Cycloserine-Isoniazid in the Treatment of Chronic, Resistant Pulmonary Tuberculosis*

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Introduction

This report concerns the clinical results observed in patients with chronic pulmonary tuberculosis in whom long-term chemotherapy had failed, who were then treated with cycloserine (CS) and isoniazid (INH). Observations were made with respect to clinical improvement, bacteriological conversion, roentgenographic improvement, closure of cavities and drug toxicity.

Material

Forty-six consecutive patients fitting the following criteria were selected: all patients had received long-term prior chemotherapy and represented failure of treatment with various combinations of SM, PAS, INH; all patients had a positive sputum; all patients were resistant to SM, PAS and INH, either in the laboratory, or clinically, or both.

All patients were Negroes, 22 males and 24 females. The age varied between 17 and 65 years. Forty-one patients were far advanced, 5 were moderately advanced. Thirty-one patients had cavitary lesions.

Four patients had previous chemotherapy with various combinations of SM, PAS, INH less than a year, 20 patients for one to two years, 22 patients for over three years. Three were sensitive to INH (5 mcg./ml.), 5 were partially resistant and 38 were highly resistant at the beginning of CS-INH therapy.

Twenty-nine patients have been treated with 750 mgs. of CS and 300 mgs. of INH per day in divided doses, 17 patients with 500 mgs. of CS and 300 mgs. of INH.

Eleven patients have been observed less than three months, six patients between four and six months, eleven patients between seven and nine months, twelve patients between ten and twelve months, six patients have been studied for more than one year.

Observations

Clinical Improvement: Symptomatic improvement was prompt and marked in most of these cases. Five patients were febrile prior to therapy with temperature ranging from 99° to 102° F. Defervescence was completed by two months in all cases. Thirty patients, or 65 per cent, gained weight: 16 patients 3 to 10 lbs.; 7 patients 11 to 20 lbs.; 4 patients 21 to 30 lbs.; and 3 patients over 31 lbs., the maximum weight gained being 69 pounds. The gain in weight occurred chiefly within the first six months period.

Bacteriological Conversions: Bacteriological conversion occurred remarkably early in the course of treatment. Fifty-four per cent of cases were negative on smear and culture at six months of therapy. After six

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months, however, a considerable number of patients became positive again and at the end of one year, only 27 per cent of cases had remained negative. No relapse occurred after a year (Table I).

Three patients who were sensitive to INH at the beginning of treatment converted and remained negative. Among five partially resistant cases, two converted within four months, but one became positive at eight months.

There was no significant difference in conversion rates between the two different doses of CS.

*Cavity Closure:* Thirty-one of the 46 cases had single or multiple cavities. Of these, only two achieved closure of cavities. One patient had maintained two cavities, 3 cm. in diameter each, throughout two years and six months of chemotherapy with SM, PAS and INH, closed these cavities within three months of CS-INH therapy. Eleven months later, however, they had reopened. Another patient with a cavity, 4 cm. in diameter, which had persisted for four years and four months of combined chemotherapy closed her cavity permanently after eleven months of CS-INH therapy. Both patients received 750 mgs. of CS daily and were resistant to INH. Two patients' cavities became smaller. Four patients' cavities became larger.

*Roentgenographic Improvement:* Both roentgenographic improvement and cavity closure were meager. Six patients, or 13 per cent, had moderate to marked improvement, graded as improvement greater than fifty per cent from the time of initial treatment and without spread of disease. Among these six patients, 3 received 750 mgs. of CS and 3 received 500 mgs. of CS. Majority of improvement occurred between three and six months. Five patients, or 10 per cent, had spread or deterioration.

Among three patients sensitive to INH, one improved markedly, two remained unchanged. Among five partially resistant, one improved moderately, two deteriorated and two were unchanged.

*Toxicity:* CS was discontinued in three cases: one because of convulsion and difficulty in talking after two weeks of treatment; one because of hyperreflexia and tremors after a week of treatment; and one because of emotional changes after two months of treatment. The former two cases received 750 mgs. of CS daily and the third case received 500 mgs. of CS. Three cases developed dizziness within two weeks of therapy. One patient had febrile reaction in a week. None of the entire group received pyridoxine.
Discussion

Bacteriological conversion was prompt and remarkable reaching its peak of 54 per cent at six months of therapy. Approximately 26 per cent of the cases became positive by the end of one year with no further relapse thereafter. It is suggested that the optimal duration of CS-INH therapy in resistant pulmonary tuberculosis should be six months followed by another regimen.

There were no significant differences between the two different doses of CS in the therapeutic efficacy and drug toxicity. The INH sensitive cases showed better results as might have been expected. Whether INH contributed to CS effects in the INH resistant cases, if any or how much, can not be determined without comparing the results of similar cases treated with CS alone.

