ETRYPTAMINE* IN THE TREATMENT OF ANGINA PECTORIS

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The nitrites have been the mainstay of our treatment of angina pectoris since their original application nearly one hundred years ago.[2, 13] Therapeutic improvements which have been utilized to allay the symptoms of this disorder have been aimed at the underlying anatomical changes in the coronary vessels. The evolution of this type of treatment has been centered on the search for nitrites of greater potency and more prolonged activity, *e.g.*, pentaerythrol tetranitrate and erythrol tetranitrate. There have been a few esoteric departures from this approach, *e.g.*, khellin [1] and ganglionic blocking agents,[9] but the aim to achieve vasodilatation or better blood flow has remained the same. A more recent concern has been the association of abnormal lipid metabolism and atherosclerosis. This has resulted in the application of hypocholesterolemic agents [11] to the treatment of angina pectoris. All of these therapeutic modalities plus surgical measures have been for the purpose of effecting a change either transient or permanent in a vascular state, already established as pathological.

The treatment of angina pectoris requires more than an anatomical approach to the problem. There are precipitating factors involved such as diet, exercise and emotional stimuli. Eskwith [5] obtained improvement in 90% of his patients with the use of tranquilizing drugs and an emphasis on the more positive elements of the physician-patient relationship. Weiss *et al.*,[15] found a higher incidence of emotional problems in a coronary group of patients as compared to a control group. Placebos reportedly relieve pain in 38% of anginal patients.[6] It is a certainty that fear, tension and anxiety play a part in the initiation and exacerbation of all disease states. A disorder that responds so well to placebos, tranquilizers and physician-patient rapport must have a large psychogenic overlay. Psychopharmacologicals would seem to be a rational approach to the treatment of this aspect of the condition.

Three years ago Cesarman [3] reported the relief of pain in angina pectoris with the administration of iproniazid (Marsilid). The therapeutic efficacy of this particular drug was attributed to its monoamine oxidase inhibiting effect. This initiated a search for other compounds, exhibiting similar properties, because the toxic side reactions of Marsilid limited the clinical application of the drug. In one series,[12] severe reactions compelled the discontinuance of this drug in all but seventeen of seventy-four anginal patients studied. Searching for an effective therapeutic agent without the toxic side reactions exhibited by the original chemical, other hydrazine compounds such as isocarboxazid (Marplan), nialamide (Niamid), phenelzine (Nardil), pheniprazine (Catron) and tersavid, were investigated for their anti-anginal properties. These drugs have varying degrees of monoamine oxidase inhibiting activity which seems to be related to the frequency and degree of untoward effect.

Coronary dilatation, oxygen sparing effect, ganglionic blockade and analgesia have been advanced as reasons [8] for the therapeutic effectiveness of these drugs but only the psychopharmacological action bears confirmation at this time. With these facts in mind it seemed feasible to evaluate a new monoamine oxidase inhibitor for the treatment of angina pectoris. This new preparation, Monase, differed from the other compounds in that it is not in the hydrazine group, has greater potency and rapidity of action and exhibits a quickly reversible effect.

* dl-α-ethyltryptamine acetate, registered by The Upjohn Company, under the trade name of Monase.

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Eighteen patients, 11 females and 7 males, aged 40 to 80, were studied for a period of twelve weeks. The symptom of angina pectoris was the major and presenting complaint in each member of this group. The etiological disease in 6 of the 7 males and in 4 of the females was arteriosclerotic heart disease. The remainder were diagnosed as hypertensive cardiovascular disease. All of the subjects exhibited electrocardiographic evidence of myocardial involvement. The social and economic status of these people ranged from that of a laborer on relief to a wealthy industrial executive. The majority were housewives, white collar workers, and skilled laborers from middle and lower income groups.

A single blind method of investigation was utilized with the modification that many of the subjects had prior acquaintance with the appearance of the chlordiazepoxide (Librium) capsule. Monase 5 mg. (1-P) and a placebo of Monase (2-P) were administered to all 18 patients for interrupted periods varying from one to two weeks each. In a like manner, a preparation of 10 mg. Librium resembling the Monase tablet was given to 16 of the patients. Similarly, 17 of the group received Librium 10 mg. capsules and 11 Librium capsule placebos. The duration of treatment for each drug was for a minimum of one week and in the majority for two weeks if the particular medication supplied was tolerated. Many had more than one course of the investigational compound interrupted by periods of administration of the other drugs and placebos in the regimen. All of the patients were evaluated for at least one week without any of the aforementioned preparations.

