THE CARDIOVASCULAR EFFECTS OF MONOAMINE OXIDASE INHIBITOR

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Monoamine compounds, to which belong tryptamine, 5-hydroxy-tryptamine (or serotonin), 5-hydroxy-tryptophan (5-HTP), dihydroxy-phenylalanine (or DOPA), phenylethylamine, tyramine, norepinephrine, epinephrine and other catacholamines and their methoxy derivatives, are destroyed in a process of oxidative deamination by an enzyme called 'monoamine oxidase', and the deaminized products are subsequently removed from the circulation. In people under depression, these monoamine compounds are either produced in small amounts, or the enzyme is present in a very high titer, destroying the monoamines in a large quantity. By administering the MAO inhibitor, the enzyme is inactivated, and is followed by marked increase of brain serotonin (1) and a moderate rise of norepinephrine. The elevation of the content of brain monoamines will bring the patient out of his depression and back to his former mode and state of psychomotor activity. It is used in psychiatry as "anti-depressant" or "psychic energizer".

The MAO inhibitor preparations that have been clinically tried are the following:—

I. *REVERSIBLE*: The "Harmine" series, the effect of which is transient, and depends upon the maintenance of the drug level in the tissues. The commercial preparation is represented by "Harmaline" (1).

II. *IRREVERSIBLE*: The effect is cumulative and more or less permanent.

A. Hydrazine Compounds: Compounds having -HN-NH- radical: The following have been tried:—
1. Iproniazid or "Marsilid";
2. Isocarboxazid or "Marplan";

3. Isonicotinoyl-N-B-N-benzylcarboxamide-ethyl-hydrazine or "Niamid" or "Nialamide";
4. Pivalylbenzhydrazine or "Tersavid";
5. Phenelzine dihydrogen sulfate or "Nardil";
6. B-Phenyl-isopropyl-hydrazine or "Catron".

B. Non-Hydrazine Compound:—

1. 1-Phenylcyclopropylamine or "Parnate"

Aside from its psychomotor effects, the MAO inhibitor has several cardiovascular effects foremost of which are on the blood pressure and on angina pectoris.

1. ON THE BLOOD PRESSURE: Several authors have reported that the MAO inhibitor can cause hypotension. Such effect is inconsistent, mostly orthostatic, slow in onset and slow in disappearance (2). The hypotensive effect is more marked when it is administered with thiazides. It cannot be reproduced in experimental animals. The exact mechanism of the hypotensive effect is not known.

   The following postulations have been advanced.

   1. Central Effect: Zoinden (2) mentioned that from animal experiments there are no indications that MAO inhibitor depressed the hypothalamus or the vasoconstrictor center of the medulla oblongata. So, the hypotensive effect cannot be central.
   2. Ganglionic Blocking Effect: Cesarman (3) believed that MAO inhibitor functioned as a slow-acting ganglionic blocker with the usual side effects of constipation, urinary retention, dryness of mouth and postural hypotension.
   3. Adrenergic Blocking Effect: Zeller (4) postulated an adrenergic blocking effect of iproniazid because of the similarity of the "fit" of hydrazide and epinephrine. Griesemer (5) demonstrated that iproniazid competed with norepinephrine at the receptor site of the smooth muscle in the blood vessels.
   4. Serotonin Effect: Haddy *et al.* (6) demonstrated that serotonin could either be a constrictor or a dilator and that it antagonized extremes of neurogenically induced tone. Since the administration of MAO inhibitor in-

creases the level of serotonin, the latter acts as a vasodilator in case of vascular hypertonus.

5. Inhibition of Carotid Sinus Baroreceptor Reflex: In anesthesized dogs, intravenous injection of 100 mg/Kg. of iproniazid causes a depression of the carotid sinus reflex, according to Leusen (7). Therefore, it may be assumed that the MAO inhibitor interferes with the blood pressure regulating mechanism.
6. Decrease of Peripheral Resistance: Maxwell *et al.* (8) reported that preliminary studies in human subjects suggested that RO4-1038, a MAO inhibitor, lowered the blood pressure primarily by decreasing the peripheral resistance.
7. Lowering of Cardiac Output: Allmark *et al.* (9) showed that iproniazid lowered the amplitude of myocardial contraction of the isolated perfused heart, while Maxwell *et al.* (8) showed that RO4-1038 actually reduced cardiac output. So, we have reason to believe that MAO inhibitor lowers the blood pressure by reducing the cardiac output.

