FAILURE OF PROPATYLNITRATE AND PENTAERYTHRITOL TETRANITRATE TO PREVENT ATTACKS OF ANGINA PECTORIS

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There is at present no widely accepted medicament which can be relied upon to abolish or diminish the frequency of attacks of angina pectoris. We report here the result of a double-blind controlled clinical trial of a new drug, propatyl-nitrate. It was originally called "etrynit," but prior to marketing in this country the name was changed to "gina." We have previously shown (Sowton and Oram, 1961) that it is as effective as glyceryl trinitrate in the treatment of an acute attack of angina pectoris, and that on rare occasions it has certain advantages over that drug.

Nordqvist and Varnauskas (1960) carried out clinical investigations of propatyl-nitrate on 65 patients for two years in Scandinavia and concluded that it is as useful as glyceryl trinitrate in the acute angina attack and that the frequency of attacks is much reduced for five hours after a 10-mg. tablet. They consider 10 mg. of propatyl-nitrate to be more effective than 30 mg. of erythritol tetranitrate, which in turn they found to be more effective than 30 mg. of pentaerythritol tetranitrate (PETN; "mycardol").

Method

The trial was designed to compare 10 mg. of propatyl-nitrate against a placebo and also against 30 mg. of PETN.

Thirty patients (22 men and 8 women) took part in the trial, all attending a cardiac clinic because of angina pectoris. The age limits were 40 to 71 (men) and 46 to 66 (women). The diagnosis of angina was made on a typical history accompanied by electrocardiographic evidence of ischaemic heart disease in all cases. No patients with aortic valve disease or anaemia (below 80% haemoglobin) were included, and in each patient the frequency of attacks of angina had remained fairly stable for at least two months. All patients were familiar with the use of glyceryl trinitrate for the treatment of acute attacks.

The three drugs were prepared by the manufacturer as apparently identical tablets, and supplied under the labels A, B, or C. They were dispensed in boxes identified only by a number, the boxes being filled and distributed in random order by the use of Fisher and Yates's (1957) statistical tables, in such a way that each patient received three boxes, each containing one drug.

Patients were asked to take one tablet sublingually three times a day whether they had pain or not, and to use glyceryl trinitrate for acute attacks. Each box contained enough tablets for one week, and the boxes were used consecutively, starting with the lowest-

numbered box. Patients kept notes during the trial and returned to the clinic after three weeks, when they were asked which tablets had been most effective and which least effective in preventing attacks of pain; they were also asked if any side-effects had been noticed.

We decided to use this method of assessment, as it is the pain of which patients with angina pectoris complain that we hope to treat. So-called objective tests, depending, for example, upon the development of electrocardiographic changes or on alterations in effort tolerance, are not necessarily closely related to the production of pain (Master and Rosenfeld, 1961). Often, too, such tests depend on the decision of the patient when to stop exerting himself. It is apparent that there can be no accurate objective test of a symptom.

Results

We assessed our results by the method of sequential analysis (Armitage, 1954; Snell and Armitage, 1957). The drugs were compared in pairs and the results plotted on a sequential analysis chart with boundaries corresponding to a 5% significance level. Until the trial had finished the drugs were known only as A, B, or C, but the identities were then determined from a key supplied by the manufacturers. Analysis in this manner failed to show a significant difference between the three preparations:

Propatyl-nitrate and Placebo	PETN and Placebo	Propatyl-nitrate and PETN
Propatyl-nitrate better .. 8	PETN better 11	Propatyl-nitrate better .. 8
Placebo better .. 17	Placebo better 13	PETN better .. 15
No difference .. 5	No difference 6	No difference 7

Discussion

Opinions regarding the value of PETN as a preventive of angina pectoris vary from it being of considerable value (Wingfield and Goldfoot, 1957; Johnson and Sevelius, 1960) to being useless (Dewar *et al.*, 1959; Phear and Walker, 1960). Winsor and Scott (1955) found PETN to be of definite value when administered sublingually, and this route was used by us to enable a double-blind technique to be employed. During the course of the trial some patients became so impressed with one set of tablets that they pleaded by letter and telephone for further supplies. One patient claimed that his average consumption of glyceryl trinitrate fell from 12 to 2 tablets a day when taking propatyl-nitrate but rose again to 12 a day when his supply ran out. This effect was obtained on three occasions and did not occur when he was supplied with PETN or with placebo tablets.

