Isoniazid and Para-Aminosalicylic Acid
Toxicity in 513 Cases:
A Study Including High Doses of INH and Gastrointestinal Intolerance to PAS*

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Introduction
In early 1956 it was demonstrated that the combination of isoniazid (INH) and para-aminosalicylic acid (PAS) provided a superior statistically significant treatment result in far-advanced and large cavitary tuberculous lesions.1 This study made a comparison between INH-PAS, streptomycin (SM)-INH, and SM-PAS (all SM was given intermittently). This year the use of high doses of INH in the treatment of pulmonary tuberculosis was again emphasized.2 Available data indicate that PAS competes with INH in the process of acetylation of both drugs. The combination of both drugs results in a higher serum level of biologically active, free, unacetylated INH.3 Thus, by adding PAS and elevating the dose of INH to 10 or 16 milligrams per kilogram of body weight per day instead of the more usual dose of about 5 milligrams per kilogram per day, an effective serum concentration of “free” INH can be attained. It is suggested that this level be at least 0.8 micrograms per milliliter of serum six hours after one-third of the total daily dose of INH and PAS is given.4

If one accepts that INH and PAS, with more elevated doses of INH, constitute one of the most effective antituberculous chemotherapeutic drug combinations at present, then one must consider the potential effects of drug toxicity or allergy and drug intolerance. There are many reports to document the multitude of allergic or toxic reactions due to PAS.5-8 However, detailed studies regarding the incidence and cause of gastrointestinal intolerance due to PAS are not readily found. Many generalities can be found regarding the “accepted” high incidence of intolerance to PAS. A quoted example is, “The well known symptoms of nausea, abdominal distress, vomiting, and diarrhea are a common experience.”9 One of us has seen gastrointestinal intolerance to PAS mount as high as 50 per cent on a single tuberculosis ward. It was of interest to note that this rate was reduced to about 15 per cent when the attitude of the ward doctor toward the “inevitable intolerance to PAS” became changed. It is believed that intolerance to PAS is directly related to the purity of the drug, and the attitude of the physician prescribing the drug which induces a iatrogenic intolerance in the patient. At two recent informal “PAS Meetings,” the problems of drug purity were discussed. Para-aminosalicylic acid varying in age from six months to three years was tested and revealed

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degrees of deterioration between 35 and 70 per cent. Para-aminosalicylic acid is a relatively unstable compound which decomposes under the influence of heat, light, moisture, time, and catalytic action of heavy metals. It has been suggested that the administration of freshly prepared and adequately controlled PAS would reduce the amount of the decomposition products of PAS that are related to gastrointestinal intolerance.

The toxic effects due to INH have been variable, but principally neurological. No great problem has existed with the use of doses of INH in the range of 300 milligrams per day. On much higher daily dosages, up to one-third of the patients developed peripheral neuropathies. The use of pyridoxine has subsequently proved to reduce or prevent neuropathies due to INH. Nevertheless, there are many physicians who maintain concern regarding the prolonged use of high doses of INH.

In light of the aforementioned comments, the purpose of this report is to suggest that PAS and elevated doses of INH, with pyridoxine, can be given to patients over prolonged periods with relative safety.

Materials and Methods

All patients treated at this hospital with INH or PAS during a nine month period (November 1, 1956 to August 1, 1957) were reviewed. This study comprises a total of 513 all of whom received INH as part of their treatment. Paraaminosalicylic acid was also administered to 303 of these 513 patients. The majority were given combined chemotherapy consisting of INH and PAS, or INH and SM. A small number of cases received triple drug therapy (INH, PAS and SM). Of the 513 who received INH, 329 (64 per cent) were given doses of 10 or 16 milligrams per kilogram of body weight per day. The remaining 184 (36 per cent) were given 300 milligrams of INH per day. All patients taking either 10 or 16 milligrams per kilogram of INH per day also received 100 milligrams of pyridoxine once daily. No pyridoxine was administered with doses of only 300 milligrams of INH per day.

The observation period on chemotherapy in these 513 patients at the time of this study was as follows. One hundred and eleven (21.6 per cent) cases received one to two months of therapy, 60 (11.7 per cent) two to three months, 133 (26 per cent) three to six months and 209 (40.7 per cent) received over six months of therapy.

In four of the five cases that exhibited toxicity to INH, the same toxic reaction was reproduced by a second course of therapy. One was accidentally given 20 to 25 milligrams of INH per kilogram daily for four to five days. The dizziness produced in this patient disappeared immediately when a lower dose was administered. The same toxic symptoms were reproduced in 22 of the 26 cases reacting to PAS. In four cases (three with G. I. intolerance and one with hematemesis) PAS was not administered a second time.

