Report on the Use of Cycloserine and Isoniazid in Twenty-seven Cases of Pulmonary Tuberculosis in Psychotic Patients

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The majority of physicians engaged in pulmonary diseases recognizes the practical need for additional drug regimens, especially in the tuberculous psychotic patient. The usual drug combinations in recent years have been, viz: isoniazid-PAS, isoniazid-streptomycin, or streptomycin-PAS.

There is a frequent appearance of drug resistance to streptomycin, as well as occasional toxic side effects. The frequent and rather severe gastro-intestinal upsets are produced by PAS. Last is the fact that isoniazid alone is not satisfactorily effective in adult pulmonary tuberculosis, unless an efficient ancillary drug is added to it.

In this condition a regimen of isoniazid and cycloserine has been found to be useful and the results of treatment in 27 cases at the State Mental Hospital, Logansport, Indiana, have been sufficiently encouraging to warrant analysis and publication.

Practically all of the patients were chronic cases, having an average duration of anti-tuberculosis treatment of 5.5 years and all in the group had received prior anti-tuberculosis chemotherapy for one year or longer. Six patients in the group had received therapeutic pneumoperitoneum; two had had temporary phrenic crush; three had thoracoplasty; and one had resectional surgery (lobectomy) after treatment with the drug regimen. In addition, all had been under intensive antituberculosis chemotherapy for prolonged periods of time with the three standard regimens of streptomycin-PAS, isoniazid-streptomycin, or isoniazid-PAS. These had been interchanged according to intolerance or toxic side effects.

The average dose in the majority of cases has been two capsules a day (each with a combination of 250 mgm. cycloserine and 150 mgm. of isoniazid, making a total daily dosage of 500 mgm. cycloserine and 300 mgm. of isoniazid). Medication had to be discontinued in only two patients; one because of grand mal convulsions with abnormal electroencephalogram findings, and the other because of marked depression with suicidal tendencies.

At the time, when the report was compiled, this combination of drugs had been in constant use by three patients for a period of 15 to 26 months; by 20 for a period of five to 15 months; and by another four for a period of less than five months.

In one, streptomycin was added to the treatment schedule, due to post-operative spread with hemorrhage following right thoracoplasty. In three cases, PAS, 6 grams daily, was added (one due to extensive bilateral toxic disease, two because of bilateral increase while on the treatment schedule).
Six patients with far-advanced disease died while under treatment (two from acute hypostatic pneumonia, one from acute cardiac failure while on the operating table, two from debility with extensive far advanced disease with tuberculous laryngitis, and one with coronary infarction). In other words, none of the deaths was attributable to the treatment schedule.

Two patients in the series improved sufficiently to have surgery (one thoracoplasty and one lobectomy) while on the treatment schedule. These had been unable to do so on the three standard regimens of chemotherapy.

Carefully evaluating the clinical progress in the series, improvement was definitely noted in 19 of the 27 patients (70 per cent). In two the disease remained static, the clinical symptoms changing insignificantly under this treatment. Only six of the 27 (22.5 per cent) have shown a distinct decline with increase in the disease.

Tubercle bacilli disappeared from the sputum or gastric culture in five cases. This is considered a good result, since the series consisted chiefly of patients with long-standing chronic disease who had received the usual three standard regimens before being put on cycloserine-isoniazid.

Evaluating progress by roentgenography, it was found that in 15 of the 27 cases there had been definite improvement, although it was only slight or initial in three of the 15 cases. In another nine cases of the series, there was no significant roentgenographic change, the picture revealing neither spread nor improvement. In only three cases of the series was the disease marked as being worse and one of them died from far-advanced disease with associated laryngitis three months after being started on the regimen.

In further evaluating the clinical findings, it was found that the general well-being was distinctly improved in 11 of the 27 cases; the appetite improved in 10 cases; the weight increased in 11 cases, but five of the patients lost weight despite the treatment. Most of them were afebrile. Reduction of cough was noted in 12 cases; reduction in expectoration was noted in an equal number of cases. Two extra-pulmonary tuberculous complications were included in this series, one of tuberculous laryngitis and one with tuberculous empyema following spontaneous pneumothorax.

In checking for unpleasant side effects, it was found that two complained of drowsiness. Grand mal convulsions were noted in one and marked depression with suicidal tendencies in one.

