

KHELLIN IN THE TREATMENT OF ANGINA OF EFFORT

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Received 28 June, 1949

Anrep, Kenawy, and Barsoum (1949) have given a historical account of the pharmacology of khellin, which is the active principle of the plant *Ammi visnaga*, from its preparation by Mustapha in 1879 and the biological studies of Samaan (1932) to their own extensive investigations, already published in various articles and now summarized and brought up to date in their latest review. They have shown that khellin, which chemically is a dimethoxy-methyl-furanochromone, is a powerful dilator of the coronary arteries of dogs and rabbits, less intense than amyl nitrite but four times as strong as aminophyllin and with the considerable merit of being prolonged in its action and, in repeated dosage, cumulative. In their clinical studies they claim that of 250 patients with angina of effort who had continuous treatment with the drug, mostly by mouth, 56 per cent showed good improvement, 34 per cent moderate benefit, and 10 per cent failed to respond. To obtain more objective results they subjected an unspecified number of patients to exercise, in order to induce pain and electrocardiographic changes, and then repeated this exercise later on the same day or on the next day, 30 minutes after an intramuscular injection of khellin, or in some cases after one or two weeks continuous treatment with the drug.

The electrocardiographic changes, RS-T depression, and T wave inversion, previously induced by the exercise are said to have been prevented when khellin was given first, and in all the patients tested the exercise tolerance is said to have improved.

The present study is concerned solely with this last aspect of the work of Anrep and his associates and an attempt has been made in a small series of carefully chosen patients, to compare khellin with glyceryl trinitrate in its capacity to prevent both anginal pain and the electrocardiographic changes that sometimes accompany it. Both drugs were given in their most active yet practical form—the glyceryl trinitrate as a tablet to be chewed in the mouth, the khellin as a liquid to be swallowed.

METHOD OF INVESTIGATION

For convenience the investigation has been limited to male patients suffering from angina of effort. The amount of exercise required to produce moderate anginal pain was determined for each patient, and this determination repeated on each test day prior to the administration of any drug to exclude spontaneous variations in the patient's condition. By this means each patient acted as his own control, and an assessment of the relative merits of glyceryl trinitrate and khellin was obtained in all cases. In two of them a further test was made with an inert control substance. Because the patient was to be exercised several times on each of two or more days to produce anginal pain, the following criteria were adopted in the selection of cases.

- (1) The patients were all men suffering from typical angina of effort.
- (2) Only patients whose exercise tolerance was limited by pain were accepted. Those in whom dyspnoea was the most prominent symptom were excluded.
- (3) It has long been known, and was confirmed in this investigation, that when exercise is repeated at short intervals (10–30 minutes) the amount required to cause pain may either increase

or decrease. Some, so to speak, "work it off," and in these cases, therefore, unless such increase was very slight and could be allowed for, the patient was rejected as unsuitable. When pain was provoked by decreasing amounts of exercise no allowance was necessary as the factor operated equally upon each drug used.

The decision to use exercise tolerance as a test in place of hypoxæmia was made deliberately, partly because exercise was felt to be safer and less alarming to the patient, and partly because it was undesirable to induce hypoxæmia more than once in the twenty-four hours in a patient suffering from coronary artery disease.

It was decided that the method of choice was to ask the patient to walk up and down a standard flight of stairs at a steady rate until he produced anginal pain. This form of exercise had the merits of simplicity and familiarity to the patient so that his performance was hardly likely to improve with practice. The number of trips made up and down this flight of stairs and the time taken over them were noted with a stop watch. It was found that the patients had no difficulty in maintaining a constant rate. In Cases 2 and 8 (Table I) tolerance was so limited that only exercise on the level was needed to induce pain.

Electrocardiograms were taken before and after exercise on each occasion. These provided in most cases useful objective corroboration of the development of myocardial ischæmia. In some instances, too, they showed that although one drug prevented both anginal pain and the cardiographic changes that previously accompanied it, the other drug abolished pain only, the cardiographic changes occurring as before. This allowed of a more accurate assessment of the therapeutic effect of the drug concerned.