All receiving isoniazid were given this drug in the form of tablets. Paraaminosalicylic acid was administered in the form of the sodium salt. No chemical additive was introduced. In order to minimize deterioration of PAS and attempt to reduce gastrointestinal intolerance, the following control measures were instituted. An order was placed with the manu-

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facturer for an estimated six weeks supply of PAS. This was delivered in polyethylene packets, sealed in nitrogen instead of air, and contained 5.57 grams of sodium para-aminosalicylate (equivalent to four grams of para-aminosalicylic acid). The date of manufacture was stamped on each lot of PAS, and the manufacturer arbitrarily indicated a 120 day expiration date. By replenishing the supply of PAS every six weeks, it was possible to deliver this drug to patients within two months of its manufacture. Precautions were taken to eliminate the possibility of mixing new orders of PAS with the waning previous order at this hospital. Exposure of the drug to light, heat, and moisture were controlled within practical limits by the pharmacy office. One packet of PAS was administered to each patient three times daily (total dose equivalent to 12 grams of para-aminosalicylic acid daily). Each packet was opened at the bedside and mixed with 3 to 4 ounces of water or fruit juice. The patient drank the dissolved medication immediately and followed it with a mouthful of fresh water.

<p>| TABLE I |</p>
<table>
<thead>
<tr>
<th>TOXIC REACTIONS TO INH OCCURRING IN 513 CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Reactions</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Chills, fever and rash. Tachycardia, jaundice, rash, and fever occurred with second dose of INH</td>
</tr>
<tr>
<td>Chills, fever, headache, tachycardia, nausea and vomiting</td>
</tr>
<tr>
<td>Fever and rash</td>
</tr>
</tbody>
</table>

*Patient discharged before time of onset of toxicity recorded.

<p>| TABLE II |</p>
<table>
<thead>
<tr>
<th>TOXIC REACTIONS TO PAS OCCURRING IN 303 CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Reactions</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Fever and rash</td>
</tr>
<tr>
<td>Exfoliative dermatitis</td>
</tr>
<tr>
<td>Chills, fever, headache, tachycardia, nausea &amp; vomiting</td>
</tr>
<tr>
<td>Chills, fever &amp; somnolence</td>
</tr>
<tr>
<td>Chills, fever, rash, somnolence &amp; eosinophilia</td>
</tr>
<tr>
<td>Gastrointestinal upset</td>
</tr>
<tr>
<td>Hematemesis (no evidence of peptic ulcer)</td>
</tr>
</tbody>
</table>

*Patient discharged before time of onset of toxicity recorded.
Observations

In Table I, data are tabulated with reference to five cases exhibiting toxic reactions to INH. All five drug reactions occurred in patients receiving 10 or 16 milligrams of INH per kilogram per day. The majority of the recorded toxic reactions were manifested within one month of the onset of therapy. The incidence of toxicity due to INH in all 513 cases was 0.97 per cent. Since all five toxic reactions occurred in patients receiving elevated doses of INH, the incidence of toxicity noted in 329 cases on elevated doses of INH was 1.52 per cent.

In Table II, 27 reactions to PAS due to allergy or gastrointestinal intolerance were noted in 303 patients. Twenty (74 per cent) of these toxic reactions were recorded to have occurred before one month of therapy was completed. The incidence of all forms of toxicity due to PAS in these 303 patients was 8.9 per cent. Sixteen (5.3 per cent) exhibited gastrointestinal complications due to PAS. The remaining 12 (4 per cent) were considered to have had allergic disorders as illustrated in Table II. If the one case with hematemesis is eliminated, it will be noted that 15 of 303 (4.9 per cent) developed the gastrointestinal symptoms of anorexia, nausea, vomiting or diarrhea that have been so frequently associated with PAS in the past. Vomiting rarely occurred. Anorexia and nausea, or diarrhea were noted more frequently. The three in Table II with chills, fever, headache, tachycardia, nausea, and vomiting were accepted as allergic reactions to PAS. The nausea and vomiting were not initial symptoms, but occurred after chills, fever, headache and tachycardia were well established.

DISCUSSION

When it was reported that the combination of INH and PAS constituted a more superior drug combination than intermittent SM with INH or PAS, then PAS no longer became a second choice drug. A primary need for PAS developed. Some physicians now became interested in the incidence and cause of gastrointestinal intolerance due to PAS. The specific cause of this intolerance has not been absolutely proved, but strong clinical and biochemical evidence exists suggesting that the cause rests with the decomposition products of this unstable drug. It is important in this respect to emphasize that only 4.9 per cent of patients in this present report developed the commonly accepted gastrointestinal symptoms due to PAS. The authors firmly believe that this low rate is due to: The methods used to deliver freshly manufactured and controlled PAS to the patient, and the education of the physician to the effect that he need not have to accept a high incidence of gastrointestinal intolerance from PAS.