II. ON ANGINA PECTORIS: Two factors are in operation in angina pectoris:

The Nervous Component and the Myocardial Ischemia. The effects of the MAO inhibitor on the nervous component are three-fold:—

1. Psychic Stimulation: The administration of the MAO inhibitor brings about a sense of well-being. Master (10) believes that the relief of the angina was at least partly due to the psychic stimulation.
2. Increase of the Pain Threshold: Emele *et al.* (11) pointed out that the MAO inhibitor had central analgesic effects, and the relief of the anginal pain was due to an increase in the pain threshold.
3. Effect on the Pain Transmission: Zbinden (2) speculated that the anti-anginal effect of the MAO inhibitor might be due to a blocking of the neurohumoral pathway responsible for the transmission of the cardiac pain, but he was not able to back up his speculation by experimental proof.

The MAO inhibitor acts on the myocardial circulation in the following ways:—

1. Coronary Dilation: Serotonin is a coronary dilator as shown by Crumpton *et al.* (12). Since the administration of MAO inhibitor markedly increases the level of serotonin, so it is possible that the relief of the anginal pain is due to serotonin-induced coronary dilation.
2. Negative Inotropic Effect on the Heart: Allmark *et al.* (9) showed that iproniazid lowered the amplitude of myocardial contraction of the isolated perfused heart. It may be possible that the action of the drug in angina pectoris is due to a negative inotropic effect on the heart.
3. Oxygen-Sparing Effect: Todd *et al.* (13) showed that there was experimental evidence that the MAO inhibitor might decrease the oxygen requirement of the tissues. Therefore. the relief of the anginal pain may be attributed to the decreased oxygen requirement of the myocardium.

DRUG POTENTION AND ALTERATION

The following drugs can be potentiated by the administration of the MAO inhibitor: General and local anesthetic agents, barbiturates, thyroid extract, corticosteroids, ganglionic blocking agents, morphine, derivatives of atropine, chloroquine and hydrochloroquine.

The thiazides can potentiate the hypotensive effect of the MAO inhibitor.

The effect of reserpine may be altered from that of sedation to excitement if the animal is pre-treated with a MAO inhibitor.

MATERIAL FOR STUDY

The patients were from the medical wards and outpatient department of the Philippine General Hospital and those from a neighboring hospital, as well as the private patients of the senior author. Prior to treatment, aside from the routine examination. the following laboratory work-up was made:

Hepatic function tests, NPN, BUN, Uric Acid, Creatinine, Cholesterol, Chest X-ray and Electrocardiograph. After a control period of three days, Nardil (*) was given at one tablet (15 mg) t.i.d., and some cases, q.i.d.

— *As An Anti-Hypertensive Agent*: In the literature, it has been frequently mentioned that some MAO inhibitors are good adjuvants to thiazides as antihypertensive agents. But in order to study its own anti-hypertensive effect, we decided not to use any thiazide. The blood pressure of the hospitalized patients was determined three times daily, lying, sitting and standing, the outpatients were checked periodically.

— *As An Anti-Anginal Agent*: The number of anginal attacks and the duration of each attack prior to the treatment were taken either from the patients' narration or from the observation of the intern(s) or resident(s) in charge during the three day control period. After starting the Nardil therapy, the patients were instructed to note down the same.

RESULTS

— *As An Anti-Hypertensive Agent*: 8 patients were under treatment: 5 male and 3 female. The age ranged from 48-65. The initial blood pressure readings ranged from 160-230/100-150. The clinical impressions were: 7 arteriosclerotic hypertension; 1 nephrogenic hypertension. The treatment period ranged from 2-10 weeks.

Sense of well-being was usually observed from the fifth day onward, but there was no appreciable effect on the blood pressure, lying, sitting or standing.

One male patient of 51 was admitted for symptoms of congestive heart failure. Upon admission, his blood pressure was 180/120 mm.Hg. He was first placed on Serpasil 0.25mg t.i.d., and Apresoline 10 mg t.i.d. The blood pressure fluctuated between 180-230/100-140 mm.Hg under such regimen Serpasil and Apresoline were suspended for three days, and Nardil 1 tablet (15mg) q.i.d. was started. He felt a sense of

* Nardil — Phenelzine dihydrogen sulfate was supplied by Warner-Chilcott Laboratories, (Phil.), Inc.

well-being on the fifth day, but the blood pressure ranged between 198-220/140-150 mm.Hg. On the seventeenth day, the patient suddenly developed cold clammy perspiration and severe nuchal pain, and the blood pressure registered 220/150 mm.Hg. Nardil was discontinued and the blood pressure was brought down slightly by intramuscular injection of Serpasil every 6 hours.