SUMMARY

1. Forty-six Negro pulmonary tuberculosis patients, all of whom had received a long term chemotherapy and were treatment failures with combination of SM, PAS and INH, were treated with CS-INH.

2. Bacteriological conversion occurred in 54 per cent at six months of therapy, 27 per cent at twelve months with 26 per cent of relapse. No relapse was found after twelve months of therapy.

3. Moderate to marked X-ray improvement occurred in 13 per cent, relapse or deterioration occurred in 10 per cent. Cavity closure occurred in 3 per cent.

4. Treatment was discontinued in three cases, or 6 per cent, because of toxicity: one because of convulsion; one for hyperreflexia and tremors; and one due to emotional changes. Other toxic symptoms were mild, temporary, and negligible.

5. It is suggested that the optimal duration of treatment with CS-INH in resistant pulmonary tuberculosis should be six months.

6. There was no significant difference between the two different doses of CS, 750 mgs. and 500 mgs. daily, in therapeutic efficacy and drug toxicity.

RESUMEN

1. Se trataron con Cicloserina e isoniaicina cuarenta y seis enfermos negros con tuberculosis pulmonar en los que el tratamiento a largo plazo con estreptomicina, PAS e isoniaicina habia fracasado.

2. A los seis meses del tratamiento se obtuvo la conversión bacteriológica en 54 por ciento, veintisiete por ciento a los doce meses con 26 por ciento de recaídas. No hubo recaídas después de los doce meses de tratamiento.

3. Mejoría radiológica moderada fue obtenida en 13 por ciento, recaída o empeoramiento en 10 por ciento. Cierre de cavidades en 3 por ciento.

4. Se suspendió el tratamiento en tres casos o sea el 6 por ciento, por toxicidad: una por convulsiones, una por hiper-reflexia y temblores y una debido a cambios emocionales. Otros síntomas tóxicos son moderados, temporales y deseadables.

5. Se sugiere que la duración óptima del tratamiento con Cicloserina e isoniaicina en tuberculosis pulmonar con gérmenes resistentes sea de seis meses.

6. No hay diferencia de significación entre las dos dosis diferentes de 750 y 500 mg. por día en cuanto a eficacia y toxicidad.

RESUMÉ

1. 46 malades de race noire, atteints de tuberculose, qui avaient tous reçu une chimiothérapie longtemps prolongée, avaient été considérés comme des échecs thérapeutiques avec les associations streptomycine, P.A.S. et isoniazide, furent traités par l'isoniazide-cyclosérine.

2. La disparition des bacilles survint dans 54% des cas après six mois de traitement, 27% après douze mois avec 26% de rechutes. Aucune rechute ne fut enregistrée au-delà d'un traitement de douze mois.

3. Une amélioration de modérée à nette survint dans 13% des cas, une rechute ou une aggravation dans 10%. La fermeture de la cavité survint dans 3%.

4. Le traitement fut interrompu dans 3 cas, soit 6% ; à cause de sa toxicité : dans un cas à la suite de convulsions, dans un autre à la suite d'hyperréflectivité et de tremblements, et dans un autre à la suite de manifestations psychiques. Les autres symptômes toxiques furent légers, temporaires et négligeables.

5. L'auteur suggère que la durée optimum du traitement par l'isoniazide-cyclosérine dans la tuberculose pulmonaire résistant aux autres médications devrait être de six mois.

6. Il n'y eut pas de différence nette selon les deux dosages différents utilisés de CS (750 mgs. et 500 mgs. par jour) ni dans l'efficacité thérapeutique, ni dans la toxicité.

ZUSAMMENFASSUNG

1. Es wurden 46 Neger mit aktiver Lungentuberkulose mit Cyklloserin-INH behandelt, nachdem sie eine langzeitige Chemotherapie gehabt und auf die Kombination von Streptomycin, PAS und INH nicht angesprochen hatten.
2. Bakteriologische Konversionen trafen bei 54% nach 6 Behandlungsmonaten, bei 27% nach 12 Monaten mit 26% Rückfällen auf. Es kam zu keinem Rückfall nach 12 Behandlungsmonaten.

3. Eine mässige bis ausgesprochene Besserung des Röntgenbefundes trat bei 13% auf, ein Rückfall oder eine Verschlechterung bei 10%. Cavernenverschluss trat bei 3% auf.


5. Es wird angenommen, dass die optimale Behandlungsdauer mit Cycloserin in Verbindung mit INH bei Fällen mit resistenter Lungentuberkulose 6 Monate zu betragen hätte.


**BIBLIOGRAPHY**


