Studies on the Use of Dioxyline Phosphate in the Treatment of Angina Pectoris

By Ralph C. Scott, M.D., Vincent J. Seiwert, M.D., Noble O. Fowler, Jr., M.D., and Johnson McGuire, M.D.

Dioxyline phosphate, on the basis of pharmacologic studies, appeared to be worthy of trial in the treatment of the anginal syndrome. The patients were studied during a control period and during alternate periods of placebo and dioxyline phosphate administration. Exercise tolerance tests were performed during each of the three periods of observation. The dosage of dioxyline phosphate was 800 mg. per day orally. Five of the 12 patients with angina experienced fewer pains while taking dioxyline phosphate than they did during either the control period or the period of placebo administration. The low incidence of serious side reactions was a conspicuous feature of the study.

PAPaverine was first suggested for the treatment of angina pectoris by Pal in 1913. Experimental it was shown to be a good coronary vasodilator in the dog. Elek and Katz, using a higher dosage of papaverine than had been used by previous investigators, reported very favorable results in patients with angina. It was therefore recommended and widely used in the prophylaxis and treatment of anginal attacks. More recent clinical studies, however, have shown it to be of little or no more value than placebo. Additional, probably unwarranted, criticism of papaverine has been the possibility of addiction, since it is an alkaloid of opium.

Recently, a synthetic compound, which is similar to papaverine in chemical structure, has been reported by Henderson, Shipley, and Chen. This compound chemically is 6,7-dimethoxy - 7' - (4' - ethoxy - 3' - methoxy-benzyl)-3-methyl-isoquinoline. It differs from papaverine in that a methyl group has been placed in position 3 in the isoquinoline ring and an ethoxy group has been substituted for one of the methoxy groups of the benzyl ring. It possesses many of the pharmacologic properties of papaverine and causes relaxation of smooth muscle. Both the hydrochloride and phosphate salts of this compound were studied and no significant difference in dilator properties were found. These workers measured its potency as a vasodilator on the coronary blood flow in dogs. They found that, when compared on the basis of equal amounts injected intravenously, the new compound caused coronary dilatation of a degree and duration equal to that of papaverine in four dogs and 5 per cent to 25 per cent greater in four other dogs. The acute toxicity of dioxyline phosphate is about one-fourth that of papaverine as measured by the intravenous injection in mice. Studies also showed the new papaverine alkaloid to have no analgesic action and no tolerance development in experimental animals by repeated administration.

Because the toxicity of dioxyline phosphate is less than that of papaverine it has been suggested that perhaps larger quantities of the former could be used in clinical medicine. An added important aspect of the new drug is that it will not be considered a narcotic. Henderson, Shipley, and Chen, on the basis of their pharmacologic studies, stated that they believed the compound warranted clinical trial.

The present study was therefore begun to attempt a clinical evaluation of the effectiveness of the new isoquinoline derivative in patients with angina pectoris.

Methods and Materials

Twelve patients with well established angina pectoris were chosen from the Cardiac Clinic at the Cincinnati General Hospital. The majority of these patients had been under observation in the clinic for several years for angina pectoris and various
medications had been used in the management of their pain.

Each patient kept a small card made in the form of a calendar on which he entered the number of pains experienced each day. All patients were allowed to take nitroglycerin tablets whenever needed. Some of the group were on digitals and administration of this was continued.

Table 1.—Effect of the Oral Administration of Dioxyline Phosphate on the Number of Anginal Attacks

