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THE RISKS OF MONOAMINE OXIDASE INHIBITORS IN THE TREATMENT OF BRONCHIAL ASTHMA

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IN the course of investigations on new tuberculostatic drugs at the Hoffmann-La Roche Laboratories, an isoniazid derivative, iproniazid, was discovered.

Although tuberculous patients treated with iproniazid gained weight rapidly, it was later realized that this apparent improvement was not paralleled by a radiologic improvement but was the result of a state of euphoria produced by the drug.¹ This fact was explained by Zeller and Barsky.² They found that iproniazid is a potent inhibitor of monoamine oxidase (MAO). For this reason, several biologically active amines (serotonin, histamine, epinephrine, norepinephrine) are not destroyed by MAO and accumulate in the central nervous system with euphoria-producing effects.

Since psychic factors seem to be of great importance in bronchial asthma and, since MAO participates in the metabolism of amines which apparently are connected with the pathogenesis of allergy, we considered that it would be of interest to try out this medication in asthmatic patients. It was expected that an accumulation of epinephrine in the body would modify favorably the asthmatic symptoms. But when iproniazid was given to 30 asthmatic patients it was found that no one improved. Contrary to expectation, 36 per cent of patients became worse some days after the drug was taken and one patient died with acute dyspnea which resembled left heart failure with pulmonary edema.³

In order to establish whether this unexpected effect was due only to iproniazid or is common to all MAO inhibitors, we decided to extend our earlier experiments to three less toxic MAO inhibitors: *N*-isonicotinoyl-*N'*-[β (*N*-benzylcarboxamido) ethyl] hydrazine (Nialamide), beta-phenylisopropyl hydrazine (Catron), and beta-isopropyl-hydrazine (Phenelzine). Comparison was made

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with *N*-dimethylaminopropyl-iminodibenzyl, another psychotropic drug which, unlike the earlier ones, does not inhibit MAO.

MATERIAL AND METHODS

Five groups were formed; each consisted of 30 adult asthmatic patients of both sexes. They all had had asthmatic symptoms for several years, 3 years as the average. They all suffered from asthmatic attacks of great intensity in spite of specific therapy. Only corticosteroid drugs were completely effective in relieving their symptoms, and sympathicomimetic drugs or aminophylline to a lesser degree.

Patients could be classified on the basis of their skin tests as having either exogenous or intrinsic asthma. However, they were all refractory to specific desensitization, elimination diet, or environmental changes.

After a thorough clinical examination, the patients were classified as:

First-Degree Asthma.—Patients with sporadic asthmatic attacks which required mild medication. Clinical examination on auscultation showed neither rhonchi nor wheezes. (Symptomatology index: 1.)

Second-Degree Asthma.—Patients with sporadic asthmatic attacks relieved by mild medication. Clinical examination showed rhonchi or wheezes at any time. (Symptomatology index: 2.)

Third-Degree Asthma.—Patients with repeated asthmatic attacks each day. In spite of parenteral medication (sympathicomimetics, aminophylline), these patients always had rhonchi and wheezes on examination. (Symptomatology index: 3.)

Fourth-Degree Asthma.—Patients who could not be controlled by subcutaneously injected Adrenaline or intravenously injected aminophylline but needed parenteral ACTH or oral corticosteroid therapy. (Symptomatology index: 4.)

Patients in Group I were treated with 150 mg. of iproniazid daily for 15 days, and a placebo during the subsequent 15 days. At the end of each series the symptoms were scored by the index described above. Sympathicomimetics, aminophylline, or corticosteroids were administered when it was necessary and were taken into account when final evaluation was made.

Patients in Group II received 75 mg. of Nialamide daily, divided into three doses.

Patients in Group III received 9 mg. beta-phenyl-isopropyl hydrazine daily, divided into three doses.

Patients in Group IV received 45 mg. beta-isopropyl hydrazine daily, divided into three doses.

Patients in Group V received 75 mg. *N*-dimethylaminopropyl-iminodibenzyl daily, in three doses, a drug without MAO-inhibiting action serving as control.

The protocol of the entire procedure in these groups was the same as in Group I, except that in Groups II, III and IV, lacking a placebo indistinguishable from the active compound, inert tablets as nearly alike as possible were used.

