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THE EFFECTS OF POSTLIGATION ADMINISTRATION OF ORG 6001 AND DISOPYRAMIDE ON EARLY ISCHAEMIA-INDUCED ARRHYTHMIAS IN THE ANAESTHETIZED RAT

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The effects of intravenous doses of Org 6001 and disopyramide (10 mg/kg) known to confer protection against early postligation-induced arrhythmias in the anaesthetized rat when given prophylactically, were assessed following postligation administration. When given 1 min after ligation both drugs greatly reduced the incidence of ventricular fibrilloflutter and completely prevented electrical deaths (45% in the controls). Protection was also seen when the drugs were given just before the expected onset of arrhythmias (4.5 min postligation).

Introduction The membrane stabilizing agents Org 6001 (Salako, Vaughan Williams & Wittig, 1976) and disopyramide (Sekiya & Vaughan Williams, 1963), when given prophylactically to pentobarbitone-anaesthetized rats, markedly reduce the severity of arrhythmias and abolish ventricular fibrilloflutter (VF) induced by acute coronary artery ligation (Au, Collins, Harvie & Walker, 1979; Clark, Foreman, Kane, McDonald & Parratt, 1980; Kane & Winslow, 1980). However, to our knowledge, there have been no studies reported on the effects of these agents when given *after* coronary artery ligation, a situation more akin to clinical practice. The aim of the present study was to assess the efficacy of postligation intravenous administration of Org 6001 and disopyramide in doses known to confer protection when given prophylactically.

Methods Male Wistar rats (325–435 g) were anaesthetized with pentobarbitone sodium (60 mg/kg given i.p.) and artificially ventilated with room air. Arterial blood pressure (BP) was recorded from the right carotid artery and the lead II electrocardiogram recorded from subcutaneous steel needles. The main left coronary artery (LAD) was ligated in one stage as described by Clark *et al.*, 1980. The incidence of ventricular fibrilloflutter (VF), the mortality and the number of premature ventricular systoles (PVS) were recorded during the 0–30 min postligation period. In this model, arrhythmias start approximately 5 min after ligation. Drugs or vehicle were therefore given (via the left femoral vein) either 1 min after ligation or just before the expected onset of arrhythmias (4.5 min postligation).

Org 6001 hydrochloride (Organon) and disopyramide phosphate (Roussel) were dissolved in distilled water. Control animals were given an equivalent volume of water (0.1 ml/100 g).

The Fisher exact test was used to detect significant differences in the incidence of VF and mortality between drug-treated and control groups and Student's t test applied to determine the significance of differences between means.

Results The mean number of PVS recorded during the 30 min postligation period, the % incidence of VF and the mortality from VF in control animals and in animals given Org 6001 or disopyramide are compared in Table 1.

When administered 1 min after ligation, both Org 6001 (10 mg/kg) and disopyramide (10 mg/kg) significantly reduced the incidence of VF (from 73% in the controls to 0 and 22% respectively). Mortality from VF was 45% in the controls whereas no deaths were observed in either of the drug-treated groups. However, the total number of PVS was not decreased by either drug. The protection conferred by Org 6001 and disopyramide was most marked during the 5–10 min postligation period when the arrhythmias are generally most severe. This was more clearly seen when protection was assessed using a weighted count; 15 ectopic beats for every second of VF being added to the total number of PVS actually recorded during successive 5 min intervals. During the 5–10 min period, the weighted count was reduced from 1165 ± 212 ectopics in the controls to 506 ± 129 and 596 ± 163 ($P < 0.05$) in the Org 6001 and disopyramide groups respectively.

When the drugs were given at 4.5 min postligation, mortality was again reduced. VF was not seen in the disopyramide-treated animals whereas an incidence of VF of 55% and 50% were recorded in the control and Org 6001-treated groups respectively. It is worthy of note, however, that 4 of the 12 animals given Org 6001 had already developed severe arrhythmias (2 were in VF and 2 in tachycardia) at the time of drug administration. Again the total number of PVS observed during the recording period was unaltered by either drug.

Values of mean blood pressure and heart rate measured prior to ligation were similar in all groups

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(96 ± 7 mmHg and 380 ± 15 beats/min in the 1 min control group).