<table>
<thead>
<tr>
<th>Patient</th>
<th>Periods of Study</th>
<th>Control</th>
<th>Placebo</th>
<th>Dioxyline Phosphate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weeks</td>
<td>Weeks</td>
<td>Weeks</td>
<td>Average No. Attacks per wk.</td>
</tr>
<tr>
<td>A. H.</td>
<td>4</td>
<td>6</td>
<td>7</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>(1-2)</td>
<td>(0-1)</td>
<td>(0-1)</td>
<td></td>
</tr>
<tr>
<td>C. N.</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>(0-7)</td>
<td>(1-16)</td>
<td>(0-8)</td>
<td></td>
</tr>
<tr>
<td>J. D.</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>(0-19)</td>
<td>(0-5)</td>
<td>(0-1)</td>
<td></td>
</tr>
<tr>
<td>M. M.</td>
<td>23</td>
<td>6</td>
<td>6</td>
<td>23.3</td>
</tr>
<tr>
<td></td>
<td>(12-36)</td>
<td>(11-32)</td>
<td>(6-29)</td>
<td></td>
</tr>
<tr>
<td>J. M.</td>
<td>8</td>
<td>15</td>
<td>6</td>
<td>15.8</td>
</tr>
<tr>
<td></td>
<td>(14-17)</td>
<td>(10-17)</td>
<td>(9-11)</td>
<td></td>
</tr>
<tr>
<td>N. G.</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>(0-1)</td>
<td>(0-1)</td>
<td>(0-3)</td>
<td></td>
</tr>
<tr>
<td>R. H.</td>
<td>7</td>
<td>8</td>
<td>6</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>(0-7)</td>
<td>(0)</td>
<td>(0-1)</td>
<td></td>
</tr>
<tr>
<td>G. S.</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>(0-1)</td>
<td>(0-3)</td>
<td>(0-1)</td>
<td></td>
</tr>
<tr>
<td>M. Wil.</td>
<td>7</td>
<td>6</td>
<td>10</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>(0-1)</td>
<td>(0-4)</td>
<td>(0-2)</td>
<td></td>
</tr>
<tr>
<td>M. O.</td>
<td>14</td>
<td>6</td>
<td>8</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td>(5-18)</td>
<td>(16-32)</td>
<td>(12-21)</td>
<td></td>
</tr>
<tr>
<td>E. C.</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>(10-17)</td>
<td>(2-7)</td>
<td>(1-10)</td>
<td></td>
</tr>
<tr>
<td>D. H.</td>
<td>5</td>
<td>6</td>
<td>8</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>(7-12)</td>
<td>(12-15)</td>
<td>(12-14)</td>
<td></td>
</tr>
</tbody>
</table>

The figures in parentheses indicate the range of attacks per week.

The study was divided into three parts. The first part consisted of a control period of observation from six to eight weeks.

Electrocardiograms consisting of three standard leads, three augmented unipolar limb leads, and the six precordial leads were taken on all patients during the control period. Two patients had normal records, one had left bundle branch block, two had the pattern of left ventricular hypertrophy, six had the pattern of nonspecific myocardial damage, and one had an intraventricular conduction defect. During this control period two exercise tolerance tests were carried out on different days. The patient walked over two steps with an ice cube in each hand up to the point of angina or severe dyspnea. If no end point was reached the test was terminated after the patient had performed the recommended number of trips for his age and weight as described by Master. An electrocardiogram, including standard leads, unipolar extremity leads and precordial leads V4 and V5, was taken prior to and immediately after completion of the exercise.

The second part consisted of a period of six to eight weeks during which the patient was given either chocolate-coated dioxyline phosphate tablets (200 mg.) four times daily, or a chocolate-coated placebo identical in shape and size. Neither the patient nor the attending physician knew the identity of the preparation administered. At the end of this second period of study another exercise tolerance test was performed as described above.

The third phase consisted of a period of six to eight weeks during which the preparation was switched so that those patients who had been on placebo were now placed on dioxyline phosphate and vice versa. Upon completion of this final phase another exercise tolerance test was performed.

**Results**

Five of the 12 patients experienced fewer pains while taking dioxyline phosphate than they did during either the control period or while taking placebo (table 1). Three of these patients (A. H., C. N., and J. D.) experienced a reduction of more than 50 per cent in the number of their pains while two (M. M. and J. M.) had a reduction of between 20 per cent and 25 per cent in the number of their pains.

Seven of the 12 patients showed no significant decrease in the number of their anginal pains while taking dioxyline phosphate. In two of these cases their pains were least frequent while on placebo therapy (table 1).

The patients in this study can be divided into three categories on the basis of the severity of their angina during the control period. We shall arbitrarily take an average of fewer than two attacks of pain per week as indicating mild angina (five cases). Those patients with more than an average of two but less than ten attacks of pain per week can be classed as moderate angina (two cases). And, finally, those with more than ten episodes of pain per week can be called severe angina (five cases). Analyzing our results according to the severity of the angina, we find one of those with mild
angina showed improvement on dioxyline phosphate, two of those with moderate angina showed improvement and two of those with severe angina showed improvement.

