ETHAMBUTOL IN THE TREATMENT OF PATIENTS WITH CHRONIC PULMONARY TUBERCULOSIS*

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There are now 13 basically different antituberculosis drugs and 7 derivatives of these drugs in use in South Africa. It is becoming increasingly difficult for the non-expert to decide on the correct dosage and combination of these drugs, especially once the initial treatment has failed to convert the sputum.

A major antituberculosis drug should be highly effective, acceptable to the patient, non-toxic and reasonably cheap. The price is important in a country where almost all patients are treated at State expense. Only isoniazid and streptomycin have in the past fulfilled the above conditions for major drugs. A new major drug should also be suitable for self-medication and for intermittent therapy and produce no cross-resistance to well-established drugs.

The literature on ethambutol hydrochloride is already extensive and most of the above conditions seem to be fulfilled. Its relatively high price makes its introduction as a first-line drug problematic. As a second-line drug it seems to be eminently suitable in view of the inacceptability of most of the presently available reserve drugs. Too often treatment is stopped by the doctor or refused by the patient because of toxic symptoms; and this happens especially with treatment containing ethionamide, pyrazinamide and cycloserine. When all three are given together they have a substantial degree of toxicity. In routine secondary treatment these drugs show a disappointingly moderate rate of success. The other four reserve drugs—rifampicin, kanamycin, capreomycin and viomycin—are very expensive, costing about 300 times as much as isoniazid.

In South Africa Dormer[1] undertook a trial with ethambutol in 47 cases of chronic pulmonary tuberculosis and Charlton[2] described the chemistry, *in vitro* and *in vivo* activity, pharmacology and adverse reactions of this drug. Its main features are its high specific activity against *M. tuberculosis, M. bovis* and other species of mycobacteria. Of 35 South African wild strains of *M. tuberculosis* tested by us on Löwenstein-Jensen medium, all were fully sensitive to 1·5 μg/ml, and 25 strains also to 0·7 μg/ml ethambutol. Twenty strains of *M. bovis* were tested in the same way and all but two were fully sensitive to 0·7 μg/ml. Seven of the sensitive strains were isoniazid-resistant *M. bovis.*

The drug's action is of a degenerative type. The bactericidal phase is preceded by a phase of bacillary multiplication lasting several days.[3,4] Dickinson *et al.*[5] proved in guinea-pigs that if the daily doses are accumulated, intermittent drug intake is superior to daily dosage. Administration by mouth is on a once-daily schedule, and both absorption and excretion occur rapidly. Its acceptability to the patients and the rarity of side-effects makes it suitable for self-medication. Its ocular toxicity is dose-associated and usually reversible on discontinuation of the drug.

The emergence of resistance to ethambutol appears to be slow. On monotherapy the following figures were given: 41% within 3 - 6 months,[6] 37% within 3 - 5 months,[7] and 58% after 6 months.[8] When given in combination with other effective drugs, the makers report 6·8% of 380 chronic cases as drug-resistant.[9]

The purpose of our study was the evaluation of the efficacy and acceptability of prolonged ethambutol treatment in chronic multi-resistant cases of pulmonary tuberculosis. Emphasis was placed on the bacteriological status and follow-up results.

MATERIAL AND METHODS

Forty-six Bantu and one Coloured patient were treated for periods of 3 - 19 months. They were hospitalized at Rietfontein (Johannesburg), Zonderwater (Cullinan), Tshepong (Pretoria), and George Stegmann (Saulspoort). All were chronic cases according to the usual definition, i.e. their strains showed resistance to the best drugs; moreover, they had bilateral pulmonary tuberculosis, and were above the age of 15 years. All had had previous therapy with primary and/or secondary antituberculosis drugs. They were chronic excreters of *M. tuberculosis.*

The 47 patients were divided into two distinct groups: Group I, comprising of 23 patients, received ethambutol (EMB) and isoniazid (INH) only. These were patients who had already received many reserve drugs and excreted INH-resistant organisms. The clinicians, however, expected some therapeutic value from the administration of INH and hoped to make the bacterial population fully catalase negative and thus attenuated. It is generally accepted[10,11] that INH may have a beneficial effect in patients with primary INH resistance, and Freerksen[12] showed in experiments on animals that INH can act like a secondary drug on INH-resistant strains. Canetti *et al.*[13] recently stated that when drug resistance has emerged during chemotherapy no further response should be expected, and this is true even for INH.

