PRELIMINARY OBSERVATIONS ON CAVODIL IN TREATMENT OF ANGINA PECTORIS

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Considerable success has been claimed for iproniazid in the treatment of angina pectoris (Cesarman, 1957; Cossio, 1957, 1958; Master, 1958; Towers and Wood, 1958). More recently, however, controlled trials have shown that the response to iproniazid may be little or no better than to a placebo (Dewar *et al.*, 1959; Snow and Anderson, 1959). Moreover, it has unpleasant and sometimes serious side-effects, particularly when used for prolonged periods (Robitzek and Selikoff, 1952; Master, 1958; Towers and Wood, 1958; Benaim and Dixon, 1958). Its most powerful known pharmacological action is the inhibition of monoamine oxidase, and it is thought that some or all of its clinical effects may be due to this. "Cavodil" (beta-phenylisopropylhydrazine), a hydrazine analogue of amphetamine, is, like iproniazid, an inhibitor of monoamine oxidase, but is much more potent in this respect (Horita, 1959). It has a prolonged action, and the effects of a single dose may last from 7 to 10 days. Like other monoamine oxidase inhibitors it may potentiate the action of barbiturates, tranquillizers, hypotensive drugs, and amphetamine compounds. Some success from this drug has recently been claimed in the relief of angina in a small series of patients (Kennamer and Prinzmetal, 1959).

We report here the results of a controlled "double blind" trial of cavodil in 28 patients with angina pectoris.

Material and Methods

Twenty-eight patients, all reliable witnesses, were selected from a larger group who had attended the department of cardiology. These patients were thought to have typical angina of effort, which had been static for at least six months. The severity of symptoms was assessed before treatment, and each patient was requested to note any side-effects and the time at which improvement, if any, occurred. Some patients were receiving treatment with long-acting nitrites and trinitrin, and this was continued during the trial. Because of the possible potentiation by cavodil patients were instructed not to take barbiturates or tranquillizers during the trial unless it was essential, when they were advised to take a smaller dose than usual. Each patient was supplied with a card to carry in a pocket stating the type of treatment he was receiving and advice regarding prescription of the above drugs and morphine should they become necessary. The dose of cavodil prescribed was one tablet (6 mg.) twice daily, with a tablet of lactose identical in appearance as a control. The tablets were dispensed by the hospital pharmacist on a "double-

blind" basis, and neither patients nor physicians knew which tablet the patient was receiving at any given time. Each tablet was given for one month, and in view of the prolonged action of cavodil a period of 14 days without tablets was given after finishing the first and before starting the second tablet. All patients were interviewed one week, two weeks, and four weeks after starting each tablet, when the standing blood-pressure was recorded and improvement or otherwise in the angina was noted. Finally the response during each four-week period was compared.

Results

One patient died from myocardial infarction during the trial and is therefore not included in the results. The remaining 27 patients completed the trial, and fall into one of four groups shown in the Table. Eleven

Effect of Cavodil on Patients With Angina

	No. of Patients	Percentage
Improvement with cavodil alone	11	41
" " control	1	4
" " both cavodil and control	12	44
No change	3	11
Total	27	100

(41%) improved with cavodil alone and derived no benefit from the placebo. Improvement in these patients was often dramatic, and most were able to discontinue trinitrin. Six of these patients had cavodil first and five the control tablet. Improvement usually began towards the end of the first week of treatment, but in some it was delayed for 14 days, the maximal effect sometimes not occurring for three weeks. Only one patient improved with the control tablet alone. Twelve (44%) patients improved with both tablets, and of these six received cavodil first and six the control. Three patients did not improve with either tablet.

Side-effects.—These were mild, and in no instance necessitated modification of the trial regime. Seven patients complained of mild transient dizziness, and this was associated with postural hypotension in four. Five complained of dry mouth while on cavodil, but four had dizziness and one had dry mouth while taking the control tablets. Other side-effects of cavodil were fatigue (3) and constipation (1), and of the control tablets fatigue (2) and insomnia (1). No difficulty with potentiation of other drugs occurred during this trial.

