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Accuracy of Self-Reported Adherence to Tuberculosis Therapy among DOTS patients in Mumbai

Abstract

Purpose: To compared self-reported adherence to DOTS therapy with urine rifampicin metabolite levels and medical records among patients in Mumbai, India.

Methods: Study subjects (N=538) were randomly selected from the DOTS centers in Mumbai, India. Self-reported adherence was ascertained by interviews; unannounced home visits were conducted, and urine samples were collected for rifampicin metabolite testing using the n-butanol test. Information from medical records was abstracted for documented receipt of drugs from the DOTS centers.

Results: Agreement between self-reported adherence and urine tests was very poor (kappa, 0.08); and between self-reports and medical records was moderate (kappa, 0.47). Receipt of drugs did not ensure adherence. Based on urine n-butanol test, 75% of patients were adherent. Physical appearance of urine for rifampicin excretion with the n-butanol extraction method indicated a high positive predictive value (95%).

Conclusion: We recommend incorporating urine tests for various drug metabolites periodically in the DOTS program to ensure treatment adherence.

Keywords: Tuberculosis; Adherence; Urine testing; Rifampicin; DOTS

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Introduction

India, the second largest populous country in the world, bears about 30% of the global burden of tuberculosis (TB) [1]. India has a long history of a national program developed for the control of TB. In 1993, the national program began incorporating the World Health Organization's Directly Observed Treatment Short Course (DOTS) drug regimen. Currently, India has the second largest DOTS program in the world, covering about 30% of TB patients in the country [2]. Despite these measures, the incidence of TB has continued to rise. A major obstacle of adequate TB control has been the development of multi-drug resistant (MDR) TB.

Non-adherence to TB therapy is a well-recognized problem that may result in MDR-TB and disease relapse [3]. Among the various drugs used in TB therapy, rifampicin resistance has been identified as a major contributing factor for MDR-TB [2]. Rifampicin, a first line agent of TB therapy, has the unique ability to kill the tubercle bacilli during its bursts of metabolism and growth [4]. It is a component drug of the DOTS regimen in both the intensive and continuous phases of treatment. Rifampicin is deacylated into 25-deacetyl rifampicin, an active metabolite that can be detected in the urine up to 24 hours.

Most DOTS centers in India rely on self-reported data on drug adherence. To our knowledge, self-reports on adherence have not been evaluated for patients attending the DOTS centers at Mumbai, India. Therefore, we conducted this study to examine the accuracy of self-reported data on adherence by comparisons with a simple urine test to detect rifampicin metabolites and to data obtained from medical records on receipt of medications.

Methods

Study Design

Prior to the study, HSRB approval was taken from the IRB committee of the University of Alabama, Birmingham and the ethics committee of Brihan Mumbai Municipal Corporation, Mumbai. We used data from a cross-sectional study conducted by us in 2003 that was designed to determine factors contributing to non-adherence to TB therapy among DOT patients in Mumbai, India. Non-adherence was defined as missing one week of treatment in a month (either a consecutive period for one week or sporadic doses of drugs totaling a week).

Study subjects were 538 patients randomly selected from 65 of the 230 DOTS centers. Eligible subjects were men and women with pulmonary TB as determined by laboratory investigations (sputum positive for acid fast bacilli and/or chest X-ray), who were 20 or more years of age and who were receiving category I or category II treatment regimen. Category I patients are newly diagnosed sputum positive patients who receive a combination of four standard anti-TB drugs: ethambutol, rifampicin, pyrazinamide and isoniazid in the intensive phase and isoniazid and rifampicin in the continuation phase for a period of at least 6 months. Category II patients are treatment defaulters, treatment failures or relapse cases who receive streptomycin administered parenterally for two months in addition to the drugs specified for category I intensive phase, and receive (isoniazid, rifampicin and ethambutol) in the continuation phase. Patients who had extra-pulmonary TB, or who were receiving Category III DOTS regimen were not included in the study. Pregnant women and patients who were too ill to be interviewed were also not included in this study.

