

Some cardiovascular problems with disopyramide

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Summary

Five patients with apparent adverse cardiovascular effects of disopyramide are reviewed. Attention is drawn to the following problems.

(1) A vagolytic effect may produce a sinus tachycardia with wide QRS complexes due to aberrant conduction or intraventricular block superficially resembling a ventricular tachycardia, or may allow increased transmission of an atrial tachycardia or atrial flutter to the ventricles by improving atrio-ventricular conduction.

(2) Although the vagolytic effect is helpful in increasing sinus rate in patients with sinus node disease, disopyramide may lead to bradycardia and asystolic cardiac arrest, and should not be used without a demand pacemaker.

(3) Dangerous ventricular arrhythmias may be provoked in susceptible subjects, as with quinidine.

(4) Rapid intravenous injection may produce transient toxic effects before the drug is distributed. The rate of injection as a loading dose for prophylaxis should be slower (2 mg/kg in 15 min) than for the urgent conversion of a resistant tachycardia (2 mg/kg in 5 min).

Although disopyramide seems less toxic than quinidine, caution is advised, as over-enthusiastic application of disopyramide, particularly with rapid intravenous injection, might tend to bring a useful new agent into disrepute.

Introduction

Although disopyramide has been used in France for many years (Desruelles *et al.*, 1967; Granier, 1968), the recent more widespread use of the drug has brought to prominence some apparent unwanted effects, and since it has been suggested that disopyramide is safe enough for use as a routine prophylactic in cardiac infarction (Kidner, 1977; Zainal *et al.*, 1977) it seems appropriate to assess the significance of some apparent adverse reactions. It is important that a promising new drug should not fall into the same position as quinidine where the use of cumulative dose schedules (Sokolow and Edgar, 1970) led to widespread disenchantment with the drug because of severe toxic effects. A sober

review assessed the mortality of simple quinidine conversion of atrial fibrillation as 3% (Thomson, 1956).

Four aspects of the cardiac effects of disopyramide noted by the authors recently seem worthy of comment: (1) adverse cardiovascular effects related to the additional vagolytic effect of disopyramide, similar to those seen with quinidine; (2) adverse effects in sinus node disease; (3) a capacity to provoke dangerous ventricular arrhythmias as is also seen with quinidine (Krikler and Curry, 1976); in addition, (4) the authors wish to stress the need for caution with intravenous injection to avoid side effects which may be related to immediate transient high plasma concentrations before distribution of the drug can occur.

Vagolytic effects

Case 1

Sinus tachycardia with bundle branch block in a female patient with hypertension, maturity-onset diabetes mellitus, and a recent anterior myocardial infarction.

This 72-year-old housewife, with acute anterior myocardial infarction, had a history of inferior infarction 5 years previously, and there was long-standing hypertension and maturity-onset diabetes mellitus. Her initial progress was stormy, with bradycardia requiring atropine therapy, and ventricular extrasystoles and ventricular tachycardia which were treated with lignocaine. On the day after admission, lignocaine no longer controlled the ventricular dysrhythmias, although doses sufficient to cause mild confusion were used. Disopyramide 2.5 mg/kg (= 180 mg) was therefore given by intravenous injection over 5 min. As the injection was nearing completion, the sinus rate increased from 80 to 120/min, with remarkable widening of the QRS complex. Maximum QRS duration was 0.16 sec. The combination of increased heart rate and QRS widening simulated a ventricular tachycardia, but a long ECG recording confirmed the gradual development of the bizarre appearance. The ECG returned to normal within 30 min of the end of the injection.

The patient noticed no ill effects from the disopyramide injection, and she later tolerated oral disopyramide.

Case 2

Restoration of 1 : 1 conduction of atrial tachycardia in acute inferior myocardial infarction.

