ETHAMBUTOL/INH. IN THE INITIAL TREATMENT OF PULMONARY TUBERCULOSIS†

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INTRODUCTION

Encouraging reports of the use of ethambutol in the initial treatment of pulmonary tuberculosis have been made. Donomae and Yamamoto[3] studied 138 previously untreated sputum positive cases by randomly allocating them into 3 groups (Group I, ethambutol 25 mg./Kg.; Group II, ethambutol 12·5 mg./Kg.; Group III, Calcium PAS. 10 gm.). All groups received INH. 300 mg. daily. Of those who completed 6 months' treatment, the sputum conversion rates were 98%, 79% and 89% respectively. Bobrowitz[1] studied 169 patients randomly allocated into 3 treatment groups (Group I, ethambutol 25 mg./Kg. for 60 days followed by 15 mg./Kg.; Group II, ethambutol 15 mg./Kg. throughout; Group III, Sodium PAS. 12 gm. daily). All groups received INH. 300 gm. daily. After 4 months, sputum conversion was 92%, 91% and 100% respectively though many patients dropped out for various reasons. Pyle[5] treated 23 patients with ethambutol 20-30 mg./Kg. and INH. 300 mg. in one dose. All became culture negative at 6 months. Bobrowitz and Robins[2] in a follow up study with an addition of 79 cases, making a total of 248 cases, demonstrated 95%, 88% and 80% sputum conversion in Group I, II and III respectively after 4 months' treatment. With these results in view we embarked on this co-operative study, of a local population, by the 4 Chest Units at Tan Tock Seng Hospital.

Objects of Investigation

1. To assess the efficacy of the Ethambutol/INH. regime on newly discovered sputum positive pulmonary tuberculosis cases by comparing with the established PAS./INH. regime.
2. To assess the incidence of side effects and toxicity to ethambutol.

MATERIAL AND METHODS

Patients, both males and females, eligible for the trial were between the ages of 15 and 60 and above 70 lbs. in weight, must be bacteriologically positive, were able to stay in hospital for the first 3 months and were prepared to continue treatment for at least 1 year and who had no previous history of anti-tuberculous chemotherapy. Those with eye conditions which prevent proper assessment of visual disturbances were not eligible.

103 cases were admitted into the trial since July 1967, and of these 46 have completed twelve months' treatment and constitute the study in this preliminary report (Tables I and II). The intake was stopped in December 1968 and the cut-off date for this report was 8.4.68.

TABLE I

AGE/SEX, DISTRIBUTION AND EXTENT OF DISEASE

	Regime	EMB./INH.	PAS./INH.	Total
	No.	51	52	103
Sex	Male	34	40	74
	Female	17	12	29
Age	15-40	22	20	42
	40-60	29	32	61
Extent of disease	Moderate	26	27	53
	Far adv.	25	25	50
		51	52	103

TABLE II

COMPLETED 12 MONTHS

Extent of Disease	No.	EMB./INH.	PAS./INH.
Moderate	25	12	13
Far Adv.	21	11	10

Allocation was randomised by an independent medical statistician and the cases were stratified

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into minimal, moderately advanced and far advanced disease by one reader throughout the trial, by the N.T.A. Classification. Of the 103 cases admitted into the trial, 53 were moderate cases and 50 were far advanced (Table I). There were 74 males and 29 females and the age distribution were about equal in both regimes. There were no minimal cases suitable for the trial.

Of the 46 cases who have completed 12 months' treatment, 25 were moderately advanced and 21 were far advanced (Table II).

The patients were allocated at random into one of two regimes, Ethambutol/INH. or PAS./INH. The daily doses were:

(*a*) Ethambutol 25 mg./Kg. for the first 8 weeks followed by 15 mg./Kg. thereafter.

(*b*) INH. 300 mg.

(*c*) Sodium PAS. 10 gm.

The drugs were given in a single dose. The allocated regime was given for 3 months as in-patient and thereafter as out-patient to complete a minimum of 18 months' treatment.

Pre-treatment investigations included a P.A. chest X-ray, two supervised spot specimens of sputum on two different days for microscopy and culture for M. tuberculosis, sensitivity tests on positive cultures to Ethambutol, INH. and PAS., and an eye examination. Follow up investigations consisted of chest X-rays at monthly intervals for the first 6 months and thereafter at the 12th and 18th months, a supervised spot specimen of sputum monthly for microscopy and culture and a repeat eye examination at the 12th month.

During the 3 months of hospitalisation, a weekly record of side effects and toxicity was made. At the out-patient follow-up, the records were made monthly. Symptoms were volunteered or obtained by indirect questioning. The 12th and 18th month X-rays were read by an independant assessor. X-rays of months 1 to 6 were read by another reader for the purpose of detecting any deterioration.

A change of chemotherapy was allowed only when there was intractable drug toxicity, when there was bacteriological deterioration which was defined as persistent positive cultures after the first 6 months of treatment and when clear radiological deterioration occurred, which persisted or spread in the presence of positive sputum and which did not resolve after a course of non-tuberculous chemotherapy. The change of chemotherapy was carried out after consultation with the independent clinical assessor.

