IPRONIAZID, NIALAMIDE, AND MEPROBAMATE IN ANGINA PECTORIS A DOUBLE-BLIND TRIAL

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The treatment of angina pectoris frequently presents a persistent problem to the physician, and new long-acting drugs are often prescribed with enthusiasm. This in itself is sufficient to produce a large percentage of satisfactory results, and for this reason only when drugs have been subjected to rigorous double-blind control studies should they be regarded as effective. During the past four years the value of the mono-amine oxidase inhibitors in the treatment of angina has been intensively studied. Recent assessments of their value (*Lancet*, 1961) have not upheld the earlier enthusiastic accounts of Cesarman (1957), Towers and Wood (1958), or Master and Donoso (1959). In addition the apparent usefulness of iproniazid in the treatment of angina has been severely limited by the development of liver damage, which has been estimated at 1 out of every 3,000–4,000 cases treated, with a mortality rate of 20–25% (Jolly, 1959). Although Shoskes *et al.* (1959) reported a significant improvement of the symptoms of angina with a low dosage (50 mg. daily) without any incidence of liver damage, other less toxic mono-amine oxidase inhibitors were clearly required (Master and Donoso, 1959). Among such drugs nialamide has been found to be relatively free of toxic hepatic effects (Robie *et al.*, 1959) and has been recommended in the treatment of angina pectoris (Wolfe and Shubin, 1959). However, like other more recently developed mono-amine oxidase inhibitors, it has not been thought to be as effective as the parent drug, iproniazid, in the treatment of angina (Russek, 1960). While this debate on the value of amine oxidase inhibitors has proceeded, it has still remained a frequent practice to recommend a mild sedative for the treatment of angina: for example, in a study of the use of sedatives in cardiovascular disease, Shapiro (1957) reported a reduction in the severity and frequency of angina following the use of meprobamate. In view of these reports it seemed desirable to attempt to compare, in a controlled trial, the respective values of iproniazid, nialamide, meprobamate, and a placebo in the treatment of angina pectoris.

Method

Thirty-seven patients with well-established angina pectoris were selected for study. (Three months was chosen as the minimum period of symptoms for inclusion in this trial, but, in fact, most patients had had angina for two to three years.) All the patients were experiencing at least one attack of angina each day, and the pain was readily relieved by rest or glyceryl trinitrate tablets. Patients with a resting diastolic blood-pressure above 100 mm. of mercury or who had suffered a recent myocardial infarction were excluded. The cause of the angina was rheumatic aortic stenosis in one of the patients and coronary artery disease in the remaining 36 patients. As it is very difficult to record objectively the severity and duration of attacks of chest pain in a trial lasting several months, patients were asked

only to note on a card the number of attacks of angina per day and also the number of tablets of glyceryl trinitrate required to alleviate the symptoms. Physical examination, a twelve-lead electrocardiogram, serum glutamic-pyruvic transaminase, supine and erect blood-pressure, and weight were recorded initially and at each subsequent six-weekly visit.

The double-blind trial was designed so that each patient would receive successive six-week courses of therapy with iproniazid 50 mg. daily, nialamide 100 mg. daily, meprobamate 400 mg. daily, and a placebo, in random order. The unknown tablets, which were all identical in appearance and labelled N, S, P, and V, were taken twice daily. The 24-week period of the trial for each patient was started, so far as was possible, in May and June, so that climatic variation would be kept to a minimum. Routine treatment with digitalis and diuretics, as indicated, and also long-term anticoagulant therapy in 20 of the patients was continued.

During the study two patients died of recurrent myocardial infarction, one patient was proved to have disseminated lupus erythematosus and was withdrawn, four patients failed to attend regularly, and two did not complete their cards as requested. Therefore 28 patients received all four types of therapy and were available for analysis.

Evaluation.—The interpretation of the results of treatment with mono-amine oxidase inhibitors in angina pectoris is particularly difficult. Allowance has to be made, on the one hand, for the initial improvement to be anticipated as a result of the extra care implicit in any clinical trial (Cole *et al.*, 1957), and, on the other hand, for the delay in the effect of mono-amine oxidase inhibitors, which may be as long as 10–14 days after beginning therapy, and which may persist for a similar period after ending therapy (Shoskes *et al.*, 1959; Master and Donoso, 1959). To reduce the effect of these conflicting factors to a minimum in assessing the value of the different types of treatment, it was decided to use only the number of attacks of pain recorded during the last three weeks of each six-week period of treatment. As the total number of attacks recorded in this manner by patients taking any one of four combinations of tablets—namely, SPVN, PVNS, VNVP, or NSPV—did not differ significantly ($P > 0.30$), we felt justified in using these results to analyse the value of the individual tablets. On completion of this analysis the code showed that N was iproniazid, S placebo, P meprobamate, and V nialamide.