A direct-writing Sanborn Visocardiette was used. In most patients at the first attendance leads I, II, III, aVR, aVL, aVF, and V1-6 were taken. Immediately after exercise, and while pain was still present, leads I, II, III, V1-6 were repeated. The time taken over these recordings had been reduced by practice to two minutes from the end of exercise. These tracings were studied, and the lead or leads that showed the maximum change were taken first on subsequent occasions.

In most of the patients who showed cardiographic changes these reverted to normal after the pain had ceased. Sometimes this reversion took ten to fifteen minutes, and in no case was the patient ever exercised again until the cardiogram had returned to its previous level. Since the patients used were all clear-cut cases of angina of effort, and the sole purpose of the electrocardiograms was to compare the effectiveness of drugs in preventing the temporary changes consequent on myocardial ischæmia, the single group of electrocardiographic criteria laid down by Levy *et al.* (1941) for the diagnosis of angina were not adopted, and the following graded classification of changes was used in its place.

0 =No change from the resting level, or less than that designated +.

+ =Any of the following:

- (1) A change in the shape of the S-T segment in any lead associated with a demonstrable S-T deviation greater than 0.5 mm. but less than 1 mm.
- (2) S-T deviation of 1 mm. in any lead.
- (3) A partial inversion of the T wave or its reversal, in any lead.

++ =Any of the following:

- (1) Inversion or reversal of the T wave in any of the leads I, II, or III.
- (2) Partial inversion or reversal of T wave in any lead with S-T deviation of 1 mm.
- (3) S-T deviation greater than 1 mm., but less than 2 mm. in any lead.

+++ =Any of the following:

- (1) S-T deviation in any lead of 2 mm. or more.
- (2) Inversion or reversal of the T wave in any of the leads I, II, or III, with at least 1mm. S-T deviation.
- (3) Inversion or reversal of the T wave in any præcordial lead.
- (4) The appearance of a transient conduction defect.

Electrocardiograms were taken with the patients sitting in all instances except Case 5, who was recumbent on each occasion.

In all but two cases the observations were made on out-patients. As far as possible the patients attended at the same time each day, and were instructed to observe the same routine as regards time of rising, meals, method of travel to the hospital, and exercise before observation. Prior to any exercise being undertaken the patients were rested until pain had been absent for at least fifteen minutes, and the pulse rate and electrocardiogram were stable.

The two patients who were admitted to hospital (Cases 2 and 8) were suffering from severe angina of effort and nocturnal angina decubitus, and had very limited exercise tolerance. They were wheeled from their bed to the room where the observations were made, and after twenty minutes rest angina was induced by gentle exercise on the flat. The patients were tested within four days of their admission to hospital, during which time there was no improvement in their clinical condition.

Only one drug was given on any one day, and in most of the cases the drugs were tested in succession within a few days of each other. The glyceryl trinitrate mg. 0.8 (gr. 1/80) was given sublingually. The extract of *Ammi visnaga* used was kindly recommended to us by Professor Anrep. Marketed under the name of ammicardine by Alpha Laboratories, Cairo, it is an alcoholic extract standardized to contain 50 mg. of khellin per ml. Routinely the manufacturer's recommendation that the preparation be warmed in water to ensure complete solution was followed. 3 ml. (i.e. 150 mg. of khellin) were diluted in 10 ml. of tepid water. Most patients complained of a burning taste on swallowing the drug. On one occasion a patient remarked that he felt very warm after taking it. On another occasion nausea was experienced but there was no vomiting. No other untoward effects were noted. A control solution of alcohol 9 parts, infusion of quassia 1 part, was administered to two patients (Cases 2 and 5) in doses of 3 ml., diluted in 10 ml. of tepid water, to exclude the possibility that ammicardine might exert its effect by virtue of the alcoholic vehicle. Quassia was added to the alcohol to provide a bitter flavour.

Chest lead positions were outlined on the thoracic wall with a gentian violet solution to ensure that subsequent tracings would be from the same area. Care was taken to prevent the spread of electrode jelly from one præcordial lead area to another. By adopting the precautions described we have tried to eliminate most of the variable factors that occur in a therapeutic trial of this kind.