RESULTS

At the end of 12 months' treatment the efficacy of the two regimes was analysed bacteriologically and radiologically.

Bacteriology

At 12 months, 2 patients on EMB./INH. gave a positive culture while 1 on PAS./INH. was positive in the moderately advanced group (Table III).

TABLE III

SPUTUM STATUS AT 12 MONTHS—MOD. ADVANCED

Regime	No.	Cult. Neg.	Cult. Pos.
EMB./INH.	12	10	2
PAS./INH.	13	12	1

In the far advanced group, there was no positive culture in the EMB./INH. regime but 2 patients on the PAS./INH. regime gave a positive culture (Table IV).

TABLE IV

SPUTUM STATUS AT 12 MONTHS—FAR ADV.

Regime	No.	Cult. Neg.	Cult. Pos.
EMB./INH.	11	11	0
PAS./INH.	10	8	2

Thus there were 2 positive cases in the EMB./INH. regime and 3 positive cases in the PAS./INH. regime for both moderate and far advanced cases. Of the 46 cases analysed 23 were in the EMB./INH. group and 23 were in the PAS./INH. group for the combined moderate and far advanced cases. The sputum conversion rates were 91% and 87% respectively (Table V).

TABLE V

SPUTUM CONVERSION RATES AT 12 MONTHS

Regime	No.	Neg.	Pos.	Con. Rate
EMB./INH.	23	21	2	91%
PAS./INH.	23	20	3	87%

Radiology

Radiological change was classified as slight, moderate, marked improvement (cavity closure and/or decrease in extent of disease of more than 3 zones), no change or deteriorated and the results are shown in Tables VI and VII. All cases showed improvement of various degrees at the end of 12 months. In the moderately advanced group the improvement shown was almost identical, with 92% showing moderate to marked improvement in both series (Table VI). In the far advanced group, 100% in the EMB./INH. regime and 70% in the PAS./INH. regime showed moderate to marked improvement (Table VII).

TABLE VI

RADIOLOGICAL STATUS AT 12 MONTHS—MOD. ADV.

Regime	No.	Slight Improvement	Moderate Improvement	Marked Improvement
EMB./INH.	12	1 (8%)	6 (50%)	5 (42%)
PAS./INH.	13	1 (8%)	6 (46%)	6 (46%)

TABLE VII

RADIOLOGICAL STATUS AT 12 MONTHS—FAR ADV.

Regime	No.	Slight Improvement	Moderate Improvement	Marked Improvement
EMB./INH.	11	0	3 (27%)	8 (73%)
PAS./INH.	10	3 (30%)	1 (10%)	6 (60%)

Of the 12 moderate cases in the EMB./INH. group, 7 had cavities initially and 6 attained closure. The remaining one showed contraction of the cavity. In the far advanced group in the EMB./INH. series, 8 cases out of 11 had cavities and 7 attained complete closure and the 8th case attained partial closure. Thus 13 out of 15 cases or 88% attained complete cavity closure and 2 or 12% attained partial closure (Table VIII).

In the PAS./INH. series, 7 of the 13 moderate cases had cavities and 5 attained complete closure, 1 attained partial closure and 1 persisted. In the far advanced cases, there were 8 with cavities initially out of the 10 cases and 5 attained complete closure and 3 attained partial closure. Thus in all, 10 out of 15 cases or 67% had complete closure of cavity, 4 or 26% attained partial closure and 1 or 7% had non-closure in the PAS./INH. series (Table VIII).

TABLE VIII

CAVITY STATUS AT 12 MONTHS

Regime	Total No. Pts.	No. with Cavity	Complete Closure	Partial Closure	Non-Closure
EMB./INH.	23	15	13 (88%)	2 (12%)	0
PAS./INH.	23	15	10 (67%)	4 (26%)	1 (7%)

Side Effects

In the EMB./INH. series, 4 patients had side effects as shown in Tabe IX. One experienced loss of appetite, one had fever associated with a rise in S.G.P.T., one had erythema and the last developed maculopapular rash due to INH.

In the PAS./INH. series, 8 patients had side effects. Four had gastrointestinal upsets (loss of appetite, nausea and vomiting), 2 had skin reaction (pruritus, urticaria and acne) and one had fever due to PAS. One patient with gastrointestinal side effects also complained of tinnitus. Thus 17% in the EMB./INH. and 35% in the PAS./INH. regime showed side effects (Table IX).

TABLE IX

SIDE EFFECTS

Side Effect	EMB./INH.	PAS./INH.
Fever	1	1
Skin	2	3
Gastrointestinal	1	4*
Neurological	0	1*
TOTAL	4 (17%)	8 (35%)

*Same patient.

