Electrophysiologic Effects of Disopyramide Phosphate in Patients with Wolff-Parkinson-White Syndrome

CHARLES R. KERR, M.D., ERIC N. PRYSTOWSKY, M.D., WARREN M. SMITH, M.D., LAURA COOK, R.N., AND JOHN J. GALLAGHER, M.D.

SUMMARY We evaluated the electrophysiologic effects of disopyramide phosphate in 12 patients with the Wolff-Parkinson-White syndrome. Electrophysiologic studies were performed during a control period and after administering i.v. disopyramide (four bolus doses of 0.5 mg/kg over 40 minutes superimposed on a continuous infusion at 1.0 mg/kg/hour). All patients were then restudied after 3 days on oral medication in doses of 800–1200 mg/day. In all patients we tried to induce reciprocating tachycardia and atrial fibrillation. The cycle length during reciprocating tachycardia was not changed by i.v. disopyramide, but increased after oral disopyramide, from 331 ± 53 (± SD) to 370 ± 68 msec (p < 0.01). This increase occurred predominantly as a result of prolongation of retrograde conduction time in the accessory pathway. Despite prolonging cycle length during reciprocating tachycardia, disopyramide did not prevent its induction. The shortest and mean RR intervals during atrial fibrillation were used to assess antegrade refractoriness of the accessory pathway. Intravenous disopyramide prolonged the shortest RR from 169 ± 18 to 226 ± 24 msec (p < 0.0001) and the mean RR from 255 ± 58 to 329 ± 62 msec (p < 0.005). Oral disopyramide prolonged the shortest RR interval from 169 ± 18 to 248 ± 36 msec (p < 0.0001) and the mean RR from 255 ± 58 to 360 ± 93 msec (p < 0.001). After oral disopyramide, the episodes of atrial fibrillation were shorter and self-terminating. No acute hemodynamic side effects were observed, but five patients developed gastrointestinal or anticholinergic side effects on oral disopyramide. Seven patients elected to have surgical interruption of their accessory pathways and five have been successfully treated with oral disopyramide for 14–33 months. Disopyramide appears to have beneficial electrophysiologic effects in patients with Wolff-Parkinson-White syndrome. Prolongation of refractoriness in the accessory pathway markedly slows the ventricular response during atrial fibrillation and therefore prevents the development of life-threatening arrhythmias.

PATIENTS with Wolff-Parkinson-White syndrome (WPW) may have two types of arrhythmias: a reciprocating tachycardia, in which the accessory pathway provides the retrograde limb of the reentrant circuit, and atrial flutter-fibrillation (AF), in which the accessory pathway provides the route whereby a rapid ventricular response may be mediated. Antiarhythmic therapy in this syndrome may theoretically be directed separately at these two arrhythmias, but in practice, many patients with reciprocating tachycardia also develop AF. Treatment can be directed toward initiating events (i.e., abolishing ectopic beats that induce reciprocating tachycardia or AF) or toward the mechanism whereby sustained arrhythmias occur (i.e., the prolongation of refractoriness in some portion of the reentrant loop so as to prevent circus movement in the case of reciprocating tachycardia or the prolongation of refractoriness in the accessory pathway to slow the ventricular response during AF).

Often, antegrade and retrograde refractoriness of an accessory pathway are difficult to assess because of encroachment on the atrial and ventricular refractory periods. However, several authors have reported a nearly direct relationship between refractoriness and the shortest cycle length during AF.1-4 Consequently, the mean and shortest RR intervals during AF present an easily interpreted measurement of drug response.

Disopyramide phosphate has proved beneficial in the treatment of atrial and ventricular arrhythmias. Its electrophysiologic effects on conduction and refractoriness have been well defined in atrial and ventricular muscle and in the atroventricular node.5-18 Its effects on sinus node function have also been described.6, 10-18

The purpose of this study was to define the electrophysiologic effects of disopyramide in patients with WPW. No antiarrhythmic agent can suppress all ectopic beats. Since the arrhythmias in WPW are frequently life-threatening, the continued occurrence of ectopic beats was anticipated, and the study was designed to emphasize the effects of disopyramide on the elements of the reentry circuit in the case of reciprocating tachycardia, and on the capacity of the accessory pathway to conduct antegrade in the case of AF.