Many patients suffering from angina of effort were tested and the twelve finally used were selected for the constancy with which their pain occurred under standard conditions of exercise. This "base line" exercise was always undertaken a second time and in several cases three or four times in order not to miss the cumulative effect upon the symptom. On a subsequent day the patient returned and a preliminary control was established without drugs as outlined above. Then the patient was given one and a half tablets of glyceryl trinitrate totalling 0.81 mg. (gr. 1/80) to suck and chew. When they had totally disappeared, usually within two minutes, he was given his standardized exercise as before. Note was made as to whether pain appeared or not, and if so for how long and at the same time the appropriate electrocardiographic leads were taken. On another day exactly the same procedure was adopted except that the patient was given ammicardine 3 ml. (khellin 150 mg.) to swallow. The first few patients tested showed that when the drug acted it did so within an hour, and accordingly exercise tests with cardiographic control were always performed at 1 or 1½ hours and sometimes also at 2, 4 and 6 hours after its administration. One patient (Case 10), whose response to 3 ml. of ammicardine was disappointing, performed a further test on a separate day with 6 ml. (khellin 300 mg.).

RESULTS

The results are given in Tables I and II. The grading of pain in the first column of Table I has been based partly on the severity but chiefly on the duration of the induced symptom, as described by the patient. In nearly all cases correlation between intensity and duration was complete, and in general it may be taken that + indicates a pain lasting less than 20 seconds, and

TABLE I
GRADES OF PAIN AFTER EXERCISE

Case No.	No drugs	After glyceryl trinitrate, 0.8 mg.	After khellin 150 mg.	Remarks
1	++	0	0	Age 64. Miner. Angina, moderate, for 2 yrs., associated with aortic stenosis. B.P. 140/125
2	+++	0	++	Age 44. Plumber. Angina, severe, for 6 months. B.P. 160/105. Later died from myocardial infarction
3	++	0	0	Age 69. Retired miner. Angina, moderate, for 2 yrs. B.P. 185/110
4	++	0	0	Age 66. Retired engineer. Angina, moderate, for 2½ yrs. B.P. 180/95
5	+++	0	0	Age 49. Priest. Angina, fairly severe, for 5 yrs. B.P. 160/100
6	++	0	0	Age 39. Salesman. Angina, mild, for 2 yrs. B.P. 170/110
7	++	0	0	Age 47. Bus conductor. Angina, mild, for 1 yr. B.P. 170/95
8	++	+++	+	Age 40. Farmer. Angina, severe, for 6 months. B.P. 130/80
9	+++	0	++	Age 48. Engineer. Angina, moderate, for 8 yrs. Myocardial infarct 7 yrs ago. B.P. 155/90
10	++	0	++	Age 45. Roadman. Angina, moderate, for 4 months. B.P. 150/90
11	+	0	+	Age 48. Miner. Angina, moderate, for 6 months. B.P. 145/90
12	++	++	0	Age 48. Miner. Angina, moderate, for 1½ years. B.P. 120/80

+++ a pain lasting more than 90 seconds. It is to be noted that these grades do not indicate the relative severity of the various patients' angina; the guiding principle was always to induce a measurable amount of pain by an exercise that did not excessively fatigue or distress him.

The results summarized in Table I show that khellin in oral doses of 150 mg. prevented anginal pain after exercise in seven cases. It permitted diminished pain in three cases, and had no effect in two. In no instance did spontaneous pain follow the administration of the drug. On two patients (Cases 5 and 8) who obtained complete relief with khellin an inert quassia alcohol mixture was without effect.

