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Efficacy of once-weekly Isoniazid-Streptomycin in preventing relapse of pulmonary tuberculosis

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Two controlled studies were undertaken to assess the efficacy of streptomycin 1 g. or 0.75 g. (by random allocation) plus isoniazid 15 mg./kg. body-weight once-weekly (the SHOW regimen) in the prevention of bacteriological relapse over a 4 year period, in patients with quiescent pulmonary tuberculosis at the end of one year of chemotherapy. In the first study which involved patients with residual cavitation at one year, bacteriological relapse requiring treatment occurred in 3 per cent of 87 patients given the SHOW regimen for 12 months as compared with 21 per cent of 94 patients on a placebo, a high proportion of the relapses in the latter occurred in the 2nd year and with sensitive organisms. In the second study on patients with no residual cavitation at one year, relapse requiring treatment occurred in 2 per cent of 98 patients given the SHOW regimen for 6 months as compared with 1 per cent of 90 patients given isoniazid approximately 4.5 mg./kg. daily for 12 months.

Previous reports from the Tuberculosis Chemotherapy Centre[1,2] have shown that maintenance therapy with isoniazid alone was highly effective in preventing relapse if given for 1 year in a dose of 150-200 mg. daily to patients with bacteriologically quiescent disease and without residual cavitation at the end of 1 year of initial chemotherapy; also when given for 6 months, a larger dose of 300 mg. daily was not so effective. Further, in patients with quiescent disease and with residual cavitation, isoniazid, even in a dosage of 400 mg. daily for 12 months was not satisfactory. Two controlled studies were, therefore, conducted to investigate the efficacy of maintenance chemotherapy with a once-weekly regimen of streptomycin plus high dosage isoniazid (SHOW) for 6 months *(i.e.* chemotherapy for a total of 18 months including 12 months of initial chemotherapy) in patients without residual cavitation at 1 year and for 12 months (i.e. total period of 24 months) in patients with residual cavitation. Patients in both studies were followed-up for a period of 4 years and the findings are presented in this report.

Material and Methods

This report is based on 369 patients with bacteriologically confirmed pulmonary tuberculosis with drug sensitive organisms who had attained bacteriologically quiescent

disease at 1 year (all of 7-9 cultures at 10, 11 and 12 months being negative). On initial admission, 56 per cent were between 25 and 46 years, the mean age being 33 years; the mean weight was 39.0 kg. (range 19.5 to 69.1 kg.) and 67 per cent were males. In the first year, all had received streptomycin (1 g. or 0.75 g. by random allocation) plus isoniazid, twice-weekly in 75 patients, daily for 1 month followed by once-weekly in 181, and once-weekly in 113; about a third had received PAS or pyrazinamide as a third drug[3,4]. Each patient was classified at 1 year as having either residual cavitation, or no residual cavitation, from postero-anterior radiographs and tomograms, and allocated at random to treatment in the second year.

Patients with residual cavitation (181 patients)

(a) SHOW regimen (12 months) : Streptomycin 1 g. or 0.75 g. (as in the first year) by intramuscular injection plus supervised oral isoniazid approximately 15 mg./kg. body-weight* administered at the same time, once a week for 12 months (87 patients); or

(b) placebo (12 months) : One tablet of calcium gluconate 500 mg. self-administered daily for 12 months (94 patients).

Patients with no residual cavitation (188 patients)

(a) SHOW regimen (6 months) : The above once-weekly regimen for 6 months followed by the placebo for 6 months (98 patients); or

(b) isoniazid regimen (12 months) : Isoniazid alone in a single oral dose of approximately 4.5 mg./kg. body-weight† daily, self-administered for 12 months (90 patients).

Management of patients : In general, patients were treated as out-patients, the SHOW patients attending the Centre once a week to receive their chemotherapy under supervision and those on isoniazid alone or the placebo visiting monthly for a supply of their tablets.

