

Evaluation of a directly observed six month fully intermittent treatment regimen for tuberculosis in patients suspected of poor compliance

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Abstract

Background - Although a priority for tuberculosis control is to achieve the maximum cure rate, compliance with chemotherapy in specific high risk groups (homeless, intravenous drug abusers, chronic alcoholics) is usually poor.

Methods - From January 1990 to December 1994 102 patients with tuberculosis (96 pulmonary, six extrapulmonary) who were poorly compliant with treatment were treated with a six month fully intermittent (twice weekly) directly observed regimen. They comprised 71 homeless subjects, 50 chronic alcoholics, 23 intravenous drug abusers, nine infected with HIV, and 11 who had previously abandoned a daily antituberculosis regimen; 53 had more than one of these risk factors. Treatment included isoniazid and rifampicin for six months and pyrazinamide during the first two months. Patients who failed to take their medication on two consecutive occasions were actively sought by telephone or by personal search.

Results - After two months of treatment 95 of the 102 patients had taken their medication regularly and 90 of them had negative cultures. Four of the remaining patients had negative cultures after three months. At the end of the six months 87 patients had completed treatment and were considered cured. Only 15 patients abandoned the treatment (13 of whom had more than one risk factor). Only three relapses occurred in the 102 patients at one year follow up and in the 88 patients followed for two years. Two patients required a change of treatment due to major side effects. Although intravenous drug abuse was the only predictor of non-compliance in the multivariate analysis, if the available variables in the second month of treatment were analysed, current poor compliance and abandonment of treatment in the past were found to be significantly associated with non-compliance.

Conclusions - This study shows the efficacy of this intermittent regimen and the effectiveness of a directly observed treatment programme.

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Keywords: tuberculosis, directly observed intermittent therapy, compliance.

The aim of all antituberculosis programmes is to increase the cure rate of patients receiving treatment.¹⁻³ Although achievement of this goal is hindered by unfavourable socioeconomic and organisational conditions in developing countries, the implementation of appropriate controlled programmes based on short term chemotherapy has proved successful in obtaining a high cure rate amongst smear-positive patients.^{4,5} In industrialised countries the high incidence of elective termination of treatment registered amongst drug abusers, the homeless, and alcoholics has become a matter of concern.⁶⁻⁹

In order to increase the cure rate it may be necessary to supervise the administration of all medications strictly¹⁰ and, in developing countries, to find low cost and effective regimens. Twice weekly treatment for 4-8 days is needed to reinstate bacillary multiplication after exposing mycobacteria to bactericidal drugs^{11,12} - this regimen not only facilitates cost reduction and supervision of treatment but has been found to be as effective as daily antituberculosis regimens.¹³⁻¹⁶

We assessed the effectiveness of a six month fully intermittent (twice weekly) treatment regimen in specific high risk groups likely to be non-compliant such as the homeless, chronic alcoholics, intravenous drug abusers, and patients who had previously abandoned daily antituberculosis treatment.

Methods

All patients with tuberculosis at risk of non-compliance who attended our hospital between January 1990 and December 1994 were eligible for inclusion in the study. The criteria for inclusion were a definitive diagnosis of tuberculosis based on laboratory identification of *Mycobacterium tuberculosis*, being homeless with no fixed abode and/or intravenous drug addict and/or a chronic alcoholic. Patients who had previously abandoned a daily antituberculosis regimen were also included provided that drug susceptibility testing excluded the presence of resistance to the drugs administered.

Intermittent antituberculosis treatment consisted of a six month regimen in which isoniazid (15 mg/kg per dose) and rifampicin (10 mg/kg per dose up to 600 mg) were given twice a week (Monday and Thursday) for six months and pyrazinamide (60 mg/kg per dose) during the first two months. According to our rate of initial resistance¹⁷ neither systematic sensitivity

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testing nor the use of a fourth drug in the first phase of treatment¹⁸ appeared to be justified. During the first two months of treatment and while waiting for the results of drug sensitivity testing ethambutol (50 mg/kg per dose) was given to patients who had previously abandoned daily antituberculosis treatment. Drug sensitivity testing was only carried out in those with a positive culture in the second month of treatment.¹⁹

Patients were requested to attend the hospital regularly for supervision of medication. At each visit they were informed about the seriousness of mycobacterial infection and the importance of compliance with the treatment regimen was stressed. They were also given a meal. A nurse supervised the procedure. Patients who failed to take their medication on two consecutive occasions were actively sought by telephone or by personal search. Most of the missing homeless were found in shelters.

A physical examination was carried out two weeks after starting treatment, at one, two, four and six months of treatment, and at six, 12, 18, and 24 months after completion of treatment. Bacteriological and biochemical investigations were performed at all visits and radiological studies were carried out at the beginning and at the end of treatment.

