Peripheral Neuritis Due to Hydrazide Derivatives*

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The antituberculous activity of isoniazid used alone or in combination with streptomycin or para-aminosalicylic acid (PAS) has been established. One of the most favorable properties of isoniazid is the low incidence of significant toxicity resulting from its use when doses of 3 to 5 mg. per kilogram per day are administered. Some of the reactions reported include toxic psychosis, convulsions, dizziness, euphoria, increased sensitivity to sympathomimetic drugs, hyperreflexia, weakness of the legs, headache, ataxia, muscle tremors, tinnitus, disturbed vision, insomnia, drowsiness, urinary incontinence, polyuria, delay in initiation of micturition, constipation, dryness of the mouth, drug fever, variations in sexual activity, pruritis, skin rash, nausea, vomiting, exertional dyspnea and transitory edema. Although this is a long list, toxic reactions are infrequent. The need for discontinuing the drug because of serious toxic reactions occurs in approximately 1 per cent of cases. It is interesting to note the dominance of toxic effects referable to the nervous system.

In our studies with isoniazid, as well as other hydrazides, we have used various dosage schedules in an attempt to evaluate therapeutic efficacy, roentgenographic response, incidence of sputum conversion, development of bacterial resistance and drug toxicity.

In the course of these studies we have observed 19 patients who have developed peripheral neuritis of varying degrees of severity. Isoniazid was administered to 15. Three received 200 mg. daily; and 11 received 400 mg. daily. These doses represent 2.5 mg. to 10 mg. per kilogram per day. Eleven of the 15 received more than 5 mg. per kilogram per day. This indicates a correlation between the size of the dose and the development of neuritis.

The isoniazid used was supplied by two manufacturers. Three patients received isoniazid alone. Nine of these 15 received 1 gram of streptomycin twice a week and 12 grams of PAS daily in addition to isoniazid. One gram of streptomycin twice a week and daily isoniazid was administered to three, one of whom had received intermittent streptomycin and daily PAS for one year.

Four were given N-isonicotinoyl-N-(hydroxypivalidene) hydrazide. In two of them 400 mg. of this compound was given daily; in one 200 mg. was administered. The third had received intermittent streptomycin and daily PAS for one year at which time 400 mg. of N-isonicotinoyl-N-(hydroxypivalidene) hydrazide per day was added. These doses correspond to 4.3 mg.

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to 11 mg. per kilogram per day. Three out of the four received over 5 mg. per kilogram per day.

Symptoms were noted as early as two weeks after the institution of therapy but in most cases appeared after the second month (Table I).

<table>
<thead>
<tr>
<th>ONSET OF SYMPTOMS AFTER BEGINNING HYDRAZIDE THERAPY</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Isoniazid</td>
</tr>
<tr>
<td>N-isonicotinoyl-N- (hydroxypropyldene) hydrazide</td>
</tr>
</tbody>
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indicating a lack of strict correlation between duration of treatment and the onset of neuritis. The most common complaints were numbness, tingling, burning sensation and pain in the extremities. Fourteen had hypesthesia which was most severe in the fingers and/or toes. As the distal interphalangeal joint area was reached there was a rather abrupt increase in sensory appreciation. The findings are tabulated in Table II.

<table>
<thead>
<tr>
<th>TABLE II: INCIDENCE OF SYMPTOMS OF NEURITIS IN NINETEEN PATIENTS RECEIVING ISONIAZID THERAPY</th>
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</thead>
<tbody>
<tr>
<td>Clinical Manifestations</td>
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<tr>
<td>Diminished vibratory sense</td>
</tr>
<tr>
<td>Hyperesthesia (pin prick)</td>
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<tr>
<td>Muscle weakness</td>
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<tr>
<td>Hyporeflexia</td>
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<tr>
<td>Hyperreflexia</td>
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<tr>
<td>Pain</td>
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<tr>
<td>Hypesthesia</td>
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<tr>
<td>Paresthesia</td>
</tr>
</tbody>
</table>

Although the findings were bilateral and had a typical "stocking and glove" distribution, in one patient there appeared to be a mononeuritis strictly limited to the distribution of the median nerve. In six the involvement was confined to the hands or was more severe in the hands, which is unusual for most types of peripheral neuritis. No changes were noted in skin color or temperature. Discontinuance of the responsible hydrazide usually resulted in improvement.

