Attendance versus compliance with tuberculosis treatment in an occupational setting — a pilot study

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Aim. To determine the prevalence of non-compliance with tuberculosis treatment at Freegold Mines.

Objectives. 1. To establish the rates of attendance and collection of anti-tuberculosis drugs. 2. To determine prevalence of non-compliance by means of urine tests.

Design. A cross-sectional study conducted over 2 weeks at mine medical stations.

Method. Urine samples were collected from tuberculosis patients 3 hours after drug ingestion. Non-compliance was established by testing these samples for rifampicin and/or isoniazid (INH) metabolites. Non-compliance was defined as a negative urine test result for these drugs in participants whose treatment regimens included one or both. Daily attendance and collection of drugs statistics are recorded in the medical station tuberculosis register. The patient rate of adherence was calculated as the observed number of days on which medication had been collected over the expected treatment days in a given period.

Results. Urine test results showed an overall prevalence of non-compliance of 14.6 ± 3.3%. The study showed that non-compliance with tuberculosis treatment was underestimated by the surveillance data. The rate of non-adherence with treatment established from the formal surveillance procedure was 0.2%. The poor response rate of patients was found to be a major problem and fewer than 40% per day returned to bring urine specimens. The mean prevalences of non-compliance established by rifampicin and INH tests were 19.5 ± 5.3% and 9.8 ± 3.9%, respectively, and these were significantly different (χ^2 = 7.44; $P < 0.05$). The proportion of false-positive results for INH and rifampicin urine tests were 21% (11/53) and 35%

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(17/48), respectively, showing that some patients were taking the wrong treatment.

Conclusions. **It is clear that attendance at the clinics does not accurately reflect compliance. Both programme compliance (dispensing of the correct treatment) and patient compliance need to be improved. This has important implications for the new national tuberculosis control policy adopted by the South African government that stresses the importance of directly observed therapy, short-course (DOTS) and a patient-centred approach.**

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Poor compliance with treatment is regarded as the major drawback of effective tuberculosis chemotherapy worldwide and as one of the principal causes of treatment failure and drug resistance.[1-4] Various methods such as directly observed therapy, short-course (DOTS), using intermittent or short-course chemotherapy, have been developed in order to improve compliance.[5] The introduction of short-course anti-tuberculosis chemotherapy to control *Mycobacterium tuberculosis* had brought high hopes to many for effective control of the disease. Short-course chemotherapy has resulted in high cure rates that can be achieved in a relatively short space of time. Low relapse rates 2 - 3 years after completion of the scheduled treatment and low levels of multidrug resistance are expected. Studies have shown, however, that success in treating tuberculosis depends not only on the efficacy of the treatment regimen, but also on social and economic factors.[6-8]

Tuberculosis is a major problem in South Africa[9,10] and needs urgent attention in the light of the increasing HIV epidemic; HIV reactivates latent tuberculosis in infected individuals and may result in a significant increase in new tuberculosis cases.[7] It is generally believed that well-implemented and well-managed tuberculosis control programmes can yield cure rates of 85% or more in smear-positive cases[2] and it has been suggested that tuberculosis control can be successful, even in populations with a high prevalence of HIV.[11]

A comprehensive tuberculosis control programme was introduced at Freegold Mines in 1977.[12] Until 1993 the incidence of pulmonary tuberculosis (PTB) had remained relatively constant at 550/100 000 men (G A Churchyard — unpublished data). Since 1993, a two-fold increase in the incidence of PTB has been recorded.[13] This increase is due in part to the impact of HIV infection. In order to reduce the increasing incidence of tuberculosis, DOTS regimens, intensive contact evaluation and patient education programmes have been introduced.

Poor compliance or non-compliance with tuberculosis treatment have been associated with drug resistance, high relapse rates and treatment failure.[11,14,15] At Ernest Oppenheimer Hospital (EOH), attendance rates of 99.8% have been reported. In view of the claim by the World Health Organisation[2,16] that an 85% cure rate should be sufficient to control tuberculosis, it is of great concern that with such a comprehensive tuberculosis control programme in place, the incidence of infection should be increasing. Anecdotal reports of patients not complying with tuberculosis treatment have been received. These include treatment drugs being thrown out of windows or found in patients' belongings and vomiting after ingestion of the drugs under DOTS. There are also reports that show that some patients are unable to absorb the drugs; this would effectively reduce the level of compliance[17] although the condition is reported to be rare and, so far, has not been reported in South Africa (P G Smith — personal communication).