One sputum specimen was examined by smear and culture every month in the second year while two specimens were examined every 3 months in subsequent years. Two additional specimens were examined at 24 months, an additional specimen at 36 and 48 months and 3 additional specimens at 60 months. Thus, 14 specimens were examined in the 2nd year, 9 each in the 3rd and 4th years, and 11 in the 5th year, making a total of 43; additional specimens were examined if a patient produced a positive culture. If a patient produced a positive culture at the 57th or the 60th month, additional sputum specimens were examined for the next 6 months. Tests

*** The dosages were 400 mg. for patients weighing below 30.0 kg. 600 mg. for patients weighing 30.0 to 44.9 kg. and 750 mg. for patients weighing 45.0 kg. or more; 6 mg. of pyridoxine was incorporated in each dose of isoniazid.**

† The dosages were 150 mg. for patients weighing below 35.0 kg., 175 mg. for patients weighing 350 to 44.9 kg. and 200 mg. for patients weighng 45.0 kg. or more.

for sensitivity to streptomycin and isoniazid were performed. The bacteriological methods and the definitions of resistance employed have been described elsewhere[3].

Bacteriological relapse and treatment : Bacteriological relapse is defined as the occurrence of two or more positive cultures in any 6 month period. Re-treatment was started only if : *(a)* the bacterial population was large, *i.e.*, 2 or more positive cultures in a 2 month period (at least one with 20 or more colonies), associated with a positive smear, or (b) there was an unequivocal radiographic spread (confirmed by an independent assessor) in the presence of positive sputum.

Results

Patients with residual cavitation at 1 year : All the 181 patients had positive cultures at the time of admission to initial chemotherapy, the first collection specimen of sputum being smear-positive in 93 per cent of the 87 patients on SHOW and in 87 per cent of the 94 patients on placebo. Moderate, extensive or gross radiographic disease was present in 78 per cent and 79 per cent respectively. In each series, 34 per cent were rapid inactivators of isoniazid. The proportions of patients who received twice-weekly, daily followed by once-weekly, or once-weekly regimens in the first year were similar in the SHOW and placebo series. At 1 year, in addition to residual cavitation, moderate or extensive radiographic lesions were still present in 49 per cent of the SHOW and 53 per cent of the placebo patients. Thus, the two series were similar on admission to the original treatment and at 1 year. The culture examination was also similar in the two series in the next 4 years (40.6 cultures in the SHOW and 40.4 in the placebo patients).

In the second year, 93 per cent of the SHOW patients received 75 per cent or more of their scheduled 52 doses, 78 per cent received 90 per cent or more. The mean percentage of doses received was 93.

Bacteriological relapse : A bacteriological relapse requiring treatment (Table) occurred in 3 (3 per cent) SHOW patients (who had received 81 per cent, 92 per cent and 98 per cent of the scheduled chemotherapy) and in 20 (21 per cent) placebo patients (P=0.001). Two of the former and 15 of the latter had an unequivocal radiographic deterioration also. Two patients on SHOW had received 1 g. streptomycin and one had received 0.75 g. Relapse occurred in one patient on SHOW and 14 patients on placebo in the second year; of these, the patient on SHOW and 10 of the placebo group had relapse by the 15th month.

Of the 23 patients, 21 (3 SHOW, 18 placebo) relapsed with organisms sensitive to isoniazid and streptomycin. One patient (placebo) had organisms resistant to both drugs. The remaining (placebo) produced cultures resistant to streptomycin but sensitive to isoniazid.

Four more patients (1 SHOW, 3 placebo) had a bacteriological relapse which resolved spontaneously *i.e.*, without re-treatment. The SHOW patient had relapse in the 60th month with sensitive organisms. The 3 placebo patients had relapses at

24, 39 and 60 months respectively. One had organisms resistant to isoniazid and sensitive to streptomycin; the others had organisms sensitive to both the drugs.

Deaths : Of the patients who did not have a bacteriological relapse, 1 SHOW and 7 placebo patients died of non-tuberculous causes during the 4 year period. The SHOW patient died suddenly of an unknown cause in the 29th month. He had been consistently negative by smear and culture for 19 months before death. The placebo patients died in the 14th, 35th, 39th, 45th, 46th, 52nd and 58th months respectively. They had been consistently negative by smear and culture for 11, 27, 34, 43, 43, 48 and 54 months respectively before death. The first two died of acute respiratory infections, the 3rd of pyrexia of unknown origin, the 4th probably of old age, the 5th committed suicide, the 6th died of an unknown cause in a maternity hospital in an advanced stage of pregnancy, and the 7th in status asthmaticus. None of these patients showed evidence of reactivation of tuberculosis.

