CLINICAL TRIAL OF TWO CORONARY VASODILATOR DRUGS

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Glyceryl trinitrate is now widely used for the rapid relief of acute episodes of cardiac pain. It is not of value in preventing pain except when taken immediately before effort. The search continues for a long-acting nitrate drug which, if taken regularly throughout the day, would prevent cardiac pain.

Two such drugs have been prepared and used in trials recently. A sustained-action nitroglycerin ("nitroglyn") was found by Huppert and Boyd (1955) to be moderately effective, while Fuller and Kassel (1955) and Heller (1956) reported good results in using triethanolamine trinitrate biphosphate ("metamine"). However, Russek *et al.* (1955a, 1955b) and Riseman *et al.* (1958) found that these two drugs were ineffective, and other clinical reports have produced further conflicting evidence.

We have been able to study the effect of these drugs on the frequency and duration of episodes of cardiac pain in 30 patients with ischaemic heart disease. This paper presents the results of our double-blind trial.

Pharmacology

Triethanolamine trinitrate biphosphate (T.T.B.) has the chemical formula:

The work of Junkmann (1940) and other European pharmacologists on the biological properties of T.T.B. has been reviewed by Fuller and Kassel (1955). It has been shown to be an effective coronary vasodilator which compares favourably with nitroglycerin (Melville and Lu, 1951), though T.T.B. has a lesser but a definite effect on the systemic blood-pressure and cardiac output than nitroglycerin (Merlen, 1951).

The mechanism of the vasodilator action is not certain. Melville and Lu (1951) showed that there is little *in vitro* nitrate-to-nitrite conversion, and claimed that the action of T.T.B. does not depend upon hydrolysis of nitrate.

Nitroglyn.—This is a porous plastic tablet impregnated with nitroglycerin so that there is a slow release and sustained action of the nitroglycerin. Gorlin *et al.* (1959) have studied the mode of action of nitroglycerin, and conclude that its primary effect is to increase the oxygen consumption of heart muscle and secondarily to cause coronary vasodilatation.

Patients and Method

Thirty patients, seven of whom were female, were studied. All had cardiac pain on effort and an electro-

cardiogram showing evidence of ischaemic heart disease. Twenty-two had had at least one myocardial infarction, and in seven this had occurred within six months of the trial. No patient was in heart failure during the trial, but three had been in left ventricular failure in the past. A Wassermann test had been done on 18 patients, and was negative in all. Three patients had mild essential hypertension, and a fourth was taking rauwolfia. Sixteen patients were taking phenindione at the time of the trial.

Three types of tablets were used, identical in shape and colour: T.T.B. 2 mg., nitroglyn 2.5 mg., and a placebo. They were coded A, B, or C, and were given in a sequence of any one of six possible combinations over a period of three weeks. For example, some patients received A the first week, B the second week, and C the third week; others had tablets in sequence B, C, A; others had C, A, B, and so on.

The sequence of tablets was varied to avoid two possible causes of error in the results. (1) If the tablets had been given in one sequence only to our seven patients with a recent myocardial infarction, the last tablet in the sequence might have seemed the most effective, as such patients often have progressively fewer attacks of cardiac pain. (2) The action of one drug might be potentiated by another when taken next in sequence, and so appear more effective.

Tablets were given on the first four days only of each week, as daily activity would tend to be more constant over this period than any other. No tablets were given on the last three days of each week, lest the action of any one drug should continue beyond the test period. Each patient took two tablets four times daily, before meals and before going to bed.

Each patient was given three cards, one for each week, and was asked to record daily the time of onset of each attack of cardiac pain, its duration in minutes, and the total number of glyceryl trinitrate tablets taken. (Patients were allowed to continue to take glyceryl trinitrate 1/100 gr. (0.65 mg.) as needed.)