Prior to initiating cycloserine-isoniazid therapy, the following laboratory studies were done, viz.: hemograms, urinalysis, 15-minute PSP, BUN, cephalin flocculation, electrocardiogram, electroencephalogram, sputum or gastric culture, x-ray films of the chest. X-ray films of the chest, hemograms and urinalysis were done every two months. The ECG, EEG, BUN, PSP and cephalin flocculation were repeated at the end of treatment. There was no significant change in the hemograms; nitrogen retention did not interfere with the treatment in any case. One
case showed an abnormal EEG during the course of treatment, which along with the association of grand mal type of convulsions caused the treatment to be terminated.

Pre-existing complicating diseases did not seem to interfere with the treatment, except in one who developed marked depression with suicidal tendencies which necessitated discontinuing the treatment. Among the complications noted were asthma, moderate arthritis, cardiac conditions and peripheral vascular disease.

SUMMARY

Twenty-seven psychotic patients with pulmonary tuberculosis have been treated with cycloserine-isoniazid for periods as long as 26 months. The majority of them had tense mental disease of several years' duration and had previously received one of the standard drug regimens. Some of them had been treated by compression or resectional surgery. Significant improvement was noted in a gratifying percentage of the patients. Reversal of infectiousness occurred in a satisfactory number; roentgenographic improvement was observed in a fair percentage; many showed improvement in well-being and appetite; there was a fairly satisfactory reduction in cough and expectoration. Complicating side effects have been fairly slight, particularly in view of the fact that all of the patients were psychotic. From this clinical experience, it is concluded that a regimen of 500 mgm. of cycloserine and 300 mgm. of isoniazid daily, in two equally divided doses, is a valuable regimen for psychotic patients who still have active disease despite treatment with one of the standard regimens.

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RESUMEN

Veintisiete enfermos de tuberculosis pulmonar y además psicóticos, se trataron con cicloserina e isoniazida por tiempos hasta de 26 meses.
La mayoría de ellos tenían la enfermedad avanzada, de varios años de curación y habían recibido antes los regímenes de drogas habituales.
Algunos de ellos habían sido tratados por compresión o resección. Se notó una mejoría de significación en un número satisfactorio de enfermos. La desaparición de la infecciosidad se observó en un número de enfermos satisfactorio; la mejora radiológica se hizo en muchos; hubo alguna reducción de la tos y de la expectoración. Los efectos colaterales complicantes han sido sensiblemente ligeros particularmente en vista de todos los enfermos eran psicóticos. Según esta experiencia clínica se concluye que el régimen de 27 caso de infección de isoniazida por día en dos dosis iguales dividida es valioso en los enfermos psicóticos que aún tienen enfermedad activa a pesar del tratamiento con las otras drogas comunmente usadas.

RESUMÉ

L'auteur rapporte 27 cas de tuberculose pulmonaire chez des malades atteints de troubles psychiques, traités par la cycloserine et l'isoniazide pendant des périodes s'étendant jusqu'à 26 mois. La majorité d'entre eux avaient des lésions avancées datant de plusieurs années, et avaient été antérieurement traités par les trois médications standard. Certains d'entre eux ont été traités par collapsothérapie ou par résection chirurgicale. Une amélioration importante fut notée dans une proportion satisfaisante. La suppression de l'infection apparaît dans un nombre de cas satisfaisant; une amélioration radiologique fut observée dans une bonne proportion; plusieurs montrèrent une amélioration du comportement et de l'appétit; il y eut une réduction vraiment satisfaissante de la toux et de l'expectoration. Les effets secondaires toxiques ont été bien légers, particulièrement si l'on considère qu'il s'agissait de malades atteints de troubles psychiques. De cette expérience clinique, l'auteur conclut qu'un programme thérapeutique de 500 mgm. de cycloserine par jour et 300 mgm. d'isoniazide, en deux doses égales, est une thérapeutique valable pour les malades mentaux dont l'affection est encore active malgré le traitement avec les médications habituelles.

ZUSAMMENFASSUNG


REFERENCES

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**ELECTRON MICROSCOPY: THE INVASIVE PROPERTIES OF MALIGNANT NEOPLASMS, INCLUDING THE LUNG**

Study of the early stages of malignant neoplastic growths with electron microscopy provides data that elucidate the mechanism of invasion. There are found deficiences of intercellular connecting processes and evidence of decreased cell cohesiveness among the malignant cells. Loss of basement membrane is also demonstrable at sites of early invasion of malignant epithelial tumors. The process of early invasion is depicted as primary loss of basement membrane, decreased cell cohesiveness, and protrusion first of cytoplasm, then of an entire tumor cell into adjacent connective tissue spaces.

It is suggested that the property of invasiveness, based partially upon the described structural characteristics, comprises a major distinguishing characteristic of malignant neoplasia.