So, we agree with Gillespie *et al.* (14) that phenelzine dihydrogen sulfate (Nardil) is not a potent antihypertensive agent, at least when it is used alone.,

— *As An Anti-Anginal Agent*: 21 patients were under treatment, 15 male and 6 female. The age ranged from 28-72. The complaints varied from substernal discomfort to typical precordial pain radiating to the left shoulder and left hand. The duration of attacks ranged from 30 seconds to 1 hour, from 2-7 times a day. The clinical impressions varied from angina pectoris, myocardial insufficiency to myocardial infarction.

The electrocardiographic findings were:— Normal 5; Borderline tracing 6; Myocardial Insufficiency 4; Myocardial Infarction 4; No electrocardiogram 2.

The blood chemistry studies were essentially normal except for hypercholesterolemia in 12 cases. All coronary vasodilators like nitroglycerine, peritrate, papaverine, etc. were suspended for 3 days prior to the institution of Nardil therapy, which we usually started at a dosage of 1 tablet (15 mg) t.i.d.

Tension and depression usually started to lift on the third day, and a sense of well being and regaining of interest usually started on the fifth day. One case, H.F., an employee in the Philippine General Hospital, felt his pain disappear 2 days after the institution of the therapy; 5 noticed the shortening of the period of pain or the lessening of the pain on the third day; 8 noticed these on the fifth day; 7 noticed the anti-anginal effect on the seventh day. Fifteen felt a complete relief of pain on the tenth day, never to come back during the period of observation; while 6 of them did not have complete relief of the anginal pain until the fourteenth day, but the anti-anginal effect was manifested in each and every one of the 21 patients under study.

One patient, M.A., was admitted in the medical ward of the Philippine General Hospital for substernal pain. He was placed under Nardil therapy by the resident. On the fourth day, while the pain was still persistent, the consultant of the service ordered the discontinuation of Nardil and the replacement by papaverine. As Nardil was not given time enough time to show the anti-anginal effect, this case was not included in the series.

SIDE EFFECTS

The following side effects have been reported by Hollander *et al.* (15). The figures show the number of cases manifesting such side effects during this study.

Side Effects	*No. of Cases Observed*
Blurring of vision	2
Dryness of mouth	8
Constipation (mild)	5
Urinary difficulty (slight)	2
Anxiety	4
Irritability	1
Insomnia	4
Weight gain, slight	2

It is worth mentioning that not a single case of jaundice was noticed, and there was no elevation of serum bilirubin. No side effect was severe enough to necessitate the disruption of the therapy.

SUMMARY

The Monoamine Oxidase Inhibitor, "Anti-Depressant" or "Psychic Energizer" has cardiovascular effects aside from its effects on the psychomotor activity. The most important cardiovascular effects are anti-hypertensive and anti-anginal The mechanism in lowering the blood pressure is not central, but postulated to be ganglionic blocking, adrenergic blocking, serotonin effect, inhibition of carotid sinus baroreceptor reflex, decrease of the peripheral resstance and/or lowering of the cardiac output. The anti-anginal effect is attributed to the psychic stimulation, increase of the pain threshold, block-

ing of the pain transmission; coronary dilatation, negative inotropic effect on the heart and/or the oxygen-sparing effect.

One of the new MAO inhibitor preparations, Phenelzine dihydrogen sulfate (Nardil) was administered to 8 hypertensive patients between the ages of 48-65, with blood pressure ranging from 160-230/100-150 mm.Hg for 2-10 weeks. No appreciable lowering of the blood pressure lying, sitting or standing was noticed.

Twenty-one patients, ranging from 38-72 years of age, with anginal attacks were given Nardil. All of them noticed the shortening of the period of pain or the lessening of the pain from the second to the seventh day, with the fastigium falling on the fifth day. All of them had complete relief of the pain: 15 on the tenth day, 6 on the fourteenth day, with no recurrence during the period of observation.

Of the twenty-two side effects mentioned in the literature, we only noticed eight, namely: blurring of vision (2), dryness of mouth (8), mild constipation (5), slight urinary difficulty (2), anxiety (4), irritability (1), insomnia (4), slight weight gain (2). Not a single case of jaundice was observed. No side effect was so serious it necessitated the disruption of the therapy.

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