Iproniazid in Angina Pectoris

A Double-Blind Study

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There has been considerable recent interest in the treatment of angina pectoris with iproniazid. In this paper the results of a careful double-blind study of its effect are evaluated.

Iproniazid (Marsilid), a hydrazine derivative of isonicotinic acid, originally employed with success as an antituberculosis agent, was later replaced by isoniazid, to avoid central nervous system stimulation as a side effect, first reported by Selikoff, et al. Since then, clinical experience with iproniazid in the field of psychotherapeutics, has shown it to be capable of reversing apathy, asthenia, anorexia, and depression in doses ranging up to 300 mg. per day. However, doses of this magnitude have also produced psychoses, both transient and permanent.

Investigation into the mode of action of this drug by Zeller and his group established it to be a potent inhibitor in vivo and in vitro of the enzyme monoamine oxidase. Shore and his co-workers found this enzyme to be involved in the metabolism of the catecholamines—norepinephrine and serotonin—in both in vivo and in vitro experiments. These catecholamines, moreover, may be of prime importance in the chemical mediation of the brain stem, especially of the centers for autonomic control. Based on these findings, the hypothesis has been advanced that the changes induced in catecholamine metabolism could be responsible for the antidepressive action of iproniazid.

Recently Cossio, in Argentina, and Cesarmain Mexico, reported remarkable amelioration of the pain in the angina pectoris syndrome secondary to ischemic heart disease. Their patients had classic symptomatology, namely, pain upon exertion relieved spontaneously by rest and nitroglycerin, though not with uniform success. Moreover, all had abnormal patterns in electrocardiograms at rest and after exercise.

Fifty milligrams of iproniazid were given 3 times daily for 3 weeks, and then the dose was reduced with symptomatic improvement. The results were impressively satisfactory, pain being reduced for as long as 6 months of therapy. Reduction in dosage did not abolish this beneficial effect, but on discontinuance of treatment pains recurred within days and up to 1 month. The course of the illness itself remained unmodified in that the abnormal electrocardiograms remained unchanged. Cesarmain followed up his initial study with a larger group of patients, given 150 mg. a day with 100 per cent satisfactory symptomatic relief. Schweitzer and Plantain and Master used the 150-mg. dose levels. Patients responded favorably in respect to their anginal pains, in from 2 to 18 days. In Schweitzer’s patients, orthostatic hypotension and other side effects at this dosage level forced the halting of medication in 46 per cent. Cossio reported also faintness, weakness, paresthesias, syncope, impotence, and muscular twitching. Furthermore, Zetzel and Kaplan reported 5 cases of hepatocellular disease accompanying iproniazid medication in doses of 50 to 150 mg. per day.
The experiences of these investigators have emphasized that iproniazid can be "very helpful in angina pectoris, but must be used with caution because of toxic side reactions," yet was also described as "the first promising drug in a whole professional career of nearly four decades." We considered that the initial promise of this drug could add a new dimension to the treatment of ischemic heart disease, and therefore, that further delineation of its utility and safety at a daily dose of 50 mg. or less was warranted. In our opinion, such an experiment could be conducted accurately only under the most stringent conditions. Fortunately, there are now available techniques of pharmacologic investigation that make possible accurate assessment of a given symptomatic therapy. Of these the double-blind method is the most successful. Katz recommends that in a well-controlled double-blind experiment each patient in the series be subjected also at several different times to both the drug and placebo. This precaution is especially important when the effect on anginal pain is tested.

**METHODS AND MATERIAL**

Using this recommendation for our model, we set up a double-blind study in our cardiac clinic, where a group of closely observed cardiac patients whose diagnoses of ischemic heart disease with angina pectoris had been confirmed over a long period of treatment. Moreover, they had received most of the well-known therapeutic agents, which could serve as a comparison with the response to any new medication. All had had complete histories and physical examinations. The laboratory studies included a complete blood count, urinalysis, electrocardiogram, chest x-ray, blood glucose, and blood urea nitrogen. Individuals previously treated for angina pectoris were re-interviewed to re-establish the diagnosis. Only patients with anterior chest pain following exertion or emotional upset, which was relieved within 20 minutes by rest, with or without sublingual nitroglycerin, were included in the study. All previous medications and treatment, i.e., sedation, digitalis, nitrates, ataractics, and diuretics including chlorothiazide were continued unchanged.

