Effects of Intravenous Disopyramide on Myocardial Function in Patients with Different Degrees of Cardiac Failure

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SUMMARY

The effects of intravenous disopyramide phosphate on myocardial function were evaluated by non-invasive indices of cardiac performance (systolic time intervals, STI) in 15 patients with atherosclerotic heart disease and different degrees of cardiac failure. Disopyramide (1.5 mg/Kg) was given intravenously over a period of 5 min. This drug induced in patients in I–II classes of NYHA a significant decrease of LVETc, while PEP, ICT, and PEP/LVET ratio rose significantly.

STI were affected much more markedly in patients in III–IV classes of NYHA. Particularly affected were contractility indices (PEP, ICT, PEP/LVET), which were reduced significantly more in patients in III–IV classes as compares to patient in I–II classes. In contrast, LVETc, which correlates to stroke volume and cardiac output, was similarly worsened by the drug in the 2 groups of patients.

Therefore, this study shows that disopyramide has relevant depressant effects on myocardial performance, simultaneously reducing stroke volume and contractility, and that the effect on contractility is more marked in patients with severe left ventricular impairment.

Additional Indexing Words:
Disopyramide phosphate Dysrhythmias Systolic time intervals Myocardial function

The effects of disopyramide on the electrophysiological properties of the heart and its action on ventricular and supraventricular arrhythmias have been recently studied.1)–7)

Moreover, it has been also demonstrated that disopyramide decreases cardiac output, coronary blood flow and myocardial contractility in intact dogs8)–9) and decreases contractility in isolated perfused rabbit hearts.9) This detrimental effect on cardiac performance induced by disopyramide was not...
prevented by previous administration of ouabain or digitoxin.\textsuperscript{9}) It has also been shown that in normal subjects doses of this drug which would prevent arrhythmias do not induce depressant effects on contractility or on other hemodynamic factors,\textsuperscript{10)} whilst they might cause alterations in cardiac performance in patients with cardiac disease.\textsuperscript{11)--15)} Thus, it seems likely that the depressant effects of disopyramide are most marked whenever ventricular myocardium is severely impaired.

Accordingly, in this study the effects of this drug on cardiac inotropism in patients with heart diseases in different functional classes of NYHA were studied. Cardiac performance was assessed by systolic time intervals (STI), which well correlate with the invasive indices of myocardial contractility.\textsuperscript{16)--23)}

**Materials and Methods**

A total of 15 patients aging between 45 and 60 were included in the study. They presented clinical and electrocardiographic signs of atherosclerotic cardiomyopathy, never associated with kidney failure. After the explanation of the goal of the study and of the methods utilized, a written consent was obtained from each of the patients. According to cardiac conditions, 8 patients were classified in the 1st or 2nd class of NYHA, while the remaining 7 were in the 3rd or 4th class. They were not receiving digitalis, diuretics or antiarrhythmic agents for at least 3 days prior to the disopyramide administration. Patients were not allowed to take any food, to drink coffee, tea or alcohol, nor to smoke for at least 12 hours before the study. In the early morning, while the patients were lying in the supine position on a comfortable examination bed, in a quiet room at the constant temperature of $20\pm1.5^\circ\text{C}$, disopyramide phosphate (1.5 mg/Kg) was given intravenously over a period of 5 min. STI were measured by recording simultaneously electrocardiogram, phonocardiogram and carotid pulse at a rapid paper speed (100 mm/sec) on a multichannel photographic polygraph (Electronics for Medicine Model DR8). STI were recorded prior to, immediately after, and at 5, 10, 15, and 30 min after the administration of the drug; systemic arterial blood pressure was also measured at the same times by cuff sphygmomanometer. The following parameters were calculated: left ventricular ejection time (LVET), from the onset of the sharp upstroke of the carotid pulse wave to the dicrotic notch; the Q-S1 interval from the onset of QRS to the first high-frequency vibration of the first heart sound; pre-ejection period (PEP) by subtracting LVET from Q-A2 interval; isometric contraction time (ICT) by subtracting Q-S1 from PEP; and PEP/LVET ratio. LVET values were also corrected for heart rate, applying the regression equation proposed by Weissler.\textsuperscript{23)} In contrast, PEP was not corrected for heart rate, since previous studies demonstrated that this parameter is not rate-dependent.\textsuperscript{24),25)} The statistical analysis was carried out by standard methods.
RESULTS