Apart from INH and EMB, 7 of the 23 patients were given additional drugs, namely PAS in 4 cases, streptomycin in 3 cases, kanamycin in 1 case, capreomycin in 4 cases, and pyrazinamide in 1 case. Their strains, however, had shown *in vitro* resistance to these drugs. The strains of the 23 patients were all fully sensitive to EMB and 3 showed *in vitro* resistance to INH at the level of 0·1 μg/ml only. In their case, the INH was expected to have therapeutic effect.

Group II, comprising 24 patients, received ethambutol, plus 1 or 2 other antituberculosis drugs to which their strains showed sensitivity *in vitro.* Participating physicians were free to use a drug of their choice, and in most cases the drug sensitivity pattern was known at the start of the trial. The test was done using the absolute

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concentration method and Löwenstein-Jensen medium at the following levels: PAS at 0·5 and 10 μg/ml, INH at 0·1 and 5 μg/ml, streptomycin at 5 and 50 μg/ml, thiacetazone at 1 and 10 μg/ml, ethionamide at 20 and 30 μg/ml, cycloserine at 10 and 30 μg/ml, viomycin at 20 and 30 μg/ml, kanamycin at 10 and 20 μg/ml, capreomycin at 30 and 50 μg/ml, pyrazinamide at 20 and 100 μg/ml, and EMB at 5 and 10 μg/ml.

PAS was given in 12 cases, kanamycin in 10 cases, capreomycin in 4 cases, cycloserine and pyrazinamide in 2 cases each, and ethionamide in 1 case, all at routine dosages.

Additional drugs given despite *in vitro* resistance were as follows: INH in 17 cases, thiacetazone in 5 cases, PAS, streptomycin and capreomycin in 2 cases each, and cycloserine, ethionamide and kanamycin in 1 case each.

In both groups the dose of ethambutol was 25 mg/kg/day in 1 dose *per os* for the first 2 or 3 months. Subsequently 15 mg/kg/day was given for another 9 or 10 months. The dose of INH was usually 600 mg/day. During hospitalization the intake of drugs was controlled, but after discharge it was not possible to ensure self-medication.

All patients showed bilateral pulmonary tuberculosis with far-advanced disease and/or extensive destruction on X-ray. One or multiple cavities were visible in 31 of the patients. Their weight was recorded, and laboratory tests such as haemoglobin value, SGPT, SGOT, and erythrocyte sedimentation rate were carried out. The history, previous treatment and clinical condition were very similar for both groups. Fourteen patients were females and 33 were males. The age varied from 20 to 76 years, with a mean of 41 years. Together they had had 94 previous admissions, which is an average of 2 admissions per patient. Admitted or known previous treatment varied from 2½ to 125 months, with an average duration of 49 months per patient. The average weight was 110 lb (50 kg), varying from 68 to 148 lb (30 - 67 kg). The clinical condition was poor in 17 cases, fair in 11, and relatively good in 6 cases. During hospitalization X-rays were taken every month and, as far as possible, the ESR and weight were measured. Eye examinations for visual acuity were also performed monthly. After bacteriological conversion and discharge, patients were referred to outpatient clinics. Satisfactory clinical data on all patients concerned could only be obtained for the first 4 months of treatment. The clinical status at that time is given in Table I.

Sputum samples were sent to Onderstepoort initially at weekly and later at 2-weekly intervals for microscopy and culture. Sensitivity tests were done at monthly intervals. As is customary today, final evaluation in this study is based on the bacteriological results. The laboratory methods used have been described elsewhere.[14] After discharge from the hospital sputum specimens were usually sent at irregular intervals varying from one to several months, although patients were supposed to report to their nearest clinic every 4 weeks. In many cases patients had to be traced in order to obtain sputum and we do not know whether they took the EMB tablets daily.

RESULTS

The term 'bacterial conversion' means the change from positive sputum culture to negative for 3 consecutive monthly sputa. Where the findings differ from this definition, the length of the negative period will be given. We define a case as a relapse when after several consecutive negative sputa, growth of *M. tuberculosis* reappears on culture. The term 'reconversion' is used when a patient's sputum first becomes negative, then positive again for a few consecutive samples and subsequently converts to negative.

