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HAEMODYNAMIC AND ELECTROCARDIOGRAPHIC EFFECTS OF INTRAVENOUS DISOPYRAMIDE (RYTHMODAN) FOLLOWING ACUTE MYOCARDIAL INFARCTION

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1 The haemodynamic and electrocardiographic effects of intravenous disopyramide were studied in fifteen patients with acute myocardial infarction.

2 Five minutes after drug injection a rise in heart rate, aortic mean and diastolic pressures and systemic vascular resistence was noted which persisted for at least 30 min. A small increase in pulmonary arterial diastolic pressure (mean = 1.5 mm Hg) occurred at 5 min only and no significant change of cardiac output was found throughout the period of the study (1 h).

3 Surface electrocardiograms revealed transient prolongation of the P-R interval and a sustained increase in the QTc interval.

4 The haemodynamic changes suggest an anticholinergic effect of the drug. There was no definite evidence of a negative inotropic effect in this study, however, these peripheral haemodynamic measurements might not have revealed a modest negative inotropic effect.

5 The electrocardiographic changes are similar to those previously reported in normals and in patients without acute myocardial infarction.

Introduction

Ventricular and supraventricular arrhythmias commonly complicate the early period following acute myocardial infarction. Disopyramide (Rythmodan) has recently been shown to be a useful drug in the prophylaxis and treatment of such arrhythmias (Selvini, 1970; Besterman Jennings, Jones, Kodner, Model & Turner, 1975). While reports indicate that in the experimental animal (Mathur, 1972) and in man (Vismara, DeMaria, Miller, Amsterdam & Mason, 1975; Sutton, 1976) disopyramide has a negative inotropic effect on the heart, none of these studies have been carried out immediately following acute myocardial infarction. It therefore appeared important to us to study the haemodynamic effect of disopyramide in this particular clinical situation.

Methods

Fifteen patients were studied after obtaining informed consent. Eleven were men and four were women. Their mean age was 53 (range 31–61) years. All the patients had been admitted to the Coronary Care Unit within 12 h of the onset of typical cardiac ischaemic pain, and they had all sustained a transmural myocardial infarction as defined by the W.H.O. criteria for 'very probable infarction'. The patients were studied within 24 h of admission. All the patients were in sinus rhythm at the time of the study; none of them had any evidence of intra-atrial, atrio-ventricular nodal or intraventricular conduction defects since admission; nor did they give a history, or have signs, of additional cardiac or pulmonary disease. The site of the infarction was anterior or anteroseptal in nine, inferior in five and true posterior in one patient.

All the patients in our Coronary Care Unit are routinely sedated with oral diazepam (Valium), but none of the patients studied had been given any other drugs in the four hour period preceeding the study. Under local anaesthesia (1% lignocaine) a 5 French gauge Swan-Ganz flow directed catheter was advanced to the pulmonary artery from an antecubital vein, and a No. 4 French gauge 80 cm nylon catheter was introduced percutaneously into the brachial artery using a Cournand needle.

Two to three hours following the insertion of the catheters the following measurements were made: (i) systemic arterial pressure (mm Hg), (ii) pulmonary arterial pressure (mm Hg), (iii) heart rate, and (iv) cardiac output (l/min). The stroke volume (ml) was derived from cardiac output and heart rate, and systemic vascular resistance (dyn s cm^{-5}) was calculated from cardiac output and the mean systemic arterial pressure; the P-R interval, the QRS duration

and the QT interval were measured from standard Lead II of the surface scalar electrocardiogram. The QT interval was corrected for heart rate (QTc). Immediately after the baseline measurements were obtained, disopyramide in a dose of 1.5 mg/kg body weight was injected intravenously over a 2 min period. Pulmonary arterial pressures, systemic arterial pressures and Lead II of the ECG were then recorded at 5, 10, 20, 30, 45 and 60 min after the injection. Cardiac output estimations were made between 10 to 20 min and at 60 to 70 min. Venous blood (10 ml) was withdrawn at 5, 10, 20, 30, 45 and 60 min for estimation of the plasma level of disopyramide.

All the pressures were recorded on a Cambridge multichannel photographic physiological recorder, using a Cambridge pressure amplifier (type 72363) and Bell and Howell pressure transducer (Series 4/422/001). The zero point for all pressure measurements was the mid axillary line at the level of the fourth intercostal space anteriorly. Cardiac outputs were measured by the dye dilution technique using a Waters (CO–4) digital cardiac output computer, and the average of three consecutive measurements was taken to be the cardiac output. The scalar electrocardiogram was recorded on a Hewlett-Packard 1500A electrocardiograph at 25 mm/s.

At the end of the study the pulmonary and systemic arterial catheters were removed, except in those patients with abnormal haemodynamic values, in which repeat measurements were necessary for the monitoring of progress and the evaluation of therapy.

Statistical analysis

The results obtained following the injection of disopyramide were compared with control values and the differences analyzed by Student's *t*-test for paired data.