I. Patients in I-II class (NYHA)

In this group of patients, disopyramide injection did not affect LVET significantly, while when corrected for heart rate (LVETc) it was reduced slightly but significantly. The maximal change of LVETc was $-15.4 \pm 5.6$ (p<0.05). In contrast, PEP, ICT, and Q-S1 were significantly elevated following the drug, their maximal change being $17.5 \pm 2.5$ (p<0.001) from the control value for PEP, $13.1 \pm 1.9$ (p<0.001) for ICT and $5 \pm 2.1$ (p<0.05) for Q-S1. As a consequence of the increased PEP, PEP/LVET ratio also rose significantly by $0.08 \pm 0.01$ (p<0.001) (Table I, Figs. 1, 2).

II. Patients in III-IV class (NYHA)

In this group of patients with more severe heart failure, disopyramide injection caused a significant decrease of both LVET and LVETc by $-21.4 \pm 5.7$ (p<0.05) and $-23.9 \pm 8.5$ msec (p<0.05), respectively. Simultaneously, a marked augmentation of PEP ($31.4 \pm 2.6$, p<0.001), ICT ($25 \pm 2.2$, p<0.001) and PEP/LVET ratio ($0.21 \pm 0.01$, p<0.001) was observed. Q-S1 interval also showed a significant rise after disopyramide from $75.7 \pm 3.0$ to $83.6 \pm 2.1$ msec (p<0.001). It is noteworthy that changes induced by the

Table I. Changes Induced by Disopyramide on Hemodynamics in Patients in I-II Classes of NYHA (A) and in III-IV Classes of NYHA (B)

<table>
<thead>
<tr>
<th>M.A.P. mmHg</th>
<th>H.R. beats/min</th>
<th>LVET msec</th>
<th>LVETc msec</th>
<th>PEP msec</th>
<th>Q-S1 msec</th>
<th>ICT msec</th>
<th>PEP/LVET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>99.0 ± 3.0</td>
<td>66.9 ± 2.8</td>
<td>298.7 ± 8.7</td>
<td>413.7 ± 6.4</td>
<td>91.2 ± 3.5</td>
<td>65.6 ± 2.6</td>
<td>0.31 ± 0.01</td>
</tr>
<tr>
<td>A After</td>
<td>104.0 ± 5.0</td>
<td>64.8 ± 2.9</td>
<td>288.7 ± 9.3</td>
<td>394.8 ± 8.1</td>
<td>108.7 ± 4.4</td>
<td>70.6 ± 3.2</td>
<td>38.7 ± 0.22</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</table>

| Before      | 126.0 ± 9.0    | 95.8 ± 5.2| 231.4 ± 8.3| 393.0 ± 3.9| 108.6 ± 2.6| 75.7 ± 3.0| 32.8 ± 0.04|
| B After     | 127.0 ± 11.0   | 94.1 ± 2.9| 210.0 ± 6.5| 369.1 ± 9.6| 140.0 ± 4.4| 83.6 ± 2.1| 57.8 ± 0.02|
| p           | NS             | NS        | <0.05      | <0.001   | <0.001    | <0.001   | <0.001   |

| ΔA          | 5.0 ± 1.5      | -2.1 ± 1.0| -10.0 ± 4.3| -15.4 ± 5.6| 17.5 ± 2.5| 5.0 ± 1.9| 13.1 ± 0.08|
| ΔB          | 1.0 ± 1.2      | -1.7 ± 1.2| -21.4 ± 5.7| -23.9 ± 8.5| 31.4 ± 3.1| 7.9 ± 2.2| 25.0 ± 0.01|
| p           | NS             | NS        | NS         | <0.01     | NS        | <0.05    | <0.01    |