The patients were seen at 2-week intervals and interviewed according to a question sheet that included presence of angina, the number of attacks of pain and of nitroglycerin tablets used, dyspnea, edema, appetite, strength, well-being, and sleep habits. The responses called for were limited to "better," "unchanged," or "worse," and reports of unpleasant reactions. With each visit, physical examinations were performed consisting of a blood pressure recording, stethoscopic examination of heart and lungs, weight, and inspection for peripheral edema. Laboratory examinations included a serum bilirubin and cephalin flocculation test at each visit to detect any hepatic toxicity, and, when possible, a final electrocardiogram at the conclusion of the study.

The tablets used were identically prepared and bottled. They were labeled "A," "B," "C," and "D." Two of these were placebo and 2 were iproniazid, and the key was withheld from all the investigators until completion of the experiment. The patients were placed on medication in random fashion according to the week in which they were taken into the project. Those seen the first week were given "A," those the second week were begun on "B" and so on for the third and fourth week. The sequence then began over again with "A" for those begun on the fifth week. Patients were followed through in alphabetic sequence with a change in letter each month. Thus, the patient begun with "C," followed up with "D" was then placed on "A" and finally "B." The dose was 1 25-mg. tablet twice daily unless it was reduced for reasons of intolerance. At the conclusion of the experiment, the key was broken and the results were analyzed.

The investigation was then continued, with 25-mg. iproniazid tablets administered daily to 11 patients who remained cooperative. We began the study with 35 patients, but were able to conclude our observations successfully, for purposes of analysis, in a total of 23. They ranged in age from 52 to 85 years; 3 were Negroes, and the remaining were white subjects; 8 were male, and 15 were female. Nineteen received all 4 trials in sequence. Of the remaining 4, 1 received 1 placebo and 1 iproniazid trial; and of the last 3, 2 had 2 iproniazid and 1 placebo trial, while the last had 1 iproniazid and 2 placebo trials. Eight began the trial sequence with "A," 6 with "B," 5 with "C," and 4 with "D."

The greater number of the 12 patients who failed to complete the study were dropped for lack of cooperation and failure to keep appointments as scheduled. Two who refused to permit the serum bilirubin and cephalin flocculation tests were dropped.

Table 1 summarizes the medical and therapeutic background of the patients. All had ischemic heart disease with the anginal syndrome. In 19
there was also hypertensive cardiovascular disease. Eighteen had previous or current cardiac decompensation, and the heart was enlarged at x-ray examination in 16. Two had normal resting electrocardiograms, but 1 demonstrated an unequivocally positive electrocardiogram after an exercise tolerance test. Seven had previous myocardial infarctions and 2 more had noted previous suspicious, but not completely confirmed episodes. The drugs previously used were continued. Seventeen patients required daily maintenance digitalis, 10 required oral or parenteral diuretics, and 4 were receiving reserpine for hypertensive therapy. All 23 were taking sublingual nitroglycerin tablets in amounts ranging from 2 to 140 tablets per week. Five others took long-acting nitrates, 3 had daily theophylline, and another took meprobamate to ameliorate the painful episodes. In summary, all patients had confirmed ischemic heart disease, due to arteriosclerotic heart disease that was complicated by hypertension in nearly half. But all one had electrocardiographic abnormalities, and most showed evidences of advanced heart disease manifested by cardiac enlargement and congestive heart failure.

Method of Evaluation

To evaluate the results we followed a modified technic of classification, used by Blumgart et al.\textsuperscript{26} for analysis of the response to thyroid irradiation by similar patients with angina pectoris. Three categories of results were used:

1. Excellent (marked improvement): patients showing a disappearance of angina or a marked decrease in the frequency and severity of attacks despite an increase in activity. This decrease was estimated as a 75 to 100 per cent reduction in attacks of pain or number of nitroglycerin tablets used per week.

2. Good (worthwhile): patients showing a moderate decrease of their angina or at least the same frequency on an increased activity level. This decrease was measured at approximately a 50 per cent reduction in attacks of pain or number of nitroglycerin tablets used per week.

3. Poor (not worthwhile): includes those with no improvement or worsening, or less than 25 per cent reduction in the number of attacks per week. In this series, we have also included those who had to discontinue the trial medication due to severe side effects.

The fortuitous selection of drugs which presented first the placebo, then 2 months of iproniazid with a final month of placebo, produced 2 consecutive months of active treatment followed abruptly by a replacement by the placebo. With the initial randomization of patients, only those 5 begun with

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<th>Table 1.—Summary of Clinical Data</th>
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*LVH, left ventricular hypertrophy; S, strain; CI, coronary insufficiency; Dig, Eff, digitalis effect; PMI, previous myocardial infarction; RBBB, right bundle-branch block; Chr. cor, chronic cor pulmonale.

