The Use of Crystalline Visammin in the Treatment of Angina Pectoris

By I. A. Nalefski, M.D., W. B. Rudy, M.D., and N. C. Gilbert, M.D.

The high incidence of unpleasant side effects following the use of crude preparations of khellin in the treatment of angina pectoris has limited its clinical use. It was felt that if this vasodilator drug were prepared free of resins, chromones, and other plant impurities, it might then be used more extensively in the treatment of coronary insufficiency. Currently, a crystalline preparation of high purity has become available. A series of patients with angina pectoris were studied using this preparation. A Starr ballistocardiograph was interjected into our study in an attempt to obtain objective evidence of any effect this drug might have on the mechanical action of the heart.

From Ancient Times the people of Arabia and the Eastern Mediterranean countries have used extracts, tinctures and other preparations made from the seeds of Ammi visnaga (Arabic khella) for the treatment of renal colic and ureteral spasms due to renal calculi. Several crystalline substances were isolated early from the seeds of this plant. The more important of these were khellin (2-methyl-5,8-dimethoxyfuranochromone), visnagin (2-methyl-5-methoxyfuranochromone), and khellol-glycoside, which is an oxyglycoside of visnagin.

Khellin, also known as visammin, was first prepared in an impure form by Mustapha in 1879. In 1931 Samaan reported on the pharmacologic action of this drug. In his experiments he utilized tinctures and extracts of the seeds as well as a crystallized material with a melting point of 153 C., which he felt was essentially pure khellin. Samaan concluded that these preparations not only relaxed all smooth muscle by direct action on the muscle fibers but also possessed a mild diuretic effect. His later studies led him to conclude that the glycoside portion of this preparation contained the active principle. In 1945 Anrep and his group confirmed the findings of Samaan. They showed, however, that khellin and visnagin were the active principles of the drug while the glycoside portion was inactive as a smooth muscle relaxant. Anrep also demonstrated that crystalline khellin had a pronounced effect in increasing coronary blood flow and that the drug had a more prolonged therapeutic effect when compared with other coronary vasodilating drugs. Gilbert and Nalefski confirmed these findings. Anrep completed his studies by treating 250 patients with angina pectoris and reported improvement in 225 cases and no improvement in 25. He noted that the drug produced only a few side effects and was not toxic with prolonged administration. He also observed that it did not affect the bleeding or coagulation time.

Following the appearance of these reports in the literature, various clinical investigations were instituted in this country. Armbrust and Levine treated 53 patients with classic histories of angina pectoris with a preparation stated to contain 75 per cent khellin and 25 per cent visnagin. They concluded that 60 per cent of their patients showed improvement since they required fewer nitroglycerin tablets, had fewer and milder attacks of pain, and could walk greater distances. They reported that nausea, anorexia and dizziness occurred in about 60 per cent of the patients treated. They concluded that khellin was of value in the treatment of angina pectoris, but its usefulness was limited by the undesirable side effects encountered. In a controlled study, Osher and Katz found that khellin therapy produced subjective and objective improvement in 16 of 19 patients with angina pectoris. They used the same preparation that the previ-
ous investigators did and reported nausea, vomiting, anorexia, insomnia and vertigo as side reactions. In the same year Dewar and Grimson reported a comparative study of the effects of khellin and glyceryl trinitrate on 12 patients. In the dosages studied, they found khellin to be less potent but longer acting than glyceryl trinitrate. They stated that khellin given in effective doses did not cause any unpleasant side effects and did relieve angina in one patient who was intolerant of both glyceryl trinitrate and theophylline ethylene diamine. Rosenman and co-workers reported their findings using Eskel, a mixture of Ammi visnaga principles. From their carefully controlled experiments they concluded that visammin (khellin) was a drug with definite therapeutic effects in angina pectoris, chronic cor pulmonale, and possibly in acute bronchial asthma. They found toxic reactions in 16 cases of the total 30 studied. Greiner and co-workers treated 39 patients with coronary artery disease and angina of effort with Eskel. Their method for evaluating this drug led them to conclude that the results on these 39 patients showed khellin to have no greater effect than lactose in the control of pain in the angina of effort. In their study, 35 of the 39 patients treated reported unpleasant symptoms at one time or another which were ascribed to the medication.

