Successful management of serious disopyramide poisoning

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Summary

A case of deliberate disopyramide overdosage is described. Circulatory collapse was treated by means of a large dose of isoprenaline, and charcoal haemoperfusion was used in an attempt to enhance the elimination of disopyramide. The suitability of this treatment regime is discussed in the light of findings from animal studies and the implications for the management of the disopyramide-poisoned patient are considered.

Introduction

The accidental or deliberate ingestion of significant overdose quantities of the antiarrhythmic drug disopyramide carries a poor prognosis. Three reports have documented such cases in all of which death ensued, either before admission to hospital or within 48 hr of admission (Hayler, Holt and Volans, 1978; Hutchison and Kilham, 1978; Powell, Smith and Carey, 1978). No reports can be traced of survival following overdose with this drug.

A case is now reported of serious disopyramide overdosage in which the patient was successfully managed using a treatment regime based on experimental findings from animal studies (Hayler *et al.*, 1979; O'Keeffe *et al.*, 1979).

Plasma disopyramide concentrations were measured using a specific gas-liquid chromatographic technique (Hayler and Flanagan, 1978).

Case history

A 21-year-old male was admitted to hospital one hour after ingesting 200 × 100-mg capsules of disopyramide (Rythmodan) which had been prescribed for his mother.

On arrival he was conscious, co-operative and orientated, but complained of dry mouth, blurred vision and paraesthesiae of the limbs. On examination he was peripherally well perfused, the pulse was irregular with a rate of 90 beats/min and BP was 90/50 mmHg. Heart sounds were normal, the chest was clear and bowel sounds were scanty. The ECG showed an irregular rhythm with variable impairment of left and right bundle branch conduction (Fig. 1).

Initial treatment consisted of gastric lavage which yielded a large quantity of fragmented capsules and the patient was transferred to the ICU.

One hour after admission he suddenly became

FIG. 1. 12-lead ECG on admission to hospital.

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confused and cyanosed, and his BP was unrecordable. The ECG monitor showed the same rhythm as on admission. A bolus of 2 mg isoprenaline was given by slow i.v. injection over 5 min, when the BP returned to 110/70 mmHg, without any change on the ECG. The patient was given oxygen and a CVP line was inserted, giving a reading of 3 cm water. Blood was taken for blood gas estimations and clinical chemistry investigations, which revealed the following, all in mmol/l:

Na⁺, 145; K⁺, 2.8; Cl⁻, 97; HCO₃⁻, 23; urea, 7.6; and the following: pH, 7.46; Pco₂, 2.0 kPa; Po₂, 18.8 kPa; base excess 8.9.

The plasma disopyramide concentration was 16.5 mg/l (effective range 2–4 mg/l (Mason, 1978).

Subsequently, blood samples were collected frequently for the monitoring of serum electrolytes and disopyramide concentrations.

Following the bolus dose of isoprenaline, an infusion of this drug at the rate of 40 µg/min was started, being gradually reduced to 13 µg/min over the first 30 min. At this time a supraventricular tachyarrhythmia developed (Fig. 2), which spontaneously reverted to sinus rhythm when the isoprenaline infusion was stopped. Thereafter, systolic BP was maintained in the range 70–100 mmHg by means of an isoprenaline infusion at the rate of 1–5 µg/min; the infusion was discontinued for periods of up to 20 min if a tachyarrhythmia of the type shown in Fig. 2 was noted.

Hypokalaemia was corrected by the infusion of 3 g KCl over 2 hr. Bladder catheterization revealed the patient to be anuric and, although 80 mg frusemide i.v. failed to produce a diuresis, 250 ml of 25% mannitol elicited a brisk urine flow of 600 ml/hr.

Five hours after admission haemoperfusion was started using a 2% acrylic hydrogel coated charcoal column (Haemocol—100, Smith & Nephew Research Ltd, U.K.) inserted into an A/V shunt in the left wrist. By that time, the BP was stable at 90/50 mmHg, without the use of isoprenaline, and a blood flow of 200 ml/min was maintained through the column. The ECG showed sinus rhythm with first degree heart block, together with left and right bundle conduction impairment, interspersed with atrial tachycardia showing a variable 1:1/2:1 conduction to the ventricles. Serum K⁺ was then 3.8 mmol/l.

During the following 2 hr there was a steady increase in BP to 120/80 mmHg and the ECG showed narrowing of the QRS complexes and a PR interval of 0.28 sec. The patient was alert but still complained of mild anticholinergic side effects. Bowel sounds were present at this time.

Haemoperfusion was continued in all for 10 hr.

FIG. 2. ECG rhythm strips. (a) Before bolus dose of isoprenaline. (b) During isoprenaline infusion. (c) Following termination of isoprenaline infusion.

After 7 hr an uncoated charcoal column was used (B-D Hemodetoxifier, Becton-Dickinson and Co., U.S.A.); blood flow through this column was maintained at 300 ml/min. Throughout the whole period of haemoperfusion, blood samples were drawn from both the column inlet and outlet lines for the measurement of disopyramide. The plasma concentrations are shown in Fig. 3, whilst the clearance data and amounts of drug removed by haemoperfusion are shown in Table 1.

Following this procedure, the patient remained in the ICU for a further 24 hr during which time the

TABLE 1. Clearance data and amounts of disopyramide removed by haemoperfusion

Cartridge type	'Haemocol 100'	'B-D Hemodetoxifier'
Perfusion time (hr)	7	3
Mean clearance (ml/min)	26.4	35.5
Mean inlet plasma concentration (mg/l)	9.6	4.4
Theoretical amount removed (mg)	106	28

FIG. 3. Plasma disopyramide concentrations. During the period of haemoperfusion, concentrations from both the column inlet (●) and outlet (○) lines are shown.