Glyceryl trinitrate in doses of 0.8 mg., prevented pain after exercise in ten cases. It had no effect on one case and on one other patient (Case 8) it actually induced pain without any exercise being undertaken. It is of interest that theophylline-ethylene diamine 0.24 g. had exactly the same effect on this man, whereas the khellin prevented pain developing after he had undertaken his

TABLE II
ELECTROCARDIOGRAPHIC CHANGES AFTER EXERCISE

Case No.	No drugs	After glyceryl-trinitrate 0.8 mg.	After khellin 150 mg.
1	+++	0	+++
2	+++	+	+++
3	+++	++	+++
4	++	+	+
5	+++	0	0
6	+++	+	++
7	+++	+++	+++
8	++	+++	+
9	++	+	++
10	0	-	-
11	0	-	-
12	0	-	-

standard walk. It may be of significance that both the former drugs caused tachycardia in him, whereas khellin did not.

So far as the development of electrocardiographic change with exercise is concerned Table II shows that both glyceryl trinitrate and khellin are less effective than they are with the pain. Out of nine patients from whom satisfactory tracings were obtained, glyceryl trinitrate completely prevented the changes in two cases. It permitted decreased changes in five, but it had no effect in one, and actually induced greater changes in another (Case 8; the same patient who developed the spontaneous pain and tachycardia). On these same nine cases khellin, however, only prevented changes in one, permitted decreased changes in three, and had no effect on the tracing in five.

The changes produced by exercise in the cardiogram and the effect upon the curves of trinitrin and khellin previously administered are shown in Fig. 1, which compares the corresponding curves of the limb leads and V2 in Cases 1-4. Similar comparisons in Cases 5-7 are shown in Fig. 2 where the appearance of V4 is shown under conditions of rest, after exercise and after exercise