Our personal experiences during the past year with the crude form of the drug showed a very high incidence of side reactions similar to those reported by others. With a few exceptions, we found that 2 tablets per day of the impure preparation which contained a total equivalent of 80 mg. of khellin would produce nausea and vomiting. Frequently, patients could not tolerate even 1 tablet per day. Only rarely could a patient with angina pectoris tolerate 3 tablets per day for intervals as long as one week.

In view of the favorable laboratory reports and the beneficial clinical results usually reported in those instances where the patient could tolerate this drug, we felt that its active principles should be investigated further. We had the distinct impression that if the side effects could be eliminated, a potent medica-

ment would be at our disposal for the treatment of coronary insufficiency.

Currently, a crystalline khellin* of 97.0 to 99.8 per cent purity having a melting point of 151 to 154 C. has become available. The physical appearance of this material is quite unlike that of the crude preparations used to date. It was felt that possibly the side effects experienced with the crude preparations would be minimized with the crystalline khellin in the absence of other plant impurities, resins and chromones. With this in mind, a series of patients were studied using the crystalline Ammi visnaga preparation.

**Method**

This investigation was conducted on 21 patients with longstanding, proved coronary artery disease, who were obtained from the Out-Patient Department of the Florsheim Cardiac Clinic and St. Luke's Hospital. In a few instances, the patients were made available for study by private physicians during hospitalization. The diagnosis of angina pectoris was based on a past history of precordial and substernal pain on effort, emotion or following the ingestion of large quantities of food. All patients obtained relief from their symptoms after rest or following glyceryl trinitrate therapy. A complete history, physical examination and pertinent laboratory data were obtained for each patient. The average age of the patients was 59, and ranged from 44 to 75 years. All had abnormal electrocardiographic and ballistocardiographic findings. The characteristics of the group and the results of khellin therapy are summarized in table 1.

Placebos were not used in evaluating the effects of this drug on the various patients. A control period of two weeks preceded the administration of crystalline khellin. During this time a record was kept of the frequency of their anginal attacks and the number of glyceryl trinitrate tablets used per day. The only drugs administered during this study were glyceryl trinitrate, crystalline khellin, phenobarbital or a mixture of phenobarbital, belladonna and crystalline khellin. Control electrocardiograms and ballistocardiograms prior to medication were made both before and after exercise tolerance tests. In all instances, these tracings were abnormal. The electrocardiograms showed the usual expected findings of coronary insufficiency.

The ballistocardiograph has been utilized by others in typical cases of angina pectoris, and it

* Khelloyd, manufactured by Lloyd Brothers, Pharmacists, Inc., Cincinnati, Ohio.
Table 1.—Effect of Crystalline Visamin on a Controlled Group of Patients with Angina Pectoris

