Long-Acting Coronary Vasodilator Drugs: Metamine, Paveril, Nitroglyn and Peritrade

By Henry I. Russek, M.D., Burton L. Zohman, M.D., Alice E. Drumm, M.D., William Weingarten, M.D. and Virgil J. Dorsett, M.D.

Recognition of the value of glyceryl trinitrate (nitroglycerine) in the treatment and prevention of anginal attacks has confirmed the belief that coronary blood flow may be influenced favorably by drug therapy and has led to a search for vasodilators capable of more prolonged action. The most popular of the newer agents which are alleged to have this desirable effect are Metamine, Paveril, Nitroglyn and Peritrade. In order to evaluate these drugs, the modifying action of each agent on the electrocardiographic response to standard exercise (Master two-step test) was recorded and compared in 21 carefully selected patients with coronary disease. Analysis of the results obtained with varying dosage administered from one to six hours prior to exercise disclosed that Peritrade was vastly superior to the other three drugs and that it alone was worthy of the designation "long-acting coronary vasodilator."

The administration of nitroglycerine (glyceryl trinitrate) in the treatment of angina pectoris has long been recognized as the most effective measure for the relief of the acute attack. Although the drug is also unexcelled prophylactically when employed prior to contemplated exertion, the relatively short duration of its action obviously does not afford prolonged protection for the patient afflicted with this disease. For many years, therefore, the search has continued for a long acting coronary vasodilator which is capable of reducing the frequency and severity of anginal attacks by routine daily administration. Although numerous drugs have been characterized by their individual sponsors as fulfilling this need, few have been able to withstand the test of time and clinical usage. In previous studies, we have compared a number of "vasodilating" agents by recording their respective actions in modifying the electrocardiographic response to standard exercise (Master two-step test) in patients with coronary disease. The results of that investigation demonstrated that only papaverine (in large dosage) and pentaerythritol (Peritrade) tetranitrate exhibited prolonged effects which were similar to those observed for shorter periods with nitroglycerine. On the other hand, whiskey, aminophylline, Roniacol (beta-pyridylcarbinol tartrate), khellin (visamin), octyl nitrate, Priscoline (tolazoline hydrochloride), tetraethylammonium chloride, Paveril (dioxyline phosphate), heparin and Dicumarol (bishydroxy-coumarin) were found to exert little or no influence on the exercise response.

At the present time a number of preparations are being widely employed because of claims that these agents are long-acting coronary vasodilator drugs. In each instance the manufacturer asserts that his drug "prevents anginal attacks or greatly diminishes their number and severity." The most popular of these agents in current usage are Metamine (triethanolamine trinitrate biphosphate), Paveril (dioxyline phosphate), Nitroglyn (glyceryl trinitrate in a sustained-action tablet) and Peritrade (pentaerythritol tetranitrate). Obviously, confirmation of these claims as well as measurement of the clinical response to each of these drugs is necessary to assess their relative value in...
therapy. The difficulty in determining the clinical effect of any agent in angina pectoris is well known to those engaged in the care of such patients. Inasmuch as the psychologic effects from placebo or other inactive drugs may significantly reduce "nitroglycerine requirements" and "frequency of attacks" whereas sedatives may accomplish a similar result by raising the pain threshold, a more reliable index of coronary insufficiency is needed than that afforded by the subjective sensation of pain.

In attempting to evaluate drugs which are alleged to have coronary vasodilator action we have been impressed with the objectivity of results obtained by means of a standard exercise test (Master two-step test) in carefully selected patients with coronary insufficiency.\(^1\) By recording and comparing the ability of specific agents to modify the electrocardiographic response to exercise, drugs exerting favorable effect could readily be identified and the duration of their action measured. To have validity, such investigation must include only those patients with coronary disease who on repeated testing under identical conditions exhibit a relatively constant positive response to a given amount of exercise. By screening a large number of patients in anticipation of the present study, we selected 21 subjects in whom the necessary criteria were fulfilled.

**Material and Method**

All 21 of the patients in this series were men between the ages of 46 and 69 years. Nine of the group had sustained myocardial infarction and 15 presented classic symptoms of angina pectoris. Arterial hypertension was present in 9 of the 21 subjects. In all patients included in this series, the control response to exercise remained constant when recorded from day to day, and, in addition, could be modified favorably by the sublingual administration of therapeutic doses of nitroglycerine just before the test. By establishing this prerequisite, it was felt that a basis for comparison could be obtained between the effect of the known vasodilator, nitroglycerine, and that of other agents with unknown or undefined action. In each of the 21 patients Metamine (triethanolamine trinitrate biphosphate), Paveril (dixoxyline phosphate), Nitroglyn (coated granules of glyceryl trinitrate) and Peritrate (pentaerythritol tetranitrate), respectively, were administered on different occasions from one to six hours before the performance of measured exercise. Medication was administered in varying dosage before breakfast in each instance. The results have been carefully recorded and compared.