Methods

Patient Population

Twelve patients (10 male and two female), mean age 24 years (range 14–54 years), underwent electrophysiologic investigation. All gave informed, written consent. The patients were selected on the basis of having experienced recurrent, uncontrolled reciprocating tachycardias or AF with a rapid ventricular response. Eight patients presented with a
### TABLE 1. Patient Data and Intervals During Sinus Rhythm

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<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Presenting arrhythmia and rate (beats/min)</th>
<th>Pathway location</th>
<th>SCL (msec)</th>
<th>PR (msec)</th>
<th>QRS (msec)</th>
<th>QTc (msec)</th>
<th>PA (msec)</th>
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<td>Mean ± SD</td>
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<td>732 ± 143</td>
<td>125 ± 23</td>
<td>113 ± 23</td>
<td>457 ± 33</td>
<td>45 ± 13</td>
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*p (comparison to control)

**Number of pairs**

*Unable to assay due to contamination of specimen.

Abbreviations: AF = atrial flutter-fibrillation; RT = reciprocating tachycardia; SCL = spontaneous cycle length; VF = ventricular fibrillation.

### TABLE 2. Intervals During Reciprocating Tachycardia and Atrial Flutter-Fibrillation

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<th>Pt</th>
<th>CL (msec)</th>
<th>AH (msec)</th>
<th>HV (msec)</th>
<th>VA(_{HBE}) (msec)</th>
<th>VA(_{min}) (msec)</th>
<th>Type</th>
<th>SRR (_{normal}) (msec)</th>
<th>SRR (_{AP}) (msec)</th>
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**Mean ± SD**

*Fibrillation requiring cardioversion during control, but not during disopyramide phosphate administration.

\(VA\(_{HBE}\)\) measured during single reentry beat.

**Abbreviations:** CL = cycle length; VA\(_{HBE}\) = ventriculoatrial interval measured to the His bundle atrial electrogram; VA\(_{min}\) = minimum VA interval; SRR = shortest RR interval; MRR = mean RR interval; AP = accessory pathway.

*p comparison to control

**Number of pairs**

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**TABLE 1. (Continued)**

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**TABLE 2. (Continued)**

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<th>HV (msec)</th>
<th>VA_{HBE} (msec)</th>
<th>VA_{min} (msec)</th>
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**DISOPYRAMIDE IN WPW/Kerr et al.**

**TABLE 1.**

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<th>PR (msec)</th>
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**TABLE 2.**

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<th>Type</th>
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<th>AH (msec)</th>
<th>HV (msec)</th>
<th>VA_{HBE} (msec)</th>
<th>VA_{min} (msec)</th>
<th>SRR normal (msec)</th>
<th>SRR AP (msec)</th>
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**DISOPYRAMIDE IN WPW/Kerr et al.**
## Table 1. (Continued)

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<th>Dose (mg/q6h)</th>
<th>Drug level (µg/ml)</th>
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<th>PR (msec)</th>
<th>QRS (msec)</th>
<th>QTc (msec)</th>
<th>PA (msec)</th>
<th>AH (msec)</th>
<th>HV (msec)</th>
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**Note:** 271 ± 40 4.8 ± 0.9 694 ± 142 127 ± 22 119 ± 24 493 ± 30 43 ± 15 70 ± 22

<table>
<thead>
<tr>
<th>Type</th>
<th>SRR normal (msec)</th>
<th>SRR AP (msec)</th>
<th>MRR normal (msec)</th>
<th>MRR AP (msec)</th>
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## Table 2. (Continued)

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<tr>
<td>490</td>
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**Note:** 370 ± 68 133 ± 63 53 ± 10 177 ± 34 133 ± 42 248 ± 36 350 ± 103 <0.01 <0.10 <0.05 <0.005 <0.001 <0.10 <0.005

<table>
<thead>
<tr>
<th>Type</th>
<th>SRR normal (msec)</th>
<th>SRR AP (msec)</th>
<th>MRR normal (msec)</th>
<th>MRR AP (msec)</th>
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were measured. The retrograde conduction time was described, previously ventricular or ventriculoatrial dissociation occurred.