Results

Those patients taking the placebo tablets had significantly more attacks ($P>0.01$) lasting from two to four minutes than patients taking either of the two trial drugs (Table I). The number of attacks of cardiac pain lasting one half to one minute and two to four minutes together, however, was about the same for each of the three tablets. Similarly the total number of attacks of all durations was the same whether the trial or the placebo tablets were given.

We concluded that, though T.T.B. and nitroglyn did not reduce the number of attacks of cardiac pain, they did benefit patients who had frequent short attacks by shortening them further. Attacks of pain lasting longer than four minutes, however, were not affected.

TABLE I.—Number of Attacks of Cardiac Pain of Different Durations in 30 Patients

Duration of Attack	Nitroglyn	T.T.B.	Placebo
1-1 minute	74	88	44
2-4 minutes	83	81	119
5-15 "	82	80	79
Over 15 "	14	7	11
	253	256	253

The 16 patients treated with phenindione and either T.T.B., nitroglyn, or placebo had fewer attacks than those who were given the trial drugs and placebo alone (Table II). The difference is highly significant ($P > 0.01$).

Finally, the 30 patients were classified according to their grade of cardiac pain (Table III). These patients had the same number of attacks when given the two drugs or placebo, irrespective of their capacity for effort; T.T.B. and nitroglyn did not benefit any one grade more than another.

The total number of glyceryl trinitrate tablets needed by patients while treated with T.T.B., nitroglyn, or

TABLE II.—Effect of Phenindione on Number of Attacks of Cardiac Pain of Different Durations in 30 Patients

Duration of Attack	Nitroglyn		T.T.B.		Placebo	
	+	—	+	—	+	—
1-1 minute ..	21	53	34	54	17	27
2-4 minutes ..	31	52	49	32	48	71
5-15 „ ..	41	41	28	52	28	51
Over 15 „ ..	6	8	3	4	8	3
	99	154	114	142	101	152

+ = With phenindione (16 patients). — = Without phenindione (14 patients).

TABLE III.—Number of Attacks Occurring in 30 Patients with Different Grades of Cardiac Pain*

Grade	No. of Patients	Nitroglyn	T.T.B.	Placebo
I ..	7	45	45	38
II ..	6	55	50	56
III ..	11	126	120	134
V ..	1	3	6	6
VI ..	5	24	35	19
		253	256	253

* No patients in grade IV.

Grades of cardiac pain: I. Pain produced only on hurrying or walking up hills. II. Pain produced when walking at an ordinary speed on the level. III. Pain that occurs even when a person walks slowly. IV. Total incapacity so that cardiac pain occurs on the slightest provocation and nearly always at rest also. V. Acute or subacute coronary insufficiency with depressed S-T segments at rest and repeated relatively long-lasting attacks of rest pain without infarction. VI. Cardiac infarction.

placebo were very similar (T.T.B. 319, nitroglyn 298, placebo 305) and substantiated the fact that neither drug in the dose given reduced the severity of the attacks of cardiac pain.

Side-effects were very few. Two patients complained of gastro-intestinal symptoms while taking the placebo tablet, and one patient developed nausea and dizziness from nitroglyn.

Discussion

When used to measure the effect of coronary vasodilator drugs on cardiac pain, subjective evidence might reasonably seem to yield less dependable results than the Master two-step effort test. This test is not without risk, however, and was thought unjustifiable in this study. The total numbers of episodes of cardiac pain are so strikingly similar for each tablet (253 for nitroglyn, 256 for T.T.B., and 253 for the placebo) that it can be strongly argued that the witness for each patient was reliable enough to make valid our frequency-duration method of assessing results of treatment.