**Results**

The 21 patients in this series performed 258 exercise tests following the administration of Metamine. The dosage employed was 2.0 to 6.0 mg. orally before breakfast. After taking the drug, exercise tests were obtained at variable intervals up to six hours but usually no more than three tests were performed in the individual case on any one day. A slight effect on exercise response was observed in only six cases in this series. In the remaining 15 patients, Metamine failed to exert a significant influence on the electrocardiograms recorded after standard exercise. Consequently, the modifying effect of this agent on exercise response must be regarded as relatively slight (figs. 1 through 4).

Paveril (dixoxyline phosphate), the synthetic analogue of papaverine, when administered in doses of 200 to 500 mg., orally, showed a significant effect in only 6 of 21 patients tested. Moreover, even in those showing favorable response the duration but not the degree of electrocardiographic abnormality was modified favorably (figs. 1 through 4). In evaluating the drug 174 exercise tests were performed. Paveril appeared to be a much less potent drug than papaverine according to this method of testing.\(^4\) Comparative studies revealed Paveril to be superior to Metamine but less effective than Nitroglyn or Peritrate (figs. 1 through 4).

In evaluating Nitroglyn, a preparation containing specially coated granules of glyceryl trinitrate (nitroglycerine), a dose of 2.4 to 9.6 mg. (\(\frac{1}{25}\) to \(\frac{4}{25}\) grain) was administered to 21 patients from one to six hours prior to the commencement of exercise. In these subjects 346 tests were performed following the administration of the drug. The dosage of 2.4 mg. (\(\frac{1}{25}\) grain) was found ineffective up to six hours after its administration in all patients tested. Similarly in 8 of the 21 patients no effect was noted even with dosage levels
as high as 9.6 mg. (\(\frac{1}{2}\) grain). In the 13 remaining patients, however, slight to moderate improvement was observed in exercise response as long as six hours after the administration of 4.8 to 9.6 mg. (\(\frac{3}{25}\) to \(\frac{4}{25}\) grain) (figs. 1 through 4). In no instance did this sustained action preparation of nitroglycerine cause a normal exercise response to be recorded.
LONG-ACTING CORONARY VASODILATOR DRUGS

FIG. 3. Master tests (lead V4) obtained in a patient with angina pectoris with and without the administration of drugs.
* T.I., time interval (minutes) between medication and beginning of test.

FIG. 4. Master test responses (lead V4) obtained in a patient with angina pectoris with and without the administration of drugs.
* T.I., time interval (minutes) between medication and beginning of test.

Even when massive dosage was employed. These findings are in distinct contrast with those observed with the sublingual preparation of the drug and with ordinary doses of Peritrate respectively (figs. 1 through 4).

Peritrate (pentaerythritol tetranitrate) was administered in a dose of 10 to 20 mg. to the 21 patients in this study. As with the other drugs the response to exercise was recorded at varying intervals up to six hours following
its administration. A total of 230 exercise tests were performed in evaluating the effects of this agent. In a dose of 10 to 20 mg., Peritrate was found to exert a marked modifying influence on the electrocardiographic response to standard exercise in 14 of the 21 patients tested. In almost all of the subjects showing favorable response, the results were comparable to those obtained with glyceryl trinitrate but the duration of action was considerably more prolonged. Thus with Peritrate an improved response could be elicited as long as five hours or more after its administration (figs. 1 through 4). The importance of taking the drug with the stomach empty is shown in figure 5.

COMMENT

In previous studies it was found that papaverine in large oral dosage is an effective coronary vasodilator. The fact that this drug is still classified as a narcotic and is an expensive medicament when prescribed in optimum dosage (at least 0.2 Gm. or 3 grains three or four times a day) has greatly hindered its use in the treatment of angina pectoris. The introduction of Paveril, the synthetic analogue of papaverine, therefore, raised the hope that an effective substitute for the natural alkaloid was now at hand. Although Paveril has been reported from animal experiments to be a more potent coronary vasodilator than papaverine, our observations indicate that the synthetic preparation has a considerably weaker action in man than the opium derivative. Comparative studies to delineate the degree and duration of action of various drugs as measured by the two-step test have indeed shown little to commend the continued use of Paveril in the routine therapy of angina pectoris. Similarly, we have been unable to confirm the claims made for Metamine as a "long acting" coronary vasodilator.

The excellence of glyceryl trinitrate in the treatment of the acute attack and in prophylaxis just prior to contemplated exertion has for many years suggested its use in a preparation so designed as to permit slow and steady absorption for prolonged protection. Nitroglyn represents an admirable attempt to achieve this goal, but from our experience appears to fall far short of the mark. Even in large dosage the release of the drug must be too slow for satisfactory clinical response; as much as 9.6 mg. (.50 grn) failed to modify the exercise response in some patients who reacted dramatically to 0.4 mg. (.150 grain) of the ordinary hypodermic preparation sublingually. Nitroglyn in massive dosage did show, however, a slight to moderate effect on the exercise response during the six-hour period following its administration in almost two-thirds of the patients tested. Nevertheless, in no instance did this sustained action preparation cause a normal exercise response to be recorded, a result contrary to common experience with glyceryl trinitrate and Peritrate respectively.