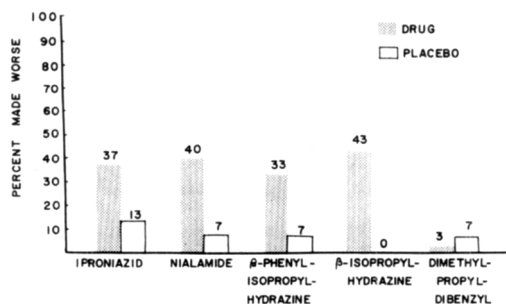


Fig. 1.—The per cent of patients with asthma in whom symptoms became worse after administration of four different monoamine oxidase inhibitors and a control psychotropic drug.

RESULTS

Thirty-seven per cent of the asthmatic patients taking iproniazid became worse as opposed to 13 per cent of those who took the placebo; and none to the same degree as those who were taking iproniazid. The symptomatology index which was 2 before the drug, remained almost the same with the placebo, but reached 3.1 after iproniazid (Table I and Fig. 1).

Forty per cent of the patients became worse with N-isonicotinyl-N-benzyl-carboxamido-ethyl-hydrazine, compared with only 7 per cent of those taking the placebo. The symptomatology index remained unchanged with the placebo but rose from 2.4 to 3.4 with the drug (Table I and Fig. 1).

Thirty-three per cent of the patients became worse with beta-phenylisopropyl hydrazine against 7 per cent of those taking the placebo. The symptomatology index rose from 1.8 to 2.7 with the drug and from 1.8 to 1.9 with the placebo (Table I and Fig. 1).

TABLE I. THE EFFECT OF FOUR MONOAMINE OXIDASE INHIBITORS AND DIMETHYLAMINOPROPYL-IMINODIBENZYL IN ASTHMATIC PATIENTS

DRUG	NO. OF CASES	UN-CHANGED %	IM-PROVED %	BECAME WORSE %	SYMPTOMA-TOLOGY INDEX	
					BEFORE TREATMENT	AFTER TREATMENT
Iproniazid	30	63	0	37	2	3.1
Placebo	30	73	14	13	2	2.1
N-isonicotinoyl-N'-[β (N-benzyl-carboxamido) ethyl] hydrazine	30	57	3	40	2.4	3.4
Placebo	30	76	17	7	2.4	2.1
β-phenylisopropyl hydrazine	30	60	7	33	1.8	2.7
Placebo	30	83	10	7	1.8	1.9
β-isopropyl-hydrazine	30	53	3	43	2.1	3.2
Placebo	30	77	13	0	2.1	1.9
N-dimethylaminopropyl-imino-dibenzyl*	30	90	7	3	2.4	2.3
Placebo	30	80	13	7	2.4	2.1

*Psychotropic drug without MAO-inhibiting action.

Forty-three per cent of the patients became worse with beta-isopropyl-hydrazine and none with the use of the placebo. The symptomatology index rose from 2.1 to 3.2 with the drug and remained almost identical with the placebo (Table I and Fig. 1).

Three per cent of the patients became worse with *N*-dimethylaminopropyl-iminodibenzyl, a psychotropic drug without any MAO-inhibiting action, and 7 per cent with the placebo. The symptomatology index remained almost identical both before and after drug or placebo. It changed from 2.4 to 2.3 with the drug and from 2.4 to 2.1 with the placebo (Table I and Fig. 1).

DISCUSSION

We reported in a previous paper that the prolonged administration of 1-isonicotinyl-2-isopropylhydrazine (iproniazid) had an adverse effect on 37 per cent of 30 severely asthmatic patients. It was considered worthwhile to ascertain whether this effect is specific for iproniazid or is common to all MAO-inhibitors.

The above experiments with three well-known and much less toxic MAO-inhibitors showed that the number of patients who became worse after taking any of these drugs was considerably higher than after taking the placebos. The average with the four MAO-inhibitors was 37 per cent (± 6).

Cortés and co-workers⁴ found that 26 per cent of their asthmatic patients became worse after taking 75 mg. of Nialamide. However, those patients suffering from pruritus and psoriasis improved. We do not know other similar clinical papers with which to compare our findings.

Moreover, Rebhun, Feinberg, and Zeller,⁵ and Rebhun and Feinberg⁶ tried iproniazid in experimental asthma and anaphylactic shock of guinea pigs and concluded that this drug has no effect at all. However, an analysis of their results shows that the number of guinea pigs that died in anaphylactic shock was greater among those receiving iproniazid than among the control animals. Furthermore, while normal control guinea pigs subjected to histamine nebulizations showed an asthmatic reaction 2 minutes after exposure, the iproniazid-treated group developed asthma in 58 seconds. It would appear that MAO-inhibitors produce an adverse reaction in both experimental and human asthma. This is, however, not the case when a psychotropic drug without MAO-inhibiting action is used, as shown by the results in Group V.