Side-effects were fairly evenly limited to all three preparations and usually consisted of headache or giddiness. Eight of the 30 patients found one tablet to be very good indeed at preventing attacks, this action being attributed to propatyl-nitrate in two cases, to PETN in three, and to the placebo in three. Although our results differ from those of the Scandinavian workers in regard to the prophylactic use of propatyl-nitrate, they are in complete agreement with the conclusions reached by Sandler (1961), who has also fully investigated propatyl-nitrate, PETN, glyceryl trinitrate, and a placebo at Sheffield by a double-blind technique.

It appears that propatylnitrate is a potent drug for the relief of acute attacks of angina pectoris but is of little or no value in prophylaxis. In our opinion there is as yet no drug which can be relied upon to abolish or diminish the frequency of attacks of angina pectoris.

Conclusion

In the doses used sublingually propatylnitrate and PETN did not differ significantly from a placebo in abolishing or diminishing the frequency of attacks of angina pectoris.

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FATTY CHANGE IN THE MYOCARDIUM OF THE NEWBORN

BY

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Recent perinatal mortality surveys have shown that in many babies dying either during or soon after delivery no cause for death apart from asphyxia can be found. Our own figures for the Glasgow Royal Maternity Hospital reveal that at least 33% of perinatal deaths have to be classified as such. Yet the term is a loose one, and the findings at necropsy vary greatly. In many, however, appearances suggestive of cardiac failure are seen. In these cases there is distension of the right heart, especially the atrium, together with congestion of the great veins. Enlargement of the liver is not generally noted, but on section blood pours from the cut surface. One other feature suggesting venous congestion is the marked distension of the umbilical vein in the ligamentum teres. This appearance was seen in babies dying shortly after delivery and was even more marked in other cases showing hyaline membrane formation. This conception of cardiac failure as a factor in death of the newborn has been suggested by many clinical observers (Rowe and James, 1957; Burnard, 1959; Brown, 1959), and Lendrum (1955) was of the opinion that it was primarily due to a left heart failure.

Obviously this failure is functional in nature, but it is the purpose of the pathologist to find, if possible, some morphological counterpart for the clinical and post-mortem appearances. It was therefore decided to examine the myocardium in these cases to determine whether the failure was accompanied by histological change or not.

Material and Methods

Altogether 72 cases were studied, 15 being stillbirths and 57 neonatal deaths. These were unselected and included infants of all degrees of maturity. Macerated stillbirths were excluded from the survey. It is the custom in this hospital to place the bodies of all babies in a refrigerator within one hour of death. Necropsies were carried out within 24 hours. Longitudinal blocks through atrium and ventricle were taken from both sides of the heart, the left block longer than the right in order to identify the side of origin. Material was fixed in buffered formalin (pH 7) and also in picric alcohol. Frozen sections were stained for fat with Sudan IV and paraffin blocks with haematoxylin and eosin and lead

tetra-acetate Schiff (L.T.A.S.). Material fixed in picric alcohol was examined for glycogen, using Best's carmine stain. Later in the survey, however, this was discontinued, as it was found that L.T.A.S. gave a relatively good estimate of the amount of glycogen present. The grading of both fat and glycogen was made on a 0, +, ++, +++ basis and was carried out in advance of the routine post-mortem histology without reference to the individual records (Fig. 1). In this there was less chance of the grading being influenced.

Results

On analysing the findings it soon became apparent that the amount of glycogen present varied greatly from case to case, but fatty change followed a much more definite pattern. In no instance did the left heart ever show more fat than the right, nor the atrium more than the ventricle. Indeed, in 50% of the cases the right ventricle showed most change, while in the remainder both ventricles were equal. Apart from the fact that the average duration of life was shorter—namely, 28 hours

Fig. 1.—Fatty change in the myocardium, grade + + +. (Frozen section stained with Sudan black.)