The findings of this study indicate that of the four drugs tested only Peritrate, (penta-
erythritol tetranitrate) is worthy of the designation, "long-acting coronary vasodilator". In two-thirds of the patients tested, this drug (in 10 to 20 mg. doses) approximated the effects of glyceryl trinitrate (nitroglycerine) on the electrocardiographic response to exercise. Peritrate, moreover, exhibited its action up to five hours or more following administration, whereas the effect of nitroglycerine persisted for only 15 to 30 minutes. It is significant however, that in most cases Peritrate did not confer protection during the first hour following its administration. This lag in its activity was to be expected since even with massive doses of nitroglycerine taken orally (not sublingually) we have observed not only an attenuation of its effect but also a latent period of 30 minutes or longer before its action could be detected. It cannot be too strongly emphasized that Peritrate should not be taken after food but only when the stomach is empty, i.e. before meals. We have repeatedly found the total action of the drug to be lost when its ingestion followed the taking of food (fig. 5). Failure to recognize this fact may be responsible for differences in opinion regarding the efficacy of this and related drugs in the treatment of patients with angina pectoris. Peritrate appears to fill adequately the need for prolonged coronary vasodilation in most patients with this disease.

**Summary**

Evaluation of vasodilator drugs in the treatment of angina pectoris continues to present a difficult problem because of the lack of objective methods of study, the element of subconscious bias on the part of both patient and physician and the unreliability of pain as a quantitative measure of underlying coronary insufficiency. It has been shown, however, that the ability of vasodilators to modify the electrocardiographic response to standard exercise (Master two-step test) in carefully selected patients provides a sound basis for assessing the relative and absolute value of each of such agents in the treatment of this disorder.

Employing this technic, a study of Paveril (dioxynline phosphate), Metamine (triethanolamine trinitrate biphosphate), Nitroglyn (coated granules of nitroglycerine) and Peritrate (pentaerythritol tetranitrate) was undertaken in 21 patients in whom control records obtained after standard exercise remained relatively constant from day to day. The results obtained with Metamine, Paveril and Nitroglyn were in sharp contrast with those observed after the administration of Peritrate. They may be summarized as follows:

1. Metamine produced little or no significant effect on exercise response as measured electrocardiographically in all patients in the series.

2. Paveril in some instances was mildly effective but its action was not sustained and its influence was never striking even with massive dosage. Only 6 of 21 patients showed significant improvement in exercise response following the use of this drug. Paveril does not appear to be as potent as papaverine in comparable dosage.

3. Nitroglyn, in spite of the logic behind its use, gave disappointing results. In the usual recommended dosage, 2.4 mg. (1/25 grain), the preparation appeared totally inert. With larger doses, 4.8 to 9.6 mg. (2/25 to 1/25 grain), Nitroglyn evoked slight to moderate improvement in exercise response for a period of six hours following its administration in almost two-thirds of the patients tested. Nevertheless, the drug failed to induce a normal electrocardiographic response to exercise in any of the 21 patients in the series, a result far surpassed by the sublingual administration of nitroglycerine and by Peritrate, respectively.

4. Peritrate, in a dose of 10 to 20 mg., showed a marked modifying influence on the response to standard exercise in 14 of the 21 patients tested. The effect of this agent was comparable to that of nitroglycerine, but its action, after a latent period of 60 to 90 minutes, could be demonstrated as long as five to six hours after the administration of a therapeutic dose. Clinical response was markedly attenuated or totally abolished, however, when Peritrate was taken after food. Of the four drugs tested only this agent appears worthy of the designation "long-acting coronary vasodilator." Peritrate appears to satisfy the
need for prolonged coronary vasodilatation in most patients with angina pectoris.

SUMMARIO IN INTERLINGUA

Nos ha interprendite un studi de Paveril (phosphato de dioxyrina), Metamina (tri-ethanolamina-trinitrato-biphosphato), Nitroglyn (granulos incrustate de nitroglycerina), e Peritrato (tetranitrato de pentaerythritol) in 21 cautamente seligite patientes in qui registraziones de controlo post exercitio standard se haveva mostrate relativemente constante ab un die al altere. Le sequente es un summario de nostre constatationes:

1. Metamina produceva pauc o nulle significative effecto super le responsa post exercitio in le electrocardiogrammas de omne le patientes in iste serie.

2. In alicun casos Paveril se monstrava lavemente efficace, sed su action non durava e su influentia eseva nunquam frappante, mesmo post.

3. Nitroglyn—ben que su uso es supportate per considerationes logic—produceva resultatos disappunctante. In le dosage normalmente recommendate (2,4 mg.), le preparato se mostrava totalmente inerte. In dosages plus grande (4,8 a 9,6 mg.), illo provocav una leve o moderate melioration del responsa a exercitio durante un periodo de 6 horas post le administra-
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HENRY I. RUSSEK, BURTON L. ZOHMAN, ALICE E. DRUMM, WILLIAM WEINGARTEN and VIRGIL J. DORSET

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