FIG. 4. 12-lead ECG 24 hr after admission to hospital.

CVP line and urethral catheter were removed. The shunts were clamped and then removed after 3 days. The ECG showed sinus rhythm (Fig. 4), and the patient was transferred to a general ward, where further recovery was uneventful. He was discharged 7 days after the overdose.

Discussion

Previous reports of disopyramide poisoning have noted an early loss of consciousness, cardiac or respiratory arrest and both tachy- and bradyarrhythmias (Hayler *et al.*, 1978; Hutchison and Kilham, 1978; Powell *et al.*, 1978). Despite intensive care and, in several cases, apparent response to resuscitation, in all instances the patient died.

The sequence of events following disopyramide overdosage has been elucidated by means of an animal model (O'Keeffe *et al.*, 1979). A consistent finding in dogs poisoned with the drug was circulatory collapse, resulting in a sudden drop in systolic BP and cardiac output, which occurred without obvious premonitory signs on the ECG. Respiratory and cardiac problems were secondary to this event. If therapy was instituted rapidly, the circulation could be restored by an inotropic drug, consistently good results being obtained with isoprenaline. In addition, experimental work has shown that the drug can be removed rapidly by charcoal haemoperfusion, up to 40% of a large overdose being removed within 3 hr (Hayler *et al.*, 1979).

Disopyramide has a mild anticholinergic action which can cause side effects such as dry mouth, blurred vision and urinary hesitancy. The patient in this case showed classic symptoms of disopyramide excess and shortly after the time of circulatory collapse the plasma disopyramide concentration was very high. The plasma concentrations were below those expected for the ingestion of 20 g disopyramide, (A. Hayler, unpublished observation) which the patient insisted he had taken, suggesting the effectiveness of the stomach wash-out. During the first 6 hr after admission to hospital, plasma concentrations fluctuated, consistent with prolonged absorption from a mass of capsules in the gut.

The key to the management of this patient was the prompt use of a large dose of isoprenaline, following the sudden loss of BP. Clinical problems subsequent to this were most probably due to high dose isoprenaline infusion and hypokalaemia.

The ECG on presentation showed an irregular rhythm with multiform aberrant complexes which, at first sight, may suggest multifocal ventricular ectopic activity. However, atrial activity is not clearly seen (the P wave becomes increasingly slurred and of low amplitude with toxic concentrations of disopyramide) and caution is necessary in inter-

preting this record, which may equally represent conducted rhythm with varying block in the His-Purkinje system.

Primary ventricular arrhythmia has been reported in association with disopyramide administration (Nicholson *et al.*, 1979; Meltzer *et al.*, 1978), but only in patients with pre-existing heart disease. In other cases, without underlying cardiac disease (Hayler *et al.*, 1978; Powell *et al.*, 1978), the suspicion exists that ventricular arrhythmias occurred secondary to circulatory collapse and were, essentially, agonal.

Where ventricular tachycardia does occur, the properties of disopyramide favour the atypical 'torsade de pointes' variety (Krikler and Curry, 1976). Under these circumstances it is advisable to maintain a normal serum potassium concentration, since hypokalaemia promotes this type of arrhythmia (Curry *et al.*, 1976). In addition, it has been emphasized previously (Hayler *et al.*, 1979) that the use of cardio-depressant antiarrhythmic drugs following disopyramide overdosage is likely to exacerbate the problem. Indeed, the authors are aware of a case of disopyramide poisoning, in which the drug was not initially implicated, in which a mistaken diagnosis of ventricular tachycardia resulted in the i.v. administration of disopyramide in an (unsuccessful) attempt at treatment!

In the present case, large doses of isoprenaline resulted in restoration of the circulation, reflecting results obtained in experimental disopyramide poisoning (O'Keeffe *et al.*, 1979). During isoprenaline infusion the ECG showed rapid conducted rhythm, up to 170 beats/min, probably representing either sinus or focal atrial tachycardia. Abrupt halving and doubling of the ventricular rate (Fig. 2) suggested intermittent 2 : 1 atrioventricular block.

As the plasma disopyramide concentrations fell, the ECG changes resolved. Atrial activity, initially with first degree atrioventricular block, became evident and the QRS complex became progressively narrower until, 36 hr after ingestion of disopyramide, the ECG was within normal limits.

Whilst symptoms and signs improved during the early period of haemoperfusion no specific benefit can be attributed to the technique in this case since it removed very little of the drug. The poor clearance of disopyramide in this case, using the Haemocol 100, was almost identical with the *in vitro* clearance determined subsequently (Hayler *et al.*, 1979), and it would appear that this column is unsuitable for the rapid elimination of disopyramide. The results using the B-D Hemodetoxifier were particularly disappointing since this column has given *in vitro* and, in dogs, *in vivo* clearances in excess of 90 ml/min for disopyramide (Hayler *et al.*, 1979). Since a good blood flow was maintained in the present case, it is

possible that the column used in this instance was defective in some respect.

The role of haemoperfusion in the treatment of disopyramide overdosage has yet to be established. The outcome in this case indicates that the prompt treatment of circulatory collapse was of prime importance, but active removal of the drug from the body might be of clinical value in a patient with a very high plasma disopyramide concentration and known cardiac disease.

As far as can be ascertained, this is the first report of an established case of serious disopyramide overdosage in which the patient has survived. Treatment was based on observations made in animal studies and the findings in this case suggest that the cardiovascular consequences of disopyramide poisoning are reversible by the timely use of an inotropic agent.

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