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, Sex, Race</th>
<th>Diagnosis</th>
<th>Duration of Angina</th>
<th>Periods of Study</th>
<th>Results of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>Cryst. visamin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Attacks per day</td>
<td>No. GTN* per day</td>
</tr>
<tr>
<td>1.</td>
<td>56, M, W</td>
<td>ASHD†</td>
<td>3 yrs.</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>2.</td>
<td>70, M, W</td>
<td>ASHD†, PMI†</td>
<td>1 yr.</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>3.</td>
<td>61, M, W</td>
<td>Hypertension</td>
<td>2 yrs.</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>4.</td>
<td>46, M, W</td>
<td>Hypertension</td>
<td>6 mo.</td>
<td>8</td>
<td>Many</td>
</tr>
<tr>
<td>5.</td>
<td>51, F, N</td>
<td>ASHD†, Recent infarct</td>
<td>3 yrs.</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>6.</td>
<td>69, M, N</td>
<td>ASHD†</td>
<td>18 mo.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>7.</td>
<td>66, M, W</td>
<td>ASHD†</td>
<td>8 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8.</td>
<td>66, F, W</td>
<td>ASHD†, Severe angina</td>
<td>1 yr.</td>
<td>Many</td>
<td>30 plus or minus</td>
</tr>
<tr>
<td>9.</td>
<td>50, M, W</td>
<td>ASHD†, Hypertension</td>
<td>8 mo.</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10.</td>
<td>75, M, W</td>
<td>ASHD†</td>
<td>2 yrs.</td>
<td>Many</td>
<td>Many</td>
</tr>
<tr>
<td>11.</td>
<td>65, M, W</td>
<td>ASHD†, Hypertension</td>
<td>3 yrs.</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>12.</td>
<td>75, M, W</td>
<td>ASHD†</td>
<td>5 yrs.</td>
<td>5</td>
<td>6-8</td>
</tr>
<tr>
<td>13.</td>
<td>57, M, W</td>
<td>ASHD†</td>
<td>3 yrs.</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>14.</td>
<td>48, F, W</td>
<td>Hypertension</td>
<td>4 yrs.</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>15.</td>
<td>44, M, W</td>
<td>Hypertension, ASHD†, Myocardial infarct</td>
<td>1 yr.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>16.</td>
<td>61, M, W</td>
<td>Hypertension</td>
<td>6 yrs.</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>17.</td>
<td>53, F, N</td>
<td>Hypertension, ASHD†</td>
<td>2 yrs.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>18.</td>
<td>71, F, W</td>
<td>ASHD†, Myocardial infarct</td>
<td>10 yrs.</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>19.</td>
<td>47, F, W</td>
<td>Myocardial infarct</td>
<td>6 mo.</td>
<td>0-1</td>
<td>1-2</td>
</tr>
<tr>
<td>20.</td>
<td>50, M, N</td>
<td>ASHD†</td>
<td>2 yrs.</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>21.</td>
<td>51, M, W</td>
<td>ASHD†, Hypertension</td>
<td>18 mo.</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

* Glyceryl trinitrate. † Arteriosclerotic heart disease. ‡ Posterior myocardial infarct.
has been found that a definite relationship exists between the symptom complex and abnormal mechanical heart action. The arbitrary grades of abnormality established by Brown\textsuperscript{12} were used in our studies to classify the degree of severity of involvement. According to the method, the ballistocardiograms are graded according to regularity of pattern, definitiveness of curves, amplitude and configuration. Four grades are used, with number one being the least and number four being the most abnormal (fig. 1). It was hoped that the ballistocardiograph could be utilized to obtain objective evidence of the effects of khellin on the heart. The instrument used was of a high frequency type designed by Starr\textsuperscript{12} and was uniformly calibrated each time with a 280 Gm. weight.

The initial dosage of crystalline khellin was 200 mg. per day given in four equal 50 mg. doses. Each patient was seen weekly. If cumulative effects appeared, a two day rest period was instituted to allow these effects to disappear, and the dosage then reduced to 100 mg. per day given in two 50 mg. doses, or even to 50 mg. once a day in a few cases. Most of the patients who manifested side reactions at the 100 mg. dosage level were given a tablet composed of:

- Khellin (crystalline) ................................... 50 mg.
- Phenobarbital ........................................... 15 mg.
- Extr. of Belladonna, U.S.P. ......................... 15 mg.

The criteria used for determining improvement in the patients were a decreased number and a lessening in severity of attacks, a reduction in the number of glycercyl trinitrate tablets, an increase in exercise tolerance and an improvement in the ballistocardiographic pattern.