Our results show that there is a small but significant effect upon the duration of shorter episodes (two to four

minutes) of cardiac pain during the treatment with nitroglyn or T.T.B., but that there is no effect upon longer episodes (over four minutes) or upon the total number for any one drug. It is possible that larger doses of both drugs would have been more effective. However, Riseman *et al.* (1958) found that 18 mg. of T.T.B. daily was ineffective, and Russek *et al.* (1955a) found that a single dose of 6 mg. of T.T.B. did not improve the effort tolerance in the Master two-step test. The absence of side-effects from T.T.B. suggests that the dose was too low (Friend *et al.*, 1954), or that it is a feeble vasodilator when given by mouth (Riseman *et al.*, 1958). We have not been able to confirm the substantial claims made for T.T.B. (Dailheu-Geoffroy, 1951; David and Rouleau, 1957).

A dose of two 2.5-mg. tablets of nitroglyn is probably not enough. Russek *et al.* (1955a) found that only 50% of the patients were any better when taking twice this dose, and Riseman *et al.* (1958) gave twice to four times the suggested dose (up to four 2.5-mg. tablets four times daily) before 57% of 14 patients were moderately or markedly improved.

The considerable improvement in patients who were being treated with phenindione and the trial drugs compared with those who were not receiving anticoagulants is very interesting. Dicoumarol has been shown to have a coronary vasodilator effect (Gilbert and Nalefski, 1949), and Graham *et al.* (1951) reported that heparin therapy coincided with a decrease in frequency of attacks of cardiac pain in 55 out of 59 patients. This latter effect, however, was shown to coincide with a change of lipoprotein pattern. The mechanism of pain relief during phenindione treatment is not known.

It is clear that T.T.B. and nitroglyn have only a small effect in patients with uncomplicated ischaemic heart disease. They may be useful drugs, however, to reduce the length of shorter episodes of cardiac pain if taken in doses at least as large as those used in this trial.

Summary and Conclusions

Two long-acting coronary vasodilators have been given to 30 patients with ischaemic heart disease to assess their effect upon the number and duration of attacks of cardiac pain. Sixteen of the patients were known to be taking phenindione.

Triethanolamine trinitrate biphosphate 4 mg. four times daily, nitroglyn 5 mg. four times daily, and a placebo were given in random sequence for three separate four-day periods, using the double-blind technique.

T.T.B. and nitroglyn reduced the duration of attacks lasting two to four minutes, but had no effect on those lasting longer. Neither drug reduced the total number of attacks.

Patients treated with phenindione and either T.T.B., nitroglyn, or placebo tablets had significantly fewer attacks of cardiac pain than those who were not receiving anticoagulant.

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A METASTASIZING CARCINOID TUMOUR WITH UNUSUAL FEATURES

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Carcinoid tumours arise from specialized epithelial cells in the gastro-intestinal tract known as Kulchitzky cells, which in recent years have been shown to secrete 5-hydroxytryptamine. The presence of excessive quantities of this substance in the blood of patients with metastasizing carcinoid tumours may produce a characteristic clinical syndrome of cutaneous flushing, diarrhoea, asthma, and right-sided valvular disease of the heart. Not all metastasizing tumours produce this syndrome, and the following case, which shows many unusual features, was originally diagnosed 22 years ago as an inoperable carcinoma of the pancreas.

Clinical Record

A retired civil servant aged 62 had his first attack of jaundice in 1927 at the age of 30; this was transient and was attributed to infective hepatitis.

In 1937 jaundice recurred, but on this occasion it steadily deepened. The liver was enlarged five fingerbreadths below the costal margin and the gall-bladder was palpable. A laparotomy by Mr. R. M. Vick at St. Bartholomew's Hospital showed a mass $1\frac{1}{2}$ by 2 in. (3.8 by 5 cm.) in the head of the pancreas and a liver studded with secondary deposits. A palliative cholecystogastrostomy was performed. No biopsy was taken. After the operation the jaundice cleared, but the colour returned to the stools for a short time only. Subsequently these became loose, pale, and offensive, five or six a day, but his main complaint over the next few years was of recurrent attacks of severe abdominal pain probably pancreatic in origin.

