The Effect of Concurrent Oral Administration of Propranolol and Disopyramide on Cardiac Function in Healthy Men

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SUMMARY Sixteen healthy men were evaluated for left ventricular performance changes and \( \beta \)-blockade after therapeutic oral doses of disopyramide and propranolol administered alone and concurrently. The volunteers were randomly assigned to receive one of two drug treatment regimens that differed in the sequence and duration of administration of the drugs. Left ventricular function was assessed by echocardiographically determined ejection fraction (EF) and systolic time intervals. Beta-blockade was assessed by changes in exercise heart rate. Both disopyramide and propranolol exhibited negative inotropic activity, as evidenced by significant, although clinically inconsequential, decreases in EF and increases in the ratio of prejection period to left ventricular ejection time. The negative inotropic effects of a single 200-mg dose of disopyramide and an 80-mg dose of propranolol were comparable, while chronic disopyramide therapy (200 mg every 6 hours for 1 week) had a greater negative inotropic effect than chronic propranolol therapy (80 mg every 8 hours for 1 week). Only propranolol had \( \beta \)-adrenoceptor blocking activity. When the drugs were administered concurrently, the negative inotropic effects of oral propranolol and disopyramide were neither additive nor synergistic.

DISOPYRAMIDE PHOSPHATE is a newly released drug that has significant type I antiarrhythmic activity.\(^1\)\(^-\)^\(^3\) Disopyramide has negative inotropic effects when administered intravenously or orally.\(^4\)-\(^10\) Antiarrhythmic agents, such as disopyramide, are frequently used in combination with other drugs to treat patients with cardiovascular disease, and it is important to recognize the potential for drug interactions. One class of drugs likely to be concurrently prescribed with disopyramide is the \( \beta \)-adrenoceptor blocking agents. Drugs in this class have negative inotropic effects. Davies and co-workers\(^11\) reported that administration in rapid succession of disopyramide (2 mg/kg) and the \( \beta \)-blocker acebutolol (0.5 mg/kg) to patients with severe coronary artery disease resulted in a significantly greater decrease in cardiac output than with disopyramide alone. The hemodynamic effects of concurrent oral administration of disopyramide and a \( \beta \)-blocker have not been reported.

We evaluated the cardiovascular effects of therapeutic oral doses of disopyramide and propranolol administered individually and determined whether their effects are additive when administered concurrently.

Protocol and Methods

Subjects

Sixteen healthy male volunteers (ages 18–29 years) participated in the study. Written, informed consent was obtained from each volunteer before participation in the study. The protocol for the study was approved by the Human Subjects Committee of the University of Kansas Medical Center. The subjects were considered healthy on the basis of a medical history, physical examination, selected laboratory tests and an exercise ECG.

Drug Schedules

The 16 subjects were randomly assigned to one of two drug treatment groups of eight each. The mean age and weight of group 1 subjects were 24.3 years and 71.6 kg, respectively; the mean age and weight of group 2 volunteers were 22.9 years and 75.3 kg, respectively. Group 1 volunteers followed drug schedule 1 (fig. 1), and group 2 volunteers followed drug schedule 2 (fig. 2). The schedules differed in the sequence and duration of administration of propranolol and disopyramide. The subjects following drug schedule 1 received a single oral dose of 80 mg of propranolol at 8:00 a.m. on day 1. Next, they took 200 mg of disopyramide orally every 6 hours from 8:00 a.m. on day 2 through 8:00 a.m. on day 8. After a washout period of 2 days, the subjects resumed taking disopyramide, 200 mg every 6 hours, at 8:00 a.m. on day 10 and continued the drug at this dose through 8:00 a.m. on day 22. At 8:00 a.m. on day 15, each subject ingested a single 80-mg dose of propranolol in addition to the disopyramide. During the final week of disopyramide therapy, 80 mg of
propranolol was concurrently administered every 8 hours.