Now we shall consider three possible ways by which the MAO-inhibitors may aggravate the asthmatic condition.

1. *The Action of MAO-Inhibitors on Adrenaline and Noradrenaline.*—All the drugs which were shown to act unfavorably in asthmatics shared the MAO-inhibiting property. This enzyme is known to participate in the metabolism of Adrenaline, noradrenaline, glutamine, 5-hydroxytryptamine, etc.

Therefore, MAO-inhibition by these drugs must produce an accumulation of these amines.

It is generally accepted that both asthma and experimental anaphylaxis can be improved with Adrenaline therapy.

Nevertheless, Danielopolu¹² claimed that when Adrenaline is administered in very small doses it may produce a paradoxical effect. Haag and associates¹³ found an adverse effect on guinea pig anaphylaxis when small doses of Adrenaline were injected before challenge with the antigen.

Franco-Browden and co-workers¹⁴ injected rats with 50 mg. of iproniazid and half an hour later injected 3 mg. reserpine per kilogram of weight. They found that in several cases this procedure produced acute edema of the lung. This is reminiscent of our experience with one iproniazid-treated asthmatic patient who died exhibiting all the symptoms of acute edema of the lung rather than the asphyxial picture of asthmatic patients.

It is also interesting that Eichler and Barfuss,¹⁵ as well as Staub,¹⁶ have demonstrated that the intravenous infusion of Adrenaline may act as a histamine liberator. Therefore, the hypothesis could be made that when a MAO-inhibitor is administered to asthmatic patients, the accumulated catechols (through their paradoxical parasymphaticomimetic or histamine-liberating action) might produce pulmonary edema and thus impair the asthmatic condition.

2. *The Action of MAO-Inhibitors on Serotonin.*—MAO metabolizes serotonin (5-hydroxytryptamine). Therefore the inhibition of the enzyme may lead to a great increase of serotonin in certain tissues.² However, the significance of this finding has been reduced since it has been proved that serotonin plays an important role in experimental anaphylaxis of mice but very little role in other mammals and humans. A revision of this problem was made recently.¹⁷ Furthermore, Udenfriend and associates¹⁸ showed that iproniazid inhibits cerebral MAO and greatly increases the amount of serotonin in the central nervous tissue but they could not demonstrate the same in other tissues or blood.

Thus, although it cannot be dismissed entirely, it is unlikely that the adverse phenomena seen during the treatment of asthma with MAO-inhibitors were due to accumulation of serotonin in tissues and the bronchopulmonary tree.

However, the accumulation of cerebral serotonin could have acted indirectly on asthmatic patients through its central excitatory effects. Nevertheless, this possibility can be dismissed too, since such central excitatory drugs as benzedrine and isopropylamine have no adverse action on bronchial asthma.

3. *The Action of MAO-Inhibitors on Histamine.*—Schayer and Karjala¹⁹ have shown that the metabolism of histamine, tagged with C-14, follows two metabolic pathways. Histaminase (diamine oxidase) would appear to play the principal role in the oxidative metabolism of histamine via the acetic imidazol acid way. On the other hand, oxidations which end in methyl-imidazol-acetic acid and acetylhistamine would seem to be performed by the MAO. Therefore, Westling²⁰ investigated the effect of iproniazid on the sensitivity of guinea pigs to histamine. He found that iproniazid increased its action. Rebhun and Feinberg⁶ claim that they cannot find any such action. Nevertheless, as we already pointed out, the negative conclusions arrived at by these authors are not faithfully reflected in the results of their own experiments. So, the possibility could be advanced that the undesirable action of MAO-inhibitors is due to accumulation of histamine in the tissues.

SUMMARY

Five groups of asthmatic patients were studied. Four groups received different MAO-inhibitors for 15 days and a placebo for a subsequent 2 week period. The fifth group received a psychotropic drug without any MAO-inhibiting action and its corresponding placebo.

Symptoms became worse in 37 per cent (± 7) of the asthmatic patients who were taking the MAO-inhibiting drugs while the patients of the fifth group (non-MAO-inhibiting drug) showed no change. These results confirm earlier findings on the unfavorable effect of iproniazid and Nialamide. It is a specific effect ascribable to MAO-inhibition, since it does not occur when a psychotropic drug without MAO-inhibiting action is used.

Different possible ways by which MAO-inhibitors may aggravate the asthmatic condition are discussed.

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