(après culture) est moins fréquente dans
début la présence de B.K. résistants à la
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e treatment.

PYRAZINAMIDE USED WITH ISONIAZID IN THE TREATMENT OF PULMONARY TUBERCULOSIS

William B. TUCKER, M. D.[1] and James H. MATTHEWS, M. D.[2]

The co-operative studies in the treatment of pulmonary tuberculosis which have been conducted by the United States Veterans Administration and Armed Forces have made possible the evaluation of the effect of various drugs in the treatment of large numbers of tuberculosis patients under well controlled and relatively standardized conditions. The participating hospitals have voluntarily accepted uniform standards regarding diagnosis, selection of cases, treatment regimens, clinical and laboratory observations for toxic manifestations, and criteria for appraisal of therapeutic effectiveness of the drugs being studied. These standards have been established by conferences composed of representatives from the hospitals, and other consultants who are experts in the treatment and control of tuberculosis. The results of the studies have been subjected to critical statistical evaluation in the Veterans Administration Central Office and have been reported to the conferences by various participating investigators usually at yearly intervals.

In all of these studies consideration has been given to the tendency which many patients exhibit to recover from tuberculosis without treatment, with the assistance of non-specific measures such as rest and diet, or with the use of collapse therapy and surgical treatment. The studies have been conducted largely by inter-regimen comparisons of test drug combinations with drug combinations of known therapeutic effect and toxicity. Insofar as is possible, all other aspects of treatment have been kept equal in the groups which differ only with respect to the drugs being tested.

Early studies clearly demonstrated that streptomycin, para-amino-salicylic acid and isoniazid exerted a significant suppressive effect on tuberculous infection. When only one of these drugs was used alone, the beneficial effect often was frequently lost after two or more months of treatment

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particularly in patients with more advanced and cavitary disease. The loss of therapeutic effectiveness was almost always associated with emergence of bacilli which were no longer susceptible to the drug being used. The concurrent use of two or more drugs greatly improved their therapeutic effectiveness and markedly reduced the incidence of emergence of drug-resistant bacilli. The prolonged concomitant administration of isoniazid and para-aminosalicylic acid became generally accepted as a very effective drug treatment regimen and this regimen has been used most often as the standard against which other drug regimens have been compared.

Additional drugs have been investigated in these studies because no combination of drugs has yet been found to be free of toxic manifestations or to be fully effective in treating tuberculous infection in all patients.

Pyrazinamide was first reported as an effective agent in the clinical treatment of pulmonary tuberculosis in 1952 by YEAGER and associates [1] and by SCHWARTZ and MOYER [2]. These studies demonstrated that pyrazinamide had a moderate tuberculostatic effect which was limited by the development of clinical resistance as susceptibility of the tubercle bacilli to the drug was lost after 6 to 8 weeks of treatment. Evidence of toxicity, chiefly the occurrence of jaundice, was observed, but this toxicity was not considered of sufficient magnitude to prevent further clinical use.

Concurrent administration of pyrazinamide with streptomycin, with para-aminosalicylic acid, and with isoniazid were studied, and in 1953 SCHWARTZ and MOYER [3] reported that pyrazinamide appeared to diminish the incidence of emergence of bacilli resistant to isoniazid. The investigation of pyrazinamide and isoniazid together was undertaken. The report of this study the following year by MOYER and SCHWARTZ [4] demonstrated the effectiveness of this treatment, particularly with regard to sputum conversion, even in the presence of persistence of radiographic evidence of cavitation. The low incidence of isolation of isoniazid resistant bacilli was confirmed. Toxicity was not considered to be a serious hazard.