It is now generally accepted that INH is one of the most important drugs available in treating tuberculosis. This can best be appreciated when one reviews the marked decrease in relapse and mortality rates in miliary, meningeal, and renal tuberculosis after INH was put into use. Present investigation at other institutions and at this institution suggest that elevated doses of INH with PAS offer a distinct therapeutic advantage. One of the purposes of this report is to suggest that elevated doses of INH can be given safely to large numbers of patients for prolonged periods of time, providing pyridoxine is also administered. The small per cent of toxic reactions to INH noted in 513 patients is about equal to the per cent of allergic reactions expected from many numbers of other drugs used in the practice of medicine. It is certainly of interest to note that none of these 513 patients developed a peripheral neuropathy. The only reactions of possible neurological significance consisted of two cases of dizziness. The only truly serious reaction occurring in all 513 patients was the case of jaundice noted in Table I. When a second dose of INH was given, the patient developed a severe toxic hepatitis. The electrocardiogram revealed R-ST changes suggesting a toxic myocarditis. This patient has presently made a full recovery from all toxic signs and symptoms. He had been receiving 10 milligrams per kilogram of INH per day plus 12 grams of PAS per day. After the rash and fever occurred, both drugs were stopped. Later INH alone was started in lower doses and it immediately precipitated jaundice, rash, fever, and tachycardia. This patient was subsequently successfully desensitized to INH.

It is important to realize that the majority of patients in this study fell within the 20 to 40 year old age group. The incidence of malnutrition, chronic alcoholism and intercurrent disease was very low.
In a study of this nature, it should be mentioned that there are occasional reports referring to the antithyroid action of PAS. No controlled study of thyroid function was made on the 303 patients in this report who received PAS. However, no palpable goiters developed and there was no obvious clinical manifestation of hypothyroidism.

SUMMARY

Toxic drug reactions in 513 patients receiving INH and 303 patients receiving PAS have been reviewed. Sixty-nine per cent were observed for over three months. All had received at least one month of therapy at the time of this study. In 303 patients taking PAS, drug allergy and gastrointestinal intolerance occurred in 8.9 per cent. Only 4.9 per cent developed gastrointestinal symptoms of nausea, vomiting, and diarrhea. Only 0.97 per cent of the 513 patients receiving INH developed toxic symptoms. Toxic reactions that did occur were derived from the 329 cases taking high doses of INH. The per cent toxicity from INH in these 329 cases was 1.52 per cent. By using the methods described in detail, the authors believe that high doses of INH plus PAS can be safely given to large numbers of tuberculosis patients for prolonged periods, provided these patients are otherwise in a state of good nutrition and do not have preexisting central nervous system or hepatic disease.

RESUMEN

Se han revisado las reacciones tóxicas que se presentaron en 513 enfermos que usaron isoniazida y 303 que tomaron PAS.

Se observaron el sesenta y nueve por ciento por más de tres meses. Todos habían recibido por lo menos un mes de tratamiento cuando se hizo este estudio. En 303 enfermos que tomaron PAS se presentó alergia a la droga y trastornos de intolerancia gastrointestinal en 8.9 por ciento. Sólo 4.9 por ciento tuvieron síntomas gastrointestinales como náuseas, vómitos y diarrea. Sólo 0.97 por ciento de 513 enfermos que recibieron HAIN tuvieron síntomas tóxicos.

Las reacciones tóxicas que ocurrieron se derivaron de 329 casos que tomaron altas dosis de HAIN. El porcentaje de toxicidad de HAIN en estos 329 casos fue de 1.52.

Usando los métodos que en detalle se describen creen los autores que las dosis altas de HAIN más PAS, pueden dase con seguridad a gran número de tuberculosos por períodos prolongados siempre que estos enfermos están por otra parte en buenas condiciones de nutrición y no tengan padecimientos previos del sistema nervioso central o afección hepática.

RESUME

Les auteurs rapportent les réactions toxiques à la médication chez 513 malades recevant de l'isoniazide et 303 malades recevant du P.A.S. 69% de ces malades furent observés pendant plus de trois mois. Tous recurent au moins un mois de traitement pendant le période que couvre cette étude. Chez 303 malades prenant du P.A.S. une allergie à la médication et une intolérance gastro-intestinale survint chez 8,9%. 4,9% seulement présentèrent des symptômes gastro-intestinaux avec nausées, vomissements et diarrhée. 0,97% seulement sur les 513 malades recevant de l'isoniazide furent atteints de symptômes toxiques. Les réactions toxiques que furent notées concernaient les 329 malades prenant de hautes doses d'isoniazide. Le pourcentage de toxicité de l'isonia- zide chez ces 329 malades fut de 1,52%. En utilisant des méthodes décrites en détail, les auteurs pensent que de hautes doses d'isoniazide associées au P.A.S. peuvent être données sans danger à un très grand nombre de malades tuberculeux pendant des périodes de temps prolongées, à condition que ces malades soient par ailleurs en état de bonne nutrition et qu'ils n'ait pas une affection nerveuse centrale pré-existante ou une affection hépatique.

ZUSAMMENFASSUNG


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