The pathogenesis of isoniazid peripheral neuritis is not known. One possible explanation is the interference with carbohydrate oxidation in nerve cell metabolism. In the oxidation of carbohydrate, nicotinic acid plays an important role as an essential constituent of co-enzyme I and II. One of the many reactions in which co-enzyme I participates is the conversion of pyruvic acid to lactic acid. It is possible that isoniazid with its similar structure might compete with nicotinic acid in this oxidative process thus producing a blocking mechanism. However, there was no
significant elevation of pyruvic acid levels in our patients. Nicotinic acid also plays a role in the Kreb Cycle as co-enzyme activator for alpha-ketoglutarate dehydrogenase. Measures will be taken to determine if there is any increase in the alpha-ketoglutarate acids.

Although none of the patients showed any of the classical manifestations of nicotinic acid deficiency, the theoretical possibility exists that nicotinic acid may be useful in the management of isoniazid peripheral neuritis. It is our intention to use large doses of nicotinic acid in the patients who do not respond satisfactorily to the withdrawal of isoniazid.

Case Report

B.F., a 22-year-old colored female was admitted to this hospital on March 23, 1953, with a history of anorexia, weakness, and productive cough of several weeks' duration. X-ray film revealed evidence of extensive pulmonary disease. The sputum showed tubercle bacilli. Streptomycin, PAS and isoniazid were started on March 23, 1953. By April 20, 1953, there was obvious clinical and roentgenographic improvement. Two weeks after treatment was started, she complained of numbness and pain in both hands. The pain rapidly became worse and she described this "as if my flesh were coming off." Neurological examination revealed paresthesias of the hands, hyperactive reflexes, and greatly diminished pin-point sensation of both hands. Vibratory sense and position sense were intact. Gradually there was voluntary limitation of movement of both hands and fingers. Three weeks after the onset of symptoms there was considerable atrophy of the intrinsic muscles of the hands, particularly the thenar eminences, with almost complete loss of movement. On June 30, 1953, isoniazid was stopped. The peripheral neuritis continued for another month and then gradually subsided.

SUMMARY

Peripheral neuritis following isoniazid has been observed in 19 patients. The chief components are paresthesias of both upper and lower extremities. There was no strict correlation between duration of therapy and onset and severity of symptoms. In most instances symptoms gradually subsided following cessation of the drug.

RESUMEN

Se ha observado neuritis periférica en 19 enfermos después del uso de la isoniazida. Los principales síntomas son parestesias en ambas extremidades inferiores. No hay estricta correlación entre la duración del tratamiento y el principio y la severidad de los síntomas. En la mayoría de los casos los síntomas ceden después de la suspensión de la droga.

RESUME

Des études du système nerveux périphérique ont été faites après un traitement à l'isoniazide chez 19 malades. Les éléments essentiels des troubles sont des paresthésies des extrémités. On ne peut noter de rapport net entre la gravité des manifestations et la longueur du traitement. Dans la plupart des cas, les signes pathologiques s'atténuèrent progressivement après qu'on eût cessé l'utilisation du produit.
REFERENCES

(g) Tempel, C. W., Pitts, F. W., Miller, F. L., Sands, J. H., FitzPatrick, M. J. and Weiser, O.: “Isoniazid-Streptomycin in the Treatment of Pulmonary Tuberculosis,” Transactions of the Twelfth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army and Navy, Atlanta, Ga., 1953, pp. 80-88.

2 References 1a, 1e, If and Ig.
3 Carr, D.: Transactions of the Twelfth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army and Navy, Atlanta, Ga., 1953, p. 143.
4 Supplied by Dr. George Mast, Nepera Chemical Company, Yonkers, New York.
5 Pyruvic Acid levels performed through the courtesy of Dr. Joseph Fazekas, Chief of Staff, District of Columbia General Hospital.

Since the preparation of this report several references to isoniazid peripheral neuritis have appeared: