DISOPYRAMIDE — SCIENTIFIC AND CLINICAL SEMINAR

On Monday 11th October, 1976 a discussion group was held under the Chairmanship of Dr. H. G. Mather at Blagdon on the anti-arrhythmic agent disopyramide (Rythmodan, Roussel). The material presented here summarises the two papers given.

The Clinical Development of Disopyramide

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Disopyramide was synthesised around 1959. Since its structure is not related to any other known anti-arrhythmics drug, one can only suppose that its discovery was serendipity. Initial studies on disopyramide led workers to conclude that disopyramide was very similar in its activity to quinidine but we now know this is not completely true. Unfortunately: the original French clinical investigations were subjective and anecdotal in nature. Perhaps medicine is more of a science than an art in the UK, while in France it tends to be more of an art than a science. Certainly, the French have a reputation for impressionistic art. As a consequence several studies were set up in the UK, Canada, South Africa, Australia, Germany and Scandinavia between 1973 and 1975 to re-examine the pharmacology of disopyramide and establish its clinical usefulness in carefully controlled trials. I was lucky enough to initiate and co-ordinate much of that particular experience, which was stimulating, fascinating and rewarding. Most of these comprehensive investigations led to an International Symposium on Disopyramide at the Royal College of Physicians in 1975.

Pharmacologically, disopyramide has anti-cholinergic activity which is about 1/200 to 1/1200 of that of atropine and this action explains the side-effects which are most often seen clinically when high doses are used or if a patient has a significant degree of renal impairment. Disopyramide is less depressant than quinidine, propanolol or verapamil on myocardial metabolism, and its haemodynamic effects are relatively small. Disopyramide is a local anaesthetic with a potency similar to that of lignocaine. It has no alpha or beta adrenergic receptor blocking activity, is not a neuro-muscular or ganglion blocker, and has no antihistaminic, diuretic, anorectic or overt CNS activity in animals. In animals, disopyramide is anti-arrhythmic against both atrial and ventricular arrhythmias. The drug was usually more active than quinidine or propranolol.

In man, slow intravenous injection of disopyramide causes a slight transient negative inotropic effect. Cardiac output is either unaffected or slightly and transiently reduced, there is either no effect on the heart rate or a slight transient increase, but the blood pressure is usually maintained or slightly and transiently increased. These minimal effects are accompanied by an increase in peripheral resistance. Disopyramide causes either no effect on conduction time in the atrium or a slight increase, while the conduction time through the His-Purkinje system and ventricle is usually increased. The conduction time through the AV node is usually unaffected by disopyramide. Animal studies have shown that phases 0 and 4 depolarisation are depressed and in man the effective refractory period is increased in both the atrium and the ventricle. There is a slight increase in the effective refractory period of the AV node.

In patients with the Wolff-Parkinson-White syndrome, the conduction time and the effective refractory period in anomalous pathways are increased, and even blocked, both in the antigrade and in the retrograde direction, making disopyramide useful in the treatment of the WPW syndrome.

Disopyramide is very effective against ventricular premature beats, atrial and ventricular tachycardia, as well as maintaining sinus rhythm following electroconversion of atrial fibrillation. There is no absolute incompatibility between disopyramide and any other anti-arrhythmic agent, but it should be used with caution in combination with other negatively inotropic
drugs. Disopyramide is contra-indicated in the presence of complete heart block and patients with severe heart failure should be digitalised prior to disopyramide therapy. To-date extensive clinical use has shown that disopyramide is strikingly free of serious side-effects.

In summary, experience shows that disopyramide is an effective and relatively safe anti-arrhythmic agent, especially against ventricular arrhythmias.

The Role of Disopyramide after Myocardial Infarction
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Between 1974 and 1975, we conducted a double blind trial in patients with post myocardial infarction to compare oral disopyramide and placebo in the Coronary Care Units of St. Mary's Hospital, Paddington and Edgware General Hospital.

We studied 95 patients with confirmed myocardial infarction, of whom 46 received disopyramide and 49 received placebo. The groups were evenly matched in their Peel prognostic indices. The mean time of entry into the trial after infarction was 8 hours in both groups. Since we were then using a relatively untried drug, we used it in the good risk myocardial infarction patients. Therefore, all unconscious patients, patients with a systolic blood pressure of less than 80 mmHg for 2 hours, patients with heart block or with obvious risks of developing anti-cholinergic problems, and patients who initially had an arrhythmia were excluded.

Immediately after acceptance into the trial, disopyramide or placebo was administered on a blind statistically randomised basis, and a 24 hours' continuous ECG tape recording started. The tapes were analysed retrospectively on an automatic arrhythmia detection system, and checked manually.

Patients were withdrawn from the trial if they developed an arrhythmia requiring treatment within the first 6 hours, since effective serum levels would not have been reached in that time.

We classified the arrhythmias into three types:

1. Ventricular premature beats (5 per minute), R. on T., bigeminy, multifocal ectopics, runs of ventricular premature beats, ventricular tachycardia and fibrillation.
2. The supraventricular tachycardias.
3. Heart block.

Twenty-one patients in the disopyramide group and 42 in the placebo group required further anti-arrhythmic treatment (p<0.005). 15 ventricular arrhythmias occurred on disopyramide, compared with 29 in patients receiving placebo (p<0.01).

Eight cases of ventricular premature beats (>5/ min.) occurred in the disopyramide group, and 21 in the placebo group (p<0.01). The incidence of multifocal or R. on T. ventricular premature beats was not significantly different between the disopyramide and placebo groups. Only 4 patients on disopyramide developed ventricular tachycardia compared with only 14 on the placebo (p<0.05). The incidence of ventricular fibrillation or supraventricular arrhythmias was not significant between the two groups.

None of the patients on disopyramide developed any degree of heart block, whereas 7 developed varying degrees on placebo (p<0.05).

There was no significant difference between the two groups in the incidence of complications observed.

Only one patient on disopyramide re-infarcted during the hospital stay, compared with 9 patients on placebo (p<0.05). There were two deaths in the disopyramide group compared with 5 on the placebo.

Disopyramide gave a significant prophylactic protection against potentially dangerous ventricular arrhythmias, but little against supraventricular arrhythmias, a surprising apparent protection against the development of heart block, a possible reduction in the extension of the original infarction and no significant predominance of side-effects.

Reference
Jennings, G., Model, D. G., Jones, M. B. S., Turner, P. P., Besterman, E. M. M., and Kidner, P. H. (1976) Oral disopyramide in prophylaxis of arrhythmias following myocardial infarction. Lancet, 1, 51-54.

References
1. The Journal of International Medical Research, 1976, 4, Supplement (1).
2. Proceedings of the Disopyramide (Rythmodan) Seminar (1977) — Viking Press Ltd., London.