (Synadrin), 60 mg thrice daily, and nifedipine (Adalat), 10 mg thrice daily, for 2 y. Before admission, attacks of angina had been mild and infrequent and there was no suggestion of any arrhythmia in his past history. The urinary retention was relieved by an indwelling catheter and an intravenous urogram (IVU) was arranged 4 d after admission. A few seconds after bolus intravenous injection of 80 ml of sodium iothalamate 70% w/v (Conray 420) the patient had a cardiorespiratory arrest. The cardiac rhythm could not be identified because of a faulty oscilloscope but a satisfactory circulatory state was restored immediately by a 100 Joule DC shock.

Ninety minutes later the patient had a further cardiorespiratory arrest. On this occasion the rhythm was identified as a ventricular tachycardia and was converted to sinus rhythm by a 100 Joule DC shock. Prenylamine was stopped and there were no further arrhythmias. Serial electrocardiograms and serum transaminases showed no evidence of a recent myocardial infarction and angina was well controlled by 100 mg/d of atenolol and 20 mg nifedipine three times per day.

Review of previous electrocardiograms showed that the QTc had been 0.41 s (normal 0.35–0.42 s) in 1974, before prenylamine was started. On the day before the
IVU the QTc was markedly prolonged to 0.59 s, and at this time the serum potassium was 3.5 mmol/l. After the first cardiorespiratory arrest (60 min after the injection of sodium iothalamate) the QTc was further prolonged to 0.65 s. After prenylamine was stopped the QTc shortened progressively to 0.57 s at 48 h, 0.44 s at 6 d and to a normal value of 0.42 s after 14 d. Before the cardiorespiratory arrest he had not been treated with any other drug known to prolong the QTc, or with diuretics.

Discussion

Prenylamine frequently causes slight prolongation of the QTc interval, for example, to a mean value of 0.44 s in one study (Oakley et al., 1980). However, prolongation may be extreme in individual patients and this may be associated with dangerous ventricular arrhythmias (Bens et al., 1973; Krikler & Curry, 1976; Puritz et al., 1977; Riccioni et al., 1980; Freestone et al., 1981; Meanock & Noble, 1981; Grenadier et al., 1982; Tamari et al., 1982). In this patient the markedly prolonged QTc on admission can be attributed to prenylamine because it was not present before the drug was started, it returned to normal after prenylamine was stopped, and the patient was not taking any other drug known to prolong the QTc. Neither hypokalaemia nor nifedipine can be held responsible as the QTc returned to normal despite an increase in the dose of this drug.

The incidence of death associated with IVU examinations has been estimated at 8.6 to 19.0 per million (Berg et al., 1973), but was 7/100,000 in one prospective study of 81,278 examinations (Shehadi, 1975). The causes of these deaths are uncertain and there was no record of electrocardiogram (ECG) monitoring. Various ECG abnormalities have been recorded during intravenous urography, including an increase in heart rate, ST segment depression, atrial and ventricular extrasystoles and QTc prolongation (Berg et al., 1973; Small & Glenn, 1968; Stadalnik et al., 1974; Stadalnik et al., 1977; Pfister & Hutter, 1980; Lawton et al., 1982).

The observation relevant to the present case was that bolus injection of sodium iothalamate prolonged the QTc by a mean of 0.07 s, with the prolongation exceeding 0.1 s in about one third of patients (Stadalnik et al., 1977). The authors believe that this patient was predisposed to ventricular tachycardia by the added effect of sodium iothalamate on the QTc, which was already markedly prolonged by prenylamine, and that the arrhythmia was precipitated by a ventricular extrasystole occurring during the prolonged QTc. The further lengthening of the QTc after the injection of sodium iothalamate, from 0.59 to 0.65 s, supports this interpretation.

Alternative explanations for the sequence of events observed have been considered. It is conceivable that the first cardiorespiratory arrest, which occurred immediately after injection of sodium iothalamate, was caused by profound hypotension rather than a cardiac arrhythmia. However, the prompt response to DC shock and the absence of other features of anaphylaxis argue against this. In any event the second episode, which was clearly caused by ventricular tachycardia, was not preceded by any haemodynamic disturbance. The possibility that the additional prolongation of the QTc interval could have been a consequence of the cardiorespiratory arrests or of defibrillation, and not injection of sodium iothalamate, was also considered. Electrocardiographic changes do occur after DC shock (Resnekov & McDonald, 1967) but QTc prolongation does not appear to have been described. These possibilities cannot be dismissed entirely, but the balance of evidence strongly favours an interaction between prenylamine and sodium iothalamate as the cause of the ventricular tachycardia.

Sodium iothalamate should be added to the list of drugs which may be hazardous to patients taking prenylamine. Other contrast media may also prolong the QTc and present a similar hazard (Stadalnik et al., 1977). The risk might be reduced by administering the contrast medium by infusion rather than as a bolus injection as the former has less effect on the QTc. Injection of contrast medium could, in theory, precipitate dangerous arrhythmias in patients taking other drugs which prolong the QTc. The authors are aware of only three reports of documented ventricular tachycardia occurring during intravenous urography (Stadalnik et al., 1974; Stadalnik et al., 1977). One of these patients was taking procainamide and had a prolonged QTc of 0.52 s and another was taking quinidine.

The authors feel that the safety of prenylamine for general use must be questioned. This is the second case of life threatening ventricular arrhythmias associated with prenylamine presenting to this unit within 5 y (Freestone et al., 1981). Prenylamine is not widely used and no more than two or three patients taking it are seen by this unit in any year. Considering this, and the other cases which have been reported it is suspected that the incidence of this serious adverse reaction may be unacceptably high. It is also of concern that this problem, which is well known to cardiologists, may not be recognized by the general physician who may attribute the development of arrhythmias and sudden death in patients with angina to the disease, and not to the treatment. The risks of prenylamine need to be quantified precisely in long term prospective studies. Until this is done the drug should be used only as a last resort in patients who cannot be managed with other antianginal drugs such as beta blockers, long acting
nitrates and calcium antagonists.

When prenylamine must be used it is mandatory to monitor the QTc with serial ECGs, to avoid hypokalaemia and to avoid any other drug which may also prolong the QTc. These precautions are stated clearly in the manufacturer’s data sheet but are not always heeded by prescribing doctors. Sodium iothalamate and other contrast media should be added to the list of drugs to be avoided in patients taking prenylamine.

References


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