The aim of this study was to determine the point prevalence of non-compliance with tuberculosis treatment in the Freegold Mine region by establishing the attendance rate and collection of anti-tuberculosis drugs and to carry out a cross-sectional estimate of compliance based on urine tests.

Study area and study population

This study was conducted at Freegold Mines medical stations in Welkom. Freegold Mines are divided into five medical zones with medical stations in each shaft. Mine workers who are diagnosed as having PTB by EOH and those discharged from the hospital collect their treatment from these medical stations. Patients collect their treatment daily from Monday to Friday as prescribed by the EOH medical officer. All patients who were on tuberculosis treatment during the week 26 June 1995 to 6 July 1995 formed the study population.

Methods

A cross-sectional study was conducted over 2 weeks to obtain a preliminary estimate of the prevalence of non-compliance. In order to detect a 1% prevalence of non-compliance (95% CI 0 - 2%) a sample of 290 PTB patients was required. Non-compliance was established by testing urine samples from these patients for rifampicin and isoniazid (INH) drug metabolites. The test for rifampicin used n-butanol (DOW Chemicals Africa — personal communication, and Nel[18]). A positive reaction to this reagent is evident up to 12 hours after drug ingestion. It is shown by a salmon-pink to cherry red colour in the upper n-butanol layer and a light orange colour where there is a trace reaction. For INH, a colour test used 10% solutions of potassium cyanide and chloramine-T.[19-21] A colour change of cherry red is indicative of positive reactions up to 24 hours after drug ingestion. In samples where trace reactions occur, a pink colour change is observed. For the purpose of this study, non-compliance was defined as having a negative urine test result for INH and/or rifampicin metabolites from participants whose treatment regimens included one or both of these drugs. Participants were dichotomised into compliers and non-compliers.

In each medical station the tuberculosis register is signed by both nurses and patients after administration of the drugs to each patient. Daily tuberculosis attendance statistics are reported and the patient rate of adherence is calculated monthly as the observed number of days on which medication was collected over the expected treatment days that month.

Determination of non-compliance

Medical stations with the highest number of tuberculosis patients were selected from each zone. In total, five medical stations were included in the study. At each medical station, patients collecting their medication were systematically selected by the choice of every fifth patient. All selected patients were asked to come back to the medical stations to give urine specimens 3 hours after drug ingestion. Changes of colour in rifampicin tests are reported to be very reliable within 8 hours of drug ingestion and can be done up to 12 hours after drug ingestion, but are then less reliable. INH reactions are known to last up to 24 hours after drug ingestion.

At the time of this study, Freegold Mines had just introduced surprise random testing of urine at the medical stations by the nursing staff as part of the tuberculosis control programme. Tests for rifampicin were undertaken immediately after collection of the specimens by nurses at the medical stations. The remaining urine specimens were refrigerated overnight and sent to the EOH laboratory the following morning, where further tests for rifampicin and INH metabolites took place. Testing of rifampicin at the laboratory was therefore a quality control measure to evaluate the medical station results. The attendance rate of tuberculosis patients for treatment at medical stations was monitored through normal clinic surveillance of tuberculosis patients.

Analysis

The prevalence of non-compliance is expressed as the percentage of negative urine test results out of the total urine samples tested for rifampicin and INH metabolites. Results for all the medical stations combined are expressed as mean values of prevalence with confidence intervals. Exact binomial confidence intervals (95%) were calculated for prevalences at each medical station. Confidence intervals based on the normal approximation (95%) to the binomial were estimated for the mean values of prevalence taken across all medical stations. False-positive results are expressed as a percentage of the total number of participants whose treatment regimens did not include the relevant drug. The overall mean estimate of non-compliance with tuberculosis treatment was calculated with the laboratory rifampicin and INH urine test results combined. An association between medical stations and prevalence of non-compliance was tested by means of a χ^2-test. This was also used to test for significant differences between the means for the different treatment regimens.