Monase was given in dosages ranging from 10 to 30 mg. daily and Librium was given in amounts of 20 to 100 mg. daily. Erythrol tetranitrate (Cardilate) was continued in those patients who had been receiving this therapy. Anti-hypertensive drugs, diuretics and digitalis preparations were administered uninterruptedly and added to the regimen when the need presented itself. Nitroglycerine was continued on an *ad libitum* basis.

A patient was reported as two plus (++) if all anginal symptoms were alleviated and no nitroglycerine was taken during the entire period that he or she was on a particular regimen. One plus (+) indicated that nitroglycerine requirements were lessened and effort tolerance increased. Zero denoted no

TABLE I

Case Number	1-P	2-P	13-P	1-C	2-C	X
1	++	++		++		++
2	+	−	++	++		−
3	++	−	++	++	−	−
4	−	−	++	++		−
5	+	−	++			−
6	++	++	++	++	++	−
7	−	0	++	++	+	0
8	−	0		++	0	0
9	++	0	++	++		0
10	+	0	++	+		0
11	−	0	++	++	+	0
12	−	0	++	++		0
13	+	+	+	+	+	+
14	++	0	++	++	0	0
15	++	++	++	++	++	++
16	+	0	++	++	0	0
17	−	0	++	++	0	0
18	++	0	++	++	0	0

1-P Monase 5 mg. tablet
2-P Monase placebo tablet
13-P Librium simulating Monase tablet
1-C Librium 10 mg. capsule
2-C Librium placebo capsule
X No medication

− angina worse
0 no change
+ improved
++ alleviated completely

change, and a minus sign signified an exacerbation of symptomatology.

RESULTS

Table I is an individual compilation and evaluation of results with the various therapeutic modalities in the 18 subjects studied. Seven of the 18 patients were completely relieved of anginal symptomatology on Monase, but 2 of these subjects (no. 1 and 15) did equally as well on a placebo and the complete absence of medication. Apparently these 2 patients were in a remission phase of their disorder. One patient (no. 6) responded well to both the drugs and placebos but relapsed when medication was withdrawn. She may have been responding to suggestion, or perhaps a true anginal condition did not exist. The remaining 4 patients reported similar improvement on Librium, but one patient (case no. 3) complained of palpitation following the evening dose of Monase. The latter had been depressed because of an environmental situation not associated with her cardiac disorder. Improvement was noted in 5 subjects on Monase therapy, but one responded equally as well to a placebo and withdrawal of medication.

Monase was associated with an exacerbation of anginal symptomatology in 6 patients, all of whom responded well to Librium capsules and 5 of these to the Librium simulating the Monase tablet. Response to Librium was uniformly good, but this may be moderated by the fact that most of these patients were drawn from a group treated with this drug prior to the Monase investigation.

A minus sign in the last column of Table I denotes that withdrawal of medication at an interval after the study was begun resulted in an aggravation of symptoms as compared with those present prior to the investigation.

Untoward reactions to Monase consisted of anxiety, insomnia, dryness of the mouth, exacerbation of angina, and palpitation. Several patients of this group in whom fluid retention occurred in the form of pretibial edema while on other monoamine oxidase inhibitors, *e.g.*, tersavid and Nardil, did not exhibit this with Monase. Repeated blood pressure recordings did not indicate either a hypertensive or hypotensive effect attributable to Monase. Interval urinalysis, serum cholesterol, and thymol turbidity determinations were unaffected by the medication.

DISCUSSION

The approach to the treatment of angina pectoris is two-dimensional *i.e.*, anatomical and psychological. The evaluation of drugs in either of these two therapeutic parameters inherently overlap and encroach upon each other. Controlled studies have their limitations. A double blind investigation may not allow for individualization of dosage and a single blind study loses a certain amount of objectivity. Physician-patient rapport is a day to day variable. Surgical measures involve great suggestibility. Psychotherapeutic and psychopharmacological methods certainly affect physiological responses. The disease itself has remissions and relapses, therefore, only prolonged and mass application of these various therapeutic modalities together with further pharmacological elucidation of individual drug activity will give us the answers that we seek.