When administered 1 min postligation, both test drugs produced an almost immediate fall in heart rate from predrug values of 393 ± 10 and 414 ± 13 to 313 ± 11 ($P < 0.01$) and 276 ± 10 ($P < 0.001$) in the Org 6001 and disopyramide groups respectively. By 5 min, heart rates were still reduced by means of 17 and 19% compared to a 5% reduction in the controls measured over the same time period. Ligation resulted in a fall in BP. Org 6001 produced a further transient fall from 73 ± 9 to 45 ± 5 mmHg whilst disopyramide produced a more prolonged increase (from 64 ± 8 to 105 ± 5 mmHg). By 9 min after drug administration there were no significant differences in BP or HR between control and drug-treated animals. Similar haemodynamic effects were observed when the drugs were given 4.5 min postligation. Values of BP and HR recorded in all groups just before the expected onset of arrhythmias (5 min postligation) are given in Table 1.

Discussion When evaluating the antiarrhythmic effects of drugs against early post-ischaemia arrhythmias, the degree of protection afforded may vary according to whether the drug is given prior to ligation, in anticipation of ischaemia or administered after ligation when ischaemia is already established. In contrast to postligation dosing, it might be expected that preligation administration would facilitate a more homogenous distribution of drug within the myocardium and allow a relatively high concentration to become trapped in the resulting ischaemic area. In addition, drugs will reach the heart before ischaemia-induced metabolic changes (e.g. lowered cellular pH) have occurred and at a time when the animals are haemodynamically stable. Prophylactic animal studies may therefore be less predictive for the clinical situation where acute treatment is instigated after the onset of myocardial infarction.

In the present study, both Org 6001 and disopyramide in doses (10 mg/kg) known to reduce the severity of ligation-induced arrhythmias when given prophylactically, were found to retain some beneficial actions when given after the onset of ischaemia.

When given 1 min postocclusion, both drugs substantially reduced the expected incidence of VF and prevented electrical deaths. The protective actions of both drugs were most marked during the 5–10 min postligation period when arrhythmias in this model are most severe. Unlike results obtained from prophylactic studies, the total recorded number of PVS in surviving animals, was not, however, reduced by either drug. This may reflect differences in drug levels achieved in the cardiac tissue at risk. In this connection it is interesting to note that a lower dose of disopyramide (2 mg/kg, i.v.) when administered pre-ligation has been reported to provide greater protection against ligation-induced VF than against ventricular ectopic activity (Kane & Winslow, 1980). However, the antifibrillatory actions observed following postligation administration may suggest that both drugs are able to penetrate the ischaemic myocardium. Kannengiesser, Lubbe & Opie (1975) have shown in rat isolated perfused hearts that flow in the centre of the ischaemic zone is approximately 18% of normal flow, thus greatly reducing drug delivery to this region.

Surprisingly, both agents also caused substantial reduction in mortality when given just before the expected onset of arrhythmias (4.5 min postligation). Both Org 6001 and disopyramide induced a modest and almost immediate bradycardia which may have contributed to the observed antiarrhythmic effects. In this respect, it is of interest that the number of PVS

Table 1 The number of premature ventricular systoles (PVS), the % incidence of fibrilloflutter (VF) and the mortality (M) observed in control rats and in rats given Org 6001 or disopyramide after coronary artery ligation

	Group	*PVS*	*VF*	*M*	*HR* (b/min)	*BP* (mmHg)
(a)	Control	1751 ± 153	73	45	365 ± 15	81 ± 7
	Org 6001	1902 ± 775	**0	*0	*327 ± 11	78 ± 9
	Disopyramide	1457 ± 405	*20	*0	336 ± 11	*105 ± 5
(b)	Control	1955 ± 647	55	36	338 ± 19	76 ± 8
	Org 6001	1337 ± 325	50	8	312 ± 22	61 ± 3
	Disopyramide	1681 ± 441	*0	0	***235 ± 10	**122 ± 10

Drugs or vehicles were given (a) 1 min or (b) 4.5 min after ligation. Values of heart rate (HR) and arterial blood pressure (BP) recorded 5 min postligation are also shown.
Values are the mean ± s.e.mean. $n = 9–12$. *$P < 0.05$; **$P < 0.01$.

was not reduced by either drug during the 15–30 min period at a time when heart rates were similar to those observed in control animals. The hypertensive action of disopyramide may also have contributed to its antiarrhythmic effect by increasing coronary perfusion pressure and/or triggering baroreceptor reflexes (see Marshall, Muir & Winslow, 1981).

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