"C," the second iproniazid tablet, did not experience 2 sequential months of the drug. This enabled us to demonstrate pointedly the cumulative pharmacologic effect of the drug.

Results

The detailed results of the trials are tabulated in tables 2 to 6.
Effect on Angina Pectoris (table 2). The first placebo administration gave a total of only 15 per cent excellent and 13 per cent good results. With the use of iproniazid, a marked improvement in response appeared with 41 per cent 'excellent' and 23 per cent 'good' the first month, and 64 per cent 'excellent' with 9 per cent 'good' the second month. Our responses were somewhat slower in appearance than those noted by other investigators, taking from 2 to 4 weeks to appear, and were apparently cumulative, judging by the increasing symptomatic benefit with time.

Substitution of the placebo caused a marked and sudden falling off of improvement with only 5 per cent claiming an excellent response and 23 per cent a good response. The total response of 'excellent' and 'good' of both placebo trials compared well, as did the iproniazid trials. The evidence for cumulation is seen in the increasing number with an excellent response in the second month compared with the first. This in turn was followed by a quick deflation on using the placebo again. This loss of therapeutic effect was also noted within 2 to 4 weeks. A statistical analysis (chi square) between the first placebo and first iproniazid trials gave a $p$ value of 0.09, or probability of 1 in 10 that these results were due to chance. Comparison between the second iproniazid and the second placebo showed a $p$ value of less than 0.001, or a probability of less than 1 in 1,000 that these findings were due to chance.

Effect on the Blood Pressure (table 3). With the first placebo 15 per cent showed increased blood pressure and 20 per cent displayed a lowering. All changes were mild and fluctuating. Similar mild changes were found during the first month on iproniazid, with 14 per cent elevated and 23 per cent depressed. By the second month on the drug, however, 40 per cent showed a blood pressure depression, severe enough in 1 patient to cause postural hypotensive symptoms with mild syncope. This was relieved by discontinuing the drug for 2 weeks, then reinstituting it at a 25 mg. per day level. Only 5 per cent showed an elevation at this time. A quick reversal appeared with switching to the placebo, and a rebound elevation was seen in 41 per cent with only 14 per cent showing a lowered blood pressure, providing evidence for a slow accumulation effect of the drug.

Effect on the Weight (table 4). Weight fluctuations were the least prominent of all observations, with 30 per cent gaining and 20 per cent losing small amounts on the first placebo. On the first iproniazid administration 23 per cent gained and 18 per cent lost weight. By the second month on iproniazid, 41 per cent had gained slightly, while the percentage losing weight remained almost exactly the same, at 18 per cent. The substitution of the final placebo produced a definite change with 54 per cent losing, while 23 per cent gained weight. This again would confirm a cumulative effect of iproniazid, manifested by better appetite and nourishment, with a sudden downward rebound of effect upon switching to the inert material.

Effect on Mood and Feeling of Well-Being (table 5). The first placebo elevated the mood of 45 per cent, while only 15 per cent felt...
worse with the tablet. These percentages remained unchanged with the first trial of iproniazid, with 46 per cent feeling better and 18 per cent worse. The second drug trial resulted in the same number (50 per cent) claiming improvement but, only 5 per cent felt worse. Uusing the final placebo tablet, however, reduced the number of those feeling better to 23 per cent, and 13 per cent again felt worse. Thus, the cumulative effect again manifested itself with a general elevation of mood for nearly the entire group under treatment, with only a single subject feeling worse. Discontinuing the active tablet reflected itself in reversal of the induced sense of well-being.

Effect on Untoward Reactions (table 6). Placebos, though pharmacologically inert, have been demonstrated to produce a wide variety of toxic reactions, and in general can worsen the symptoms of up to 20 per cent of an experimental population.27 Similarly, during the first placebo attempt, 1 mild and 1 severe reaction in 10 per cent of the group were produced. The first use of iproniazid, however, produced a definite increase in incidence of reaction to 23 per cent mild and 4 per cent severe. Repeated nausea and vomiting forced us to discontinue the drug "B," but the subject successfully took "C" in the same dose level. "B" and "C" were both iproniazid. By the second month, 36 per cent experienced mild and 14 per cent severe side reactions. One patient with a postural hypotensive reaction, required halving of the dose. However, this total of 50 per cent of reactions included for the most part, mild and relatively unimportant symptoms, but, the increasing number of reactions, again demonstrates a culmination of pharmacologic effect of the drug. Return to the placebo brought 16 per cent mild and 5 per cent severe reactions.