Protocol

The right atrium, coronary sinus and right ventricle were rapidly paced beginning at cycle lengths of 500-600 msec with progressive shortening until atrioventricular or ventriculoatrial dissociation occurred. Antegrade and retrograde refraction periods of the normal and accessory pathways were measured by programmed stimulation from the same three sites. These methods have been described in detail. Reciprocating tachycardia was induced by bursts of rapid pacing or by premature stimulation from the atria or ventricle; frequently, it arose spontaneously during refractory period determination. During reciprocating tachycardia the site of the accessory pathway was determined by atrial mapping, as previously described, and the cycle length, retrograde conduction times, and antegrade conduction times were measured. The retrograde conduction time was recorded as the earliest ventricular activation to both His bundle atrial electrogram (VAHBE) and earliest atrial electrogram (VAearly A). The antegrade conduction times were recorded as conventional AH and HV intervals.

AF was then induced by bursts of atrial pacing at cycle lengths of 60-200 msec. During AF, the shortest and mean RR intervals were recorded, noting whether ventricular activation occurred over the normal or an accessory pathway. The mean RR interval was calculated as the mean RR interval that occurred over at least 15 seconds.

After the control measurements were taken, disopyramide was administered intravenously. Five patients received a bolus dose of 2.0 mg/kg, followed 30 minutes later by a repeat bolus dose of 2.0 mg/kg. In seven patients, an infusion of disopyramide phosphate was started at 1.0 mg/kg/hour and was accompanied by a bolus dose of 0.5 mg/kg over 5 minutes. After a 5-minute observation period, a repeat dose of 0.5 mg/kg was given over 5 minutes. This was repeated to a total of four such bolus doses. The infusion at 1.0 mg/kg/hour was continued throughout the duration of the study. In both regimens, the electrophysiologic testing during reciprocating tachycardia and during AF was repeated 10-30 minutes after the final bolus dose. The repeat cycle could not be performed at a precise time after the last bolus because of the variability in the induction of arrhythmias and the positioning of catheters. Blood pressure was closely monitored during drug administration. Blood was then drawn immediately after electrophysiologic testing to determine serum concentration (determined by Searle Laboratories).

After the initial study, all patients were started on oral disopyramide in doses of 150-200 mg every 6 hours. The oral dose was increased to 200-300 mg every 6 hours. After 2-5 days on this regimen, the patient was returned to the electrophysiology laboratory and either all catheters were reinserted or only the coronary sinus catheter, which had been left in place, was connected to the stimulator and the studies were repeated. Studies were performed 2-3 hours after an oral dose of the drug. Serum levels were determined before and after the final study.

Statistical Methods

The control values were compared independently to measurements made after the final i.v bolus and after the final oral dose of disopyramide. Comparisons were made in each case using the paired t test. In some cases, not all measurements could be taken because of technical problems or because only one catheter was used. In these cases, comparisons were performed only on data points for which paired data were available.

Results

All patients completed the three electrophysiologic investigations. No significant acute side effects were noted with i.v. disopyramide. Patients 1 and 2 had mild, transient hypotension after the bolus doses, but both remained asymptomatic.

Table 1 is a summary of measurements during sinus rhythm. Disopyramide did not affect baseline conduction intervals during sinus rhythm. There was marginal prolongation of the QRS complex and the corrected QT interval, but this proved difficult to assess because of the varying degrees of preexcitation.

During reciprocating tachycardia, i.v. disopyramide caused a slight prolongation of the minimum ventriculoatrial interval, but this was not sufficient to significantly prolong cycle length. On the other hand, oral disopyramide in a mean dose of 279 ± 33 mg every 6 hours caused a significant prolongation of cycle length of reciprocating tachycardia, from 331 ± 53 to 370 ± 68 msec (p < 0.01) due to a prolongation of the minimum ventriculoatrial interval from 100 ± 27 to 133 ± 42 msec (p < 0.01) (table 2, figs. 1 and 2). In no case did the QRS duration change during reciprocating tachycardia and in no case was the ventriculoatrial interval measured during bundle branch block aberrancy. There was no difference in conduction through the atrioventricular node (as reflected by the AH interval) after either i.v. or oral disopyramide.