The clinical and radiological assessment after 4 months of EMB treatment as given in Table I illustrates the amazing improvement which occurred in many of these desperate cases. The majority of seriously ill patients had a dramatic clinical change for the better. Patients in group II, where EMB was combined with other effective drugs, showed resolution of infiltration more often than patients on EMB and INH only, but failure of infiltration to clear was due mostly to fibrosis.

The therapeutic history and the resistance pattern at the start of the trial are given in Table II. Five to 6 different drugs had been used previously, and in almost all cases the patients' strains were resistant to INH and streptomycin and several reserve drugs.

The bacteriological results as summarized in Tables III and IV and Fig. 1 will be described in more detail. The sputum of patients in group I, given EMB and INH only, converted in 12 cases. Conversion occurred in 4 cases in the 1st month, in 5 cases in the 2nd, in 2 cases in the 3rd, and in 1 case in the 4th month. No further cases became negative after 4 months. The higher the colony count at the start of therapy, the later conversion occurred. In 3 of the 12 cases we could only examine 2 consecutive negative sputa.

TABLE I. CLINICAL AND RADIOLOGICAL ASSESSMENT AFTER 4 MONTHS OF ETHAMBUTOL TREATMENT

Therapy	*Clinical status*	*Weight changes*	*Resolution of infiltration on X-ray*	*Alteration in size of cavities on X-ray*
Group I (EMB+ INH) 23 cases	20 felt, looked and were much better 1 no change 1 died (pneumonia) 1 died (1 month after withdrawal of EMB)	16 showed weight increases of 1·3 - 16·3 kg (average 6·2 kg) 7 no information	9 improved (3 slight, 4 moderate, 2 marked) 10 no change 4 no information	13 improved (1 closure, 7 much smaller, 5 somewhat smaller) 2 no change 8 no information
Group II (EMB+ other drugs) 24 cases	14 felt, looked and were much better 9 no information 1 deteriorated	14 showed weight increases of 0·4 - 10·8 kg (average 4·9 kg) 1 lost 6·2 kg 9 no information	18 improved (7 slight, 4 moderate, 7 marked) 1 deteriorated 2 no change 3 no information	11 improved (4 closures, 1 much smaller, 6 somewhat smaller) 1 deteriorated 4 no change 8 no information

TABLE II. KNOWN PREVIOUS CHEMOTHERAPY HISTORY AND BACTERIAL RESISTANCE AT START OF ETHAMBUTOL TREATMENT

	INH	*SM*	*PAS*	*TH*	*ETH*	*CS*	*CAP*	*PZA*	*VM*	*KM*	
up I (EMB + INH) 23 cases											
rugs received previously	23	23	18	10	9	6	1	12	2	5	Mean of 5 drugs
vitro bacterial resistance acquired	22	22	16	18*	16†	6	4‡	5	4	6	Resistant to mean of 5 drugs
up II (EMB + INH + other drugs) 4 cases											
rugs received previously	24	24	21	14	15	14	4	16	7	10	Mean of 6·5 drugs
vitro bacterial resistance acquired	23	22	11	18*	15	10	4	2	4	5	Resistant to mean of 5 drugs

= isoniazid; SM = streptomycin; PAS = para-amino salicylic acid; TH = thiacetazone; ETH = ethionamide; CS = cycloserine; CAP = preomycin; PZA = pyrazinamide; VM = viomycin; KM = kanamycin.
istance to 1 μg TH occurs naturally in South Africa.
treatment can cause ETH resistance.
istance to CAP can be caused by use of KM or VM.