Results

The haemodynamic effects and electrocardiographic effects of disopyramide are shown in Table 1. The heart rate (Figure 1) rose significantly 5 min after the injection of disopyramide and continued to be significantly elevated for 30 min. There was no significant elevation of systemic arterial systolic pressure (Figure 1) but the diastolic pressure was significantly elevated at all times and the mean systolic arterial pressure at 5, 10 and 30 min only. Pulmonary arterial end diastolic pressure (Falicov & Resnekov, 1970) and mean pulmonary arterial pressure showed a significant rise 5 min after injection; subsequent measurements, however, did not show any significant change from control values. The pulmonary systolic pressure remained unchanged. The cardiac output

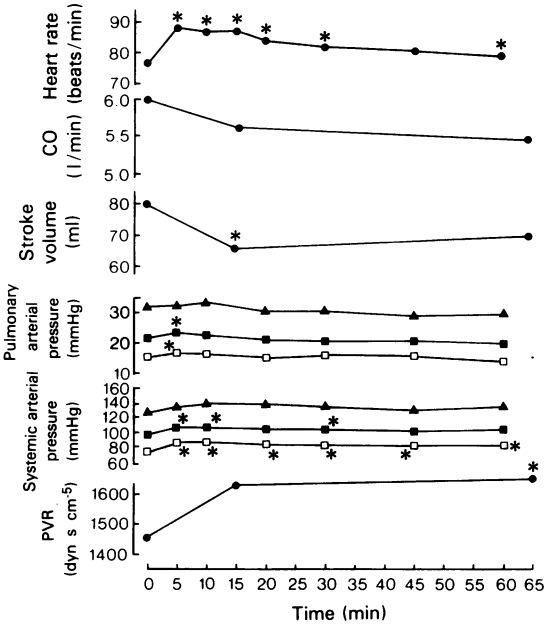

Figure 1 The haemodynamic effects of intravenous disopyramide. ▲ systolic, ■ mean, □ diastolic pressure.
*Indicates significant values ($2P < 0.05$)

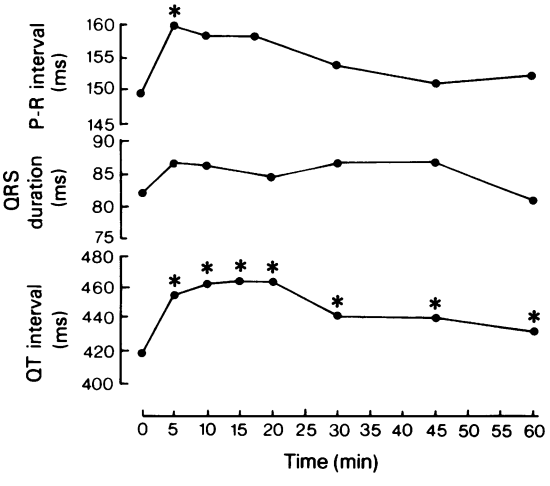

Figure 2 The electrocardiographic effects of intravenous disopyramide. *Indicates significant values ($2P < 0.05$)

Table 1 Haemodynamic and electrocardiographic effects of disopyramide after myocardial infarction

		Time after injection of disopyramide (min)					
		5	*10*	*15–20*	*30*	*45*	*60*
Systemic arterial pressure (mm Hg)	Systolic	6.9 ± 16.4	9.8 ± 18.5	8.7 ± 20.0	6.3 ± 11.9	1.4 ± 16.3	7.7 ± 19.8
		NS	NS	NS	NS	NS	NS
	Diastolic	10.5 ± 8.9	10.4 ± 10.4	7.7 ± 9.3	7.3 ± 6.7	5.9 ± 8.7	8.2 ± 10.3
		$2P < 0.001$	$2P < 0.005$	$2P < 0.02$	$2P < 0.005$	$2P < 0.05$	$2P < 0.01$
	Mean	9.6 ± 11.4	10.0 ± 14.4	7.3 ± 14.4	6.9 ± 7.2	5.3 ± 8.9	6.9 ± 13.9
		$2P < 0.01$	$2P < 0.025$	NS	$2P < 0.01$	NS	NS
Pulmonary arterial pressure (mm Hg)	Systolic	0.3 ± 3.2	1.4 ± 7.2	−1.3 ± 4.0	−1.2 ± 4.9	−3.0 ± 5.1	−2.5 ± 4.9
		NS	NS	NS	NS	NS	NS
	Diastolic	1.5 ± 1.6	0.9 ± 2.5	−0.3 ± 2.0	0.9 ± 5.4	−0.6 ± 2.1	−1.5 ± 2.2
		$2P < 0.005$	NS	NS	NS	NS	$2P < 0.02$
	Mean	1.7 ± 2.8	1.1 ± 2.7	−0.3 ± 2.7	−0.7 ± 3.9	−0.7 ± 2.7	−1.6 ± 2.8
		$2P < 0.05$	NS	NS	NS	NS	$2P < 0.05$
Cardiac output (l/min)			−0.4 ± 1.7 (10–20 min)				−0.5 ± 1.6
			NS				NS
Heart rate (beats/min)		11.9 ± 7.5	10.5 ± 6.0	11.2 ± 6.0	5.7 ± 7.5	4.5 ± 8.8	2.9 ± 5.3
		$2P < 0.001$	$2P < 0.001$	$2P < 0.001$	$2P < 0.02$	NS	$2P < 0.05$
Stroke volume (ml)			−14.3 ± 22.0 (10–20 min)				−10 ± 21.5
			$2P < 0.025$				NS
Peripheral vascular Resistance (dyn s cm^{-5})			170 ± 349 (10–20 min)				188 ± 240
			NS				$2P < 0.025$
P-R Interval (ms)		10.8 ± 13.8	9.2 ± 15.6	9.2 ± 15.6	4.6 ± 16.1	1.8 ± 14.0	3.1 ± 11.1
		$2P < 0.02$	NS	NS	NS	NS	NS
QRS duration (ms)		4.6 ± 7.8	3.8 ± 6.5	2.5 ± 6.3	0 ± 4.1	0 ± 4.5	−1.5 ± 3.8
		NS	NS	NS	NS	NS	NS
QTc interval (ms)		37.3 ± 24.0	42.8 ± 18.7	45.6 ± 12.5	22.8 ± 15.4	22.9 ± 20.2	13.3 ± 15.4
		$2P < 0.001$	$2P < 0.001$	$2P < 0.001$	$2P < 0.001$	$2P < 0.005$	$2P < 0.02$