In 1944 he developed oedema due to hypoproteinaemia (serum albumin 2.6 g./100 ml.). Treatment with a high-

protein low-fat diet and intravenous infusions of plasma resulted in a rise in serum albumin, disappearance of the oedema, and some improvement in the steatorrhoea. Shortly after discharge from hospital he had a further attack of jaundice, thought to be a serum hepatitis.

In 1952 he became jaundiced again, the serum bilirubin rising over three weeks to 32.5 mg./100 ml. A laparotomy was performed by Professor I. Aird at Hammersmith Hospital, the operation note being as follows: "The liver was grossly enlarged, with about a dozen hard white nodules characteristic of a carcinoma deposit. In the head of the pancreas and related to the termination of the common bile duct there was a stony-hard tumour encircling not only the common duct but also the lower part of the portal vein. The remainder of the pancreas presented to palpation and vision the characteristic appearances of chronic pancreatic obstruction. The common bile duct was grossly distended and there was only a tiny fistulous opening between the gall-bladder and duodenum. This was closed and a Roux-en-y choledochojunostomy performed. Biopsies were taken from the liver and from the pancreatic mass through the lumen of the common bile duct. The appearances of the liver were exactly those described at the first operation."

Histological report (Dr. E. D. Williams): "Naked-eye examination of the liver biopsy showed one main nodule of tumour tissue (0.8 cm. diameter) and two smaller ones. On microscopy these consisted of clumps and strands of closely packed polygonal cells embedded in a meshwork of loose fibrous tissue. In some areas there was a tendency to an acinar structure and in one part there were well-formed tubules. The tumour nuclei were remarkably uniform in size and shape, and only occasional mitoses were seen. The clear vacuolated cytoplasm contained a few granules which did not stain with the Masson silver technique or with the diazo reagent. The pancreatic biopsy was badly distorted and consisted mainly of dense fibrous tissue, but in one area at the edge of the specimen there was similar tumour tissue to that described above. Despite the absence of specific granules, the histological appearances were typical of a carcinoid tumour."

The patient made a good recovery from the operation, though the steatorrhoea and recurrent bouts of abdominal pain continued. He also complained of nocturnal polyuria and cramp in the hands and feet, suggestive of tetany, but never had any attacks of flushing or cyanosis.

Results of Examination

In 1958 he was readmitted for further assessment. He was thin with a dry, scaly skin and slight, pitting oedema of the ankles. Trousseau and Chvostek signs were negative. The liver edge was hard but regular, and was palpable three fingerbreadths below the costal margin. There was no splenomegaly or ascites. The cardiovascular system was normal apart from a soft systolic murmur at the apex.

Investigations.—Haemoglobin, 12.9 g./100 ml.; M.C.H.C., 30%; white-cell count, 6,000, with a normal differential; sternal marrow, normal. Serum electrolytes: sodium 130, potassium 4.1, chloride 99, bicarbonate 25, calcium 4.0, phosphate 1.9 mEq/l. Serum proteins: albumin 3.6 g., globulin 3.0 g./100 ml.; serum amylase 170 units. 5-hydroxyindole acetic acid excretion, 10.5, 10.7, and 9.2 mg. per 24 hours (normal range 3–13 mg.). Liver-function tests: serum bilirubin, 0.3 mg./100 ml.; thymol turbidity, 0 unit; alkaline phosphatase, 21 units; serum G.O.T. 25 units/ml., serum G.P.T. 25 units/ml. Bromsulphthalein test, less than 10% dye retention at 30 minutes. Prothrombin time, 14.5 seconds (normal 10–11 seconds). Liver biopsy, only normal tissue obtained. Intestinal absorption tests: stool examination, numerous undigested meat fibres; no fat-forming organisms on culture. Glucose tolerance, normal. Starch tolerance, abnormal; no significant rise in blood sugar after 50 g. of starch by mouth. Fat balance (75 g. intake): first three days, average daily excretion 64.7 g.; second three days, average daily excretion 38 g. Radioactive fat studies (labelled with

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