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Key passages

THE COMPARATIVE VALUE OF DRUGS USED IN THE CONTINUOUS TREATMENT OF ANGINA PECTORIS ¹

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The most difficult problem in devising a plan of observation on treatment was how to provide adequate control. With this object we adopted a scheme of treatment with placebo. Even then particular attention had to be paid to a number of factors which conspired to upset the value of control observations. Thus, it was always necessary to learn in every case the number of attacks produced by a known amount of exertion in a definite period, and the severity of these attacks and their duration when rest was taken, from their onset. Spontaneous variation in the severity of the pain, and occasionally the tendency to periods of relative freedom from attacks (remissions), had both to be considered. Gain or loss in body-weight, weather conditions, unusual emotional influences, and intercurrent illnesses, all had to be taken into account when assessing the value of the remedies tested, and appropriate notes were made on a specially printed form at each attendance. One of two placebos² was prescribed for a fortnight at the first attendance. Patients were instructed to make personal records of each attack, noting the nature of the exertion which had induced the pain, and the duration of the several attacks when rest was the only treatment accorded. Particulars of the frequency, severity, and duration of the anginal attacks prior to observation were also taken. Later, between trial periods of active drugs, control periods (placebo only) of two, four, or more weeks were introduced.

All patients were ambulatory; they visited the clinic at fortnightly or monthly intervals. Any untoward symptom due to the drug was noted. In order to avoid mental suggestion the drugs were prescribed in a mixture form whenever possible, and a simple colouring agent added where necessary. The following drugs were tested: sodium nitrite, mannitol hexanitrate, erythrol tetranitrate, potassium iodide, luminal, chloral, morphine, papaverine, phenacetin, diuretin, calcium diuretin, euphyllin, belladonna, digitalis, lacarnol, and harmol. Mannitol hexanitrate, erythrol tetranitrate, phenacetin, and calcium diuretin were prescribed in tablet form. Care was taken in arranging the order in which these drugs were prescribed so as to avoid giving two important drugs over consecutive periods, and an intervening period was often allotted during which the patient was given a placebo.

Control periods. (Placebo.) The value of remedies in relieving anginal pain cannot be judged unless the observations are properly controlled. The literature on the treatment of angina gives no indication that this side of the problem has been considered, although it is recognized that the disease pursues a varying course in regard to severity quite apart from any form of treatment. Gallavardin (25) pointed out that spontaneous remissions occur in about 8 per cent. of patients and sometimes last for years. His observations dealt with such long periods of remission that it is likely that

coronary thrombosis explained most of them. No facts seem to be available on variations in the severity of symptoms during the course of angina of effort over weeks or months. This knowledge is essential if we are to have control of therapeutic investigations. A contribution to this problem is furnished by our control observations.

Sixty-six patients were treated with a placebo for periods of four to twenty-six weeks. In some patients the periods of placebo treatment were consecutive, but usually they were separated by periods during which active drugs were taken. The results are discussed here in four different groups according to the frequency of anginal attacks during successive observation periods when compared with an initial test period of fourteen days. The four groups indicating different degrees of clinical response to treatment are defined as follows: (a) great improvement, indicating a decrease of more than 50 per cent. in the number of attacks; (b) moderate improvement, indicating a decrease of less than 50 per cent. in the number of attacks; (c) no improvement; (d) worse.

Of the 66 patients who received placebo treatment for more than one test period of fourteen days, 18 (27 per cent.) showed great improvement (a), which included complete relief from attacks for one or more observation periods. Seven (10.5 per cent.) showed moderate improvement (b), 22 (33.5 per cent.) showed no improvement (c), and 19 (29 per cent.) were worse (d).

In the first group (a), 12 out of the 18 patients had a reduction of 50 per cent. or more in attacks during more than one-half of the period of observation. The minimum period of observation of the cases in this group while taking a placebo was six weeks, the maximum period twenty-six weeks, and the average period 12.6 weeks. The minimum period of complete relief was two weeks, the maximum period fourteen weeks, and the average 5.1 weeks. In the second group (b), all 7 patients had moderate improvement for at least half the period of observation. The minimum period of observation in this group was four weeks, the maximum fourteen weeks, and the average 7.1 weeks. If the results in groups (a) and (b) are considered together they show that 25 (37.5 per cent.) out of the 66 patients had improvement ranging from slight reduction in attacks, up to complete freedom for one-half or more of the observation period.