Statistical analysis of the number of attacks observed during the control period and while receiving the placebo revealed a mean difference of 0.72 attacks for 12 subjects, being less with the placebo than in the control period; the difference was not statistically significant \(t = .62, p = 0.6\). In comparing the number of attacks during the placebo and with the test drug, a statistically significant difference was observed \(t = 3.27, p = <0.01\). In this group there was a mean difference of 1.58 attacks, there being fewer attacks in the drug treated group. Statistical analysis of the control period and the drug treated period revealed an average of 2.3 fewer attacks in the drug treated period. However, this was not a statistically significant difference \(t = 1.88, p = 0.1\). It may seem paradoxical that the difference observed between the drug and control periods was not statistically significant when the mean difference in number of attacks was greater between the test drug and control periods than between the drug and placebo periods. The reason for this is that there was a wider scatter on both sides of the mean difference for the test drug and control periods than for the test drug and placebo periods.

**Exercise Tolerance Tests**

Exercise tests were performed 53 times on the 12 patients. A positive test as indicated by the occurrence of angina or severe dyspnea was obtained in eight of these patients during the control period. A positive test as indicated by RS-T segment depression of 0.5 mm. or more in standard leads I or II, in the precordial leads, or in aVL or aVF, a change in direction of the T waves, or the appearance of conduction defects was obtained in eight patients. At the time of the test, four of these patients with positive tests were on digitalis medication, a fact which renders interpretation doubtful.

Exercise tests were performed on every patient following placebo therapy. Following the course of dioxyline phosphate treatment each patient was given an exercise tolerance test with the exception of one patient (N.G.) who will be discussed below. Only one of the 11 cases tested showed any increased ability to make more trips before experiencing angina or severe dyspnea while on dioxyline phosphate medication than either during the control period or while on placebo tablets. This patient (C.N.) was forced by dyspnea to stop during both the control period and the period of placebo administration. He performed 19 and 14 trips during the control period and 29 during the period of placebo medication. However, following dioxyline phosphate therapy he was able to perform a double Master test (32 trips); he developed dyspnea but it was not severe enough to cause him to stop.

Only one of the nine patients (J.D.) who had a positive exercise test as indicated by the electrocardiographic changes mentioned above showed a negative test after dioxyline phosphate.

One patient (N.G.) after being on dioxyline phosphate six weeks experienced severe precordial pain radiating to the left shoulder and also to the right arm. The pain was not relieved by nitroglycerin. He was admitted to the Cincinnati General Hospital. The electrocardiogram was interpreted as showing subepicardial ischemia. He was given anticoagulants and discharged after six weeks. No exercise tolerance test, therefore, could be performed at the completion of his course of dioxyline phosphate.

**Side Effects**

Five of the 12 patients experienced unpleasant side effects while on dioxyline phosphate. Two patients (E.C. and G.S.) complained of nausea on the first day of treatment but had no further untoward effects. One patient (R.H.) was nauseated and felt weak and tired for the first two days of treatment; he subsequently had no further complaints. This same patient during a subsequent course of dioxyline phosphate therapy had no side effects except occasional slight epigastric burning. A fourth patient (N.G.) complained of occasional gaseous distension with slight epigastric burning. A fourth patient (N.G.) complained of occasional gaseous distension with slight nausea while on dioxyline phosphate. The fifth patient (J.D.) experienced nausea, flatulence and slight epigastric burning; this patient voluntarily re-
duced his dose to one tablet three times a day. In no instance were the side effects of such a disagreeable nature that dioxyline phosphate had to be discontinued.

Of considerable interest is the fact that 6 of the 12 patients had various complaints while on placebos. These consisted of nausea, nocturia, frequency, constipation, a feeling of gaseous distention, difficulty in urination, and a metallic taste. In one instance (J. D.) these sensations caused the patient to reduce the dose; in another case (M. M.) the patient stopped the placebos because she attributed her symptoms to the tablets.