The increasing number of reactions with prolonged use of the drug emphasized the need to determine its effectiveness at the lower dose level of 25 mg. per day. Eleven patients were placed on this amount and followed for at least 1 month further. Nine of them acted as favorably as with the higher dosage. In 2, a return to the 50-mg. level was necessary. Two patients (19 per cent) experienced mild untoward reactions on this dose. The laboratory studies showed no abnormalities of liver function with the serial determinations of serum bilirubin and cephalin flocculation. No signs of hepatotoxicity were detected in any subject. One month after discontinuing the study, 1 patient was admitted to the hospital for the treatment of painless icterus. The gallbladder was not visualized after both oral and intravenous cholangiography, cholecystasis with cholecystitis was therefore seriously considered as the etiologic background. Her course was benign and she was discharged in 4 weeks in an asymptomatic condition.

The repeat electrocardiograms were likewise without significant change. Of the 17, 12 remained unchanged, 4 improved slightly, and 1 became worse. No patient experienced an acute myocardial infarction during this observation. One subject demonstrated transient signs and symptoms of a minor cerebrovascular accident, probably a small cerebral artery thrombosis. She remained ambulant and participated through the study with rapid and complete resolution of her episode within 2 weeks.

Discussion

Beecher has specified the requirements for appraising drugs, the efficacy of which is tested by the patients subjective responses. These conditions include (1) cooperative in-

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<th>Iproniazid</th>
<th>Placebo</th>
<th>Iproniazid</th>
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<tbody>
<tr>
<td>Improved</td>
<td>9</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Unchanged</td>
<td>8</td>
<td>8</td>
<td>10</td>
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<tr>
<td>Worsened</td>
<td>3</td>
<td>4</td>
<td>1</td>
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Table 5.—Effect of Iproniazid on Mood and Feeling of Well-Being

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<thead>
<tr>
<th>Placebo</th>
<th>Iproniazid</th>
<th>Placebo</th>
<th>Iproniazid</th>
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</thead>
<tbody>
<tr>
<td>Mild</td>
<td>1</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>10</td>
<td>11</td>
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Table 6.—Untoward Reactions of Placebo and Iproniazid
individuals who report on response, (2) the use of a double unknown (placebo-double blind), (3) randomization of order, (4) correlation of data, and finally, (5) mathematical evaluation. Our study fulfills all these criteria, including also the stringent condition proposed by Katz,\textsuperscript{25} i.e., presentation of the unknowns, on 2 separate occasions. Most important in a small group is the statistical correlation, which was highly significant in this study. Thus, investigation of 10 times the number under the same conditions should not change our finding of a positive symptomatic benefit with the use of iproniazid.

We consider that this study provides a new opportunity for reevaluation of the drug at the recommended dose level of no more than 30 mg. per day. The percentage of relief of symptoms was as high in this study as in those previously reported with 150 mg. doses. Moreover, we were successful even with doses of 25 mg., and a likely further reduction is indicated once symptomatic improvement is attained. The demonstration of a gradual accumulation of pharmacologic effect over the 2-month period emphasizes the need for patience in awaiting the desired response. The drug should be reduced at stepwise intervals of 1 or 2 weeks until the lowest effective dose is reached. Thus, the quandary so aptly described by Master\textsuperscript{29} may be solved.

This worker using the recommended dosage of 150 mg. per day in 74 patients found that ‘‘In my long experience with innumerable drugs for coronary heart disease, none has approached the subjective relief attained by iproniazid.’’ However, because of the high number and serious nature of untoward side effects, he was forced to discontinue the use of iproniazid, pending the development of a similar but less toxic compound. It is our opinion, that except for a possible specific hepatotoxicity, other reported side effects are manifestations of overdosage. We did not find that such untoward side effects were necessary correlation to a positive drug response; for example, while postural hypotension diminished on reduction of the drug, the symptomatic relief of anginal pain persisted.