The high figures indicating improvement in this series emphasize an earlier remark that most of the observations made on the continuous treatment of angina have been based on uncontrolled data.

TABLE XIV

Summarizing the Effects of Thirteen Drugs in the Continuous Treatment of Angina Pectoris Compared with the Effects of Control Treatment with Placebo

Drug.	No. of patients.	Patients arranged in groups according to response to treatment.				Average no. of attacks in each patient during average test period.
		Great improvement.	Moderate improvement.	No improvement.	Worse	
		(a)	(b)	(c)	(d)	
Placebo	66	18	7	22	19	29
Sodium nitrite	42	5	3	21	13	38
Placebo		12	5	11	14	30
Mannitol hexanitrate	21	2	1	13	5	41
Placebo		6	2	9	4	32
Erythrol tetranitrate	20	0	0	13	7	89
Placebo		7	1	8	4	57
Potassium iodide	47	13	5	20	9	22
Placebo		15	5	15	12	26
Luminal	59	8	14	30	7	22
Placebo		17	7	21	14	29
Chloral	56	19	13	15	9	19
Placebo		17	4	20	15	30
Morphine	48	16	11	15	6	21
Placebo		15	3	16	14	32
Papaverine	31	9	7	8	7	27
Placebo		9	3	11	8	29
Phenacetin	20	6	4	6	4	33
Placebo		7	1	6	6	26
Diuretin	53	10	5	30	8	24
Placebo		17	5	18	13	27
Euphyllin	37	7	3	16	11	36
Placebo		12	3	12	10	31
Belladonna	15	1	1	7	6	48
Placebo		4	2	5	4	35
Digitalis	19	3	1	8	7	34
Placebo		4	2	7	6	25

Summary

A series of 90 patients with angina pectoris of effort was observed over a period of two and a half years, with special reference to the comparative value of certain drugs used in continuous treatment. Syphilitic angina pectoris was excluded, and coronary thrombosis was only considered as a complication.

Each patient attended fortnightly, and the various drugs were administered over periods of two to four weeks at a time, or longer. In this way their effects upon the frequency and severity of attacks could be compared. As a control in each case a placebo was regularly substituted for an active drug. The following drugs were tested: sodium nitrite, mannitol hexanitrate, erythrol tetranitrate, potassium iodide, luminal, chloral, morphine, papaverine, phenacetin, diuretin, ephyllin, belladonna, digitalis, lacarnol, and harmol.

The comparative results are outlined in Table XIV and in the graph. With one exception, they show that a measure of improvement appears to result from every remedy tried, and at least as great an improvement during treatment with placebo. This universal efficacy can only be explained by natural variations in the severity of the symptoms, which give a spurious value to each remedy. If any drug had proved to be superior there might have been grounds for recommending it in the continuous treatment of the disease, but no such precedence could be made out. Though scarcely convincing, there was some reason to think that chloral, morphine, papaverine, and phenacetin had a trifling influence in controlling the group incidence and severity of attacks.

We have been unable to convince ourselves that any drug tested is worthy even of trial in the routine treatment of the disease. Though not widely applicable, a drug might of course be effective in individual cases, and examples were sought for, but, with a few exceptions, were not found. The nature of the underlying cause of angina pectoris alone would seem to make the quest for a satisfactory form of treatment on these lines unlikely of attainment.

If, as we are convinced, none of these remedies are capable of lessening the frequency or severity of anginal attacks, there is all the greater need for a study of the application of those general measures known to control them, and to promote the wider use of vasodilators, such as trinitrin, which

are so often successful in the palliative treatment or even in the prevention of particular attacks.

We wish to acknowledge great indebtedness to our chief, Dr. John Parkinson, whose encouragement, criticism, and help alone made this investigation possible. To other members of the Honorary Medical Staff, who allowed us to observe the treatment of their patients, we owe our best thanks.

This investigation was made while one of us (W. E.) worked under the Paterson Bequest to the Cardiac Department, and the other (C. H.) as Medical First Assistant to the Hospital and Gillson Scholar to the Society of Apothecaries.