ABLE III. BACTERIAL STATUS AT END OF LABORATORY INVESTIGATIONS

of treatment average length	*Group I EMB monotherapy (treated 11 months)*		*Group II EMB + other drugs (treated 9 months)*	
	No.	*%*	*No.*	*%*
ersion	12	52	16	67
nversion	3	13	0	0
pse	3	13	1	4
stently posi-e	5	22	7	29
Total patients	23	100	24	100

E IV. INFECTIOUSNESS OF PATIENTS' SPUTA AT 3-MONTHLY INTERVALS*

	Time lapse after start of EMB treatment					
	3 months	*6 months*	*9 months*	*12 months*	*14 - 15 months*	*17 - 18 months*
ersion to negative	28	22	17	13	10	6
nversion	—	0	1	0	2	0
pse	—	1	0	3	3	1
istently positive	19	14	9	5	1	0
otal No. of patients†	47	37	27	21	16	7

ups I and II combined. Average time under bacteriological observa- 10 months.
rapid decrease in the number of patients was due to discharge and ire to report to clinics.

here were 3 cases of reconversion in group I. Their ures initially showed 25 - 50 colonies. The first case ame negative within the 1st month, then scantily posi- again from the 3rd to 7th months, and subsequently ative during the 8th to 14th months. The 2nd case became negative within the 1st month, was positive n the 12th to 14th months and reconverted during 15th month, a situation which persisted until the end the study. The 3rd case became negative in the 3rd nth, was positive during the 7th to 12th months, and negative sputa from the 13th to 19th months.

hree cases in group I showed a relapse which appeared ing the 6th, 10th and 14th months respectively. In first case treatment was stopped after 4 months due ransfer to another hospital. The strains isolated after relapses were sensitive to 5 μg/ml EMB *in vitro*.

Five cases showed persistently positive cultures. The strain from one of these patients did not develop resistance to 5 μg/ml EMB. The other 4 cases developed partial resistance to 5 μg/ml EMB after 9, 8, 10 and 12 months respectively. No significant changes in the level of resistance to other drugs occurred during the period of observation.

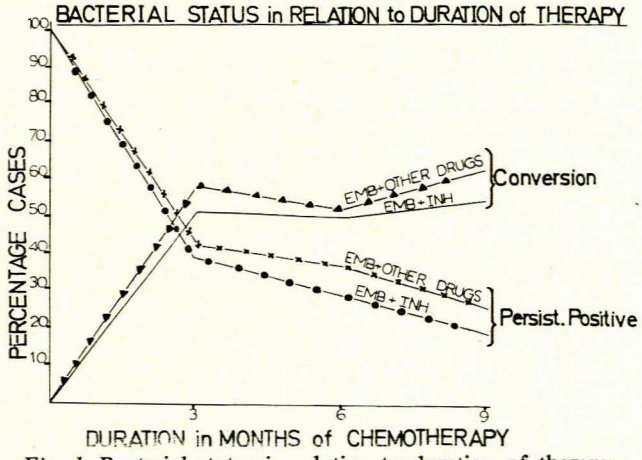

Fig. 1. Bacterial status in relation to duration of therapy.

The 24 cases in group II, who received EMB combined with other effective drugs, showed conversion in 16 patients, persistently positive sputa in 6, relapse in 1, and intermittently negative sputa in another case. The conversion occurred in 2 cases after 1 month, in 8 cases after 2, in 3 cases after 3, and in 1 case after 8 months. The group contains 2 cases from whom 1 or 2 colonies were isolated after a period of negative sputa. They can be regarded as converters. Another patient had a highly positive sputum after 1 month, was negative after 2 months, then moderately positive during the 3rd to 6th months, and in the 7th month 4 colonies were isolated. In the 8th month his sputum was again negative.

Three of the persistently positive cases showed moderate to numerous colonies on culture throughout. Another case was highly positive until the 3rd month, and then the excretion gradually decreased to 11 colonies at 6 months. Two patients showed a marked decrease of organisms with several single colony isolates for a period of a few months before excreting higher numbers of organisms again. These could have been called relapses. The one case shown as a relapse in Table III was negative during the 1st year of therapy but produced a positive sputum at the 17th month.

The resistance pattern to other antituberculosis drugs in strains isolated from patients in group II was very similar to the pattern for patients in group I. But, contrary to group I patients, no resistance to EMB emerged. Two patients on kanamycin and 1 on PAS acquired resistance to the drug concerned.

DISCUSSION

A comparison of the results obtained in the 2 different groups shows a higher rate of conversion and a lower rate of relapse in the group on EMB treatment combined with other effective drugs than in the group that received EMB and INH only. This was to be expected as all were chronic cases of tuberculosis with poly-resistance of the excreted organisms. The use of one effective drug alone in cases of advanced pulmonary tuberculosis will lead to emergence of resistance to that drug. The total conversion rate however is nearly the same in both groups if reconversion is added. It is 65% for EMB 'monotherapy' and 67% for combined EMB therapy.