Comparative studies were designed and pursued for 2 years in a number of the co-operating hospitals in which patients were treated by random assignment with one of four combinations of drugs. These were isoniazid and pyrazinamide, isoniazid and para-aminosalicylic acid, isoniazid and streptomycin, and streptomycin and para-aminosalicylic acid. Daily dosage of isoniazid was 300 mg., of pyrazinamide was 3 grams, and of para-aminosalicylic acid was 12 grams. Streptomycin was given 1 gram twice a week. The report of these studies made by Mrs. LIVINGS [5] in 1956 indicated that the combination of isoniazid and pyrazinamide appeared to be slightly but not significantly superior to isoniazid and para-aminosalicylic acid, and significantly superior to the drug combinations where streptomycin was used twice a week.

Beginning in 1956, the study was confined to a comparison of the treatment regimen of isoniazid and pyrazinamide with the regimen of isoniazid and para-aminosalicylic acid. The dosage was as previously listed. Only

patients who had proven active cavi
positive sputum, and who had received
were eligible for the study. Each pa
regimens on a random basis without re
The randomization was not under cont
patient, having been determined by a pe
patients being treated.

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patients who had proven active cavitary pulmonary tuberculosis with positive sputum, and who had received no previous anti-tuberculosis drugs, were eligible for the study. Each patient was assigned to one of the regimens on a random basis without regard to any aspect of his disease. The randomization was not under control of the physicians treating the patient, having been determined by a person who had no knowledge of the patients being treated.

An analysis of the results of this study revealed that there were 237 patients treated with isoniazid and para-aminosalicylic acid and 219 patients treated with isoniazid and pyrazinamide upon whom reports were available during at least 4 months of treatment.

The patients in the two groups were checked to determine if the groups were comparable. All patients were male with one exception. 73 % of each group were white Caucasian, the others being American Negroes except one in each group who was of some other race. Approximately an equal proportion of patients in each group had bilateral disease. This disease had been progressive in 93 % of each group prior to treatment. Only 4 patients in one group and 2 in the other had surgical or collapse therapy in effect at the time treatment was initiated. The patients treated with isoniazid and para-aminosalicylic acid tended to be slightly older and to have slightly more extensive disease than did those in the isoniazid and pyrazinamide groups, but the latter group had a few more patients with multiple cavities, particularly among those whose largest cavity exceeded 4 cm. in diameter. A careful study of these background factors revealed that none of the differences in the groups were significant and the two groups were accepted as comparable.

Comparison of the effectiveness of the two treatment programs was made by recording the incidence of overall improvement by x-ray, of any unfavourable x-ray change occurring during treatment, of cavity closure, and of sputum conversion. This information was tabulated at 4-month intervals during the first year of treatment in patients remaining in the study at each interval. No consistent superiority of either regimen was shown on the basis of change by X-ray, either favourable or unfavourable. Cavity closure was observed to occur somewhat earlier in the group treated with isoniazid and para-aminosalicylic acid. Sputum conversion apparently occurred slightly more rapidly with isoniazid and para-aminosalicylic acid although at the end of one year slightly more of the patients treated with isoniazid and pyrazinamide were negative. None of these differences were statistically significant. (Table 1).

Both para-aminosalicylic acid and pyrazinamide were shown to be effective in preventing the emergence of isoniazid resistant tubercle bacilli.

Significant toxicity which was attributable to the isoniazid occurred in 5 patients. This was a hypersensitivity reaction in 3 patients, peripheral neuritis in one and nausea, vomiting and a paranoid reaction in one patient which was believed to have been due to isoniazid. No significant difference

TABLE I

Comparison of high-dosage pyrazinamide with para-aminosalicylic acid as companion drug to isoniazid*

In Original Treatment Pulmonary Tuberculosis

	Isoniazid and P.A.S.		Isoniazid and Pyrazinamide	
	4 mos.	8 mos.	4 mos.	8 mos.
No. of Cases	237	159	219	115
	Percent			
Marked or Moderate X-ray Improvement	15	80	67	83
Closure of cavities	19	44	13	37
Conversion of sputum (by culture)	45	73	41	78
Isoniazid resistance (1 mcg.)	1	2	4	4
Toxicity sufficient to cause discontinuation of drug	4	5	8	13

* Daily dosages of drugs : isoniazid, 300 mg.; P.A.S., 12 gms.; pyrazinamide, 3.0 gms.

in the incidence of isoniazid toxicity occurred in the two groups. Toxicity attributed to para-aminosalicylic acid of sufficient severity to force discontinuation of treatment occurred in 19 patients or 7 % of 267 originally starting treatment. This developed chiefly during the first 4 months of treatment and consisted of gastrointestinal intolerance (abdominal discomfort, anorexia, nausea, vomiting and diarrhea) in 13 cases and hypersensitivity reactions (chills, fever, dermatitis and/or eosinophilia) in the other 6.