Subjects following drug schedule 2 received a single oral dose of 200 mg of disopyramide at 8:00 a.m. on day 1. Propranolol, 80 mg every 8 hours, was started at 8:00 a.m. on day 3 and continued through 8:00 a.m. on day 22. At 8:00 a.m. on day 15, each subject ingested a single 200-mg dose of disopyramide in addition to the 80-mg dose of propranolol. During the final week of propranolol administration, 200 mg of disopyramide every 6 hours was also taken.

The subjects in each group were hospitalized in the Clinical Research Center at the University of Kansas Medical Center on the evenings before days 1, 8, 15 and 22 of the study. They remained hospitalized until completion of the pharmacodynamic tests on days 1, 8, 15 and 22. Subjects received no medication for at least 1 week before participation in the study and were instructed to take only the study medications during the investigational period. The subjects fasted (except for water) from 10:00 p.m. on the evening of admission until 2 hours after the 8:00 a.m. dose of propranolol and/or disopyramide was taken on days 1, 8, 15 and 22.

Pharmacodynamic Tests

Identical tests to evaluate the cardiovascular effects of the drugs were performed on both groups. The tests were performed just before (0 hour) and 1, 2, 3, 5 and 7 hours after the 8:00 a.m. dose of drug(s) on days 1, 8, 15 and 22. The following tests were performed: 1) resting supine blood pressure and heart rate; 2) echocardiographic measurement of left ventricular chamber dimensions; 3) systolic time intervals; and 4) a standardized exercise test (not performed at 7 hours).

The subjects rested in the supine position at least 5 minutes before beginning the pharmacodynamic tests. Resting supine heart rate was determined from an electrocardiographic tracing. Blood pressures were determined using sphygmomanometry (phase IV of the Korotkoff sound was used as the diastolic pressure). Echocardiograms were obtained with the subjects in the supine position using an EkoSector I ultrasound system (Smith Kline Instruments, Sunnvale, California). Simultaneous echoes were recorded from the left posterior ventricular wall and interventricular septum. From these tracings the left ventricular internal dimensions during diastole (LVIDd) and systole (LVIDs) were measured as described by Pombo et al.12 Mean values for LVIDd and LVIDs from 10 consecutive cardiac cycles were used to calculate left ventricular ejection fraction (EF). EF is expressed as a percentage of total left ventricular volume. The volunteers remained supine for determination of systolic time intervals (QS, left ventricular ejection time [LVET] and preejection period [PEP]) by previously described technique.13 The systolic time intervals for 10 consecutive cardiac cycles were measured and mean values were calculated. Calculation of the ratio PEP/LVET was done using PEP and LVET values not corrected for heart rate.

Finally, the subjects performed an exercise test in which they stepped on and off a platform 18 inches high at a rate of 30 steps/min for 3 minutes. The volunteer’s heart rate was monitored continuously by electrocardiography and the heart rate after 3 minutes of exercise was recorded. Between each series of tests on days 1, 8, 15 and 22 the subjects remained sedentary.

Blood Collections

Blood samples for determination of disopyramide levels were obtained just before and at intervals after the 8:00 a.m. dose of each drug on days 1, 8, 15 and 22. Plasma disopyramide levels (total concentration) were determined by gas chromatography.14

Statistical Analysis

Intragroup Differences

Differences between mean values for each variable at the six consecutive time periods (0, 1, 2, 3, 5 and 7 hours) for an individual study period (day 1, 8, 15 or 22) were examined using one-way analysis of variance (ANOVA) for repeated measurements.16 Considering 0 hour as the control, statistical differences between the mean of the control period and the mean of subsequent time periods were investigated for significance by the use of Dunnett’s test.16 Differences between the mean values of a variable at identical time periods (e.g., 0 hour) on the four test days (1, 8, 15 and 22) were also examined by ANOVA. The exact location of significant differences between means of each variable was investigated by use of the Newman-Keul’s test.16
Intergroup Differences

The t test was used to examine for significant differences between mean values at identical time periods on a study day in group 1 and the same or different study day in group 2.