**Dosage**

Ten of the 12 patients were maintained on a dose of 200 mg. of dioxyline phosphate four times daily. One patient (J. D.), because of side effects as noted above, reduced his dose to one tablet three times daily. One patient (M. M.) experienced unpleasant effects, curiously enough, while on placebo and reduced her dose to one placebo tablet three times a day. Since the attending physician did not know the identity of the tablet, he continued this dose into the second period of study. Accordingly this patient was maintained on three tablets only of dioxyline phosphate even though the latter had caused no side effects. This patient may well have been able to tolerate 800 mg. per day.

**Discussion**

As has been previously pointed out, the evaluation of any therapeutic agent in the treatment of angina pectoris is extremely difficult. The frequency and severity of anginal seizures depend upon the temperature, the amount of exertion, the emotional stress to which the patient is subjected, the size and nature of his meals, and many other immeasurable factors. There is frequently spontaneous improvement in a patient's anginal seizures without any specific medication. This may be attributed to the development of collateral circulation, or to the result of an acute myocardial infarct with destruction of the anoxic portion of the myocardium which had been the cause of the pain.

In order to attempt to assess the value of a drug in angina pectoris the problem must be approached as objectively as possible. The patients should be observed for a control period during which no coronary vasodilator is administered with the exception of nitroglycerin. Then the patient should be given either the drug to be studied or a placebo identical in size, appearance, and taste. The identity of the tablet should not be known to the physician who is following the patient. This should eliminate any possibility of suggestion on the part of the physician.

In addition to this some objective means of study such as the exercise tolerance test or anoxemia test should be done during the control period and at the end of each subsequent period of study. We believe the exercise tolerance test is more physiologic and less hazardous than the anoxemia test.

It is well recognized that positive tests are not diagnostic of angina, since they have been reported in apparently normal subjects as well as in those with neurocirculatory asthenia. On the other hand some patients with unquestionable angina do not have a positive test. Perhaps the chief value of these tests in the evaluation of a therapeutic agent in angina pectoris is to observe if there is any serial change in a given patient's record. In other words, if during the control period the patient with angina has a positive test and then at the end of the period with the active drug has a negative (or possibly a less positive) test, this suggests that the vasodilator may have produced a more effective coronary blood flow. However, if the test also becomes negative at the end of the period of placebo study the conclusions are obvious.

In the present study there were 5 of the 12 patients studied who had fewer pains while taking dioxyline phosphate than either during the control period or while taking a placebo. In only one of the cases was there any increase in exercise performance after taking dioxyline phosphate. One patient was hospitalized during the period of dioxyline phosphate medication for an episode of what appeared to be coronary
insufficiency. One might speculate that had he not been on a vasodilator, a frank myocardial infarction may have resulted. This problem obviously cannot be answered.

The low incidence of serious side reactions while taking dioxylene phosphate was a conspicuous feature of this study. In no instance were these side effects sufficiently troublesome to necessitate discontinuing the drug. This is in contrast to the toxic symptoms encountered by Gray, Riseman, and Stearns, in their use of papaverine; they encountered 5 of 11 patients with either nausea or abdominal cramps to such a degree that either the drug had to be discontinued or the dosage reduced from 800 mg. to 400 mg. per day. This would seem to indicate that dioxylene phosphate in equivalent dosage causes less troublesome side effects than does papaverine.

Summary and Conclusions

1. The effect of 6,7-dimethoxy-7-(4'-ethoxy-3'-methoxybenzyl) - 3 - methyl - isoquinoline (dioxylene phosphate) has been studied in 12 patients with angina pectoris.

2. These patients have kept a daily record of the number of their pains during a control period and during alternate periods of placebo and dioxylene phosphate medication.

3. The physician who followed the patients did not know whether they were receiving placebo or dioxylene phosphate.

4. Five of the 12 patients experienced fewer pains while taking dioxylene phosphate than during either the control period or while taking a placebo.

5. Exercise tolerance tests were done during the control period and upon completion of the period of placebo and dioxylene phosphate administration. Two patients showed improvement in the test following dioxylene phosphate.

6. The usual dose was 200 mg. four times daily.

7. Side effects were encountered in five patients but were not severe and in no instance did dioxylene phosphate have to be discontinued.

8. This study indicates that dioxylene phosphate is worthy of trial in patients with angina pectoris.

Acknowledgment

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References


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