To assess the pharmacological effectiveness of intermittent antituberculosis treatment the following variables were analysed: percentage of patients with negative cultures at two months of treatment; number of patients with positive cultures at three months of treatment (pharmacological failures); percentage of patients in whom medication was discontinued or changed due to side effects; number of relapses at 24 months after completion of treatment; and number of patients cured (culture negative). Depending on the number of doses taken at the second, fourth, and sixth month, patients were divided into those who had taken all the required doses, those who had taken 75–99% of the required doses, those who had taken 50–75% of doses, and those who had taken less than 50%. Before finishing the programme patients were also classified into those who were compliant and those who had abandoned treatment.

DATA ANALYSIS

Statistical analyses were carried out by using the χ^2 test (with Yates' continuity correction when needed) and the odds ratio (OR) with 95% confidence intervals (CI). A logistic regression model was used to analyse predictive variables of non-compliance at the time of diagnosis and at the end of the second month of treatment. A p value of <0.01 was considered to be statistically significant. All calculations were performed with the SPSS-PC and EGRET statistical packages.

Results

During the study period (January 1990 to December 1994) 104 patients with culture positive tuberculosis were included in the study, al-

Table 1 Compliance with intermittent antituberculosis treatment (n=102)

Percentage of doses taken under nurse supervision	No of patients attending to take drugs regularly		
	2nd month	4th month	6th month
100%	59	40	37
75–99%	32	37	38
50–74%	4	10	11
<50%	0	1	1
Abandonments	7	14	15
Culture negative ^a	90	88	87

^aSputum conversion.

though two patients were excluded later because of side effects leaving a study population of 102 patients for analysis. Their age ranged from 18 to 87 years (mean 41.3 years) and 84 were men. Homelessness was registered in 71 patients, chronic alcoholism in 50, intravenous drug abuse in 23, and abandonment of previous treatment in 11. At least two of these conditions was present in 53 patients. Nine patients were seropositive for the human immunodeficiency virus (HIV), all of whom used heroin by the intravenous route. Pulmonary tuberculosis was diagnosed in 96 patients and extrapulmonary tuberculosis in six. Smear positive *M tuberculosis* was found in 94 patients and eight were smear negative.

Table 1 shows the rate of compliance of the patients throughout the six month treatment period. At the end of the second month 95 patients attended the sessions regularly and 90 had negative cultures. Of the five patients with positive cultures one was lost to follow up shortly afterwards and four had negative cultures at three months. None of these five patients exhibited resistance to the drugs administered. At the end of the fourth and six months 88 and 87 patients, respectively, continued taking medications and all of them had negative *M tuberculosis* cultures. At the end of six months only 15 patients had abandoned treatment, 13 of whom had more than one risk factor at the time of inclusion in the study. Two patients who discontinued treatment (both during the first month) sought medical care 13 and 18 months later because of active pulmonary tuberculosis; none of the other patients appear to have been treated at the other hospitals in Gran Canaria.

The results of univariate analysis are shown in table 2. Abandonment of treatment occurred more frequently in women, in those aged under 55 years, and in those with extrapulmonary tuberculosis, smear positive tuberculosis, HIV seropositivity, homelessness, chronic alcoholism, intravenous drug abuse, abandonment of treatment in the past, and poor adherence to treatment at the second month. The five women who dropped out were intravenous drug abusers and indigents (table 2). Low compliance at two months was the only variable significantly associated with abandonment of treatment (p<0.0001).

At the time of diagnosis intravenous drug abuse was the only statistically significant variable in the multivariate analysis (OR 4.62; 95% CI 1.21 to 17.54; p=0.02) although homelessness, chronic alcoholism, and abandonment

Table 2 Results of univariate analysis. Predictors of poor compliance

Variable	Total	Cured	Abandonments (%)	Odds ratio (95% CI)
Age				
18–39 ^a	49	41	8 (16.3)	
40–54	37	31	6 (16.2)	0.99 (0.38 to 2.53)
>55	16	15	1 (6.2)	0.34 (0.04 to 2.77)
Women ^a	18	13	5 (27.7)	
Men	84	74	10 (11.9)	0.35 (0.10 to 1.15)
Extrapulmonary TB ^a	6	4	2 (33.3)	
Pulmonary TB	96	83	13 (13.5)	0.31 (0.05 to 1.75)
Smear negative ^a	8	7	1 (12.5)	
Smear positive	94	80	14 (14.9)	1.22 (0.13 to 10.78)
HIV seronegative	93	81	12 (12.9)	
HIV seropositive	9	6	3 (33.3)	3.38 (0.79 to 14.38)
Homelessness				
No ^a	31	28	3 (9.6)	
Yes	71	59	12 (16.9)	1.90 (0.50 to 7.19)
Drug abuse (iv)				
No ^a	79	70	9 (11.4)	
Yes	23	17	6 (26.0)	2.75 (0.88 to 8.54)
Chronic alcoholism				
No ^a	52	46	6 (11.5)	
Yes	50	41	9 (18.0)	1.68 (0.55 to 5.12)
Abandonment of treatment in the past				
No ^a	91	79	12 (13.2)	
Yes	11	8	3 (27.3)	2.47 (0.59 to 10.3)
Compliance 2nd month				
100% ^a	58	58	1 (1.7)	
>75%	32	28	4 (12.5)	8.29 (1.20 to 57.05)
50–75%	4	1	3 (75.0)	174 (30.18 to 10003.15)
<50%	7	0	7 (100) ^b	406 (75 to 2197.77) ^c
Total	102	87	15 (14.7)	