Three (1 SHOW, 2 placebo) of the patients who had a relapse requiring treatment subsequently died. The SHOW patient, who relapsed in the 31st month, did not respond to re-treatment as he was extremely irregular in his drug intake, and died of tuberculosis in the 56th month with organisms sensitive to streptomycin and isoniazid. One placebo patient died after a spontaneous pneumothorax in the 19th month, having produced only negative cultures in the preceding month; the second, who had her elapse in the 15th month, left Madras before re-treatment was completed, and died in the 34th month, probably of tuberculosis.

No autopsies were performed.

Drug toxicity : One patient (female, aged 25 years) had the dosage of streptomycin reduced from 0.75 g. to 0.5 g. in the 21 st month due to severe giddiness. Another (SHOW-a slow inactivator of isoniazid) developed peripheral neuropathy in the 14th month which responded to a pyridoxine supplement of 8 mg. daily, the SHOW regimen being continued.

Factors of prognostic significance : The prognostic significance of various factors on relapse requiring treatment was examined in the placebo series. The factors studied were age, sex, weight, isoniazid inactivation status, the smear grade and extent of cavitation on admission to initial treatment, the total extent of radiographic lesion on admission and at the start of the relapse study, the treatment regimen, the percentage of chemotherapy received and the month of sputum conversion in the first year.

It was observed that the incidence of relapse requiring treatment was relatively high in patients who had a heavy bacterial content of sputum on admission to initial treatment and in patients who had a late sputum conversion. Thus, 26 per cent of 68 patients with a 3-plus or 2-plus smear initially had a relapse requiring treatment compared with 8 per cent of 26 patients with a 1-plus or negative smear ($P=0.04$); 43 per cent of 23 patients who had a sputum conversion at 4 months or later had a relapse requiring treatment as compared with 14 per cent of 71 patients who had converted by 3 months ($P<0.01$). Multiple regression analysis involving all the factors showed

that the only factor with a statistically significant prognostic value was the speed of sputum conversion.

Patients with no residual cavitation at 1 year : All 188 patients had culture positive disease on admission to (initial chemotherapy, the first collection specimen of sputum being smear positive in 88 per cent of the 98 SHOW patients and 91 per cent of the 90 isoniazid patients. Cavitation was present initially in 95 per cent and 94 per cent respectively, and moderate, extensive or gross radiographic disease in 57 per cent and 66 per cent respectively. The proportions of rapid inactivators were 31 per cent and 29 per cent respectively. The proportions of patients who received twice-weekly, daily followed by once-weekly, or once-weekly regimens in the first year were similar in the SHOW and isoniazid series. At 1 year, no residual radiographic lesion was present in 5 per cent of the SHOW patients and 6 per cent of the isoniazid patients, 67 per cent in each series had trivial, slight or limited disease, and 28 per cent in each series had moderate or extensive but non-cavitated lesions. Thus, the two series of patients were similar on admission and at 1 year. They had a high and similar intensity of bacteriological examination, the average number of cultures being 41.6 in the SHOW and 40.8 in the isoniazid series during the 4 year period.

In the second year, 98 per cent of the SHOW patients received 75 per cent or more of their scheduled 26 doses, including 85 per cent who received 90 per cent or more. The mean percentage of doses received was 97. Each isoniazid patient was given a month's supply of isoniazid at a time for self-administration. The mean percentage of isoniazid collected was 98, 45 per cent having collected 100 per cent of their doses.

Bacteriological relapse : A bacteriological relapse requiring treatment (Table) occurred in 2 (2 per cent) SHOW patients, at 20 months (1 g. streptomycin) and 30

TABLE. BACTERIOLOGICAL RELAPSE DURING THE 4 YEAR PERIOD OF FOLLOW-UP RELATED TO CAVITATION STATUS AT ONE YEAR AND TREATMENT DURING THE SECOND YEAR.