Pyrazinamide was discontinued because of toxic reactions which were believed to be due to this drug in 33 cases or 13 % of the 261 cases originally starting treatment. Twenty-one of these developed evidence of hepato-cellular dysfunction manifested by liver function test abnormalities. This was shown by increase of bromsulphalein retention, cephalin flocculation, alkaline phosphatase or serum glutamic oxalacetic transaminase, or rising serum bilirubin levels. An additional 6 were clinically jaundiced also, and the remaining 6 had gastrointestinal symptoms which were believed to be prodromal symptoms of hepatic disease.

The liver toxicity which developed in the pyrazinamide and isoniazid group was reversible when the drugs were stopped promptly as soon as symptoms occurred or when abnormal liver function tests were noted. Nevertheless, this is considered a serious toxic manifestation and it is

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Comparison of low-dosage pyr acid as companio

In Original Treatmer

I. A

No. of Cases
Marked or Moderate X-ray improvement
Closure of cavities
Conversion of sputum (by culture)
Relapse bacteriologically
Isoniazid resistance (1 mcg.)
Toxicity sufficient to cause discontinuation of drug

II. Cases with cavities

No. of Cases
Marked or Moderate X-ray improvement
Closure of cavities
Conversion of sputum (by culture)
Isoniazid resistance (1 mcg.)

* Daily dosages of drugs: isoniazid, 300

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TABLE II

Comparison of low-dosage pyrazinamide with para-aminosalicylic acid as companion drug to isoniazid*

In Original Treatment Pulmonary Tuberculosis

I. All Cases

No. of Cases	Isoniazid and P.A.S.		Isoniazid and Pyrazinamide	
	4 mos. 134	8 mos. 87	4 mos. 135	8 mos. 87
	Percent			
Marked or Moderate X-ray improvement	62	84	64	70
Closure of cavities	18	44	21	43
Conversion of sputum (by culture)	40	70	44	68
Relapse bacteriologically	—	2	—	1
Isoniazid resistance (1 mcg.)	4	3	7	9
Toxicity sufficient to cause discontinuation of drug	5	11	5	14

II. Cases with cavities more than 4 cm. in diameter

No. of Cases	36	23	35	20
	Percent			
Marked or Moderate X-ray improvement	69	91	65	69
Closure of cavities	4	21	0	15
Conversion of sputum (by culture)	31	61	23	40
Isoniazid resistance (1 mcg.)	5	16	6	25

* Daily dosages of drugs: isoniazid, 300 mg.; P.A.S., 12 gms.; pyrazinamide, 1.5 gms.

known to us from other sources that if pyrazinamide is continued in the face of evidence of liver damage, an irreversible acute yellow atrophy of the liver will result in death. For this reason, it has been recommended that pyrazinamide not be given with isoniazid except to patients who are hospitalized under daily observation of physicians who clearly understand the hazards of the treatment. All these patients are required to have a brom-

sulphalein retention of not more than 7 % when tested 45 minutes after the administration intravenously of 5 mg. of the dye per kilogram body weight prior to treatment and liver function tests are repeated at frequent intervals throughout the course of treatment. The liver toxicity is not confined to any time interval but may occur at any time during the use of these drugs even though they may have been well tolerated previously by the patient.