This 56-year-old man with an acute inferior myocardial infarction had ventricular fibrillation and was resuscitated in the Accident and Emergency Department. On arrival in the Coronary Care Unit, he had atrial tachycardia at a rate of 150/min and a ventricular rate of 75/min due to 2 : 1 atrio-ventricular block. Repeated episodes of ventricular tachycardia interrupted the atrial tachycardia and did not respond to 100 mg i.v. of either lignocaine or phenytoin. Disopyramide 100 mg was given by i.v. injection over 5 min, and immediately after this the ventricular rate increased to 150/min owing to restoration of 1 : 1 conduction of the atrial tachycardia. Sinus rhythm was ultimately achieved after intravenous propranolol.

Sinus node disease

Case 3

Asystolic cardiac arrest in a patient with sick sinus syndrome and hypertension complicated by acute renal failure.

This 60-year-old man, a known hypertensive with a history of recurrent supraventricular tachycardia, was admitted to hospital with persistent atrial tachycardia which did not respond to intravenous propranolol 8 mg and disopyramide 100 mg. A single DC shock of 30 J restored sinus rhythm. The next day he became anuric, with consequent hyperkalaemia, hyponatraemia and hypocalcaemia; this was probably due to prolonged hypotension in the presence of renovascular disease. Twenty-four hour ECG tape monitoring showed periods of sinus arrest and bradycardia consistent with 'sick sinus syndrome'.

Although the renal failure improved, atrial tachycardia recurred 3 days after admission, and responded to i.v. disopyramide 100 mg. Disopyramide 100 mg 6 hourly orally was prescribed, but the tachycardia recurred in spite of this treatment and, during the subsequent 3 days, i.v. disopyramide 100 mg was given on at least 3 occasions; propranolol 40 mg thrice daily orally was also given.

Eight days after admission, sinus bradycardia 48/min and ventricular ectopics required treatment with i.v. atropine. Tachycardia recurred several hours later, and did not respond to 50 mg i.v. disopyramide. Eight hr after this dose, a further 100 mg dose of disopyramide was given. Thirty min after the injection, sinus bradycardia developed and

progressed to asystole requiring resuscitation. Temporary cardiac pacing was eventually needed; the patient later died from left ventricular failure and pulmonary embolism.

Ventricular arrhythmia

Case 4

Ventricular fibrillation in a patient with cardiomyopathy. This 39-year-old woman commenced disopyramide 100 mg thrice daily because of multiple, multifocal ventricular extrasystoles which were thought to be due to a cardiomyopathy of the congestive type. She was also receiving treatment with frusemide 80 mg daily and potassium supplements. Five months later she was admitted for investigation. Cardiac catheterization confirmed the diagnosis of congestive cardiomyopathy; 24-hr ECG tape monitoring still showed multiple ventricular extrasystoles and the dose of disopyramide was increased to 200 mg thrice daily. This produced no obvious benefit, but after 3 days the patient sustained cardiac arrest due to ventricular fibrillation. During the subsequent 12 hr, at least 30 electroversions (DC shocks) were performed to correct ventricular tachycardia or fibrillation. Drug therapy with intravenous disopyramide, propranolol and lignocaine was ineffective. Phenytoin 700 mg suppressed the dysrhythmia, but a slow ventricular rhythm took its place and temporary cardiac pacing was required. All anti-dysrhythmic drugs except propranolol were stopped, and the patient made a steady recovery. Ultimately propranolol was also discontinued because it was not preventing extrasystoles. At outpatient follow-up 6 weeks later the patient felt well but the extrasystoles persisted.

Rapid intravenous injection

Case 5

Transient right bundle branch block after i.v. disopyramide for atrial ectopic beats and atrial fibrillation in a man aged 55 years with transient impairment of renal function after coronary arterial vein grafting.