The mechanism of action of this drug is beyond the limits of our investigation. Specification as to its mode of action points to some change in the catecholamine metabolism within either the myocardium or myocardial blood supply. Raab\textsuperscript{26} in a recent review of the chemical control of the metabolism and function of the heart, pointed out that the neurohormones, norepinephrine and acetylcholine, are liberated and react locally within the heart. Moreover, circulating epinephrine and norepinephrine are avidly absorbed by the myocardium. Insofar as the oxygen consumed during the cardiac recovery phase is augmented by the catecholamines and reduced by acetylcholine, these neurohormones regulate the energy metabolism of the heart. The exact pharmacology of catecholamines in myocardial metabolism and function is still being evolved. Lochner et al.\textsuperscript{30} found that the oxygen saturation of the coronary sinus rose in the intact dog after the intravenous infusion of epinephrine, norepinephrine, and acetylcholine. Feinberg and Katz\textsuperscript{31} using a different technic, found that infusion of catecholamines also diminished the coronary arteriovenous oxygen difference, while increasing the coronary blood flow and the available oxygen to the myocardium. Infusions of iproniazid in the isolated mammalian heart increased the coronary blood flow\textsuperscript{32} moreover, Pletscher and Pellmont also found a long-lasting rise in the catecholamine content of the heart of guinea pigs.\textsuperscript{33} These observations point to a plausible sequence of events in which long-term administration of a potent monoamine oxidase inhibitor initially increases the catecholamine content of the myocardium. These neurohormones can dilate the coronary vessels, increasing the oxygen supply to the myocardium while enhancing its metabolic utilization of the available oxygen. This pharmacologic action has a favorable effect on angina pectoris secondary to ischemic heart disease.

In addition to the pharmacologic effects upon anginal pain the more favorable emotional outlook experienced by patients while on iproniazid for 2 months contrasted with the
marked let-down sensed on sudden switching to a placebo must not be overlooked. Others have emphasized the strong effect of emotions on the course and prognosis of angina pectoris. There seems little doubt that such a more optimistic outlook exhibited by our patients was a potent factor in their achieving symptomatic relief from pain.

**Summary**

An evaluation of iproniazid in the syndrome of angina pectoris in ischemic heart disease is presented. A “double blind” experiment was performed with 4 unknowns, 2 of which were iproniazid and 2 placebo given separately at monthly intervals. The use of iproniazid was judged effective in relieving the pains of a total of 64 per cent and 73 per cent of the group on 2 separate periods, while the placebos were effective in only 30 per cent on 2 separate periods. These differences, analyzed statistically, were shown to be significant. The effects of this drug were slowly cumulative as evidenced by an increasing rate with time of both therapeutic effectiveness and of untoward reactions. Iproniazid at the dosage level employed also produced a mild hypotensive effect and an elevation of mood, and aided in maintaining body weight. There was no change in the clinical course or in the progression of the primary heart disease.

The initial dose level of 50 mg. per day was reduced satisfactorily to 25 mg. per day in 9 of 11 subjects. Doses over 50 mg. per day should be used only initially and not in ambulatory patients. When a therapeutic response is achieved, the maintenance dose of iproniazid should be continually reduced in stepwise fashion at 1- or 2-week intervals until the minimum effective dose is found for the individual patient.

**Summary in Interlingua**

Es presentate un evaluation de iproniazido in le therapia del syndrome de angina de pector in morbo de corde ischemic. Esseva execute un experimento “bis-occulte” con quatro medicationes incognoscite: 2 de iproniazido e 2 de un preparato ficticie. Illos esseva administrate separateme e a intervallos mensual. Le uso de iproniazido esseva considerate como resultante in un alleviamento del dolores in un total de 64 e 73 pro cento del casos studiate in 2 differente periodos experimental. Le uso del preparatos ficticie produceva un alleviamento del dolores in solmente 30 pro cento del casos in 2 periodos. Le analyse statistic mostrava que iste differrentias esseva significative. Le efectos del droga esseva lentemente cumulative. Isto esseva apparente per le progressive efficacia therapeutic e le progressive augmento del reactions adverse. Iproniazido in le dosage usate produceva etiam un leve effecto hypotensive. Illo elevava le spiritus del patientes e esseva de adjuta in mantenier lor pesos corpore. Esseva notate nulle alteration del curso clinico o del progresso del morbo cardiace primari.

Le dosage diurne de initialmente 50 mg esseva reducece satisfactormente a 25 mg in 9 ex 11 subjectos. Doses de plu que 50 mg deberea esser usate solmente al iniito e non del tuto in patientes ambulatori. Quando un responsa therapeutic es obtenute, le dose de mantenencia de iproniazido deberea esser reducece continuamente a intervallos de 1 o 2 septimanas usque le efficace minimo es determinate pro le patiente individual.

**References**


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Circulation. 1959;20:17-24
doi: 10.1161/01.CIR.20.1.17
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

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