Effects of Erythrol Tetranitrate and Amotriphene on Exercise Tolerance Tests in Angina Pectoris

By Arthur Ruskin, M.D.

OBJECTIVE EVIDENCES for angina pectoris, in the absence of proved myocardial infarction or grossly abnormal electrocardiograms, are more or less limited to abnormal electrocardiographic changes induced by exercise or hypoxemia. Similarly, while termination or prevention of angina is notoriously unreliable in the evaluation of "coronary dilator" drugs, their effects on provoked abnormalities in the electrocardiogram may be considered objective, if not completely reliable.

Consequently, we compared the effects of sublingual erythrol tetranitrate (Cardilate*) and amotriphene (Myordilt)† in selected patients with angina pectoris, who repeatedly showed positive Master exercise tests.

Material and Method

"Standardized" two-step exercise tolerance tests were performed. Thirty-six patients with angina pectoris who had repeated (two to four) positive Master tests on placebos corresponding to the two drugs (infra) were selected for the study. Eight of them had had myocardial infarction 6 or more months previously, but showed no electrocardiographic residues beyond Q waves. None was receiving digitalis.

Our strict criteria of a positive exercise tolerance test were (1) flat S-T depressions totaling 3 mm. or more in leads I, II, III, V₂, and V₄ or (2) less marked S-T depressions, plus inversions of the T wave in leads I, II, V₂, and V₄ or with induced arrhythmias or conduction defects or both. Doubtful positive tests included borderline S-T depressions plus low negative changed to positive T-waves.‡

Sublingual erythrol tetranitrate 30 to 45 mg., oral amotriphene 50 to 75 mg., or a corresponding placebo was administered 45 to 60 minutes before the exercise test. These drug dosages were empirically found to cause the greatest number of reversals, i.e., in some cases smaller doses failed to reverse clearly placebo-positive Master tests. Identical drug and placebo tests were repeated from two to four times each on different days at approximately the same time in the afternoon. As a check on the longer acting nitrate, in three patients who had shown positive and three patients who had exhibited negative Master tests following the administration of erythrol tetranitrate the exercise tests were repeated within 5 minutes after 0.6 mg. of nitroglycerin by mouth.

In 20 cases clinical evaluation of the two drugs and placebos was done in 3-week periods each, arranged in varying Latin-square sequences and often repeated, especially in doubtful cases. Records exact as possible were kept by the patients of the number, kind, length, and severity of their pains, and the daily dosage of nitroglycerin tablets required. We thus had two comparative placebo and drug periods for cross-evaluation of their efficacy.

Results

Exercise tolerance tests positive following placebo were reversed by sublingual erythrol tetranitrate in 26 of 36 cases (72 per cent; figs. 1 and 2), while seven continued to be positive and three were doubtful (table 1). Three positive and three negative tests after the drug checked equally so after nitroglycerin (0.6 mg.).

Headache was a side effect in one quarter to one third of the cases, but it occurred infrequently if the patient was placed on a small dose first and this dose was gradually increased to the desired level. Excluding the large doses of the exercise test, it was mild, transient, and annoying in six of the 36 cases. Weakness, nausea, dizziness were fleeting and infrequent (table 2). Intermittent claudication was reduced on exercise in one case, but remained unchanged in another.

Oral Amotriphene resulted in six negative (fig. 2), four doubtful, and 26 positive (fig. 1) tests—a reversal of 16 per cent of the patients

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†WIN-5494, Winthrop Laboratories, New York, New York.

‡The latter occur most commonly in mentally disturbed patients in our experience.
exhibiting positive Master tests following placebos (table 1). Side effects from amotriphene were perhaps less frequent and severe, consisting primarily of headache, nausea, or dizziness on rare occasions (table 2). Intermittent claudication was unaltered in the two patients showing it.