Results

Less than 40% of the patients recalled actually returned to give urine specimens each day at most of the sampling stations. Out of 523 mineworkers with *M. tuberculosis* who were asked to come back to give urine specimens, 270 returned. The number of patients on each treatment regimen who were tested is shown in Table I. A large proportion of participants (66.7%) were on treatment regimens that included both INH and rifampicin. The remainder were on treatment regimens that included either INH or rifampicin in combination with other drugs. In total, 270 urine specimens were tested for rifampicin and INH metabolites over a 2-week period. The same urine specimen was tested for rifampicin metabolites at both the medical stations and the hospital laboratory. Two sets of rifampicin test results, those tested at the medical station and the laboratory, are presented (Fig. 1).

Table I. Frequency distribution of patients by treatment regimens in medical stations A-E

Station	INH and other drugs	Rifampicin and other drugs	INH, rifampicin and other drugs	Neither INH nor rifampicin	Total	%
A	9	10	33	1	53	19.6
B	8	5	22	0	35	12.9
C	6	7	39	3	55	20.4
D	15	6	57	4	82	30.4
E	4	9	29	3	45	16.7
Total	42	37	180	11	270	100
Per cent	15.6	13.7	66.7	4.1		

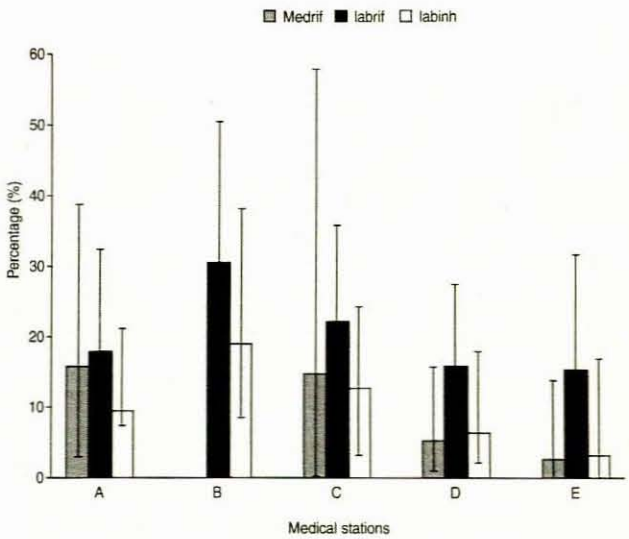

Fig. 1. Percentage of urine samples negative for rifampicin and INH tests performed by the medical stations (Medrif) and the laboratory (Labrif, Labinh).

The prevalence of non-compliance established by the different urine test methods for each medical station is shown in Fig. 1. Medical station B did not perform urine tests for rifampicin. For each drug tested, there was no significant difference in urine test results between the medical stations. Similarly, there was no significant difference in results between medical stations, regardless of whether tests were carried out at medical stations or the laboratory (Table II). A mean prevalence of non-compliance of 7.1 ± 4.5% was found in respect of the urine test for rifampicin done by the medical stations. The laboratory urine test results showed mean prevalences of non-compliance with rifampicin and INH for all five medical stations combined to be 19.5 ± 5.3% and 9.8 ± 3.9%, respectively.

The mean prevalence of non-compliance in respect of rifampicin test results differed significantly depending on whether the test was done at the laboratory (19.5 ± 5.3%) or by the medical station (7.1 ± 4.5%)($\chi^2 = 8.79$; $P < 0.05$). However, there was also a significant difference between mean prevalences of non-compliance with rifampicin and INH (19.5 ± 5.3% and 9.8 ± 3.9%) when both were tested at the laboratory ($\chi^2 = 7.44$; $P < 0.05$). The mean prevalence of non-compliance in respect of rifampicin and INH combined for each medical station (Fig. 2) did not differ among the five medical stations ($\chi^2 = 7.36$, respectively; df = 4; $P > 0.05$). Because of the difference between the medical station and laboratory rifampicin results, an overall prevalence of non-compliance was estimated using the laboratory results for rifampicin and INH. The overall prevalence of non-compliance among those who returned to give urine samples was 14.6 ± 3.3%.