We examined the effect of the drug on atrial and ventricular refractoriness. Intravenous disopyramide prolonged the functional refractory period of the atrium (p < 0.01) but had a variable effect on the effective refractory period. Oral disopyramide prolonged both effective and functional refractory periods (p < 0.025). In only six patients was ventricular refractoriness assessed. Intravenous disopyramide had no consistent effect on ventricular refractoriness,
The effects of disopyramide phosphate in the intravenous and oral form on the various components of the reentrant pathway during reciprocating tachycardia. The p values represent comparisons with control. The values shown are the cumulative means of seven patients.

whereas the oral preparation prolonged the functional refractory period of the ventricle (p < 0.005), but not the effective refractory period.

We examined the effects of disopyramide on the shortest and mean RR intervals during AF and the shortest atrial pacing cycle length at which 1:1 atrioventricular conduction occurred over the accessory pathway. These were both used as reflections of refractoriness in the accessory pathway. The shortest RR interval during AF (fig. 3A) was prolonged from 169 ± 18 to 226 ± 24 msec with i.v. disopyramide (p < 0.0001) and from 169 ± 18 to 248 ± 36 msec with the oral drug (p < 0.0001). The mean RR interval (fig. 3B) was prolonged from 255 ± 58 to 329 ± 62 msec with i.v. disopyramide (p < 0.005) and from 255 ± 58 to 350 ± 103 msec (p < 0.0005) with oral disopyramide. These highly significant prolongations of ventricular response during AF indicate a significant prolongation of refractoriness induced by disopyramide. Figure 4 shows ECG tracings of patient 7 during AF before treatment (fig. 4A), after treatment with quinidine sulfate (fig. 4B), and after treatment with oral disopyramide (fig. 4C). Quinidine with therapeutic blood levels did not reduce the ventricular response, whereas disopyramide in a dose of 300 mg every 6 hours markedly reduced the ventricular rate.

The shortest atrial cycle length at which 1:1 antegrade conduction occurred over the accessory pathway was frequently difficult to assess because of failure of atrial capture during atrial stimulation.* Consequently, numerical mean values could not be assigned to these values. However, with i.v. disopyramide, the shortest cycle length with 1:1 conduction over the accessory pathway definitely prolonged in four patients8-10, 11, 21 and with oral disopyramide it prolonged in seven of nine patients in whom it could be assessed.1, 4, 5, 9, 12

Often, antegrade or retrograde refractoriness in the accessory pathway could not be measured because atrial or ventricular refractoriness was longer than accessory pathway refractoriness.* Intravenous disopyramide definitely prolonged antegrade refractoriness in patients 9 and 12, but could not be assessed in the others. Oral disopyramide prolonged antegrade refractoriness in patients 1, 10 and 12 and retrograde refractoriness in patients 1, 2, 5, 7 and 12.

Therefore, indirect assessment of refractoriness by observing the ventricular response during AF and by direct observation in several individual patients suggested that disopyramide prolongs refractoriness in the accessory pathway.

As well as decreasing the ventricular rate during AF, disopyramide made the induction of fibrillation more difficult and reduced the duration of the fibrillation. Although precise quantification of the difficulty in inducing AF was not performed, induction of AF after disopyramide required shorter pacing cycle lengths, longer duration of pacing bursts, and more pacing bursts. Three patients required DC cardioversion during the control study, but after disopyramide all episodes of AF reverted spontaneously to sinus rhythm. Although disopyramide reduced the severity and duration of AF and prolonged the cycle length of reciprocating tachycardia, it did not reduce the frequency or ease of induction of reciprocating tachycardia. In patient 5, reciprocating tachycardia could not be induced in the control state, but could be repeatedly induced with disopyramide.