Differences were considered statistically significant if the p value was less than 0.05.

Results

Group 1

The mean supine heart rates, systolic and diastolic blood pressures, EF, PEP/LVET and exercise heart rates for the subjects in group 1 are recorded in Table 1. Mean resting heart rates increased 15–30% during each study period, the maximum rate occurring 3 hours after drug ingestion. The heart rates on day 8 (after 1 week of disopyramide) were significantly higher (p < 0.05) than at the corresponding test periods on days 1, 15 and 22 (i.e., after propranolol alone or concurrently with disopyramide).

There were small but statistically significant (p < 0.05) decreases in systolic and diastolic blood pressures 1, 2, 3 and 5 hours after combined disopyramide and propranolol ingestion on day 15, and decreases (p < 0.01) in diastolic blood pressures 2, 3, 5 and 7 hours after combined drug ingestion on day 22. However, comparison of blood pressures at identical times on each of the four study periods (i.e., interday comparisons) did not reveal any significant differences.

The mean (± SD) EF before drug administration (0 hour) on day 1 was 72 ± 5%. EF fell slightly after a single 80-mg oral dose of propranolol, reaching a nadir of 65 ± 7% (p < 0.01) at 2 hours before returning toward predrug levels. The changes in mean PEP/LVET were inversely related to the changes in EF. The PEP/LVET at 0 hour was 0.31 ± 0.04 and increased to 0.35 ± 0.04 (p < 0.05) at 1 hour; subsequent PEP/LVET ratios were not significantly different from the predrug values. During chronic disopyramide therapy (day 8), the mean predose (0 hour) EF was 69 ± 7% and decreased slightly but insignificantly after the next dose of disopyramide. The lowest EF after chronic disopyramide dosing

Table 1. Summary of Pharmacodynamics in Group 1

<table>
<thead>
<tr>
<th>Day of study</th>
<th>0 (before drug)</th>
<th>1 (after drug)</th>
<th>2 (2 hours)</th>
<th>3 (1 hour)</th>
<th>5 (1 week)</th>
<th>7 (2 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting supine HR (beats/min)</td>
<td>61 ± 7</td>
<td>63 ± 7</td>
<td>67 ± 11†</td>
<td>70 ± 9‡</td>
<td>63 ± 7</td>
<td>65 ± 9</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>108/67</td>
<td>105/71</td>
<td>104/68</td>
<td>101t/63</td>
<td>103/64</td>
<td>104/65</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>72 ± 5</td>
<td>66 ± 6‡</td>
<td>65 ± 7‡</td>
<td>68 ± 6</td>
<td>69 ± 7</td>
<td>69 ± 4</td>
</tr>
<tr>
<td>PEP/LVET</td>
<td>0.31 ± 0.04</td>
<td>0.35 ± 0.04‡</td>
<td>0.33 ± 0.06</td>
<td>0.32 ± 0.05</td>
<td>0.31 ± 0.03</td>
<td>0.30 ± 0.03</td>
</tr>
<tr>
<td>HR after 3 minutes of exercise</td>
<td>171 ± 12</td>
<td>129 ± 13‡</td>
<td>125 ± 12‡</td>
<td>130 ± 10t</td>
<td>137 ± 12‡</td>
<td>ND §</td>
</tr>
</tbody>
</table>

*Values are mean ± SD. See text for interday comparative statistics.
†Significantly different from 0-hour value of same study day (p < 0.05).
‡Significantly different from 0-hour value of same study day (p < 0.01).
§Test not performed at this hour.
Abbreviations: HR = heart rate; PEP/LVET = ratio of preejection period to left ventricular ejection time; ND = not done.
(64 ± 6% at 2 hours after a dose) was not significantly different from the lowest EF after the single dose of propranolol administered on day 1. After chronic administration of disopyramide (day 8), the mean 0-hour value for PEP/LVET was significantly higher ($p < 0.05$) than the 0-hour ratio on day 1 and increased to a peak of 0.39 ± 0.07 2 hours after the next disopyramide dose. However, the mean peak PEP/LVET during this disopyramide dosing interval was not significantly different from the highest value after a single dose of propranolol (day 1).