This patient had a triple coronary artery vein graft. His chest was reopened for control of a bleeding aortic puncture wound; recovery was very stormy, and a total of 70 units of blood was transfused. On the 4th day after operation the chest was opened again to remove packing material, and atrial fibrillation developed. This was treated successfully with electroversion but recurred on the 5th day after operation. Disopyramide 100 mg 8 hourly i.v. was prescribed. This treatment prevented the atrial fibrillation, but atrial ectopic beats persisted. During this stage of recovery the patient was jaundiced owing to multiple transfusions, and had some impairment of renal function (blood urea up to

44 mmol/l). He was being treated with frusemide, erythromycin, gentamicin, hydrallazine, i.v. feeding and vitamin supplements.

The ECG monitor showed obvious widening of the QRS complex with only a slight increase in heart rate (from 82 to 90/min) while the disopyramide injection was being given; similar changes in heart rate at other times did not affect the QRS width. The 100 mg injection was given over 15 min, and the QRS changes appeared a few minutes after the start of the injection. The ECG returned to normal shortly after the end of each injection, and remained normal until the next injection. Administration of disopyramide was changed to a much slower intravenous injection over one hr for each 100-mg dose, and the problem did not recur.

Discussion

The *anti-cholinergic actions* of disopyramide, although said to be less than those of quinidine (Danilo and Rosen, 1976) may produce minor inconveniences such as dry mouth, or more serious problems such as urinary retention (Donald, 1977; Large and Todd, 1977) or acute glaucoma (Trope and Hind, 1978). From the cardiovascular point of view the tendency to a sinus tachycardia from vagal blockade may help minimize vagal bradycardia in acute cardiac infarction and may also reduce the vagal depression of conduction at the atrio-ventricular (AV) node which is such a frequent reflex effect from acute inferior infarction; such an action may account for the relative rarity of heart block during disopyramide therapy of acute cardiac infarction (Zainal *et al.*, 1977) in spite of the well established adverse effect of disopyramide on His-Purkinje conduction (Ranney *et al.*, 1971). The suggestion that disopyramide does not cause AV block (Zainal *et al.*, 1977) is in this respect misleading (Ross, Vohra and Sloman, 1978). The wide QRS pattern noted in case 1 (above) in sinus tachycardia induced by vagal blockade may have been due to a rate-dependent bundle branch block (aberrant conduction) but may also have been accentuated by an adverse effect of disopyramide on His-Purkinje conduction after toxic doses of lignocaine. The improvement of atrioventricular node conduction by vagal blockade is generally beneficial but may produce an adverse effect as in case 2 by allowing 1 : 1 conduction of a fast atrial tachycardia, particularly if the atrial rate is slowed by the drug, a situation analogous to that generally recognized in quinidine treatment of atrial flutter. Preliminary AV nodal blockade with digitalis or a β -blocker might have prevented an improvement in AV conduction on disopyramide, but there is not at present adequate information about the response to combination of these drugs with disopyramide for firm recom-

mendations to be made, and it might be wiser to regard atrial flutter or atrial tachycardia with block as contra-indications to the use of disopyramide.

The vagolytic effect of disopyramide seems to have allowed its use on some patients with sinus node disease whose bradycardia had a strong autonomic component. However, this does not imply safety in all patients with sick sinus syndrome since adverse effects have been described (Reid and Williams, 1977) and it may suppress all effective pacemakers (Seipel and Breithardt, 1970), as was seen in case 3, although it is difficult to exclude a natural variation in the disease process. The combined oral and i.v. doses used may well have been excessive in the presence of impaired renal function. As with other anti-arrhythmic drugs extreme caution is advised in the use of disopyramide in treatment of sick sinus syndrome, and preliminary insertion of a demand pacemaker seems advisable if disopyramide is to be used to suppress tachycardia in this situation.