Interviews

A structured face-to-face questionnaire that elicited information on adherence to treatment and on potential risk factors that may contribute to non-adherence was administered. As a part of the questionnaire, patients were required to recall the most recent date and time when drugs were taken. Information on adherence to treatment schedules and receipt of medications from the medical records maintained at the DOTS centers was obtained. For a random sample of 102 patients who were in the continuation phase of treatment of Category I or II, we conducted unannounced interviews at their homes, administered the questionnaire and obtained a

urine specimen, four to six hours following estimated ingestion of the drugs. About 20 ml of urine was collected during the visit and transported in a cooler to the laboratory attached to the DOTS centers.

Urine test for rifampicin

We used the n-butanol color test to detect rifampicin metabolites in urine. One of us (SB), blind to patient's identification and adherence status, performed the testing. The urine samples were thawed to room temperature. The physical appearance (color) was recorded as rifampicin produced an orange-red coloration of the urine. For the n-butanol test, a 10 ml urine sample was pipetted into a test tube and 2 ml n-butanol was added. To augment mixing, the tube was inverted gently a few times. The test tube was allowed to stand for about 30 seconds, to allow the n-butanol to separate. The appearance of a cherry-red color in the upper n-butanol layer indicates a concentration of $\geq$ 50 µg/ml of rifampicin in the urine. Decreasing concentrations of rifampicin are indicated by decreasing color of the butanol layer, salmon pink to light orange.

Analysis

We performed the analysis by doing the following comparisons. Self-reported-adherence to DOTS regimen was compared to adherence status as determined from urine n-butanol test results; self-reported-adherence to receipt of drugs from medical records; and physical appearance of urine to urine n-butanol test results. Agreement between each set of information sources was determined using the kappa coefficient (κ) and the associated 95% confidence intervals (k values near 1 suggest very high levels of agreement). Using the n-butanol test as the gold standard, the sensitivity, specificity and positive predictive value for self-reported adherence was computed. Sensitivity was calculated as the number of subjects who reported adherence and had a positive urine test, divided by the total number of subjects with a positive urine test. Specificity was computed as the number of subjects who reported non-adherence and had a negative urine test, divided by the total number of subjects with a negative urine test. The PPV was calculated as the number of subjects with a positive urine test who also reported adherence, divided by the total number of subjects who reported adherence. Self-reported adherence and the urine test results by subject characteristics such as age, gender, surrogate measures of socio-economic status (literacy, employment status), marital status, number of household members and the treatment regimen category was compared.

Using the urine n-butanol test as a gold standard, we examined the usefulness of using physical appearance of urine (orange-red color) in correctly classifying patients' adherence to rifampicin. To do this, we computed the positive predictive value of the physical appearance of the urine as the number of patients with a positive n-butanol test among those whose urine was orange-red in color. We also computed the sensitivity and specificity of the physical appearance of the urine. Sensitivity was defined as the proportion of patients with a positive n-butanol test and who also had orange-red color of urine. Specificity was defined as the proportion of patients who had a negative n-butanol test and who did not have orange-red color urine.

Results

The self-reported adherence status and urinary n-butanol test results for the subgroup of 102 patients who participated in the urine testing for rifampicin metabolites. are provided in Table 1.

Table 1: Self-reported adherence status and urinary n-butanol test for rifampicin metabolites*

Self-reported adherence status	Adherent	Non-adherent
Adherent	70	22
Non-adherent	6	4
Total	76	26

**Using urinary n-butanol as the gold standard, self-reported adherence status had a sensitivity of 92%, and specificity of 15% (κappa=0.09, p value = 0.26, 95% CI=-0.09-0.28). Assuming adherence status in the Mumbai DOTS screening population was represented in this sample, the positive predictive value of self-report was 76%, and the negative predictive value was 40%.*

The sensitivity and specificity of self-reported adherence were 92% and 15%, respectively. There was very poor agreement between subjects' report of adherence to DOTS regimen and urine n-butanol test (κ=0.09, 95% CI=-0.9-0.28). Most of the disagreement was due to patients falsely reporting adherence to DOTS regimen. Of 92 patients who reported adherence, 22 (24%) were not corroborated with urine findings. Patients' recall problems contributed to a small part to the disagreement. Six out of ten patients who reported non-adherence to DOTS regimen had a positive urine test. Of the 102 patients, 76 (75%) were adherent to the drug regimen based on urine testing. The agreement between self-reports of adherence and urine testing for n-butanol for subgroups of subjects characterized on the basis of age, gender, education, employment status, marital status, household members and treatment category was very poor ranging from -0.14 to 0.25 (Table 2).