**Results**

**Toxicity.** Dosages of 200 mg. per day of pure crystalline khellin can be tolerated by most patients for only limited periods. Reduction of the daily dose to 100 mg. in two divided doses markedly reduced the severity of the side effects. When the daily dose of 100 mg. was given in four divided doses, only four of 21 patients experienced side effects after six weeks of treatment. These four patients no longer experienced nausea when the dose was further reduced to 50 mg. daily in two divided doses.

In addition to elimination of side effects by reduction of dosage, it appears that the concomitant administration of phenobarbital may control the undesirable symptoms. In six of our series of cases, nausea and insomnia were experienced on doses of 100 mg. per day, but when the tablet containing khellin, phenobarbital and belladonna was given in equivalent dosage, side effects were eliminated in five of the cases. Furthermore, it was found that the side effects of even the higher doses could sometimes be eliminated by simultaneous administration of suitable amounts of phenobarbital. The drug had no effect on pulse or blood pressure.

Of the 21 patients studied, two were maintained on 200 mg. of the drug per day for four weeks with nervousness as their chief complaint. Another tolerated this same dosage for three weeks before the development of nausea, vomiting and nervousness. Two others were on this dosage without side effects for two weeks, and another for one week. The remainder of the 21 patients showed manifestations of vertigo, headache, diarrhea, nausea, vomiting and insomnia after only two days of

\[\text{Fig. 1. The above series of ballistocardiograms illustrate first a normal tracing for comparison with others showing increasing amounts of abnormal mechanical heart action.}\]
treatment on 200 mg. When the daily dosage was reduced to 100 mg. and given in two equal doses, about 50 per cent of the patients still complained of a bothersome nausea, but when it was divided into four equal doses, only four of this latter group of patients experienced side effects after six weeks of treatment. These same four patients still showed a small amount of nausea on a single 50 mg. daily dose, but this was eliminated by giving two doses daily of 25 mg. each. Two patients refused to continue taking the drug after experiencing side effects at the 200 mg. dose level. One patient with an intractable angina, which became refractive to glycercyl trinitrate, tolerated 300 mg. per day for eight weeks and complained only of a slight insomnia which was controlled by phenobarbital.

Angina Pectoris. Crystalline khellin improved the cardiac status of the 19 patients who remained on the drug and invariably each patient commented on his ability to withstand more exertion. Five of the patients still experienced anginal pain. However, it was less severe and less frequent. All of these patients showed improvement for variable periods of time after the drug was discontinued. This probably can be attributed to the cumulative effect of the drug.

The control ballistocardiograms showed no common characteristic abnormality. All tracings taken during this control period were abnormal, with those nearly normal becoming more abnormal after exercise. In general, the tracings made after the crystalline khellin was administered tended to assume a more normal configuration. Calculations for cardiac output were not attempted because of the abnormality of the tracings. Cardiac strength determinations were also difficult to make and were not dependable because of the abnormality of the curves. It was of interest to note that after the patients received the crystalline khellin, their ballistocardiograms did not show the deterioration following exercise tolerance tests as they previously did before medication. Figure 2 illustrates serial ballistocardiograms of one of the patients treated. It was felt that the ballistocardiograph gave objective evidence of the favorable influence of the drug on the disease process present in these patients. No significant changes in the electrocardiographic pattern were noted during the treatment period.

Comment

Sufficient laboratory investigations have been conducted by competent investigators to establish the fact that this drug does reduce the tonicity of smooth muscle. The present study was primarily undertaken to compare the incidence of toxic manifestations of crystalline khellin with that of crude preparations being used to date. The pharmacologic reports on khellin by early investigators stressed the absence of toxic effects following its use. However, this was not confirmed by the clinical investigations conducted with the crude products prepared and used in this country. Anrep called attention to the fact that since the publication of his observations, a considerable number of preparations of Ammi visnaga were being offered to the public. He warned that crude extracts of this drug could cause undesirable effects. He advised that all preparations of it which were to be used orally or parenterally should first be freed from injurious impurities and that the final concentration of the active principle should be carefully standardized. It might be concluded that the discrepancies of the earlier clinical reports with current observations may be due to the use of a drug prepared
by different methods and containing various amounts and varieties of impurities.