Cavitation status at one year	Treatment in the second year	Total No. of patients	Patients who had a bacteriological relapse requiring treatment					
			No.	%	Year of relapse			
					Second	Third	Fourth	Fifth
Cavitated	SHOW (12 months)	87	3	*3*	1	1	0	1
	Placebo	94	20	*21*	14	1	1	4
Non-cavitated	SHOW (6 months)	98	2	*2*	1	1	0	0
	Isoniazid	90	1	*1*	0	1	0	0

months (0.75 g. streptomycin) respectively, and 1 (1 per cent) isoniazid patient, at 36 months, all 3 after the cessation of chemotherapy. Both the SHOW patients had received 100 per cent of their scheduled chemotherapy and the isoniazid patient had collected 100 per cent of his doses. One SHOW patient had a strain resistant to streptomycin and sensitive to isoniazid and the other had organisms sensitive to both drugs; the isoniazid patient had a strain resistant to isoniazid but sensitive to streptomycin. All the three also had clear cut radiographic deterioration.

Two other patients (1 SHOW, 1 isoniazid) had a bacteriological relapse, with drug sensitive organisms, at 45 and at 60 months respectively, but their sputa reconverted spontaneously.

Deaths : During the follow-up 5 SHOW and 3 isoniazid patients died, all of non-tuberculous causes. The SHOW patients died in the 20th, 31st, 46th, 51st and 54th months respectively. The first died of severe diarrhoea, the second suddenly, probably of a cardiac cause, the third of severe anaemia, the fourth of a massive haemoptysis, and the fifth of an acute abdomen. Their sputa had been consistently negative by smear and culture for 17, 27, 37, 47 and 53 months respectively before death. The 3 isoniazid patients died in the 35th, 36th and 52nd months respectively. The first two died of unknown causes, and the third probably of acute enteritis. Their sputa had been consistently negative by smear and culture for 31, 31 and 48 months respectively, before death. None of the patients showed evidence of reactivation of tuberculosis. No autopsies were performed.

Drug toxicity : Four SHOW (2 slow, 2 rapid inactivators) and 5 isoniazid (4 slow, 1 rapid) patients had symptoms suggestive of peripheral neuropathy. Seven patients (2 SHOW, of whom 1 was a slow inactivator, and 5 isoniazid, of whom 4 were slow inactivators) were given vitamin B complex tablets containing pyridoxine. The remaining 2 were not given any symptomatic treatment. None of the 9 patients complained subsequently. One SHOW patient had facial paraesthesia which could be controlled by antihistamines. All 10 patients had their maintenance chemotherapy without interruption.

Discussion

Although in the last few years short course chemotherapy has been studied and effective regimens identified[5,6] the regimens currently being introduced into clinical practice include expensive drugs such as rifampicin and pyrazinamide. Further, these drugs are not readily available in many developing countries and hence the regimens may be inapplicable in service programmes. It therefore still remains important to investigate duration of conventional chemotherapeutic regimen with the currently available drugs, and maintenance regimens for the prevention of relapse.

The present studies demonstrate the value of the SHOW regimen (streptomycin plus isoniazid once a week) when given for 12 months to patients with bacteriologically

quiescent disease and with residual cavitation, and for 6 months to those without residual cavitation, Thus, only 3 per cent of patients with residual cavitation who received it relapsed, in contrast to 21 per cent on a placebo (P=0.001); the protection obtained (84 per cent) is highly satisfactory. In an earlier study[2] when isoniazid alone in a dose of 400 mg. daily was given for 1 year as maintenance chemotherapy to patients with residual cavitation, the protection obtained was 54 per cent. In patients with non-cavitated quiescent disease at 12 months, 2 per cent of the SHOW patients had a relapse compared with 1 per cent of patients who received isoniazid daily for 12 months. In this respect it is relevant that in an earlier study in the Centre[2] the relapse rate in patients with non-cavitated disease without maintenance chemotherapy was 12 per cent.

The SHOW regimen requires only once-weekly attendance. As it is fully supervised, the amount of chemotherapy actually received by the patients is known precisely and if doses are missed, defaulter action can be instituted immediately. The regimen is highly effective, is relatively inexpensive where facilities for giving injections already exist, and toxicity is low. In view of these advantages, a shorter duration of maintenance chemotherapy with the regimen is now being studied.

In many rural areas of the developing countries, regimens containing streptomycin will not be readily applicable because of the lack of injection facilities. Hence, the efficacy of a fully supervised once-weekly oral regimen of PAS plus isoniazid is now under study at this Centre.

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