Table II. Chi-square test results for INH and rifampicin for differences between medical stations

Urine test method	χ^2	df	*P*-value
Rifampicin results tested by medical stations	3.59	3	$P > 0.05$
Rifampicin results tested by laboratory	3.63	4	$P > 0.05$
INH results tested by laboratory	2.91	4	$P > 0.05$

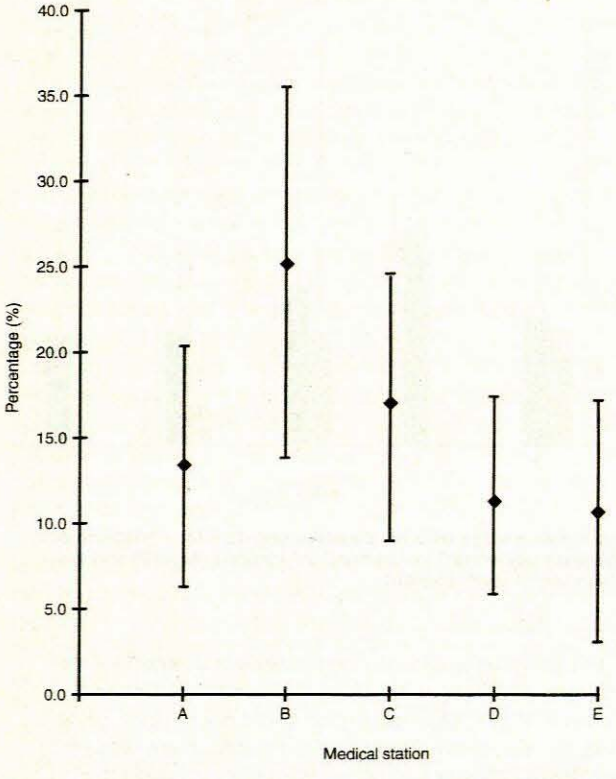

Fig. 2. Mean prevalence of non-compliance with rifampicin and INH combined at each medical station.

The rate of non-compliance with tuberculosis treatment established on the basis of attendance at the different medical stations over the same 2-week period was 0.2%. For most medical stations, the apparent rate of attendance was 100% per day.

Fig. 3 shows the percentage of false-positive urine test results for rifampicin and INH as a proportion of the participants whose treatment regimens did not include these drugs. The mean prevalences of INH and rifampicin false-positive urine tests were 21 ± 11% (11/53) and 35 ± 13% (17/48), respectively. The overall prevalence of false-positive results was 28 ± 9%. Four per cent (11/270) of all urine samples were from patients whose treatment regimens did not include rifampicin and INH. However, 45.5% and 9.1% (5 and 1) of these tested positive for rifampicin and INH, respectively, but the overall numbers involved are very small.

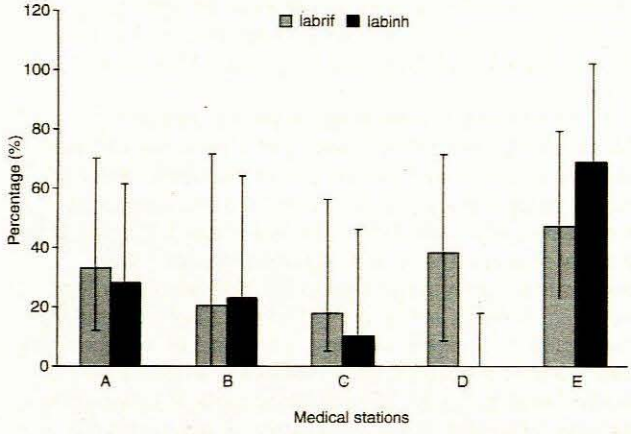

Fig. 3. Percentage distribution of false-positive urine test results for rifampicin and INH tests performed by the laboratory.

Discussion

Compliance with chemotherapy is a well-known problem in the management of tuberculosis. DOTS has been recommended as the best method to improve poor compliance or non-compliance[3,14,22] and has led to significant decreases in relapse rates and drug resistance.