MAP = mean arterial pressure; H.R. = heart rate; LVET = left ventricular ejection time; LVETc = left ventricular ejection time corrected for heart rate; PEP = pre-ejection period; Q-S1 = Q-S1 interval; ICT = isometric contraction time. All numbers are mean±1SE.
drug were more marked in this group than in the group of patients in classes I–II, at least for the indices of contractility. Actually, by comparing changes induced on STI by the drug in the 2 groups of patients, it was shown that the increase in PEP, ICT, and PEP/LVET ratio following disopyramide was significantly greater in patients in III–IV classes, as compared to those in I–II classes (Fig. 2). In contrast, LVETc, which correlates to stroke volume, was similarly worsened by the drug in the 2 groups of patients (Fig. 2). These changes of STI became evident after 5–10 min and disappeared about 30
Fig. 2. Changes induced by disopyramide on systolic time intervals in patients in I-II classes of NYHA (solid columns, n=8) and in patients in III-IV classes of NYHA (dotted columns, n=7). Note that contractility indices are more severely affected in patients in III-IV class of NYHA as compared to those in I-II class.

* Different from I-II class of NYHA, p<0.05
** Different from I-II class of NYHA, p<0.01
All numbers are mean±1SE.

Discussion

The efficacy of disopyramide in interrupting different types of arrhythmias has been demonstrated. In particular, this drug proved to be specially active on ventricular arrhythmias, such as ventricular tachycardia and threatening premature ventricular contractions. Moreover, the hemodynamic effects of this antiarrhythmic and its depressant action on cardiac contractility were explored in the experimental animal as well as in healthy men. However, little information is available concerning its effects on cardiac performance in patients with heart disease and the possible different actions of disopyramide in subjects with different degrees of cardiac failure. To evaluate cardiac performance, the non-invasive measurement of STI was preferred to invasive indices. The reason for this choice was that in obtaining the indices of cardiac performance invasively, results could be altered by the emotional stress and the consequent catecholamines release always connected with invasive studies. Furthermore, invasive indices cannot be corrected for heart rate and, thus, changes in this parameter can lead to a misinterpretation of the data. The results of this study confirm the depressant effects of the drug on cardiac performance, as shown by changes in most of the
examined parameters in the absence of changes in the heart rate and systemic blood pressure. Also LVET in patients in I–II classes did not change significantly; however, this value corrected for heart rate showed a small but significant reduction. Since LVETc is closely correlated to left ventricular stroke volume, its reduction indicate that disopyramide affects negatively cardiac output. Similar results were obtained in patients in III–IV classes, although in this group the reduction in LVETc appeared to be more marked. However, the reduction of this index in the 2 groups of patients did not differ significantly, thus showing that stroke volume is decreased almost similarly, independently from the degree of cardiac failure. Disopyramide also induced in this group of patients a significant increase in PEP, ICT, and PEP/LVET ratio, thus showing that this drug has a deleterious effect on left ventricular contractility in patients with cardiac failure. This deleterious effect appears to be more evident in patients in III–IV classes of NYHA, i.e. in subjects with severe impairment of cardiac function, as compared to those in I–II classes, since in the former there is a significant greater increase of these indices of cardiac contractility. Therefore, these results indicate that disopyramide affects cardiac performance in patients with cardiac failure and that heart contractility is affected more severely in patients with severely impaired heart function.

In conclusion, since it is likely that many patients presenting arrhythmias will also suffer from cardiac failure, the results of this study suggest that caution should be payed in the treatment of arrhythmias with disopyramide in patients with severe left ventricular impairment.

REFERENCES


