Diphenidol Treatment of Arrhythmias*

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The antiarrhythmic activity of diphenidol, an antiemetic, has been demonstrated both in electrophysiologic studies of patients and in experimental arrhythmias in animals. Accordingly, 18 patients with tachyarrhythmias were treated with intravenous diphenidol in doses of 0.5 to 1.5 mg/kg. In six patients with atrial arrhythmias, there was no notable effect. Similarly, 12 patients with premature ventricular contractions were treated and studied. In six of them, ectopic beats were abolished, at least transiently; in three the number of ventricular premature contractions decreased; in two there was no effect; and in one, the number of premature beats was increased. Of the total number of 18 patients, 14 suffered adverse effects related to the central nervous system. These adverse effects were of such severity as to suggest that further studies with diphenidol as an antiarrhythmic are not warranted.

Diphenidol (Voltont)‡ has antiarrhythmic activity in animal models.1-4 Its effectiveness in human digitalis-induced arrhythmias has been reported recently.5 No mention of adverse effects from diphenidol is made in that report. In the study here in reported, 18 patients with arrhythmias were treated with diphenidol intravenously. Although antiarrhythmic activity was demonstrated, 14 of these patients developed adverse effects related to the nervous system, which were of such severity that the study had to be terminated.

METHODS

Eighteen patients (ages 47-80) were studied after the investigative nature of the study had been disclosed to them and their written consent obtained. In the group, two patients had atrial premature beats, two had atrial fibrillation, and two had atrial flutter. The other 12 were treated for frequent ventricular premature beats. Of 11 patients who had received cardiac glycosides, none was considered to have digitalis intoxication.

An intravenous infusion of 5 percent dextrose or of 0.9 percent saline solution was established as a route for administration of medications. Two placebo injections of either saline or 5 percent dextrose solution were made 5 minutes apart. Then, at 5-minute intervals, the following doses of diphenidol were administered: 0.2 mg/kg, 0.3 mg/kg, 0.5 mg/kg and 0.5 mg/kg. If significant antiarrhythmic or adverse effects occurred, the dosage schedule was interrupted.

For this study the electrocardiogram was monitored continuously on an oscilloscope and recorded at frequent intervals on a direct writing electrocardiograph at the bedside. A continuous tape recording (Avionics Research Products electrocardiograph) was also made. The tapes were subsequently scanned and the rate, rhythm, and count of premature beats were determined during the third and fifth minute of each five-minute segment. The sampling periods were selected arbitrarily, but were used consistently for all the recordings.

RESULTS

With regard to any antiarrhythmic effect, placebo injections proved negative. Diphenidol produced no effect in either patient with atrial fibrillation (Table 1). In both patients with atrial flutter, the atrial rate slowed slightly (10 percent) after treatment, with a concomitant decline in ventricular rate but no change in the 2:1 atrioventricular block. In the two patients with atrial premature contractions, there was no change in the incidence of premature beats after treatment.

Ventricular premature beats were abolished, at least transiently, in six patients, decreased in three, remained unchanged in two, and increased in one after diphenidol treatment. Of the six patients in

<table>
<thead>
<tr>
<th>Table 1—Antiarrhythmic Effects of Diphenidol</th>
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<tbody>
<tr>
<td>Rhythm</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Atrial flutter</td>
</tr>
<tr>
<td>Atrial premature contractions</td>
</tr>
<tr>
<td>Ventricular premature contractions</td>
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<td></td>
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</table>
DIPHENIDOL

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4)111C.
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fourteen

patients

were

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two

received

0.5

mg/kg;
one

received

1.0

mg/kg;
and

three

received

1.5

mg/kg
total
dose

diphenidol

Table 2—Ventricular Premature Contractions

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Digitalis</th>
<th>Diphenidol dose (mg/kg)</th>
<th>Placebo 1st dose (mg/kg)</th>
<th>Placebo 2nd dose (mg/kg)</th>
<th>Diphenidol VPC (count per minute)</th>
<th>Diphenidol (time after total dose)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>1.5</td>
<td>40 30 42</td>
<td>0 30 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>1.5</td>
<td>11 19 14</td>
<td>3 1 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>0.5</td>
<td>15 11 12</td>
<td>0 0 6</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>No</td>
<td>1.0</td>
<td>9 8 11</td>
<td>14 17 18</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>No</td>
<td>1.5</td>
<td>7 5 5</td>
<td>6 6 8</td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>1.0</td>
<td>38 40 37</td>
<td>38 44 41</td>
<td></td>
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</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>1.5</td>
<td>13 11 9</td>
<td>1 0 0</td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>1.0</td>
<td>2 2 3</td>
<td>0 0 0</td>
<td></td>
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</tr>
<tr>
<td>9</td>
<td>No</td>
<td>0.5</td>
<td>15 17 9</td>
<td>0 0 0</td>
<td></td>
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</tr>
<tr>
<td>10</td>
<td>Yes</td>
<td>0.5</td>
<td>17 14 12</td>
<td>5 2 5</td>
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<tr>
<td>11</td>
<td>Yes</td>
<td>1.0</td>
<td>17 16 18</td>
<td>12 12 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>No</td>
<td>1.0</td>
<td>10 8 4</td>
<td>11 5 12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The duration of the antiarrhythmic effect varied from 20 to 240 minutes, with an average effective time of 88 minutes.

