THE PHARMACOKINETICS OF INTRAMUSCULAR DISOPYRAMIDE PHOSPHATE

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At present both oral and intravenous formulations of the anti-arrhythmic drug disopyramide (DSP) are commercially available. It was considered that an intramuscular (IM) preparation may also be useful, particularly if the drug is to be given outside hospital as a prophylactic in the very early stages of myocardial infarction. The specific objective of this investigation was to determine the plasma concentration profiles and pharmacokinetic parameters of DSP following IM injection to patients with ischaemic heart disease.

Seven patients (5 males, 2 females) aged 48-64 years were included in the study. All patients showed evidence of ischaemic heart disease and their condition was defined as "uncomplicated" with no evidence of cardiac arrhythmia. Each patient was given 150 mg of IM disopyramide phosphate (supplied by Roussel Laboratories) by deep injection into the gluteal muscle. Fifteen blood samples were collected over a period of 8 hrs after administration and DSP concentrations were measured by high pressure liquid chromatography (Meffin et al, 1977). Log serum concentration vs time data were analysed by non-linear regression.

Table 1. Summary of the absorption and disposition parameters of DSP after IM injection to 7 patients with ischaemic heart disease.

	Tmec (min)	Cp_{max} (μg/ml)	T_p (min)	k_a (min^{-1})	$at_{\frac{1}{2}}$ (min)	β (h^{-1})	$\beta t_{\frac{1}{2}}$ (h^{-1})	Tth (h)	AUC (μg/ml/h)	Cl (L/h)	V_d (L)
Median	4.0	3.7	22.8	0.13	5.3	0.09	7.3	5.5	33.5	4.5	37.9
Range	1.0	2.7	1.2	0.1	0.1	0.08	3.6	1.6	17.1	2.4	20.6
	12.0	6.9	39.3	6.3	6.8	0.19	9.0	11.3	62.6	8.8	58.9

A one-compartment model was sufficient to describe the data in six patients. In one patient, in whom extremely rapid absorption was observed, a finite distribution phase was identified and these data were fitted to a 2-compartment model.

The overall absorption profile indicated that this preparation was suitable for clinical usage. Serum DSP concentrations in the therapeutic range (2-7 μg/ml) were achieved in all cases and an attractive feature was the rapidity with which the minimum effective concentration was achieved (Tmec) - within 12 mins in all patients. However the rate constant of absorption (k_a) showed significant interindividual variability, in common with findings for other drugs given by the IM route (Gibaldi, 1977). The median value (7.3 h) observed for the elimination half life ($\beta t_{\frac{1}{2}}$) was in agreement with previous findings (Bryson et al, 1982). The median time during which DSP serum concentrations were maintained within the therapeutic range (Tth) was acceptable (5.5 h). However the group values for the parameters were again spread over a relatively wide range.

Due to potential interindividual variability in absorption, IM injection may not be the ideal parenteral route of administration for a drug with a narrow therapeutic range. However the use of a specially prepared IM formulation of DSP could be justified in specific circumstances provided that the dose is individualised and that therapeutic and clinical monitoring facilities are available.

Meffin, P.J. et al (1977) J. Chromatography 132: 503-510.
Milo Gibaldi (1977) "Biopharmaceutics and Clinical Pharmacokinetics" Pub. Lea & Febiger.
Bryson, S.M. et al (1982) J. Clinical & Hospital Pharmacy, 7: 37-42.

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