An additional study has been undertaken in which the daily dosage of pyrazinamide is reduced to determine if this will reduce the risk of liver toxicity without impairing the therapeutic efficacy of the drug. In this study isoniazid in 300 mg. daily dosage was given concurrently with pyrazinamide in 1.5 gm. daily dosage in one regimen compared with the standard isoniazid and para-aminosalicylic acid regimen. All other aspects of this study were the same as listed in the previous study. This study has not been completed but a preliminary analysis has been made of 135 patients treated with the isoniazid and reduced dosage pyrazinamide and 134 patients treated with isoniazid and para-aminosalicylic acid.

The background factors of these patients were evaluated and the groups were considered comparable. The therapeutic efficacy of the reduced dosage pyrazinamide with isoniazid, when considered on the same basis as in the previous study, appeared to be equal to that of isoniazid and para-aminosalicylic acid in all except the far advanced cases with large cavities, where the pyrazinamide treated group did not appear to do quite as well (Table 2). This group of severely ill patients is small and no reliable conclusions have yet been reached from this most recent study.

The early results do suggest that the reduction of the daily dosage of pyrazinamide may have resulted in a reduction of the incidence of hepatotoxicity. When it does occur it is just as severe and as serious as the liver toxicity occurring during the administration of 3 grams daily of pyrazinamide.

RESUME

Pyrazinamide Used with Isoniazid in the Treatment of Pulmonary Tuberculosis. — A controlled co-operative study of pyrazinamide and isoniazid treatment of pulmonary tuberculosis conducted by hospitals of the United States Veterans Administration and Armed Forces has been reported. Patients treated with this combination of drugs were compared with a group of similar patients treated with isoniazid and para-aminosalicylic acid. Daily dosages of these drugs were isoniazid 300 mg., pyrazinamide 3 gm. and para-aminosalicylic acid 12 gm. The therapeutic efficacy of the two drug combinations was found to be similar. The para-aminosalicylic acid has the disadvantage of producing severe gastrointestinal symptoms as well as hypersensitivity reactions in some patients. The pyrazinamide has the disadvantage of producing liver damage which may be serious unless treatment is given under close medical supervision. The study is now in progress to attempt to determine if reducing the daily dosage of pyrazinamide to 1.5 gm. daily with isoniazid will reduce the risk of efficacy.

Utilisation de la Pyrazinamide avec tuberculose pulmonaire. — Un trava de la tuberculose pulmonaire par la dans les hôpitaux de l'Administration États-Unis.

Les malades traités avec cette combir avec un groupe de malades semblables amino-salicylique. Les doses quotidienr 3 g pour la pyrazinamide et 12 g pou L'efficacité thérapeutique des deux a similaire.

L'acide para-amino-salicylique a com festations gastro-intestinales sévères air chez quelques malades.

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Utilisation de la Pyrazinamide avec l'Isoniazide dans le traitement de la tuberculose pulmonaire. — Un travail d'équipe contrôlé sur le traitement de la tuberculose pulmonaire par la pyrazinamide et l'isoniazide a été fait dans les hôpitaux de l'Administration des Vétérans et des Forces Armées des États-Unis.

Les malades traités avec cette combinaison médicamenteuse furent comparés avec un groupe de malades semblables traités par l'isoniazide et l'acide para-amino-salicylique. Les doses quotidiennes furent de 300 mg pour l'isoniazide, 3 g pour la pyrazinamide et 12 g pour l'acide para-amino-salicylique.

L'efficacité thérapeutique des deux associations médicamenteuses fut trouvé similaire.

L'acide para-amino-salicylique a comme inconvénient de produire des manifestations gastro-intestinales sévères ainsi que des réactions d'hypersensibilité chez quelques malades.

La pyrazinamide a, comme désavantage, de produire des altérations hépatiques qui peuvent être sérieuses, si le traitement n'est pas fait sous contrôle médical étroit.

L'étude maintenant en cours cherche à déterminer si la réduction de la dose quotidienne de pyrazinamide à 1,5 g avec association à l'isoniazide, peut réduire le risque de toxicité sans affaiblir l'efficacité thérapeutique.

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