The serum levels of disopyramide are listed in table.
Most patients attained a higher blood level after chronic oral therapy than after the i.v. regimen. The mean level of 4.8 ± 0.9 µg/ml after oral medication was significantly greater than the mean level of 3.6 ± 0.7 µg/ml after i.v. disopyramide (p < 0.005). However, although the increase in cycle length and ventriculoatrial intervals during reciprocating tachycardia and the prolongation of shortest and mean RR intervals during AF appeared greater after oral than after i.v. disopyramide, there were no statistically significant differences between the electrophysiologic effects using these two regimens. Furthermore, we correlated the electrophysiologic response to the measured blood levels of the drug by a regression analysis and found that there was no apparent relationship between drug levels and change in cycle length, ventriculoatrial intervals, or shortest and mean RR intervals.

No patient developed acute hemodynamic side effects during i.v. infusion. Five patients developed gastrointestinal or anticholinergic side effects on oral medication. Six of 12 patients elected initially to have surgical interruption of their accessory pathway. In three cases, this was due to side effects of disopyramide and intolerance or ineffectiveness of other medications. In two cases, surgical treatment was chosen over lifelong medical therapy. In patient 7, the accessory pathway conducted only in the retrograde direction; disopyramide slowed reciprocating tachycardia, but did not reduce its frequency, and surgery was performed. Patient 2 remained on the oral drug for 14 months; although he tolerated it well, he had recurrent episodes of AF that required cardioversion three times. He subsequently underwent successful surgical interruption of his pathway.

Patients 1, 4, 5, 6 and 9 have continued on oral disopyramide during a follow-up of 12–33 months. All five of these patients had originally presented with AF. One patient has had mild constipation. All five have been well controlled on doses of 1000–1200 mg/day, with no episodes of rapid AF and no episodes of reciprocating tachycardia.

Discussion

The electrophysiologic effects of disopyramide phosphate have been studied in sinus node, atrioventricular node and atrial and ventricular muscle.6-18 The effects of the drug reflect a balance between the direct prolongation of refractoriness and the anticholinergic effect of the drug.26-27 In clinical studies, disopyramide has been shown to be effective in reducing both premature ventricular or atrial complexes and atrial arrhythmias.6, 25, 29, 32-38

Spurrell et al.9 examined the effects of i.v. disopyramide, 2 mg/kg, in three patients with WPW. They showed prolongation of antegrade conduction time over the pathway during sinus rhythm, retrograde conduction time during reciprocating tachycardia, and antegrade and retrograde refractoriness of the pathway after drug administration. Bennett10 studied the effects of i.v. disopyramide in six patients with WPW and showed a prolongation of the shortest and mean RR intervals during AF and a variable effect on reciprocating tachycardia.

In this study we have shown that disopyramide has two major electrophysiologic effects on the accessory pathways of patients with WPW. First, it slows conduction retrogradely through the pathway, as evidenced by prolongation of the ventriculoatrial intervals during reciprocating tachycardia. This resulted
in the prolongation of the cycle length of the tachycardia with the oral drug. Second, it prolongs refractoriness in the antegrade direction, as evidenced by the prolongation of the shortest and mean RR intervals during AF, by the prolongation of the shortest atrial cycle length with 1:1 conduction over the pathway, and by the prolongation of directly measured refractoriness in patients in whom it could be assessed.

These electrophysiologic effects may have variable efficacy in controlling reentrant arrhythmias in patients with WPW. If conduction velocity in the reentry circuit is slowed more than the refractoriness of the accessory pathway in the retrograde direction is prolonged, the window during which premature complexes can enter the circuit and initiate a tachycardia may be prolonged, resulting in easier induction of the reentrant tachycardia. This explains why reciprocating tachycardia was induced after disopyramide in patient 5, whereas it could not be induced in the control state. Disopyramide may have variable effects on other parts of the reentrant circuit, as seen in the variable AH intervals. Spurrell et al. reported variable effects on the AH interval with disopyramide, possibly because of the anticholinergic effect of the drug. Consequently, the effect on the reciprocating tachycardia may be variable.

