A COMPARATIVE TRIAL WITH COMBINATIONS OF RIFAMPICIN, ETHAMBUTOL AND ISONIAZID (HYDRONSAN) IN PREVIOUSLY UNTREATED CASES OF PULMONARY TUBERCULOSIS*

B. A. DORMER, M.B., B.S., B. HYG., D.P.H., M.D., T.D.D. AND P. L. SALINGER, M.B., CH.B., M.D., *King George V Hospital, Durban*

SUMMARY

The results of a randomized, single-blind, between-patient trial of various combinations of rifampicin, ethambutol, and an INH salt in 100 previously untreated cases of pulmonary tuberculosis are presented. As in earlier trials by the South African State Health Department, 100% of cases on a combination of rifampicin plus INH or INH salt achieved bacteriological conversion within 12 weeks with a mean conversion time of approximately 5 weeks. It is suggested that properly used, rifampicin should be considered for first-line therapy of pulmonary tuberculosis.

Earlier studies undertaken by the State Health Department of the Republic of South Africa have been reported elsewhere.[1-3] This communication concerns a trial of various combinations of rifampicin, ethambutol and a glucuronide salt of INH (Hydronsan) in 100 previously-untreated cases of pulmonary tuberculosis.

MATERIALS AND METHODS

A randomized, controlled single-blind trial of drug combinations was conducted on previously untreated moderately advanced cases of pulmonary tuberculosis (Table I). Patients were screened for admission to the trial: all of them were between 16 and 60 years of age, had had no previous anti-tuberculosis therapy and their sputa were positive for *M. tuberculosis*. If culture of a sputum proved negative *ab initio,* the patient was considered not to have fulfilled the criteria for inclusion and was replaced. There was also radiological evidence of moderately advanced or advanced pulmonary tuberculosis in all cases.

TABLE I. TREATMENT COMBINATIONS

No. of cases	*Rifampicin 450 mg daily*	*Ethambutol 25 mg/kg daily*	*Hydronsan 2 g daily*
25	+	+	+
25	+	+	−
25	+	−	+
25	−	+	+
100	75	75	75

+ = present.
− = absent.

Following selection, patients were allocated according to a completely randomized plan to 4 treatment groups. Each patient was maintained on a trial therapy for 16 weeks when assessments of pre- and post-trial chest X-rays, sputum bacteriology, haematological and biochemical findings were made by one of the authors (P.S.) who was unaware of the treatment given. Sputum was examined by direct smear microscopy and culture, weekly for the first month and fortnightly thereafter; blood tests and chest X-rays were done at the commencement and then every 4 weeks; liver function tests were carried out at commencement and completion of the trial. The clinical progress was recorded.

*Date received: 25 January 1971.

Comparability of Treatment Groups

Subsamples were checked by statistical analysis for pre-treatment homogeneity as follows:

1. *Sex distribution*
   No significant difference $\chi^2_{3DF} = 3{\cdot}783$ $P>0{\cdot}20$
2. *Age distribution*
   No significant difference (class intervals of 5 years starting at 16 - 20). $\chi^2_{3DF} = 2{\cdot}041$ $P>0{\cdot}50$
3. *Body weight*
   The rifampicin plus hydronsan group had significantly lowered initial body weight than the other treatment groups. Duncan's new multiple range $P<0{\cdot}05$ test.
4. *Haemoglobin*
   The mean sq. between samples = 4·94 F = 1·584 $P>0{\cdot}20$
   The mean sq. within samples = 3·12
   No significant difference.

Thus, excepting for the lower body weight of the rifampicin-plus-Hydronsan group, the groups were homogeneous in other respects.

The drugs were given in the following dosages:
Rifampicin—450 mg daily on an empty stomach
Ethambutol—25 mg/kg daily
Hydronsan—2 g daily (≡ 666 mg INH)

RESULTS

The responses were judged by clinical, radiological, bacteriological and biochemical criteria. No significant differences were apparent between the 4 treatments in improvement in body weight and haemoglobin, and consequently a difference in clinical observation was not to be expected. Analysis of total and differential white cell counts revealed no differences between treatments and no blood dyscrasias were observed.

Significant differences were observed in the other criteria. The sputum culture conversion time (Table II) is significantly ($P<0{\cdot}01$) quicker in the rifampicin-treated groups and, as would be expected, the cumulative frequency of conversion (Fig. 1) is noticeably different, too, showing marked superiority of the rifampicin groups. (Conversion of sputum at the 16th week of trial must be regarded as tentative, since no subsequent negative sputum is available for confirmation. Consequently, the cumulative frequency curves are drawn up to the 14th week only.)

The proportion of cases showing marked radiological clearing after 16 weeks of trial is higher in the rifampicin-treated groups than in the ethambutol-plus-Hydronsan group. Table III shows the radiological clearing.

TABLE II. SPUTUM CULTURE CONVERSION (MEAN TIME EXPRESSED IN WEEKS)

Treatment	*All combinations*	*Rifampicin + ethambutol + Hydronsan*	*Rifampicin + ethambutol*	*Rifampicin + Hydronsan*	*Ethambutol + Hydronsan*
% converted (each group out of 25 cases)	97	100	96	100	92
Geometric mean* (weeks)	5·8	5·0	5·6	4·7	8·8†
Arithmetic mean* (weeks)	6·8	6·1	6·8	5·3	9·7†

0·5 > P > 0·01—Duncan's new multiple range test, modified according to Kramer.
*Only converted cases have been included in calculating means. Four cases in the ethambutol + Hydronsan group have a possible conversion time of 16 weeks and have been included as 'converted' despite no subsequent sputum cultures being available to confirm conversion.
†Means significantly higher than those of other 3 treatments.