Ingestion of 80 mg of propranolol in addition to 200 mg of disopyramide on day 15 was associated with a significant ($p < 0.05$) decrease in EF and an increase in PEP/LVET at 1 and 2 hours after dose. However, these changes were not significantly different from those seen during a dosing interval during chronic disopyramide therapy alone (day 8). Insignificant changes in EF and PEP/LVET were observed after 1 week of propranolol and 3 weeks of disopyramide (day 22) administration. In addition, the mean EFs on day 22 were not significantly different from those during previous study periods. The mean PEP/LVET ratios after the 8:00 a.m. drug dose on day 22 were consistently lower ($p < 0.05$) than the values at identical times measured after either 1 week of disopyramide administration alone (day 8) or after 2 weeks of disopyramide plus a single dose of propranolol (day 15).

The baseline (0 hour) exercise heart rate on day 1 was 171 ± 12 beats/min. One hour after a single dose of propranolol the exercise heart rate decreased to 129 ± 13 beats/min, and remained significantly below ($p < 0.01$) the baseline rate through 5 hours. Disopyramide did not significantly alter exercise-induced tachycardia or the β-adrenergic blocking activity of propranolol, as measured by exercise heart rate.

The steady-state plasma disopyramide level immediately preceding a drug dose on day 8 was 2.78 ± 0.53 μg/ml. The mean peak level was 3.86 ± 0.73 μg/ml and the time to peak was 2.5 hours. The disopyramide levels gradually decreased to a mean level of 2.44 ± 0.48 μg/ml at 7 hours. The plasma disopyramide levels on day 22 closely paralleled those seen on day 8, with a 0-hour level of 2.64 ± 0.81 μg/ml, a peak of 3.64 ± 0.63 μg/ml at 2.5 hours and a gradual decline to 2.51 ± 0.68 μg/ml at 7 hours.

**Group 2**

The mean supine heart rate, systolic and diastolic blood pressures, EF, PEP/LVET and exercise heart rates in group 2 subjects are recorded in table 2. As in group 1, the resting heart rates were lowest at 0 hour and peaked at 3 hours. A single dose of disopyramide raised the mean resting heart rate at 2, 3 and 5 hours ($p < 0.01$), as well as at identical times after administration on subsequent study days (8, 15 and 22) when the volunteers were also receiving propranolol, although less than when receiving disopyramide alone.

A significant decrease in diastolic blood pressure was observed only at 2, 3 and 5 hours after propranolol ingestion on day 8 ($p < 0.05$). The mean diastolic pressures at 1 through 7 hours during chronic propranolol therapy (day 8) were lower ($p < 0.01$) than those at corresponding times after a single dose of disopyramide. The diastolic pressures at 2, 5 and 7 hours after chronic propranolol plus a single dose of disopyramide (day 15) were also lower ($p < 0.05$) than after disopyramide alone. Blood pressures on day 22 (chronic propranolol and chronic disopyramide therapy) were similar to those after a single 200-mg dose of disopyramide.