Discussion

Eleven (41%) patients improved with cavodil alone, while only one (4%) improved with the control tablet. Twelve (44%) patients improved with both tablets, so that a total of 23 (85%) patients improved on cavodil as compared with 13 (48%) who improved on the control tablet. Though this trial was of short duration and on a small number of patients, the results contrast favourably with a similar recent trial in this department of iproniazid (Snow and Anderson, 1959). The improvement in individual patients was often very striking, and the figures are encouraging, suggesting that cavodil may become a useful drug in the management of anginal pain. The assessment of any new drug in the treatment of angina is notoriously difficult, for angina is a subjective sensation which improves in a proportion of patients involved in a clinical trial no matter what treatment they receive. Moreover, in the natural course

of the disease phases of increased and decreased pain occur. For this reason caution must be exercised in pressing the claims of a new preparation before extended trials have been made. We believe, however, in view of our results, that such trials of cavodil are fully justified and should be undertaken.

Summary

A controlled "double-blind" trial of cavodil has been made in 28 patients with angina pectoris.

Improvement occurred in almost twice as many patients with cavodil as with the control tablet, and in some patients this improvement was remarkable.

It is suggested that an extended trial of this drug is fully justified and should be undertaken.

Side-effects were minimal and unimportant.

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EPIDEMIC OF CHRONIC NEPHRITIS OF UNKNOWN AETIOLOGY

BY

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Since 1957 a remarkable increase in the number of persons suffering from chronic nephritis has been observed in some regions of Yugoslavia. In certain villages this outbreak has shown all the main signs of an epidemic. As a similar occurrence has not been described before and therefore no experience has been obtained concerning this condition, extensive investigations have been undertaken in the affected area. It was found in the neighbourhood of Lazarevac, a city of Serbia, that cases of chronic nephritis have occurred in great numbers in three of the villages situated in the inundated area of the river Kolubara (Milojčić *et al.*, 1958). Epidemiological inquiry established that most of the persons attacked were adults over 30 years of age; only 10–14% were children under 14 years old. Incidence in women was 10–30% greater than in men. The illness is confined to certain families and is restricted to those parts of the villages which are situated in the inundated area. In these families the morbidity rate is from 38 to 44%. Of the whole population of these

villages 1–6% became ill with characteristic symptoms, as 30–36% suffered only from albuminuria, the first sign of renal disease.

The patients are agricultural workers, employed under average economic conditions. Their diet is mixed, contains milk products and meat, and does not differ from that of the healthy villagers. The water-supply is unhygienic, the wells being shallow and liable to pollution. However, no intestinal infection has been registered during the past 25 years, nor has there been any epidemic among domestic animals or trouble with rodents. Mosquitoes are present in great numbers, but malaria has not been unusually prevalent. No effect of seasonal influence has been observed on the spread of illness; nor has a diffusion of illness by contact been noticed, since uninundated areas of villages have been spared though continual contact existed with affected families. No other epidemics of infectious diseases in this region are remembered, and no trace of scarlet fever, sore throat, or other streptococcal infection has been reported among the patients.

Onset

It is significant that about 90% of the patients have not been aware of the onset of the illness. The starting-point is imperceptible, and subjective symptoms are so infrequent, even in the final stage, that the patients pay no great attention to them. For that reason many are not conscious of their illness until the physician tells them. The most common symptoms are lassitude, fatigue, anorexia, headache, and gastric pains. The only objective symptom is albuminuria, and that is the first sign of renal disease (Danilović *et al.*, 1957). The remaining urinary findings are uncharacteristic, red cells and casts mainly being absent. Oedema and hypertension are seldom present. Urea is usually within normal limits until the final stage, when uraemia begins, death following shortly. Patients are apyrexial, thin, and anaemic, and have a characteristic dark-coloured skin. Inspection of the fundus oculi has not indicated any change.

Clinical Picture

The illness is characterized by a gradual development from the beginning of albuminuria to the final uraemic stage. The renal lesion develops throughout the years; it may be detected in children as albuminuria, reaching the final stage of renal failure only at the age of 40 or over. Acute cases, with a rapid and definite beginning of the disease, do not occur. The mortality rate is 3–5%. At necropsy the kidneys show interstitial chronic inflammation, localized mainly to the tubules.

Because of the uncharacteristic clinical picture, the possibility of some form of chronic poisoning has been under consideration. This theory was discarded as soon as it was established that the illness lasts for several decades in some families, and that sometimes all members of a family died of chronic nephritis. Though the illness was known long ago, only the obvious increase in the number of cases has drawn the attention of specialists to it. Water and food have been analysed for various toxic elements, such as mercury, arsenic, phenols, aniline, cresols, insecticides, and radioactive substances, but without positive results. In the flour used by some families lead was found in the proportion of 0.3 mg./kg. As this flour comes from the little village mills it was decided to investigate the millstones concerned. Some of these had a high proportion of lead