The agreement between adherence status as obtained from self-reports to those based on medical records was on the lower range of moderate agreement (kappa = 0.47) (Table 3). Of 441 patients reporting adherence and whose medical records documented receipt of drugs, 64 had urine testing done which indicated that 57 (89%) were adherent and 7 (11%) were non-adherent. This suggests that medical records documentation of receipt of drugs does not ensure adherence. Of 52 patients who reported adherence and whose medical record indicated non-adherence, 28 had urine tests available of which 15 (54%) were non-adherent and 13 were adherent (46%). Of 35 patients who self reported non-adherence and whose medical records also indicated non-adherence, 10 had urine testing done of which 4 were found to be non-adherent and 6 were adherent. All of these findings suggest that both patient and the health care system factors may account for the disagreement. Besides false reporting, patients may have recall problems or may have had unused drugs from previous visits. Although a smaller problem, it is clear that medical records may not always capture all clinic visits.

Table 2: Sensitivity and positive predictive value and kappa coefficients for self-reported adherence using urine n-butanol test as a gold standard, according to selected subject characteristics

	True Positive (N)	False negative (N)	False positive (N)	True negative (N)	Sensitivity (%)	Positive predictive value (%)	κ (95% CI)
Age (years)							
20-39	52	4	14	1	93	79	-0.01 (-0.20 - 0.18)
40+	18	2	8	3	90	69	0.20 (-0.13 - 0.53)
Gender							
Male	40	4	12	4	91	77	0.19 (-0.08 - 0.45)
Female	30	2	10	0	94	75	-0.09 (-0.19 - 0.02)
Education (school years)							
≤ 5	35	6	9	3	85	80	0.11 (-0.18 - 0.41)
5+	35	0	13	1	100	73	0.10 (-0.08 - 0.28)
Employment status							
Unemployed	46	3	11	4	94	81	0.25 (-0.02 - 0.52)
Employed	24	3	11	0	89	69	-0.14 (-0.28 - -0.01)
Marital status							
Married	38	3	14	3	93	73	0.13 (-0.11 - 0.37)
Single/other	32	3	8	1	91	80	0.03 (-0.25 - 0.32)
Number of household members							
0-3	17	2	2	1	46	90	0.23 (-0.31 - 0.77)
3+	53	4	20	3	93	73	0.08 (-0.12 - 0.27)
Treatment category, continuous phase							
Category I	34	2	9	1	94	79	0.06 (-0.21 - 0.33)
Category II	36	4	13	3	90	74	0.11 (-0.15 - 0.36)

κ = Kappa. 95% CI = 95% confidence interval

Table 3: Self-reported adherence status and drug receipt documented in medical records

	Medical records	
Self-reports	Adherent	Nonadherent
Adherent	441	52
Nonadherent	10	35
Total	451	87

κ=0.47, p=0.00, 95% CI=0.36-0.58. κ = Kappa. 95% CI = 95% confidence Interval

A comparison of the use of physical appearance (red to orange discoloration in urine) as a measure of rifampicin excretion with the biochemical test (n-butanol extraction method) indicated that the predictive value for a positive physical appearance was high (95%) (Table 4). The sensitivity and the specificity were 99% and 85%, respectively.

Discussion

This study found that adherence to treatment based on the urine test was 75%. The accuracy of self-reported adherence to TB therapy was very poor when compared to the gold standard of the urine n-butanol test. The agreement between self-reports of adherence and medical records' documentation of clinic visits was higher than the urine chemical test; however, we noted that documentation of receipt of drugs does not ensure patient adherence and that medical records may not capture all clinic visits.