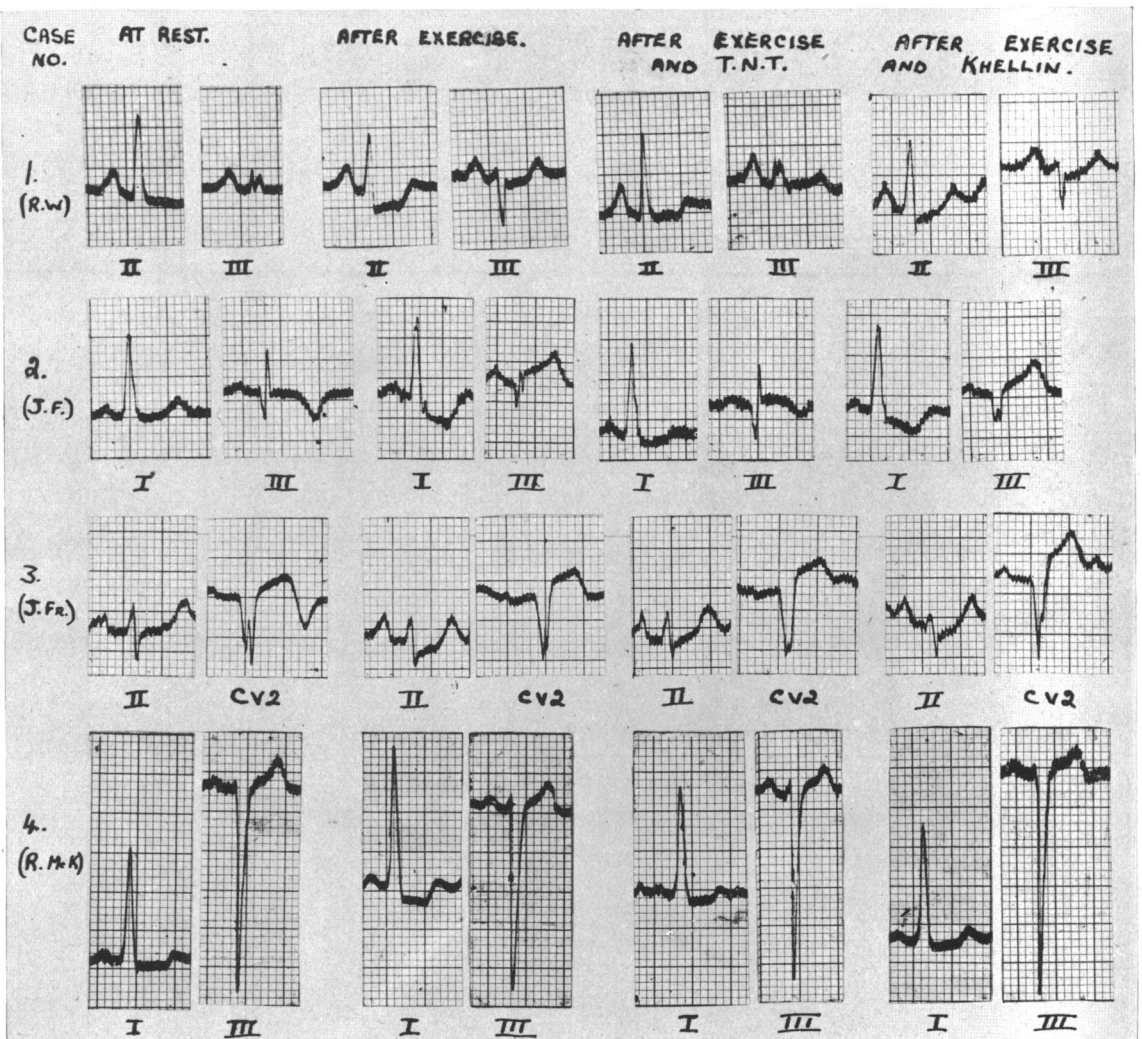


FIG. 1.—Electrocardiograms illustrating the changes induced by exercise in limb leads and lead V2, and the influence of khellin and glyceryl trinitrate in modifying them.

when trinitrin and khellin had been previously given. Fig. 3 shows the record in Case 8 (referred to above); it is seen that trinitrin produces a deformity in the S-T segment in lead II comparable to that of exercise while producing a greater degree of acceleration of the heart. Exercise after the administration of khellin failed to produce any S-T deviation.

On this evidence khellin in a single dose of 150 mg. is less effective, but probably longer acting, than glyceryl trinitrate 0.8 mg. (gr. 1/80), except in the occasional patient, who, perhaps because of tachycardia, develops spontaneous pain with the latter drug. On the question as to whether a