This study demonstrates a poor response rate to testing on the part of participants (< 40% per day during the 2-week sampling period). This poor response rate can be attributed to a number of factors. These include the fact that workers staying in communities outside the mines may find it difficult to go back to the medical stations after working hours, and some workers may have felt that the process of urine testing encroached on their leisure time. Non-responders are likely to have a higher risk of non-compliance with their treatment than those who respond. The true prevalence of non-compliance is therefore likely to be higher than the rate of 14.6 ± 3.3% estimated in this study. A better estimate of the true value of non-compliance with treatment at these medical stations needs to be established.

The policy of Freegold Mines is that each medical station carries out surprise random urine tests for rifampicin to ensure compliance. When we started this study, none of the medical stations had done these tests, although they all had supplies of the necessary reagents from the EOH laboratory. During the study two of the five stations (A and C) conducted few tests — 20 and 7, respectively — and station B performed none (Fig. 1). As a result of such small

numbers, there is great uncertainty about non-compliance, as shown by the confidence intervals in Fig. 1. This is likely to be the reason for the difference that was found between the mean prevalences of non-compliance established by medical stations and the laboratory results. Because of great uncertainty in medical station results, these were not included in overall calculations of non-compliance.

When the prevalence of non-compliance with tuberculosis treatment established through surveillance procedure (0.2%) was compared with the urine test method (14.6%), it became clear that the rate of non-adherence, as measured by surveillance, is a gross underestimate of actual non-compliance. If routine surveillance is to be used to estimate compliance, a much more rigorous way of doing it must be developed and tested against the results of random urine tests.

An analysis of the urine test results for the individual drugs showed that there were more negative tests for rifampicin than for INH; the means of non-compliance for these two drugs differed significantly. Out of the 11 participants whose treatment regimens did not include the tested drugs, 6 (54.5%) tested positive for these drugs (Fig. 3). This gives an indication of pitfalls in the control programme. Although this needs further investigation, it is clear that some patients take the wrong drugs. De Cock and Wilkinson[23] point out that multiple regimens offered to tuberculosis patients can cause confusion. At times, medical officers change treatment regimens for various reasons. It was found that treatment regimens prescribed after last consultations with medical officers at the hospital were sometimes not given, and that patients continued with the old treatment regimen. Observations during administration of the tuberculosis treatment showed that DOT varied greatly among the five medical stations and was not always consistent with Freegold Mines' tuberculosis DOTS policy. As a result of understaffing in different medical stations, patients were not fully supervised according to the DOTS procedure.

Conclusion

This study was undertaken to determine the prevalence of non-compliance of patients with tuberculosis treatment under the DOTS approach at Freegold Mines, where availability of drugs and accessibility to health care centres present no problems. With the increasing incidence of tuberculosis, partly as a result of HIV infections, we felt it necessary to identify and tighten control over factors that may have as great an impact, but that can be controlled. The findings of this pilot study show that even with the DOTS approach, some patients do not take their drugs and that daily surveillance may not necessarily give a true reflection of what is actually happening.

Quantitative follow-up studies and qualitative studies to look at risk factors for non-compliance with tuberculosis treatment in the mine setting are planned. This study has shown that for the benefit of the tuberculosis control programme and before these studies can be undertaken in these mines, some areas need to be improved. These include improving patient response rates to testing. Nursing staff need to be encouraged to undertake rifampicin urine tests at the medical stations. This will assist them in identifying non-compliers. Besides reinforcing the attendance results, this can help to predict the outcome of the treatment and to detect patients who have problems with their treatment regimens. Some medical stations are understaffed and patients are left to get their own treatment. This calls for alternative means of treatment administration which may require peer or community involvement. Communication between medical officers and the nursing staff needs to be strengthened to avoid continuous administration of drugs that have been changed.

DOTS and patient-centredness are two key elements of the guidelines of the WHO global programme on tuberculosis control.[24] Since this has been adopted as a national policy in South Africa, it is of the utmost importance that DOTS be correctly implemented so that it will achieve the desired outcome.

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