Adverse Effects

Fourteen of the 18 patients developed adverse central nervous system effects (Table 3). Two of those without adverse effects received only 0.5 mg/kg total dose. Usually the first effect noted was drowsiness, soon replaced by manifestations of central nervous system stimulation such as restlessness, agitation and confusion. These symptoms were very poorly tolerated by the patients who often tried to climb from bed, becoming acutely uncooperative and detaching their monitoring electrodes and infusion equipment. One patient appeared to hallucinate. Six patients also developed parasympatholytic symptoms of dry mouth, hot feeling with or without flushing, or both. These adverse effects lasted from a few minutes to as long as six hours, but abated in most patients in 30 to 60 minutes. Later interviews with the patients substantiated the magnitude of the adverse effects, some of the patients indicating that they would not accept the drug again.

A decline in systolic and diastolic blood pressure of 20 mm Hg for 60 minutes was seen in one subject whose total dose was 0.5 mg/kg. No other changes in blood pressure occurred.

In two patients, dyspnea developed. One of these developed increased pulmonary rales which cleared gradually after being treated with intravenous furosemide. The other patient spontaneously improved in ten minutes.

Table 3—Adverse Effects of Diphenidol

<table>
<thead>
<tr>
<th>Effect on Patient</th>
<th>IV Dose (mg/kg)</th>
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<tbody>
<tr>
<td></td>
<td>0.5</td>
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<tr>
<td></td>
<td>(n=4)</td>
</tr>
</tbody>
</table>

A. Central Nervous System

Central

Drowsiness 2 3 3
Restlessness 3 4
Confusion 1 2
Hallucinations 1
Paresthesias 1 1
Slurred speech 2
Parasympatholytic
Dry mouth 1 3
Hot, flushed 3

B. Cardiovascular

Hypotension 1

Worsening of congestive failure 1 1

C. Patients without any adverse effects 2 0 2

*As a patient may have had more than one adverse effect, the total of adverse effects exceeds the number of patients affected.

Discussion

The cardiovascular effects of diphenidol have been summarized by Mandel et al.4 (1) Electrophysiologic studies showed depression of dv/dt, shortening of the action potential duration, rightward and downward shift of the membrane responsiveness curve, depression of action potential amplitude and overshoot, and suppression of ouabain or epinephrine induced automaticity; (2) hemodynamic studies showed no significant effect on cardiac output, total peripheral resistance, arterial pressure, stroke volume or coronary flow at effective antiarrhythmic doses; (3) antiarrhythmic studies showed diphenidol to reverse digitalis induced tachyarrhythmias while shortening the A-H
time (His bundle electrograms) which had been prolonged by the digitalis. Diphenidol also protected against glycoside lethality. In our laboratory, diphenidol 3-6 mg/kg reversed ouabain-induced ventricular tachycardia in seven of eight dogs (unpublished observations).

In the human studies reported here, an antiarhythmic action for diphenidol is confirmed. There was a reduction in ventricular premature contractions in 9 of 12 patients. However, the marked adverse effects of diphenidol would appear to preclude its clinical usefulness. These predominantly central nervous system effects could not have been predicted from the cardiovascular studies in anesthetized animals, but might have been anticipated from the known pharmacologic and toxic effects of the drug.6,7 Diphenidol's action as an antiemetic and its induction of drowsiness, confusion and hallucinations in man all indicate CNS activity. Excitement, tremors, ataxia and convulsions occur when toxic doses are given to dogs.

Animal studies have also shown diphenidol to have parasympatholytic activity.6 Thus, the complaints of dry mouth, flushed hot feeling and even some of the central nervous system effects might have been expected on this basis.

Although observations in man support the antiarhythmic action of diphenidol, they also demonstrate an unacceptable frequency and severity of adverse effects. No effects, therapeutic or adverse, were noted at the lowest dose studied (0.2 mg/kg), but at 0.5 mg/kg two patients had significant complaints and this dose was effective in only two of the 18 patients treated. It would therefore be likely that lower doses would prove to be ineffective. Furthermore, the duration of the adverse effects seems to be similar to the duration of the antiarhythmic effect. While the animal studies and the report of Cecena5 indicate that diphenidol would be especially effective against digitalis induced tachyarrhythmias, this hypothesis was not tested here as such patients were not available in our study.

It may be, as suggested by Mandel,8 that “further investigation of antiemetic or antivertigo agents should be carried out since these drugs may be a possible source of new antiarhythmic agents.” However, adverse central nervous system effects from these agents must also be anticipated in view of their mechanism of antiemetic action and in view of our experience with diphenidol.

REFERENCES

7 AMA Drug Evaluations, 1st ed. Chicago, American Medical Association, 1971, p 49