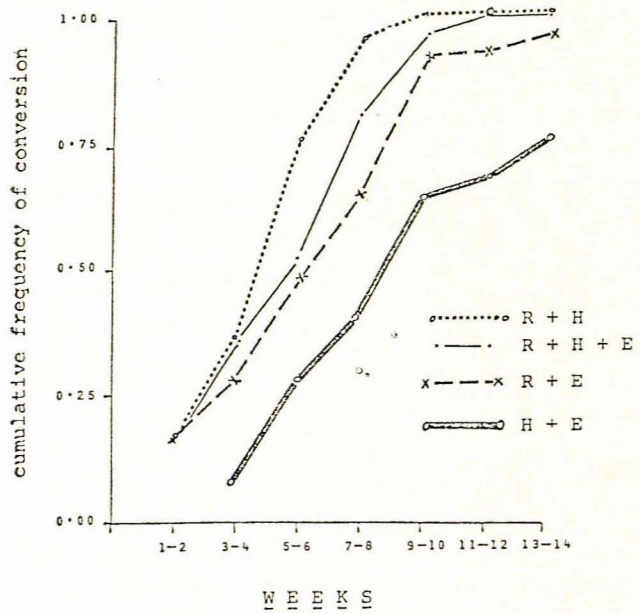

Fig. 1. Cumulative frequency distribution of sputum culture conversion. R = rifampicin; H = Hydronsan; E = ethambutol.

TABLE III. RADIOLOGICAL CLEARING

Treatment	*No. of cases*	*Proportion showing marked clearing*	
		Actual No.	*%*
Rifampicin + ethambutol + Hydronsan	25	13	52
Rifampicin + ethambutol	25	11	44
Rifampicin + Hydronsan	25	13	52
Ethambutol + Hydronsan	25	6	24

The rifampicin-treated cases show a statistically significantly higher incidence of marked clearing than the ethambutol + Hydronsan-treated cases (0·50 > p > 0·01, χ^2 analysis).

Analysis of the liver function tests shows a significantly higher incidence of pathological findings in the ethambutol-plus-Hydronsan group than in the other groups. It is not clear why the ethambutol-plus-Hydronsan-plus-rifampicin group does not show the same picture; in no case, however, was there any clinical evidence of liver dysfunction, nor was treatment ever discontinued for this reason (Tables IV and V).

TABLE V. STATISTICAL ANALYSIS OF TABLE IV. (RIFAMPICIN PRESENT VERSUS RIFAMPICIN ABSENT)

Measurement	*Statistical test*	*P*	*Comment*
Bilirubin	Exact probability	0·484	Not significantly different.
Alkaline phosphatase	—	—	Obviously not significantly different on inspection.
SGOT	χ^2 1d.f.	<0·01	Difference highly significant.
SGPT	Exact probability	0·005	Difference highly significant.

DISCUSSION

Our earlier studies in previously untreated pulmonary tuberculosis compared the efficacy of rifampicin plus INH versus streptomycin plus INH and showed a clear-cut bacteriological advantage for rifampicin plus INH. The present study confirms this efficacy and further demonstrates the superiority of rifampicin plus INH salt over ethambutol plus INH salt. The results also indicate that the addition of ethambutol to rifampicin plus INH does not enhance the response and, moreover, we conclude that in our patients, rifampicin appears to be a more active drug, not only than ethambutol, but also than INH. This was first suggested by Canetti.[4] Sputum conversion has been observed in 100% of our cases on rifampicin plus INH or INH salt within 12 weeks and the geometric means of the conversion time is approximately 5 weeks. Two further significant features in our trials with rifampicin involving over 200 cases have been the consistently

TABLE IV. LIVER FUNCTION TESTS

Treatment	*Bilirubin*		*Alkaline phosphatase*		*SGOT*		*SGPT*	
	No. observed	*No. abnormal*	*No. observed*	*No. abnormal*	*No. observed*	*No. abnormal*	*No. observed*	*No. abnormal*
R + H + E	23	0	23	4	25	1	24	0
R + E	24	0	23	1	25	1	24	0
R + H	25	0	25	3	25	3	25	0
E + H	23	1	22	2	23	7	23	4
Total								
R present	72	0	71	8	75	5	73	0
R absent	23	1	22	2	23	7	23	4

good response to a 450 mg dose, and the remarkably good tolerability as evidenced by patient acceptance and the absence of haematological or liver function disturbances. The effect of ethambutol plus INH salt in previously untreated pulmonary tuberculosis is disappointing by comparison with rifampicin combinations.

While much of the early work in pulmonary tuberculosis with rifampicin was done on polyresistant cases, we feel the need for highly effective first line-therapy in an attempt to achieve a cure rather than temporary improvement. The response to rifampicin combined especially with INH has been so promising, that it seems wrong to reserve it for respiratory cripples. Clearly, the drug should not be used indiscriminately, since this might lead to the development of resistant strains of bacteria. However, under proper supervision, we believe that rifampicin should be used in the management of previously untreated cases. It promises shorter initial hospitalization and earlier ambulant treatment. We believe that really effective treatment when the patient first presents may prove far less costly in the long run than using present first-line therapy, which, while producing satisfactory results in the majority of cases (about 85%) does not seem to provide sufficient improvement to prevent a significant proportion of apparent successes from relapsing, despite prolonged maintenance treatment. With rifampicin-plus-INH combinations we have noted a consistently satisfactory response in 100% of cases and there is a theoretical anticipation[5] of a better stability of results and lower relapse rate. Freerksen *et al.*[6] conclude that with rifampicin plus INH plus ethambutol there exist good chances of shortening treatment.

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