It was apparent from the onset of our investigations that crystalline khellin used in dosages in excess of those required to obtain the desired therapeutic effect would produce toxic symptoms similar to those obtained with the crude forms of *Ammi visnaga* used earlier. We were impressed with the fact that we were dealing with a potent drug and also realized that each patient required an individual adjustment of the amount of the drug required to relieve him of his symptoms. In this respect, this drug is not unlike digitalis.

It is universally recognized that the evaluation of the efficacy of any drug in the treatment of such a capricious disease as angina pectoris is subject to many pitfalls. The enthusiasm of the investigator for a drug frequently leads to faulty conclusions. An attempt to de-emphasize this factor was made in this investigation by using patients with the anginal syndrome who had been observed for a number of years, by evaluating the frequency and severity of attacks before and after medication, by considering the number of glyceryl trinitrate tablets used, and by utilizing objective evidence obtained with the ballistocardiograph. In this investigation the latter proved to be especially valuable because this instrument affords a physiologic approach to a physiologic problem in that it records mechanical heart action. It must be stressed, however, that this instrument was used in a qualitative manner since the tracings obtained before and after medication were still too abnormal to quantitate. The improvement in the appearance and amplitude of the complexes supplied us with evidence which is difficult to argue against. Seventeen of the 19 patients studied showed improvement in the appearance of the complexes of the ballistocardiograph.

The high incidence of unpleasant side effects observed with the use of the crude preparations of khellin in the past has limited its clinical value. Using the crystalline preparation, we were able to control the anginal symptoms in 80 per cent of the patients treated with a dose ranging from 50 to 100 mg. per day. The drug is absorbed rapidly from the stomach, and relief from the symptoms is noted within 15 to 30 minutes following its ingestion. Its cumulative effect is well established. Consequently, it is not unreasonable to assume that 50 mg. could temporarily raise the serum concentration of this drug to a toxic level. The crude preparations as used by other investigators required 100 to 300 mg. to control the anginal symptoms. However, at this level a very high incidence of unpleasant side effects was present. Therefore, it appears that the crystalline preparation eliminates toxic effects which may well be produced by the impurities present in the crude preparations.

It has not yet been established whether the toxic effects observed are produced by direct action on the gastrointestinal tract or by a central effect. Preliminary investigations are now under way to determine whether parenteral preparations would allow a higher blood concentration of this drug to be used without experiencing toxic effects. To date, six dogs have been given intravenous injections of crystalline khellin dissolved in a solution of saccharin. Each animal received toxic doses of 280 mg. of this preparation over a five day period. During this time the animals remained in good health, enjoyed a good appetite, and showed no evidence of toxicity. Five days after the last dose was given, two of the six animals died. The gross pathologic findings on these dogs at autopsy were a generalized vasodilatation and bleeding from the orifices. Further studies are now being conducted. It must be concluded that the pharmacodynamics of this drug are still little understood.

**Summary**

1. The action of crystalline khellin, the active principle of *Ammi visnaga*, has been evaluated in cases of angina pectoris. Dosage, therapeutic efficacy and toxicity are discussed.

2. Seventeen of the 19 patients treated with this preparation showed a good response. Two other patients discontinued therapy after the development of severe side effects.

3. Untoward reactions were minimal when 50 to 100 mg. per day of the drug were used.
This amount given in divided doses was sufficient to control the symptoms of angina pectoris in 80 per cent of the cases.

4. The results indicate that crystalline khellin is a beneficial drug in the treatment of angina pectoris. It can be used in small dosages, and in therapeutic amounts exhibits essentially no toxic effects.

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