The baseline EF was 73 ± 7%, comparable to the value in group 1. One hour after administration of a single 200-mg oral dose of disopyramide, EF fell to 62 ± 7% ($p < 0.01$). Subsequently, EF gradually returned toward baseline levels. Concomitant with the decrease in EF was a marked increase in the mean PEP/LVET, from 0.31 ± 0.06 at 0 hour to 0.37 ± 0.08 at 1 hour ($p < 0.01$). During chronic propranolol administration (day 8), the mean EF at 0 hour was 75 ± 4% and did not decrease significantly after a dose of propranolol. Similarly, on day 8 there were no significant changes in mean PEP/LVET. Ingestion of 200 mg of disopyramide in addition to the propranolol dose on day 15 decreased the EF to 70 ± 4% at 2 hours ($p < 0.01$) and increased the PEP/LVET to 0.36 ± 0.04 at 1 hour ($p < 0.01$). However, these changes did not exceed the changes after a single oral dose of disopyramide. On day 22 (after 3 weeks of propranolol and 1 week of disopyramide), the mean EF decreased from 71 ± 3% at 0 hour to a minimum of 64 ± 5% at 1 hour ($p < 0.01$); EF subsequently returned to 72 ± 3% at 3 hours and remained at this level for the duration of the study period. On day 22 the mean PEP/LVET at 0 hour was 0.35 ± 0.03, significantly higher ($p < 0.01$) than the 0-hour value during the three previous study periods. However, the mean PEP/LVET ratio did not increase significantly after drug administration on day 22. During a dosing interval during chronic disopyramide and propranolol therapy (day 22), the minimum values for EF were not significantly less and the peak values for PEP/LVET were not significantly greater than those after a single dose of disopyramide alone or with chronic propranolol therapy (days 1 and 15, respectively).

A single dose of disopyramide did not affect exercise-induced increases in heart rate. The exercise heart rate was significantly lower ($p < 0.01$) during chronic propranolol therapy (day 8) than after a single dose of disopyramide (day 1). Even chronic administration of disopyramide did not alter the effect of propranolol on exercise-induced tachycardia.

In group 2, the mean peak plasma disopyramide levels were similar after single doses of disopyramide on days 1 and 15 (2.24 ± 0.82 μg/ml and 2.64 ± 0.70 μg/ml, respectively). The time to peak level was 1.5 hours on both days. Mean levels 7 hours after dose were 1.49 ± 0.52 μg/ml on day 1 and 1.77 ± 0.60 μg/ml on day 15.
Table 2. Summary of Pharmacodynamics in Group 2

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<th></th>
<th></th>
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<td>2</td>
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<tr>
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<tr>
<td></td>
<td>22</td>
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<td>PEP/LVET</td>
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<td>0.37 ± 0.07‡</td>
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<td>112 ± 6</td>
<td>109 ± 3†</td>
<td>111 ± 4</td>
<td>116 ± 6</td>
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</tbody>
</table>

*Values are mean ± so. See text for interday comparative statistics.
†Significantly different from 0-hour value of same study day (p < 0.05).
‡Significantly different from 0-hour value of same study day (p < 0.01).
§Test not performed at this hour.
Abbreviations: HR = heart rate; PEP/LVET = ratio of preejection period to left ventricular ejection time; ND = not done.

Intergroup Differences

Ingestion of a single 200-mg dose of disopyramide (day 1) by group 2 volunteers did not significantly decrease the mean EF or increase the mean PEP/LVET more than a single 80-mg dose of propranolol (day 1) in group 1 volunteers (fig. 3). However, administration of disopyramide, 200 mg every 6 hours, for 1 week had a significantly greater (p < 0.05) effect on EF and PEP/LVET than administration of propranolol, 80 mg every 8 hours, for 1 week (fig. 4).

The effects on EF and PEP/LVET of a single dose of disopyramide in group 2 volunteers were equivalent to those after a dose at the end of 1 week of disopyramide therapy in group 1 (fig. 5). Although the effects on PEP/LVET and exercise heart rate of a single dose and 1 week of propranolol treatment were comparable, the EF during a dosing interval after 1 week of propranolol (day 8) in group 2 was significantly less (p < 0.05) than after an initial single dose of propranolol (day 1) in group 1 (fig. 6).

Despite differences in the sequence of addition of
chronic therapy of one drug to chronic therapy with the other, after 1 week of therapy with both drugs (day 22 in both groups), there were no differences in EF, PEP/LVET and exercise heart rate (fig. 7).

