Ethionamide and Isoniazid in Previously Untreated Cases of Pulmonary Tuberculosis*

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Material and Methods

Cases of newly diagnosed pulmonary tuberculosis were treated with ethionamide 1 gm. daily (in the form of uncoated tablets) and isoniazid 400 mg. daily. Patients with gross cavitation and extensive disease were excluded. Examination of urine for albumin, blood and bile was carried out weekly; liver function tests (serum albumin, and globulin, serum bilirubin, thymol turbidity, alkaline phosphatase) monthly; chest x-ray film and culture of sputum or bronchial lavage specimens monthly. Specimens of respiratory secretions were concentrated by Petroff's method and cultured on Löwenstein-Jensen medium. Sensitivity tests were carried out by incorporating the drugs in Löwenstein-Jensen medium in the following strengths: isoniazid 0.2, 1, 5 and 50 micrograms/ml.; and ethionamide 5, 10, 20 and 40 micrograms/ml. Sensitivity test media were controlled by means of the standard strain H37 R.v.

Clinical and Radiologic Results

Of 32 patients with organisms initially sensitive to ethionamide and isoniazid, 26 completed six months' therapy and six failed to do so, in two instances because of death from disease other than tuberculosis, and in four instances because of the development of toxic reactions to ethionamide. Clinical and radiologic progress was satisfactory in all of the 26 patients who completed the six months' period. Of these 26 patients, five had initially six lung zones affected by disease; three had four zones; four had three zones; eight had two zones; and six had one zone. After six months, three had four zones affected by disease; five had three zones; six had two zones; and 12 had one zone.

Cavitation was initially present in 17 of the 26 cases. These 17 cases had all together 30 cavities, 23 less than one inch in diameter, and seven more than one inch in diameter. After six months, cavities had closed in 14 of the 17 patients who originally had them. Three still had a single cavity each. Follow-up showed that they closed after seven, eight and eleven months' treatment respectively. Their general condition improved satisfactorily and all but two gained weight.

Bacteriologic Results

If bacterial conversion is defined as a negative monthly culture followed by at least one subsequent negative monthly culture and no further positives during the period of observation, only one of the 26 patients completing six months' therapy remained unconverted at the end of the period. In 12 cases conversion occurred at one month; in six at two months; in three at three months; in two at four months; and in two at six months. The two converting at six months have now been followed for ten months in one case and for over a year in the other and cultures have remained negative.

In the case in which the sputum was still positive at six months, the patient was a man of 59 years who initially had extensive disease involving all lung zones: five cavities were present. He had refused streptomycin. Sputum conversion occurred after seven months. He died from coronary thrombosis after nine months' therapy. Histologic examination of the lungs postmortem showed healed tuberculous disease in the right lung and almost healed disease in the left. No cavity was found.

No evidence of emergent bacterial resistance to ethionamide or isoniazid was noted in any of the cases.

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Further Follow-up

Eight patients have now received ethionamide and isoniazid therapy for at least a year. Five failed to complete the second six months' treatment, in three instances because of toxic reactions to ethionamide and in two instances because of death unrelated to tuberculosis.

Clinical and radiologic progress was satisfactory in all of the eight cases completing one year's treatment. Initially, two of these eight patients had six lung zones affected by disease; one had four zones; one had three zones; two had two zones; and two had one zone. At the end of the year, one had three zones affected, and seven had one zone. Initially, five of these eight patients had cavitary disease. At the end of the year, all cavities had closed. Bacteriologic conversion occurred after one month's treatment in seven cases and after six months in the remaining case. No evidence of emergent bacterial resistance was noted in any of the cases.

Two patients died of coronary thrombosis after eight and nine months' therapy, respectively. In both cases, sputum had converted, there had been no evidence of drug resistance, cavities had closed, and progress had been in every way satisfactory.

Toxicity

Six patients complained of nausea and malaise at the start of treatment, but in all, symptoms improved and disappeared within a week. Four failed to complete six months' therapy because of toxicity from ethionamide. In one case, treatment had to be stopped after six weeks because of the occurrence of severe mental depression in a young man. On withdrawal of ethionamide, he recovered within a week. In the other three cases, treatment had to be stopped because of the development of jaundice which appeared after five months' treatment in two cases and after four months' treatment in the third. On withdrawal of therapy, the patients felt better in a day or two and liver function tests returned to normal within two months. Challenge with ethionamide in the first case encountered produced nausea and increased disturbance of liver function. In two further cases, transient disturbance of liver function was noted.

Three patients who had completed six months' therapy failed to complete one year's therapy because of drug toxicity. Treatment had to be stopped after seven months in one case because of complaints of persistent nausea. In the remaining two, therapy was withdrawn because of the onset of neurotoxicity. One, after eight months' therapy, complained of burning in the feet and legs, and in the hands and forearms; he also had an unsteady gait and there was impairment of proprioception. The other after ten months' therapy complained of insomnia, burning of the feet, and difficulty with micturition. In both cases, symptoms disappeared after drug treatment was stopped and pyridoxine given. Therapy was later continued with isoniazid 400 mg. daily and PAS 12 gm. daily and there was no further trouble.

The above instances of ethionamide toxicity have been considered with others and discussed elsewhere."

Discussion

The results of isoniazid plus ethionamide proved an effective therapeutic combination. Satisfactory clinical, radiologic, and bacteriologic progress was achieved in 26 patients treated for six months and was maintained in eight who were observed for at least a further six months. Bacteriologic conversion occurred in every case (in all except one by six months) and there was no evidence of emerging microbial resistance to either drug.