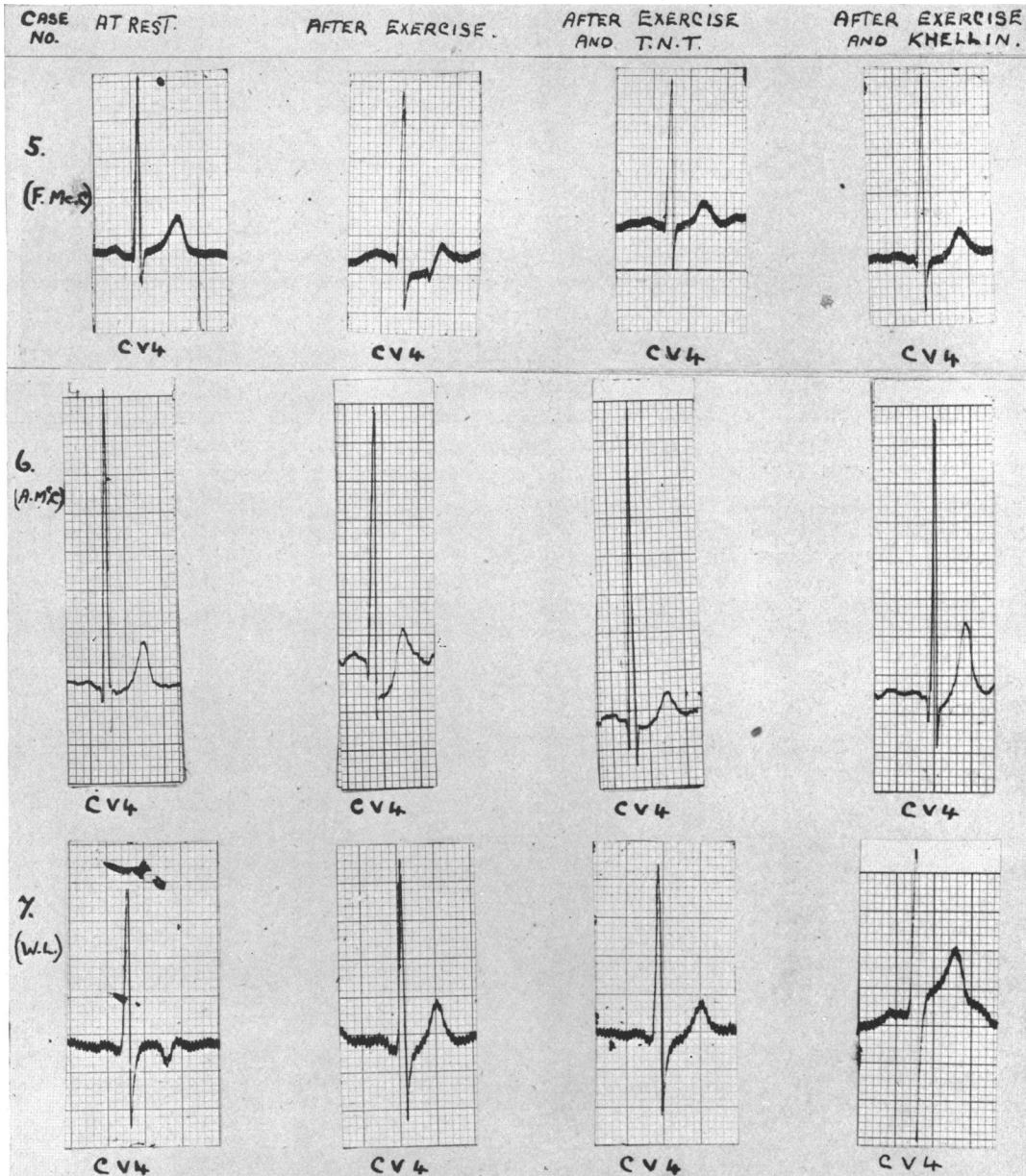


FIG. 2.—Effects of exercise and khellin and glyceryl trinitrate on lead V4.

larger dose and repeated administration would have more intense action we have no evidence. A more extended series with longer periods of observation and adequate control with inert substances will be required.

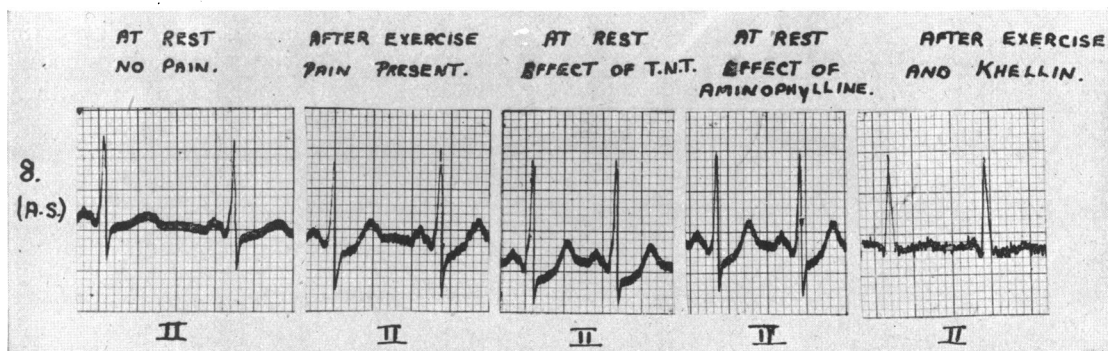


FIG. 3—Case 8. Induction of cardiographic changes by exercise. Both glyceryl trinitrate and aminophyllin induced similar changes (in association with tachycardia). Khellin allowed exercise to be taken without these changes occurring in the cardiogram.

SUMMARY

The comparative efficacy of certain doses of khellin and glyceryl trinitrate in preventing angina of effort and the electrocardiographic changes that may accompany it was tested in twelve patients.

In the doses studied, khellin is less potent but longer acting than glyceryl trinitrate.

Khellin, in doses that were effective, 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.

The drug appears to warrant further study.

Our thanks are due to Professor D. Burns for facilities in his Dept. of Physiology and to the King's College Research Fund for a grant towards expenses.

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