Visual Toxicity

Three patients in the EMB./INH. regime had eye changes as shown in Table X. Two had slight deterioration of visual acuity and the other showed slight contraction of the temporal fields though his visual acuity remained the same in the right eye and improved on the left from 6/18 to 6/9. In the PAS./INH. regime, there were 4 cases with slight deterioration of visual acuity. All the patients had no complaints and all were above 50 years except one female who was aged 19 and on the EMB./INH. regime. The drugs were continued in all the 7 cases and there was no further deterioration.

TABLE X

VISUAL TOXICITY

	EMB./INH.	PAS./INH.
Impairment of visual acuity	2 (9%)	4 (18%)
Colour vision	0	0
Fundi	0	0
Fields	1 (4%)	0
TOTAL	3 (13%)	4 (18%)

Defaulters

Two patients in the PAS./INH. regime defaulted (i.e. absent for more than 4 weeks), one after 4 months and the other after 5 months of treatment and both have been excluded from the analysis. None defaulted in the EMB./INH. regime.

Interruption of Treatment

Drugs were interrupted for two weeks in a patient in the EMB./INH. regime at the third month because of severe ulcers of the legs. These turned out to be tuberculous erythema induratum and the drugs were continued. One patient in the PAS./INH. series was late for drugs for more than a week, but less than two, on two occasions.

Cost of Drugs

From Table XI, it could be seen that the average initial cost of the EMB./INH. regime was about 15 times that of the PAS./INH. regime. After 8 weeks, the average cost of the former was still about 10 times that of the latter. But since this report was written the cost of ethambutol has fallen to about a third of its original price.

TABLE XI

RELATIVE COST OF DRUGS

300 mg. INH.	S$0·004
10 gm. PAS./300 mg. INH.	0·07
800 mg. EMB./300 mg. INH.	0.77
1,000 mg. EMB./300 mg. INH.	0·95
1,200 mg. EMB./300 mg. INH.	1·14

DISCUSSION

From the results of this study, ethambutol (25 mg./Kg. for the first 8 weeks, thereafter 15 mg./Kg.) in combination with 300 mg. INH. daily in one dose was as effective as 10 gm. PAS. with 300 mg. INH. daily in the initial treatment of moderately and far advanced pulmonary tuberculosis. These results agree with those of Bobrowitz[1] and Donomae and Yamamoto.[3]

Radiologically, in the far advanced patient, moderate to marked improvement was obtained in 100% in the EMB./INH. series and 70% in the PAS./INH. series. In the moderately advanced cases, the improvement was the same in the two series. In the EMB./INH. series, complete cavity closure was attained in 88% and partial closure in the remaining 12%. In the PAS./INH. series, however, the corresponding figures were 67% and 26% with 7% having persistent cavitation. Our results contrast with those of the studies of the United States Public Health Services reported by Murray[4] which showed that the EMB./INH. patients with cavitated disease did not respond as well when compared with the PAS./INH. series.

Side effects were commoner in the PAS./INH. series. Visual toxicity was about equal though one patient in the EMB./INH. series showed contraction of temporal fields attributable to ethambutol. The other visual toxic effects were unimpressive and might be due to the effects of age.

Patient acceptance of the EMB./INH. regime was excellent as gauged by the spot tests of urine for ethambutol. One disadvantage of the EMB./INH. regime is its cost. If the cost of ethambutol can be significantly reduced, then this regime can well replace the PAS./INH. regime which has a higher incidence of side effects. However, ethambutol still has a place if there is severe intolerance or reaction to PAS. or in the retreatment of tuberculosis.

SUMMARY

A controlled clinical trial on the efficacy, side effects and toxicity of ethambutol (25 mg./Kg. for 8 weeks, thereafter 15 mg./Kg.) in combination with INH. 300 mg. daily in one dose in the initial treatment of pulmonary tuberculosis was made. This was compared with a standard combination of Sodium PAS. 10 gm. and INH. 300 mg. daily.

A total of 103 moderately and far advanced cases had been admitted randomly since early July 1967 and this paper reports the results in 46 cases (23 EMB./INH. and 23 PAS./INH.), who had completed one year's treatment.

The sputum conversion rates were 91% and 87% respectively for the two regimes.

Radiologically, moderate to marked improvement was attained in 100% in the far advanced cases in the EMB./INH. series and 70% in the PAS./INH. series. In the moderately advanced

cases, moderate to marked improvement was obtained in 92% in both series. Complete cavity closure was attained in 88% and 67% respectively. Partial closure was attained in 12% and 26% respectively. There was persistent cavitation in 7% in the PAS./INH. series.

Side effects were encountered in 17% in the EMB./INH. patients and 35% in the PAS./INH. patients.

Impairment in visual acuity occurred in 9% and 18% respectively. One patient on the EMB./INH. regime had contraction of temporal fields though his visual acuity improved. There was no colour defect detected in all the cases.

There were two defaulters in the PAS./INH. series, but none in the EMB./INH. series.

The comparative costs of the two regimen are illustrated. Ethambutol seems a good substitute for PAS. if the cost can be significantly reduced.

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