In group I, which was virtually on EMB monotherapy, the rate of relapse was higher than in group II. In the 3 cases of reconversion on EMB monotherapy, resistance to 5 μg/ml EMB emerged in their last positive cultures during the relapse period, i.e. in the 4th, 5th and 6th months respectively. Reconversion to negative occurred without a change in therapy.

As regards the cases which persistently excreted *M. tuberculosis,* none of those on combined EMB treatment developed drug resistance, while 4 of the 5 cases on EMB monotherapy showed a resistance to 5 μg/ml EMB after 7 - 12 months of treatment. This indicates that these patients continued to take the drug as outpatients.

The most likely explanations for the maintenance of sensitivity to EMB is that our *in vitro* method was not sensitive enough to detect resistance. After this trial we changed the lowest concentration of EMB incorporated in the medium to 2 μg/ml. However, Gyselen *et al.*[15] using 2 μg/ml of ethambutol for *in vitro* tests also found that, contrary to experience with other drugs, the failure to convert to negative was as a rule not accompanied by demonstrable drug resistance. The *in vitro* difference between sensitive and resistant strains is very small.[13]

It should be emphasized that all but 1 of the 28 successfully treated cases converted within the first 4 months of EMB treatment. Usually conversion was earlier when the number of cultivable bacilli was low at the start. The bacteriological relapses in group I on EMB monotherapy occurred after 3, 6, 7, 10, 12 and 14 months respectively, but most of these patients were desperate cases and no miraculous results could be expected. In this trial the only known relapse after combined EMB treatment occurred during the 17th month.

Our over-all results are comparable to those published elsewhere. On EMB monotherapy the rate of conversion after 6 months is 51% for 163 chronic cases described in the literature; in this trial it was 50%. For a 12-month period the rate from the literature is 35% of 98 cases and in our study it was 46%. Out of a total of 163 cases 28% were reported to be persistent excreters 6 months after starting EMB, and the same figure was obtained in our series. The 3 months on combined EMB treatment evaluation of 191 published chronic cases shows conversion in 130 patients, i.e. 68% compared with 58% conversion in our 24 patients.

Although clinical and radiological assessment of our series is only complete for the first 4 months, it is evident that improvement was usually rapid and significant. The clinical change was often dramatic in patients who were very ill. The improved status was usually maintained. Radiological changes were difficult to evaluate because of the extent of the disease. One patient on EMB monotherapy who remained persistently positive and showed EMB resistance, died after an intercurrent pneumonia.

The striking therapeutic response was coupled with a high degree of acceptability of the drug and the absence of hypersensitivity and side-effects. As for toxic reactions, we have on record only 1 patient who complained of weakening of vision after 4 days of treatment with 25 mg/kg EMB per day. The dosage was reduced to 15 mg/kg/day and his vision returned to normal.

The follow-up study was greatly hampered by the number of patients who disappeared before completion of treatment and could not be traced.

SUMMARY

Ethambutol was used in the re-treatment of extensive chronic pulmonary tuberculosis. Most patients' bacterial strains were resistant to all major drugs. During the first 2 months 25 mg/kg was administered *per os,* thereafter 15 mg/kg body-weight. In group I, 23 patients were treated with ethambutol plus isoniazid (INH), which was virtually a monotherapy because of resistance to isoniazid. In group II, 24 patients were treated with ethambutol plus 1 or 2 other effective secondary drugs.

Ethambutol brought about rapid and significant clinical and also radiological improvement. Reversal of infectiousness was achieved in 65% in group I and 67% in group II. In group I, 13% of patients relapsed, and in group II the rate was 4%. A great proportion of patients disappeared due to the length of the trial. Sputum conversion was usually obtained within the first 3 months.

Ethambutol was found to be a very effective drug in the re-treatment of chronic tuberculosis, and quite suitable for long-term administration. Ethambutol in the dosage used was very well tolerated and caused no significant ocular side-effects. It should always be given in combination with 1 or more effective antituberculosis drugs.

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