The variables involved in the investigation of the monoamine oxidase inhibitor group of drugs are most vividly portrayed in the literature regarding their application in angina pectoris. Cesarman [3] reported 97% improvement in his group of patients, and Fife *et al.*[7] using the same drug reported equal efficacy with the use of a placebo.

The degree of side reaction *e.g.*, hypotension, may be related to the improvement observed with this antidepressant collection of compounds. Russek [14] reported 59% improvement in anginal patients treated with isoniazid compared to 29% in those to whom tersavid was administered. Cossio [4] observed therapeutic effectiveness in 65% of his patients on Marsilid. An additional reason for differing reports by various investigators may be that we overlook the individual characteristics of the drug being used and attempt to equate all results with the monoamine oxidase inhibiting activity that they have in common.

The anginal patients reported here were a tense and easily excitable group of subjects. Both realistic fear and less warranted apprehensive anticipation were the predominating affects observed. Depression was not an outstanding characteristic. Certainly a drug considered to be psychostimulating or psychoenergizing and antidepressant would not seem to be the logical therapeutic choice for this type of person. Sedatives, tranquilizers, and anti-anxiety drugs would seem more suitable in these cases, as indicated in the response of these and other patients[10] to Librium. On the contrary, Monase outperformed Librium and many of the monoamine oxidase inhibitors in a group of depressed patients that I have treated.

Placebo reaction must be considered in several respects. Wolf and Pinsky[16] reported that pharmacologically inert placebos produce a wide variety of toxic reactions and aggravate symptoms in as many as 20% of an experimental population. A number of our patients responded adversely to placebos. If a placebo should follow an effective antianginal preparation or be given during a remission period of the disorder, there is the likelihood that the patient may be conditioned to an alleviation of fear and anxiety and hence may retain this healthy attitude for some time. This situation may also work in reverse. Therefore, it is most difficult to be certain of any conclusions in an investigation in which the course of observation and study does not entail a prolonged period of time.

Summary

Eighteen patients suffering from angina pectoris were subjected to a single blind study in order to evaluate the therapeutic efficacy of Monase.

Monase was not very effective in alleviating the symptoms of angina pectoris in this particular group of patients. Anxiety and tension rather than depression were the precipitating factors initiating anginal symptomatology in the subjects in this series. Therefore, a potent psychoenergizer effective in disorders associated with depression, or conceivably in an anginal patient where depression might exist, would have no beneficial effect in conditions in which anxiety and tension predominate.

References

1. Anrep, G., and Barsoum, G. S.: *Am. Heart Journ.*, 37:531, 1949.
2. Brunton, T. L.: *Lancet*, 2:97-98, 1867.
3. Cesarman, T.: *Arch. Inst. Cardiol. Mexico*, 27: 563, 1957.
4. Cossio, P.: *Am. Heart Journ.*, 56:113-118, 1958.
5. Eskwith, I. S.: *Am. Heart Journ.*, 55:621, 1958.
6. Evans, W., and Hoyle, C.: *Quart. Journ. Med.*, 2:311, 1933.
7. Fife, R., Howitt, G., and Stevenson, J.: *British Med. Journ.*, No. 5174:692, 1960.
8. Griffith, G. C.: *Progress in Cardiovascular Diseases*, 3:119, 1960.
9. Hirshleifer, I., Schwartz, G., and Fuerst, H.: *N.Y. State Journ. Med.*, 52:575, 1952.
10. Hirshleifer, I.: *Current Therapeutic Research*, 2:501-508, 1960.
11. Hollander, W., and Chobanian, A.: *The Boston Medical Quarterly*, 10:1, 1959.
12. Master, A. M., and Donoso, E.: *Annals of New York Academy of Sciences*, 80:1020, 1959.
13. Murrell, W.: *Lancet*, 1:80-81, 151-152, 225-227, 1879.
14. Russek, H. I.: *Angiology* (pt. 2), 76-80, 1960.
15. Weiss, E., Dolin, B., Rollin, H. R., Fischer, H. K., and Beysler, L. R.: *Arch. Int. Med.*, 99: 628, 1957.
16. Wolf, G., and Pinsky, R. A.: *Journ. Am. Med. Assoc.*, 155:339, 1954.