Editorial:
Disopyramide Phosphate (Norpace)
A New Antiarrhythmic Drug

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Disopyramide Phosphate (NORPACE) was recently approved and released in the United States for clinical use as an antiarrhythmic drug. The electrophysiologic, pharmacologic and hemodynamic properties, clinical application and toxicology of this drug have been extensively studied in this country and abroad. Some of the studies have been published in two symposia.1 2

Disopyramide has both membrane depressant and anticholinergic effects. Electrophysiologic studies of disopyramide in human subjects have demonstrated that it usually shortens spontaneous cycle length, slightly prolongs the relative refractory periods of atrium, ventricle and the His-Purkinje system, and increases the duration of the P wave and QRS complex. It does not affect atioventricular nodal conduction time, but may prolong the His-Purkinje conduction time. Most of these effects are concentration-dependent. The overall depressant effects may be nullified by the associated anticholinergic properties.

The two papers published in this issue of Circulation have reviewed admirably the electrophysiologic effects of disopyramide in man and have clarified the clinical application of disopyramide in patients with sinus node dysfunction and in those with bundle branch block.3 4 Disopyramide may have deleterious effects in patients with sinus node dysfunction, so it should be administered with caution to these patients. In contrast, disopyramide can be given safely to hemodynamically stable patients with bundle branch block without resulting in second or third degree atioventricular block.

Intravenous administration of disopyramide in a dose of 1.5 – 2 mg/kg produces no measurable hemodynamic effect in patients with normal left ventricular function, but may cause a transient negative inotropic effect on the myocardium in those with abnormal left ventricular function.

The drug is rapidly and almost completely absorbed from the gastrointestinal tract when taken orally. Maximum plasma levels are usually reached 1–3 hours after ingestion of a dose, and the plasma half-life of the drug is about 6 hours. The range of therapeutic plasma concentrations is 2–4 µg/ml, which may be achieved with a 100 or 150 mg dose four times a day. About 70% of the drug is excreted in the urine and the remainder via the biliary system into the feces.

Long-term administration of disopyramide to human volunteers and patients causes no appreciable change in body weight, blood pressure, heart rate, serum electrolytes, or in hepatic, renal or hemopoietic function. Oshrain and associates in our medical center have followed 59 patients who have been on disopyramide therapy for 5 years. None of these 59 patients has developed serious complications resulting from the drug.

Disopyramide is effective in the suppression of ventricular premature beats and ventricular tachycardia in about 80% of the patients who are placed on the therapy. It also has been successful in controlling and preventing refractory ventricular tachycardia.5 Disopyramide given orally appears to be effective in the prevention of potentially serious arrhythmias in patients with acute myocardial infarction.6

The efficacy of disopyramide in the management of atrial tachyarrhythmias is less impressive. It has been used in the conversion of paroxysmal atrial tachycardia as well as of atrial fibrillation with a success rate ranging from 20–50%. The rate of success for conversion of atrial fibrillation to sinus rhythm depends on the duration of arrhythmia.7 The conversion rate is much higher when the duration of atrial fibrillation is less than 7 days. The drug also has been effective in controlling paroxysmal atrial tachycardia in patients with Wolff-Parkinson-White syndrome.

The therapeutic effect of disopyramide is similar to that of quinidine in the management of both ventricular and atrial arrhythmias, but disopyramide is tolerated better than quinidine by a large proportion of patients.

The recommended dose in an average person is 100 mg or 150 mg four times a day. In most patients a loading dose is not required. The maximum daily dose should not exceed 1600 mg. In patients with renal functional impairment the daily dose requirement may be considerably curtailed. We will learn from clinical practice how to regulate the dose to fit the patient.

The most significant side effects of disopyramide are caused by its anticholinergic properties. These side effects include dryness of mouth and tongue, urinary retention, constipation, abdominal discomfort, blurred vision, dizziness, headache and nausea. Male patients with prostatic hypertrophy and female patients with diabetic bladder are prone to develop urinary retention. Ten of over 200 patients followed personally by Oshrain developed obstructive symptoms and required either prostatectomy or discontinuance of the drug while they were on disopyramide.
therapy. Mental depression, impotence and hypotension are occasionally observed, especially in those patients with a high plasma level of the drug.

The depressant effect of disopyramide on cardiac muscle may be accentuated when extracellular potassium concentration is increased. Therefore, in hyperkalemic states, toxic manifestations of disopyramide may be observed, even though the plasma level of the drug appears within therapeutic range. Conversely, the therapeutic effect of disopyramide may be significantly reduced if the serum potassium level is excessively low.

Hayler and co-workers reported the death of five patients who deliberately took overdoses of disopyramide. The uniform clinical finding was an early loss of consciousness after apnea. Cardiopulmonary resuscitation was unsuccessful. Postmortem examination revealed gross pulmonary edema probably secondary to left ventricular failure.

Disopyramide administration is contraindicated in patients with acute pulmonary edema, uncontrolled congestive heart failure, cardiogenic shock, glaucoma, and urinary retention. It should be used with caution or temporarily withheld in patients with advanced atrioventricular block or sinus node dysfunction. The drug may be harmful to patients with sinus node dysfunction with sinus pause, sinoatrial exit block or secondary pauses. Since the safety of disopyramide in pregnancy has not been established, the drug should not be given to pregnant women.

Several workers have stated that disopyramide should be given with caution if the patient has received a β-blocking agent because of the development of hypotension. In general, no adverse interaction has been observed between disopyramide and lidocaine.

In summary, disopyramide is an effective oral antiarrhythmic agent, especially for the management of ventricular arrhythmias. The most frequent side effects are dryness of mouth and urinary retention attributable to its anticholinergic properties. It has been used for long-term therapy without serious adverse effects or toxic manifestations. Since a large number of patients cannot tolerate quinidine and cannot continue to take procainamide because of a lupus-like syndrome, disopyramide may be a useful alternative to these two drugs to control ventricular and atrial arrhythmias. However, in patients with certain conditions, the drug is contraindicated and in other conditions, including sinus node dysfunction, it should be used with caution.

References
Disopyramide phosphate (Norpace): a new antiarrhythmic drug.
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