The tendency to serious ventricular arrhythmias associated with quinidine therapy, usually with prolongation of the QT interval leading to the 'torsade de pointes' form of ventricular tachycardia and eventually to ventricular fibrillation (Krikler and Curry, 1976) seems to be shown by disopyramide although its effect in prolonging QT interval is less than that of quinidine (Ranney *et al.*, 1971; Danilo and Rosen, 1976). Syncope with 'torsade de pointes' has been reported in another patient receiving disopyramide and may be analogous to case 4, although hypokalaemia was an added factor in this patient (Casedevant *et al.*, 1975). Case 4 had severe underlying heart disease, and in this situation with recurrent arrhythmia it is difficult to relate any particular incident to treatment. Ventricular arrhythmias were a feature of fatal deliberate disopyramide overdose (Hayler, Holt and Volans, 1978) and there is clearly a risk of such dangerous toxic effects; the ventricular tachycardia (Siklos, Chalmers and Evans, 1978) or increase in ventricular extra-systoles (Härkönen, 1978) described after disopyramide may have an analogous basis.

In case 5 the transient adverse effect seems to be related to rapid intravenous injection of disopyramide which would produce transient high plasma concentrations. Impairment of His-Purkinje conduction producing bundle branch block is a well recognized effect of the drug and it is reassuring that the changes reversed quickly, presumably as the plasma concentration decreased with distribution of the drug to the tissues. The widening of the QRS complex associated with tachycardia and the added effect of lignocaine in case 1 may have similar basis. In both these patients and in the other cases the adverse effects followed soon after the i.v. administration of disopyramide, raising the suspicion that

the recommended rate of injection of 100 mg in 5 min may be too fast and run the risk of transient unduly high plasma concentrations. Other patients with coronary artery disease developing widened QRS complexes and complete heart block after rapid intravenous injection of disopyramide have been described (Camm, 1977). The very slow infusion (100 mg in one hr) in case 5, was appropriate for i.v. maintenance therapy. The rapid initial injection of 2 mg/kg in approximately 5 min was designed to produce a dramatic response in refractory ventricular tachycardia (Vismara *et al.*, 1977) where some risk of toxicity can be accepted. It ought not to be recommended for routine use as a loading dose.

In a pharmacokinetic study designed to determine the best way to establish steady therapeutic plasma concentrations of disopyramide by infusion, it seemed that the best loading dose was 4 mg/kg in the first hour, given as 2 mg/kg over at least 15 min and a further 2 mg/kg over 45 min (Rangno *et al.*, 1976). Subsequent experience suggests that this loading dose may be unduly large and rapid for some patients with myocardial infarction. Even in normal subjects, 100 mg i.v. over 10 min may cause hypotension and bradycardia (Ashford, Carmichael and Kidner, 1979). As a compromise between the rapid attainment of consistent effective plasma concentrations and the avoidance of acute toxicity the authors suggest a loading dose of 2 mg/kg, given over 15 min, although the data suggest (Vismara *et al.*, 1977) that even with a simultaneous infusion (0.4 mg/kg/hr) effective plasma concentrations may be lost after 2 hr; and a further smaller bolus dose (1 mg/kg) may be needed to maintain an effective plasma concentration.

In spite of its potent quinidine-like activity, accentuation of heart failure has not been a major problem with the use of disopyramide by the present authors, although animal work suggests that an adverse effect can be demonstrated and the combination with β -blocking drugs may be particularly hazardous (Cross and Raftery, 1976). The general fear of an adverse effect of quinidine on myocardial function may have been overrated as the main cardiovascular effects produced at therapeutic doses are probably due to venous vasodilatation (Markiciewicz *et al.*, 1976; Mason *et al.*, 1977), and in the past have been misinterpreted as myocardial depression.

Although the problem has not been fully assessed particularly with regard to combination with other drugs such as β -blockers and verapamil, where hypotension is reported (Ross, Vohra and Sloman, 1978), disopyramide appears to be a relatively safe drug in patients with some evidence of impaired myocardial function (Vismara, Mason and Amsterdam, 1970) and is deserving of further exploratory

study as a first-choice anti-arrhythmic drug. The authors' anxiety is that excessive use and, particularly, fast i.v. injection should not bring it into premature undeserved disrepute.

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