Results

Angina.—The average number of attacks of angina pectoris experienced by all patients during the final three weeks of treatment with 50 mg. of iproniazid was 38, with 100 mg. of nialamide 40, with the placebo 43, and with 400 mg. of meprobamate 48. These results do not differ significantly. Individual patients showed striking improvement to each type of therapy. Taking a reduction in the number of attacks of angina in any one period of treatment to 25% of the average level as an "excellent" response (Blumgart *et al.*, 1955), there were three excellent responses on iproniazid, three on nialamide, three on meprobamate, and four on the placebo. These results appeared to be independent of the order of therapy, and were not more frequent during the first six weeks of the trial. These responses occurred in nine different patients. A further method of analysis would be to use a non-parametric method of ranking,

by which the number of pains experienced by each individual during each type of therapy would be "ranked" 1-4. With this method the average ranking of iproniazid was 2.3, placebo 2.4, nialamide and meprobamate both 2.6 (see Table). Those patients with severe angina (more than five attacks a day) and those taking long-term anticoagulants did not differ in their response from the group as a whole.

Results of Treatment of Angina Pectoris (Last Three Weeks of Six-week Treatment Period)

	Iproniazid 50 mg.	Nialamide 100 mg.	Meprobamate 400 mg.	Placebo
Average No. of angina attacks	38	40	48	43
No. of "excellent" responses	3	3	3	4
Average ranking	2.3	2.6	2.6	2.4

Postural Fall of Blood-pressure.—The postural changes of blood-pressure recorded were very variable throughout this trial. The average changes were as follows: iproniazid -10/5, meprobamate -10/2, nialamide -10/5, and placebo -10/5. The maximal changes recorded were iproniazid -60/30, meprobamate -30/20, nialamide -30/20, and with the placebo -60/0. The maximal postural changes of blood-pressure did not correlate with the excellent responses of the angina.

Liver-function Tests.—The serum glutamic-pyruvic transaminase activity of all the patients was below 25 units at the beginning of the trial. Two marginally elevated readings were noted during the study: 39 units in one patient receiving nialamide and 49 units in one patient receiving iproniazid. In both patients the level fell below 25 units during the following six-week period.

Minor Toxic Effects.—Minor toxic effects such as insomnia, tiredness, giddiness, or constipation were recorded in eight patients receiving iproniazid, two receiving meprobamate, two receiving the placebo, and one receiving nialamide.

Electrocardiograms.—There was no significant change in any of the electrocardiograms of the 28 patients who completed the trial.

Weight.—No consistent changes were noted.

Deaths.—Two patients died of recurrent myocardial infarction during this trial. In both instances the diagnosis was confirmed at necropsy. One patient was receiving meprobamate and the other the placebo at the time of death.

Discussion

In a double-blind trial of this type it is often difficult to decide the dosage of the agents under examination. In this study the dose of iproniazid was limited by the danger of toxicity and by the reported difficulty of patients tolerating even the moderate dosage of 150 mg. daily (Master, 1958). The small but reportedly effective dose of 50 mg. (Shoskes *et al.*, 1959) was therefore chosen. Similarly, relatively small but reportedly effective daily doses of nialamide 100 mg. (Wolfe and Shubin, 1959) and meprobamate 400 mg. (Shapiro, 1957) were selected.

We have been unable to show in this trial that in these doses iproniazid, nialamide, and meprobamate differ significantly in their effect on the symptoms of angina either from each other or from the inert placebo. Furthermore, there appeared to be no significantly different response in the patients with severe angina or those receiving anticoagulants.

As the number of excellent responses in the trial was the same with each type of therapy as well as with the placebo, it seems very probable that these periods merely reflect temporary changes in the course of the disease or in the spontaneous activity of the patient concerned, and illustrate the necessity of judging the efficacy of anti-anginal remedies in a controlled trial. In one of the few controlled trials of iproniazid which showed a significant improvement in the symptoms of angina pectoris (Shoskes *et al.*, 1959), the order of giving the unknown tablets appears to have significantly influenced the outcome of the trial. In this study, however, where the order of administering the tablets did not produce significantly different results, we have been unable to confirm their findings. In view of the considerable number of double-blind trials (Dewar *et al.*, 1959; Snow and Anderson, 1959; Fife *et al.*, 1960; Phear and Walker, 1960; Allanby *et al.*, 1961; Murphy *et al.*, 1961), in addition to this study, which have failed to confirm the value of the mono-amine oxidase inhibitors in the treatment of angina pectoris, it seems increasingly difficult to be convinced that earlier enthusiastic reports of improvement based on uncontrolled trials were not due to temporary changes in the mental outlook of the individual patients concerned or to natural variations in the symptoms of angina pectoris.

Summary

In a double-blind trial of the respective value of iproniazid 50 mg. daily, nialamide 100 mg. daily, meprobamate 400 mg. daily, and an inert placebo in the treatment of 28 patients with angina pectoris, it was found that the incidence of chest pain did not differ significantly during any of the courses of therapy. The effect of each course of treatment on the postural change of blood-pressure was very variable. No serious side-effects requiring the discontinuation of therapy occurred, but minor complaints were more common with iproniazid than with any of the other forms of treatment.

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