Effect of Khellin on Coronary Artery Insufficiency as Evaluated by Electrocardiographic Tests

By Maurice M. Best, M.D. and Walter S. Coe, M.D.

The effectiveness of khellin in 9 patients with angina pectoris was evaluated electrocardiographically by means of the exercise tolerance, anoxemia and ergonovine tests. Normalization occurred in the majority of the previously abnormal tests following khellin therapy. A beneficial effect was noted on symptoms accompanied by a reduction in nitroglycerin requirement. Mild toxicity, as a result of khellin therapy, was observed in 3 cases.

Khellin is a crystalline substance isolated from the seeds of the plant Ammi visnaga, which grows abundantly in the Eastern Mediterranean region. It has been used for centuries for the treatment of conditions characterized by spasm of smooth musculature. The drug has been shown by Samaan to relax smooth muscle by direct action on the muscle fibers.

The pharmacologic action of khellin on the coronary circulation has been studied by Anrep, Barsaum, Kenawy, and Misrabty. In heart-lung preparations they observed that concentrations of the order of 1 in 200,000 resulted in increases in coronary blood flow of 3 to 4 times the initial volume. In dogs they demonstrated the action of khellin in therapeutic doses to be largely selective on the coronary vessels since action on systemic blood vessels and blood pressure is negligible.

Clinical evaluation of the drug in angina pectoris was recently reported by Anrep and his co-workers. In a series of 250 cases, 56 per cent showed good subjective improvement, 34 per cent showed moderate improvement and 10 per cent were classified as failures. Some of their patients were studied objectively by utilizing the effect of exercise on the electrocardiogram following intramuscular injection of khellin.

Method and Technique

Selection of Patients. The 9 patients selected for this study fulfilled the following criteria: history of classic angina pectoris on exertion; no evidence of congestive heart failure, hyperthyroidism or anemia; no recent myocardial infarction; and at least 1 of 3 electrocardiographic tests for coronary insufficiency positive.

Medication. All patients were observed through at least a one-month control period. They then received khellin,* 50 mg. (one tablet) orally three times a day for a period ranging from two to four weeks. All patients received one placebo tablet three times a day for at least one month. Four patients received these tablets before and five at the completion of khellin therapy. The placebo tablets were identical in appearance and indistinguishable in taste from the khellin tablets. Daily nitroglycerin consumption was recorded throughout each period. The observer who recorded symptomatic response and nitroglycerin consumption was unaware which type of tablet the patient was receiving. All patients remained ambulatory and continued their usual activities throughout the periods of study.

Electrocardiographic Evaluation. The following tests were done before treatment, at completion of khellin therapy, and following placebo administration:

* The khellin used in these studies was supplied through the courtesy of Merck and Company, Rahway, New Jersey.
Fig. 1. Effect of khellin on nitroglycerin requirement.

Fig. 2. Patient M. S., 65 years of age. Five-year history of angina pectoris. Exercise tolerance test, Pretreatment electrocardiograms show depression of RS-T segment in Leads II and III; T waves in Leads I, II, III and V, become upright. No changes in tracings during khellin period. During placebo period the form of the pretreatment tests has been resumed,

(1) Exercise tolerance test, as described by Master and associates6 with graded exercise on standard steps. The patients rested 15 minutes and then performed the standard amount of exercise as indicated by tables based on sex, age and weight, and completed the de-

terminated exercise in one and one half minutes. Electrocardiograms consisting of Leads I, II, III, and V₁ were recorded before exertion. These were repeated immediately on cessation of exercise and at intervals of 3, 5, and 8 minutes thereafter. In the event of pain, an immediate electrocardiogram was recorded and nitroglycerin, 0.43 mg. was given.

Criteria for a positive test consisted of a depression of the RS-T junction of at least 1 mm. in any lead, conversion of an upright T wave to an isoelectric or inverted T in Leads I, II, or V₁; or conversely the conversion of an inverted T wave to an upright T wave in these leads. The appearance of multifocal ventricular premature contractions was also considered an abnormal response.