**Discussion**

This study confirmed the negative chronotropic properties of propranolol. Disopyramide neither exhibited β-adrenergic blocking effect, as measured by acute inhibition of exercised-induced increase in heart rate, nor altered the negative chronotropic effect of propranolol. These findings are not surprising, because disopyramide was found devoid of β-blocking effect in experimental animals.¹⁷

Rangno et al.¹⁸ reported a mild transient decrease in supine blood pressure in three patients given disopyramide who had been taking propranolol chronically. Although fluctuations in blood pressure were documented in this study, we did not observe any clinically significant changes with the various drug regimens used in the healthy subjects.

Both propranolol and disopyramide exhibited negative inotropic activity in normal volunteers, as evidenced by decreases in the left ventricular EF determined by echocardiography and increases in the PEP/LVET ratio. The peak changes in EF and PEP/LVET occurred 1–3 hours after drug ingestion, corresponding with the time of peak disopyramide levels determined in our investigation and the time of peak propranolol levels after oral dosing reported in the literature.¹⁹ By the end of a dosing interval (5–7 hours after drug ingestion) EF and PEP/LVET usually returned to predose levels.
Ventricular performance after an initial single oral dose of disopyramide and after a dose at the conclusion of 1 week of chronic administration was equivalent. Therefore, repeated dosing of disopyramide resulting in higher serum levels does not result in a greater negative inotropic effect. However, the negative inotropic effect seen after 1 week of propranolol therapy was less than that seen after an initial dose of propranolol, suggesting development of tolerance to propranolol in these healthy subjects. We cannot explain the reason for this finding.

There are few studies comparing the negative inotropic effects of antiarrhythmic agents. Using an in vitro method, Hammermeister and co-workers compared the effects on myocardial contractility of propranolol, phenytoin, lidocaine, quinidine and bretylium, but not of disopyramide. When compared at concentrations comparable to the maximal human therapeutic concentration, phenytoin had the greatest negative inotropic effect. The effects of propranolol, quinidine and lidocaine were equivalent, and slightly less than that of phenytoin, while procainamide and bretylium had no negative inotropic effects. In our study, intergroup comparison revealed that the initial 200-mg oral dose of disopyramide had no greater negative inotropic effect than the initial single 80-mg oral dose of propranolol; however, 1 week of disopyramide therapy had significantly greater negative inotropic effect than 1 week of propranolol therapy. Because of its negative inotropic activity, the use of propranolol in patients with compromised cardiac function has been discouraged. Although our conclusions regarding the relative effects of disopyramide and propranolol may not be applicable to patients with impaired ventricular performance, disopyramide, with greater negative inotropic activity than propranolol in healthy subjects, should also be used with caution in patients with cardiac decompensation. Vismara et al. reported a patient with extensive coronary artery disease and left ventricular dysfunction in whom the long-term dose of disopyramide had to be reduced because of probable worsening of pump function by the drug. Recently, Story and co-workers reported a patient with previous myocardial dysfunction who developed reversible cardiogenic shock most likely due to oral administration of disopyramide.

Concomitant administration of propranolol and disopyramide did not result in a greater negative inotropic effect than that seen with disopyramide alone. However, this result in healthy subjects should not be interpreted to mean that the patient with cardiac disease who does not develop clinically significant heart failure on disopyramide will not develop failure after the addition of propranolol to his drug regimen. Such a patient may be dependent on sympathetic drive for maintenance of an adequate cardiac output and the addition of propranolol may block a compensatory mechanism.

In summary, both propranolol and disopyramide exhibit negative inotropic effects in normal volunteers, but disopyramide had relatively more effect than propranolol, especially after chronic administration of the doses used in this study. Only propranolol displayed β-adrenergic receptor blocking activity. When administered concurrently, the negative inotropic effects of oral propranolol and disopyramide are neither additive nor synergistic. In healthy humans, the negative inotropic effects of propranolol and disopyramide administered orally, individually or concurrently were not clinically significant. However, in patients with decreased ventricular performance, administration of propranolol or disopyramide alone or in combination may depress it further, causing or worsening clinical heart failure. Therefore, use of these drugs in this group of patients must be approached with caution.

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