Ethionamide toxicity was, however, a major drawback. Treatment had to be stopped within six months in four cases, in one instance because of the occurrence of severe mental depression, and in the remaining three because of the development of jaundice. Depression from ethionamide has not infrequently been encountered, and occasional cases of ethionamide jaundice have been reported. Although it appears that jaundice may be a not infrequent side effect of ethionamide-isoniazid therapy using the dosage levels here em-
ployed, it should be pointed out that the results in the present investigation probably give an exaggerated impression of the likely incidence of ethionamide hepatotoxicity, since an equal number of patients were concurrently treated with the same dosages of both drugs plus streptomycin 1 gm. daily, and there was no instance of jaundice in the triple drug series.

Peripheral neuritis from ethionamide has been reported by several workers, and treatment had to be stopped in two patients because of its occurrence between six months and one year from the start of treatment. Isoniazid is, of course, also potentially neurotoxic and the possibility that it contributed to the development of peripheral neuritis cannot be excluded. Ethionamide treatment had to be discontinued in one further case after seven months because of the development and persistence of nausea.

Troublesome gastrointestinal side effects—nausea, malaise and gastralgia—occurred frequently soon after the commencement of therapy in the original clinical trials of ethionamide carried out by Brouet et al., but although these side effects were encountered initially in six cases in this series, they proved comparatively transient.

Experience with ethionamide in this investigation (and experience with other patients to be reported elsewhere) suggests that despite good therapeutic results, the incidence of drug toxicity with a dose of 1 gm. daily is too high to be acceptable. However, there is evidence that it may be possible to lower the dose of ethionamide when given with isoniazid without impairing the therapeutic efficiency of the combination. From experimental work with mice, Grumbach considers that a dose of 0.5 gm. or even 0.25 gm. of ethionamide daily may be adequate if accompanied by a high dose of isoniazid; and Rist reports that analysis after eight months of a controlled trial shows that sputum conversion occurred as often with an isoniazid-ethionamide regimen in which 500 mg. of isoniazid with 832 mg. of ethionamide were the maximum daily dosages, as with an isoniazid-PAS regimen in which the daily drug dosages were 300 mg. of isoniazid and 12 gm. of PAS. Moreover, the emergence of bacterial resistance occurred less frequently and toxic reactions were no more common with isoniazid-ethionamide than with the isoniazid-PAS therapy.

Further experience with ethionamide is needed before any firm assessment of its place in therapy can be made, but in the meantime it would appear to be a valuable alternative to PAS as a companion for isoniazid.

**Summary**

Patients with newly diagnosed pulmonary tuberculosis were treated with a combination of ethionamide 1 gm. daily and isoniazid 400 mg. daily. Twenty-six patients were observed for at least six months and eight for at least one year. Clinical, radiologic, and bacteriologic progress was satisfactory in all these cases. Conversion of sputum was achieved in every case, and there was no evidence of emergence of bacterial resistance to either drug.

The incidence of ethionamide toxicity which occurred, however, indicates that a daily dose of 1 gm. of the drug is too high for routine use. Side effects observed were nausea, jaundice, mental disturbance, and peripheral neuritis.

The excellent results in patients who could tolerate the ethionamide-isoniazid therapy warrant further trial of this drug combination, since the use of a lower dosage level of ethionamide may make it acceptable in regard to toxicity without sacrificing its therapeutic effectiveness.

**Resumen**

Se trataron enfermos con tuberculosis recién diagnosticada con una combinación de etionamida, 1 gramo diario con 400 mg. de isonicáida.

Se observaron veintiséis enfermos por lo menos durante seis meses y ocho durante un año, cuando menos. La evolución clínica, radiológica y bacteriológica fueron satisfactorias en todos los casos.

La conversión de los esputos se obtuvo en todos los casos y hubo evidencias de aparición de resistencia a ninguna de las drogas. La frecuencia de la toxicidad de la etionamida, tal como ocurrió, sin embargo, indica que una dosis diaria de 1 g. de la droga es demasiado alta para su uso de rutina. Los efectos colaterales fueron náuseas, ictericia, trastornos mentales y neuritis periférica.
Los resultados excelentes en los enfermos que pudieron tolerar la asociación etionamida e isoniazida autorizan el ensayo ulterior de ella puesto que el uso de una dosificación más baja de etionamida puede ser aceptable en lo referente a la toxicidad sin sacrificio de su efectividad.

RESUMÉ

Des malades atteints de tuberculose pulmonaire récemment découverts furent traités par une association d'etionamidé à la dose d'un grammes par jour et d'isoniazide à la dose de 400 mg. par jour. 26 malades furent observés au moins pendant six mois, et huit pendant au moins un an. Le progrès clinique, radiologique et bactériologique fut satisfaisant dans tous les cas, et il n'y eut aucune preuve de l'apparition d'une résistance bactérienne à aucun produit.

Cependant la fréquence avec laquelle apparaissent les manifestations de toxicité pour l'etionamidé indique que la dose quotidienne d'un gramme est trop élevée pour la pratique courante. Les effets toxiques observés furent la nausée, l'ictère, les troubles mentaux et des atteintes du système nerveux périphérique.

Les excellents résultats obtenus chez les malades qui purent supporter le traitement par l'etionamidé-isoniazide justifient la poursuite ultérieure de cette association chimiothérapeutique puissant l'emploi à un dosage plus faible d'etionamidé peut la rendre acceptable en ce qui concerne la toxicité sans sacrifier son efficacité thérapeutique.

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REFERENCES