(2) Anoxemia test was performed according to the method of Levy and his co-workers. A mixture of 10 per cent oxygen and 90 per cent nitrogen was administered through a gas machine equipped with a flutter valve so that no rebreathing occurred. Periodic analysis by the method of Haldane of the gas mixture revealed the oxygen content to remain constant at 10 ± .02 per cent. By means of a simple push button 100 per cent oxygen could be immediately substituted for the reduced oxygen mixture. A control electrocardiogram consisting of Leads I, II, III, and V₁ was obtained initially.

Table 1.-Effect of Khellin on Electrocardiographic Tests for Coronary Artery Insufficiency

<table>
<thead>
<tr>
<th>Patient</th>
<th>Exercise Tolerance Test</th>
<th>Anoxemia Test</th>
<th>Ergonovine Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control*</td>
<td>Khellin</td>
<td>Control*</td>
</tr>
<tr>
<td>M. H.</td>
<td>—</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>J. W.</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>F. H.</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>B. W.</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>L. H.</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>J. B.</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>W. J.</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>M. S.</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>E. J.</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

+ Positive test.  
— Negative test.  
0 Test not performed.  
* Post-treatment placebo results were identical with pretreatment control studies.
The oxygen-nitrogen mixture was then given for 20 minutes. Electrocardiograms were recorded at intervals of 5 minutes during the period of reduced oxygen administration and for 15 minutes thereafter. In the event of pain an immediate electrocardiogram was recorded and 100 per cent oxygen administered.

Criteria for a positive test were similar to those of Levy: the sum of the RS-T deviations in all leads totals at least 3 mm., or a reversal in the direction of the T wave in Leads I and V4 if accompanied by RS-T depression of 1 mm. or more. We also considered the appearance of multifocal ventricular premature contractions to be an abnormal response.

Tests were performed on the patients prior to treatment. Fourteen were positive. Ten (71.4 per cent) of these 14 positive tests reverted to negative following khellin therapy. Two tests remained positive and two tests were not repeated. One patient (B. W.) developed chaotic heart action following ergonovine and another patient (E. J.) refused to permit the anoxemia test to be repeated. All tests reverted to their pretreatment status with placebo therapy.

**Occurrence of Pain during Testing**

Precordial pain occurred during 17 (68 per cent) of the 25 pretreatment tests. Pain occurred on 4 (17.3 per cent) occasions during testing at the completion of khellin therapy. One patient (L. H.) experienced pain during the initial exercise tolerance test but had no pain on subsequent testing following khellin and placebo periods.

**Symptomatic Response**

Eight patients noted an increase in exercise tolerance and a decrease in number and severity of anginal attacks while under treatment with khellin as contrasted to the control period, as shown in table 2. One patient reported symptomatic improvement with placebo tablets. The only patient (E. J.) in whom no subjective improvement occurred was thought to have syphilitic involvement of the coronary ostia.

**Effect on Nitroglycerin Requirement**

The effects of khellin and placebo tablets on average weekly nitroglycerin requirements as compared with those of the control period are summarized in figure 1.

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**Table 2.** Nine Patients with Coronary Artery Insufficiency Treated with Khellin

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Etiology</th>
<th>Duration of Angina</th>
<th>Duration of Khellin Therapy</th>
<th>Symptomatic Improvement</th>
<th>Toxic Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. H.</td>
<td>56</td>
<td>F</td>
<td>Arteriosclerotic</td>
<td>3 years</td>
<td>3 weeks</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>J. W.</td>
<td>52</td>
<td>M</td>
<td>Arteriosclerotic</td>
<td>4 years</td>
<td>4 weeks</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>F. H.</td>
<td>68</td>
<td>F</td>
<td>Arteriosclerotic</td>
<td>4 years</td>
<td>2 weeks</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>B. W.</td>
<td>65</td>
<td>M</td>
<td>Arteriosclerotic</td>
<td>6 years</td>
<td>2 weeks</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>L. H.</td>
<td>69</td>
<td>F</td>
<td>Arteriosclerotic</td>
<td>4 years</td>
<td>3 weeks</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>J. B.</td>
<td>50</td>
<td>M</td>
<td>Arteriosclerotic</td>
<td>3 years</td>
<td>2 weeks</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>W. J.</td>
<td>81</td>
<td>M</td>
<td>Arteriosclerotic</td>
<td>10 years</td>
<td>2 weeks</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>M. S.</td>
<td>65</td>
<td>F</td>
<td>Arteriosclerotic</td>
<td>5 years</td>
<td>2 weeks</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>E. J.</td>
<td>35</td>
<td>M</td>
<td>Syphilis</td>
<td>3 years</td>
<td>2 weeks</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

(3) Ergonovine test was performed by the method of Stein. Each patient was required to rest at least 20 minutes and a control electrocardiogram consisting of Leads I, II, III, and V4 was recorded. Ergonovine maleate, 0.2 mg. was injected intravenously very slowly. The electrocardiogram was repeated immediately upon completion of the injection and at intervals of 3, 5, 15, and 30 minutes. Tablets of nitroglycerin, 0.43 mg., were given immediately if pain occurred.

The criteria for a positive test were depression of the RS-T segment of 1 mm. in any lead or conversion of an upright to an isoelectric or inverted T wave in Leads I, II, or V4.

**Results**

**Effect on Electrocardiographic Tests**

The responses of the individual patients to the exercise tolerance, anoxemia and ergonovine tests are shown in table 1. Twenty-five
**Toxic Effects of Khellin**

Nausea and vomiting were the only toxic effects noted. These occurred in 3 patients but were not so severe as to limit the use of the drug.

**Discussion**

Angina pectoris is generally thought to be due to a decreased coronary circulation which becomes inadequate when coronary filling is impaired by spasm or other factors or when cardiac work is increased. It may be due to an inability of the arteriosclerotic arteries to dilate but the presence of some degree of vasospasm is suggested by the classic response to the nitrates.

Direct measurement of coronary artery blood flow in man is not feasible. Estimation by means of coronary sinus catheterization following saturation of the blood by nitrous oxide as developed by Bing and his co-workers is not applicable to problems of exercise tolerance. The electrocardiogram is probably the best means of evaluating the adequacy of coronary blood flow during periods of increased myocardial demand in man.

The conversion to a normal pattern of 71.4 per cent of the previously abnormal electrocardiographic tests of coronary insufficiency would indicate that khellin in the dosage used is helpful in preventing myocardial anoxia. The action may be that of vasodilatation of the coronary arteries as suggested by Anrep and associates and confirmed by their direct measurements in the dog. In man with arteriosclerotic disease of the main coronary arteries, the drug may cause dilatation of collateral vessels sufficient to permit more blood to reach anoxic areas of the myocardium.

Subjective response to any drug in angina pectoris is difficult to evaluate. The majority of these patients during treatment with khellin noted an increase in ability to exercise without pain, used less nitroglycerin per week and had less pain during testing procedures as compared to the pretreatment control period. In only one patient was improvement sustained while on placebo tablets.

Limited supplies of available khellin restricted its dosage and the number of patients studied. It would seem that khellin may be an effective means of improving anoxia of the myocardium secondary to coronary artery disease. The drug warrants further experimental and clinical study.

**Summary**

(1) Of 14 abnormal electrocardiographic tests of coronary insufficiency obtained in 9 patients, 10 (71.4 per cent) reverted to normal with khellin therapy. This beneficial effect was not noted with placebo therapy.

(2) Eight of the 9 patients noticed an increase in exercise tolerance and a decrease in number and severity of anginal attacks while under khellin treatment.

(3) Nausea and vomiting of moderate severity occurred in 3 patients during khellin therapy.

(4) It would seem that khellin is of value in the treatment of angina pectoris.

**Acknowledgments**

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