Reentrant arrhythmias may also be controlled by abolition of premature atrial and ventricular complexes that may initiate the tachycardia. Disopyramide reduces ectopic complexes from both of these sites. Therefore, in certain circumstances, one might expect disopyramide to reduce the frequency of episodes of reciprocating tachycardia. Because of the variability of the effect of disopyramide on the elements of the reentrant circuit and on the initiating events of reciprocating tachycardia, the efficacy of the drug cannot be predicted in patients with WPW. Therefore, disopyramide, like other type I drugs, may increase, decrease or have no effect on the frequency of reciprocating tachycardia.

The prolongation of antegrade refractoriness of the accessory pathway produces very significant beneficial effects in patients with atrial fibrillation. The prolongation of refractoriness produces a reduction in the ventricular response during atrial fibrillation, and therefore, will help to reduce the risk of hemodynamic impairment and ventricular arrhythmias. This response was seen consistently in all patients who demonstrated antegrade conduction over their accessory pathways. As well as reducing the severity of the episodes of AF, disopyramide frequently curtailed the duration of the arrhythmia. The prevention of induction of the arrhythmia is another means by which a drug may be beneficial in patients with AF and WPW. Disopyramide has been shown to be beneficial in preventing atrial arrhythmias. Our study confirms this: Generally, AF was more difficult to induce after disopyramide. Although our long-term follow-up on oral therapy involved only five patients, the results suggest that oral disopyramide may be effective in controlling AF in patients with WPW.

The electrophysiologic effects of disopyramide appear similar to those of quinidine and procainamide. As with disopyramide, these drugs may also have variable effects on reciprocating tachycardia and, indeed, may exacerbate symptoms. Quinidine and procainamide may slow the atrial rate during AF and paradoxically increase the atrioventricular conduction and ventricular rate. We did not see this response with disopyramide.

Wellens et al. reported that other type I drugs (quinidine gluconate, procainamide and ajmaline), administered acutely, do not significantly prolong antegrade refractoriness in patients in whom the refractory period is initially short (i.e., in those patients with a

**Figure 4.** Twelve-lead ECGs from patient 1 during atrial fibrillation. (A) In the control state, his shortest RR interval was 150 msec. (B) Quinidine sulfate in an oral dose of 400 mg every 6 hours (blood level 5.9 mg/l) did not significantly reduce the ventricular response. (C) Disopyramide phosphate in an oral dose of 300 mg every 6 hours (blood level 5.5 μg/ml) prolonged the shortest RR interval to 230 msec and greatly reduced the ventricular rate.
rapid ventricular response to AF). Our study suggests that disopyramide differs from other type I drugs in this respect. We had eight patients in whom the shortest RR interval was initially less than 200 msec, and disopyramide produced a marked prolongation of this value in all eight. Furthermore, some patients who did not respond to other drugs responded to disopyramide (fig. 4). Thus, failure of one type I drug should not preclude a trial of another agent.

There appeared to be no statistically significant correlation between serum drug levels and electrophysiological response. This may be explained in part by variation in individual sensitivity to drugs and by the variable direct and parasympathetic effects of the drug. Chronic therapy may result in the appearance of electrophysiologically active drug metabolites and in a different tissue distribution of the drug, neither of which is accounted for by a comparison of electrophysiologic effect and measured serum drug level.

The negative inotropic effect of disopyramide has been shown to cause hemodynamic impairment in patients with diminished left ventricular function. Although most patients with WPW are young and have normal ventricular function, disopyramide should be used with caution in any patient with possible myocardial dysfunction.

From this study, we conclude that disopyramide has a beneficial effect in patients with WPW. The primary importance of this drug is in the control of AF, where it prolongs refractoriness in the accessory pathway and slows the ventricular response. It may have an added beneficial effect of preventing the induction of AF. Consequently, disopyramide is apparently effective in patients with WPW in whom a history of AF with a rapid ventricular rate is elicited. It provides an alternative to quinidine and procainamide in these cases. However, because of the variable effects of these agents and the risk of development of more severe arrhythmias, these patients should have AF induced electively while taking these medications.

References

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