In cases of reversal of a positive Master test by either drug, subjective symptoms on exercise such as precordial pain and dyspnea were also frequently reduced or eliminated. Daily anginal attacks on sublingual erythrol tetranitrate and oral amotriphene were respectively 0.92 and 0.94 versus placebo 2.17 and 1.94.

Ectopic beats, usually ventricular in origin, were infrequent in the control electrocardiogram, and often appeared or increased greatly on exercise after the placebos. Bigeminy and multifocal beats occurred in many cases. These arrhythmias were generally the same, e.g., in one case—paroxysmal ventricular tachycardia, on repeated exercise tolerance tests.

Premature beats produced or increased by the drug or on exertion were twice as frequent following erythrol tetranitrate as after

<p>| Table 1 |
| Master Exercise Tests after Placebo, Erythrol Tetranitrate, and Amotriphene |</p>
<table>
<thead>
<tr>
<th></th>
<th>Placebos</th>
<th>Erythrol tetranitrate</th>
<th>Amotriphene</th>
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<tbody>
<tr>
<td>Positive</td>
<td>36</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td>Doubtful</td>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>26</td>
<td>6</td>
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</tbody>
</table>

| Table 2 |
| Symptoms (Per Cent) Noted after Erythrol Tetranitrate, Amotriphene, and Placebos |
| --- | --- | --- |
| Erythrol tetranitrate | Amotriphene | Placebos |
| Headache Definite | 24 | 6 | — |
| Mild | 14 | 12 | 12 |
| Dizziness Definite | 14 | 6 | 4 |
| Mild | 4 | — | — |
| Weakness Definite | 14 | — | 12 |
| Mild | 4 | — | — |
| Nausea | 14 | 6 | — |
| Vomiting | 4 | — | — |
ERYTHROL TETRANITRATE AND AMOTRIPHENE

L. G. 62 yr. W. M.
Angina Pectoris

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
<th>III</th>
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<tr>
<td></td>
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<td>PLACEBO CONTROL</td>
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<th>V₂</th>
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<tr>
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<td>PLACEBO EXERCISE</td>
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<td>CARDIATE EXERCISE</td>
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<th>V₂</th>
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<td>MYORDIL EXERCISE</td>
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Equal reversal of positive exercise tolerance test by erythrol tetranitrate and amotriphene
—unusual case.

Amotriphene. Both drugs equally reduced or abolished premature beats on exercise. Similarly, in about 10 per cent the premature beats following the two drugs or the Master test remained about the same as in the tests following the placebos (table 3). Otherwise, the electrocardiograms were essentially unaltered by either drug.

Discussion

It is evident that sublingual erythrol tetranitrate is potent in reversing the electrocardiographic signs of coronary insufficiency in the majority of cases of angina pectoris (72 per cent). This corroborates previous reports of the efficacy of certain nitrites in coronary disease.²⁻⁶

Amotriphene, on the other hand, clearly reversed positive exercise tolerance tests in only 16 per cent. Experimentally⁷⁻⁹ and clinically¹⁰ it has been reported to have coronary dilator and anti-arrhythmic effects. It did decrease ectopic beats on exercise about as often as erythrol tetranitrate, but also produced them at times, though less frequently than erythrol tetranitrate. In any case, it would seem that premature beats as such should weigh little in the evaluation of a positive or negative Master test.

Although less definite, the evidence suggests that both erythrol tetranitrate and amotriphene reduce the number of anginal attacks in half. The parallelism between the objective and subjective findings for erythrol tetranitrate does not hold however for amotriphene.

Table 3

<table>
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<th>Ectopic Beats (Per Cent) in the Exercise Tolerance Tests Following Erythrol Tetranitrate and Amotriphene in Contrast to Placebos</th>
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<td>Drug alone</td>
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</tr>
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<td>8</td>
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and the latter’s clinical worth must remain
sub judice. Other drugs, especially those pro-
ducing sedation or monoamine oxidase inhibi-
tion, e.g., iproniazid, show the same disparity
between apparent alleviation of angina and
no objective evidence of abolition of coronary
ischemia.11,12 This anti-anginal effect is, of
course, hardly consonant with the resulting
greater availability of catecholamines, which,
despite coronary vasodilatation, produce rela-
tive coronary ischemia.