^a Reference category; ^b $p < 0.0001$; ^c Approximate estimation.

of previous treatment almost reached statistical significance ($p \geq 0.1$). At the end of the second month of treatment abandonment of past treatment was significantly associated with non-compliance (OR 8.87; 95% CI 1.15 to 68.15; $p < 0.05$).

Only three relapses occurred in the 102 patients followed up for one year and in the 88 patients followed for two years. The relapse rate at two years was 3.4%. The three relapses at one year occurred in an indigent patient, a patient who was an intravenous drug abuser and a chronic alcoholic, and another who had been non-compliant with treatment in the past.

Two patients were excluded from the analysis because of side effects which required a change of treatment (a case of “flu-like” syndrome attributed to the intermittent use of rifampicin and one of hepatitis associated with isoniazid). Eleven patients experienced transient side effects including gastric symptoms (seven), itching (three), and arthralgia with hyperuricaemia (one).

Discussion

At present the ideal antituberculosis regimen consists of daily administration of isoniazid and rifampicin for six months, reinforced with pyrazinamide during the first two months. In areas with high rates of primary resistance ethambutol is added in the initial phase.^{13–16} Regimens based on partial or fully intermittent administration of drugs are well established and have also been recommended. These include an initial two month period of daily administration, the use of four drugs in the initial phase, and the administration of drugs three times per week.^{13 15 20–26} However, a few studies of fully intermittent twice weekly regimens have been carried out with discouraging results.^{27–29} In the study by Paramasivan *et al*²⁸ only 80% of patients were culture negative at the end of

treatment, 49% did not complete the short course chemotherapy regimen, and no data on relapses were given. We have obtained much better results using the same intermittent anti-tuberculosis regimen which indicates the importance of directly observing drug taking in the success of this therapeutic strategy. Our findings are similar to those obtained in New York city,^{30 31} adopting similar measures although with far fewer resources. Supervision of drug taking from the beginning of treatment has been extensively recommended when factors such as poverty, homelessness, intravenous drug abuse, or anticipation of non-compliance are present, otherwise a very low cure rate will be achieved.^{7–9} In tuberculosis control programmes for high risk groups developed in Gran Canaria in 1988 and 1989³² 87% and 83%, respectively, of the patients abandoned antituberculosis treatment. These findings, and the results of the present study in which low compliance at two months was the only variable significantly associated with abandonment of treatment, further confirm the importance of directly observed administration of drugs. It is therefore necessary to develop special compliance-related strategies for high risk populations (such as those described in this study) including supervision of drug taking in patients on methadone maintenance programmes.³³

According to the recommendations of the American Thoracic Society,³⁴ for a short term chemotherapy strategy to be considered acceptable both therapeutic failures and relapses should not exceed 5% and adverse effects of treatment should not cause a change in the therapeutic regimen in more than 5% of patients. The present results fulfil these specifications (no failures, relapse rate of 3.4% in 88 patients followed for over two years after completion of treatment, 1.9% adverse effects) and the high rate of negative cultures at the end of the second month (94.7%) confirms the effectiveness of six months of fully intermittent (twice weekly) tuberculosis treatment. These figures are similar to those obtained in islanders treated with a standard course of medication.³²

The main problems with the treatment of tuberculosis are supervision of the patients until they are cured and the cost of achieving this in developing countries. Both problems could be solved with the supervised treatment under study as it would be necessary to observe 52 drug administrations directly to control the entire treatment, fewer than the 60 that would be needed for daily supervision during the first two months of the recommended regimens by the International Union against Tuberculosis and Lung Disease and the World Health Organisation.^{4 5 13 14 35 36} On the other hand, doses of rifampicin (the most expensive drug) in the intermittent regimen are equal to those used in daily regimens. This, together with the fact that treatment is provided on an outpatient basis, results in a substantial reduction in the cost of treatment.

In summary, this study shows the effectiveness of a fully intermittent antituberculosis regimen from the beginning of treatment, and the efficiency of an incentive programme in

which administration of the medication was directly supervised by the nursing staff. This regimen may constitute a valuable strategy in tuberculosis control programmes in developing countries and for treating high risk patients in whom non-compliance is anticipated, especially in industrialised countries.

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