Table 4: Physical appearance of urine and urinary n-butanol test results

Urine physical appearance	Urine n-butanol test	
	Positive	Negative
Positive	75	4
Negative	1	22
Total	76	26

Using urinary n-butanol as the gold standard, physical appearance of urine had a sensitivity of 99%, and specificity of 85% (κ=0.87, p=0.00, 95% CI=0.75-0.98). Assuming urine physical appearance in the Mumbai DOTS screening population was represented in this sample, the positive predictive value of physical appearance was 95%, and the negative predictive value was 96%.

A recent study conducted in Australia found a sensitivity of 76% and a specificity of 56% when self-reports of adherence to anti-TB therapy were compared with urine isoniazid levels [5]. Studies that have examined adherence to anti-TB therapy by validating self-reports with urine tests for metabolites of isoniazid, rifampicin and pyrazinamide [6,7] have found varying range of drug adherence patterns, ranging from 60% to 100%. Our results thus fell within the range of adherences reported by other studies.

The DOTS program in India has been expanding rapidly since 1998 [8]. In both 2000 and 2001, the country accounted for more than half the global increase in the number of patients treated under DOTS and by early 2002, more than a million patients were being treated under the program in India [8]. Under the DOTS program attempts are made to facilitate adherence. The doctor explains the treatment schedule to the patient and the TB health visitor visits the home of the patient, speaks with the patient and his/her family, emphasizing the importance of adhering to the treatment schedule. During the intensive phase, the patient is requested to come to a convenient DOTS center three times per week to receive the drugs under direct observation. However, during the continuation phase there is no direct supervision of drug intake, the patient visits the center once a week to collect medications until the completion of treatment. The TB health worker monitors the therapy, manages drug reactions and takes 'defaulter retrieval action' – i.e. should the patient fail to appear at the DOTS center on more than two occasions, the health visitor goes the patient's home and brings them in for treatment. The DOTS based treatment has several advantages: it provides high cure rates, it, has been shown to reduce the emergence of MDR TB, [9] it improves the longevity of AIDS patients by controlling TB among them [10] and it has been certified by the World Bank as "one of the most cost-effective of all health interventions" [11].

In this study, we noted a non-adherence of 25% based on the urine tests. Non-adherence to TB treatment has been shown to greatly increase the risk for development of MDR TB. In a retrospective study done in Japan to determine the attributable risk factors to emergence of multi-drug resistant TB, non-adherence to

treatment was found be a major risk factor (odds ratio 21.0: 95% CI= 4.10-107.63) [12]. Other studies have shown that DOTS is the best way to prevent MDR TB [13, 14]. Thus, it is very crucial to validate the accuracy of self-reports of adherence periodically among this population. In this study, we found that simple urine tests may be used to monitor adherence. The n-butanol test for rifampicin has been found to have 100% sensitivity and 100% positive predictive value, if urine is collected within 2-6 hrs of ingestion of rifampicin [15, 16]. It is a very inexpensive test that is acceptable to the patients because it is non-invasive. We also found that the physical appearance of urine is a good substitute for chemical testing of urine for rifampicin metabolite.

The study has some limitations. As the cost of testing multiple drugs was prohibitive (cost of one isoniazid strip in India is approximately $4.00) we were able to test for rifampicin metabolites only. It has been suggested that there could be differences in adherence to different drugs when patients are on multi-drug regimens [6]. Although, we collected the urine sample within 2-6 hours of reported ingestion of rifampicin, there is a potential of recall bias. If the time period following ingestion was greater than 6 hrs, the sensitivity of the n-butanol test might have been lower [15].

Conclusion

Treatment adherence cannot be guaranteed even if the patient is enrolled in a DOTS program. Periodic testing of urine should be used in conjunction with patient education to ensure that adherence to the therapy is complete. Such a strategy may also motivate patients to report their medication intake more accurately. We recommend that the urine tests for various drug metabolites should be made part of the management under the DOTS program and all the patients getting their treatment for TB should be periodically tested to ensure compliance.

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Conflict of Interest

We declare that we do not have any conflict of interest associated with the presented work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by us. NS, SB and GA conceived and designed this study. Data collection and analysis was carried out by NS, SB, GA, DS and PKV. The manuscript was prepared by NS, SB, GA, DS and PKV.

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