The results are given as difference between stated time and control expressed as mean difference ± s.d., together with significance from Student's paired *t*-test

(Figure 1a) was not altered but the stroke volume was significantly decreased 10 min after the injection and systemic vascular resistance was significantly elevated at 60 min.

Disopyramide produced a significant prolongation of the P-R interval after 5 min (Figure 2). The QTc interval was significantly increased at all times following injection of the drug, whereas the QRS duration showed no significant change.

The disappearance of disopyramide from the plasma showed a biexponential pattern similar to that found by other workers (Marrott, Ruttley, Winterbottam & Muir, 1975). The actual levels were (given as mean $\pm$ s.d. in mg/l): 4.48 ± 2.62, 2.65 ± 1.16, 2.12 ± 0.8, 2.01 ± 0.61, 1.75 ± 0.67 and 1.60 ± 0.5 at 5, 10. 20, 30, 45 and 60 min respectively following the end of disopyramide injection.

Discussion

There have been no previous studies of the haemodynamic effects of disopyramide after acute myocardial infarction. It has been shown in animal experiments that disopyramide has an anticholinergic action (Mokler & Van Arman, 1962) and Mathur (1972) found a large reduction in contractile force using the drug in anaesthetized dogs in a dose of 1 mg/kg body weight. Similar effects have been observed in humans by Vismara *et al.* (1975) who observed the haemodynamic effects of intravenous disopyramide in twelve patients during routine cardiac catheterization.

It seems that disopyramide has an anticholinergic effect causing an increase in heart rate but no rise in cardiac output. The increase in systemic vascular resistance can also be explained on the basis of an anticholinergic effect because acetyl choline causes vasodilatation but acetyl choline receptors on parasympathetic nerve endings may be blocked by anticholinergic drugs. There is no evidence from this study of a negative inotropic effect of disopyramide because only a small rise of pulmonary arterial diastolic pressure occurred at 5 min after injection of the drug and the increase of heart rate by 11.9 beats/min at this time was possibly the true reason for this rise, the left ventricular pressure not being correctly reflected by the pulmonary artery end diastolic pressure under these conditions. However the measurements made of pressure and flow are peripheral, have an indirect relationship to left ventricular function, and therefore might not have revealed a modest reduction in left ventricular inotropic state. A negative inotropic effect of the drug might have been masked by the effect of vagal withdrawal on cardiac output (Berry, Thompson & Miller, 1959).

In clinical practice a bolus dose of 1.5 mg/kg body weight is often followed by a continuous infusion of 0.4 mg/kg body weight to maintain the plasma level and with this regime a potential negative inotropic effect of the drug might become manifest. Further studies are necessary to assess the effects of disopyramide administered in this manner. There is evidence that a negative inotropic effect of the drug becomes unmasked when sympathetic compensatory mechanisms are withdrawn by beta adrenergic blockade (Davies, Joshi, Fadayomi, Henderson & Muir, 1978) and therefore caution is necessary when disopyramide is administered intravenously to patients taking beta adrenergic blocking drugs.

Mathur (1972) and Marrott *et al.* (1975) have shown that disopyramide increases atrio-ventricular conduction time and our finding of prolongation of the P-R interval 5 min after injection of the drug would support that observation. This increased P-R interval is small (mean increase at 5 min = 11 ms). The prolongation of the QTc interval is marked and persistent up to 60 min.

In conclusion, the use of disopyramide for the prophylaxis of serious ventricular dysrhythmias in uncomplicated myocardial infarction is unlikely to lead to any severe haemodynamic disturbance although, on the basis of previous studies, caution is necessary in those patients with left ventricular failure, and in those patients taking β-adrenergic receptor blocking drugs.

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