Headache from erythrol tetranitrate was in
our experience no more frequent than from
nitroglycerin. It occurred infrequently when
the dose was reduced and gradually increased
to the same level. In fact, the large doses (30
to 45 mg., which are two or three times the
usual dose) employed in the exercise tolerance
tests did not cause headache in some cases.
Only two patients, not included in the 20
cases rotated on the various regimens, were
unable finally to tolerate 15 mg. doses of the
drug. Nor were angina pectoris or adverse
electrocardiographic effects produced or ag-
gravated by the large test doses of erythrol
tetranitrate, whereas failure of coronary dial-
tation13,14 or severe coronary insufficiency15
has occurred from heavy doses of the fast-
acting nitroglycerin, in part as a result of
hypotensive ischemia.

Summary

Sublingual erythrol tetranitrate is a potent
drug in counteracting coronary insufficiency,
as evidenced by reversal of positive electro-
cardiographic exercise tolerance tests in 72
per cent of 36 cases and reduction of anginal
attacks in them by more than 50 per cent.

Comparative studies with amitriptyne indi-
cate some subjective alleviation of angina, but
objective reversals of the electrocardiographic
effects of exercise in only 16 per cent of the
cases.

Side effects of erythrol tetranitrate, par-
ticularly headache, are seen in a minority of
cases and are often circumvented by starting
with a small dose and gradually increasing it
as necessary.

Alleviation of ectopic beats on exercise
occurred equally in a minority of cases on the
two drugs.

References

1. Master, A. M.: The two-step exercise electro-
2. Risse, J. E. F., Altman, G. E., and Korets-

ky, S.: Nitroglycerin and other nitrates in
the treatment of angina pectoris. Circulation
The treatment of angina pectoris. New England
4. Altman, G. E., Risse, J. E. F., and Korets-

ky, S.: Sublingual erythrol tetranitrate in
the treatment of angina pectoris. Effect of
varying the dose and rate of administration.
5. Russek, H. K., Zohman, B. L., Drumm, A. E.,
Weingarten, W., and Dorset, V. J.: Long-
acting coronary vasodilator drugs: Metamine,
paveril, nitroglycin and peritate. Circulation 12:
169, 1955.
6. Russek, H. I.: Evaluation of the nitrates in
the treatment of angina pectoris. Circulation 18:
774, 1956.
7. Robb, J. R. R., and Green, H. D.: Comparative
effects of WIN 5494 on left coronary flow.
8. Karczmar, A. G., Bourgault, P., and Elpern,
B.: Antiaccelerator and certain other phar-
macologic and coronary dilator actions of new
polymethoxyphenyl derivative. Fed. Proc. 17:
383, 1958.
9. Farah, A., and Birnbaum, L.: Decelerator and
antiarrhythmic properties of amitriptyne. J.
10. Harris, R.: Clinical observations on a new
coronary vasodilator (WIN 5494). Am. J.
11. Cesarman, T.: Serendipity y angina de pecho
in forme preliminar sobre un hallazgo tera-
peutico. Arch. Inst. Cardiol. de Mexico 27:
563, 1957.
12. Master, A. M.: Iproniazid (Marasilid) in angina
effect of nitroglycerin on the coronary
circulation and myocardial metabolism in man.
14. Gorlin, R., Brachfeld, N., Bopp, P., and
MacLeod, C.: Physiological diagnosis of dis-
15. Proger, S. H., and Ayman, D.: Harmful effects
of nitroglycerin with special reference to coro-
nary thrombosis. Am. J. M. Sc. 184: 480,
1932.

Circulation, Volume XXIII, May 1961
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Circulation. 1961;23:681-684
doi: 10.1161/01.CIR.23.5.681

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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