Original Article

A pilot study to determine the occurrence of concomitant diseases and drug intake in patients on antituberculosis therapy

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Abstract

Introduction: Altered pharmacokinetics of antituberculosis (anti-TB) drugs due to interaction with non-TB medications or concomitant diseases may lead to suboptimal plasma levels of the affected drugs and hence contribute to the emergence of drug resistance in mycobacteria. Yet, few studies have investigated the prevalence of concomitant drug intake or concurrent diseases in patients on anti-TB therapy (ATT). The objective of this study is to study the prevalence of concomitant diseases and intake of non-TB drugs in patients on ATT. **Methods:** Adult patients who were undergoing treatment for TB at a directly observed treatment short-course (DOTS) center were interviewed to find out any concomitant drug intake and ailments they were suffering from. Data were also collected from the patients' treatment cards. **Results:** A total of 105 patients were interviewed for the study over a period of 1 month. Among these, 66 (62.9%) patients reported having taken a non-ATT drug in the last 3 months, 61 (58.1%) of which were drugs that may affect the ATT. A comparable number of patients (61 [58.1%]) reported suffering from one or the other concurrent illnesses or symptoms while on DOTS, including one patient with AIDS and eight with diabetes mellitus. Fluoroquinolones had been prescribed to four patients while on DOTS. **Conclusion:** A large proportion of the patients with TB were found to be on non-TB concomitant medications including drugs with potential for interactions that are capable of affecting ATT outcomes. It is, therefore, important that the patients and prescribing physicians be aware of any possible drug interactions.

Keywords: Antitubercular therapy, drug–disease interactions, drug–drug interactions

Introduction

Tuberculosis (TB) is a chronic infectious disease which can be classified in various ways, based on the anatomical site, history of previous treatment, drug resistance, or HIV status.[1] Based on the anatomical site, TB is classified as pulmonary or extrapulmonary. Both types of diseases require treatment with multiple drugs for a minimum period of 6 months. During this long period, it is very likely that the patient may suffer from a concurrent illness. It is then reasonable to expect that a patient on anti-TB therapy (ATT) may also take other non-TB drugs at some point and that such drugs may interact with ATT.

Among anti-TB drugs, rifampin and isoniazid are most often implicated in drug interactions. Rifampin induces the metabolism of many commonly used drugs such as anticoagulants, anticonvulsants, other antimicrobials, antihypertensives, oral contraceptives, glucocorticoids, immunosuppressants, sulfonylureas, and theophylline.[2,3] Isoniazid, on the other hand, inhibits the metabolism of a number of drugs such as anticonvulsants, theophylline, benzodiazepines, and acetaminophen.[4] Ethambutol has been reported to have important drug–drug interactions through inhibition of human

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organic cation transporters. In particular, HIV or diabetes patients taking ethambutol may experience significant drug–drug interactions.[5]

While the effect of anti-TB drugs on metabolism of other drugs is well established, data on the reverse scenario are scarce. Recently, the potential of such interactions and their impact on TB outcomes have been recognized.[6] Drugs which affect the activity of cytochrome P450 enzymes may alter the drug levels of anti-TB drugs, leading to variability of drug response.

While a lot of attention has been given to drug interactions between anti-TB and anti-HIV drugs,[7] many other drugs have the potential to affect anti-TB drug metabolism. The use of such common over-the-counter drugs such as antacids may interfere with absorption of anti-TB drugs.

Certain diseases too may have important effects on patient outcomes in TB. HIV infection is well known to increase the susceptibility to TB, and antiretroviral therapy and anti-TB drugs are known to interact with each other.[8] Inadequate control of diabetes mellitus also predisposes the patient to TB. Diabetics are thrice more likely than nondiabetics to develop active TB[9] but may respond poorly to ATT, with higher rates of treatment failure and death. Some of the newer oral antidiabetic drugs can interact with anti-TB drugs and lower their efficacy. Suboptimal concentrations of isoniazid and rifampin are commonly found in TB patients with diabetes. Diabetics are also more likely to have toxicity due to ATT.[10]

In addition to the above metabolic changes, there could be other serious consequences of concomitant drug use of TB patients. Use of second-line antibiotics such as fluoroquinolones for a concurrent infection may encourage the emergence of drug resistance and make these second-line drugs useless for TB treatment. It is hence recommended that these antimicrobials not be used in a patient suspected or confirmed to have TB.

Therefore, the present study was conducted to estimate the prevalence of concomitant drugs or diseases in patients on directly observed treatment, short course (DOTS). We also assessed the awareness of TB patients regarding the use of other drugs during TB therapy.

Methods

Ethical considerations

Clearance was obtained from the Institutional Human Ethics Committee before starting the study (permission letter number: IHEC-LOP/2015/STS 0057–2015, dated May 12th, 2015). Informed consent was obtained from all participants before inclusion in the study in English or Hindi as preferred by the patient.

Study design and site

The study was a cross-sectional survey conducted at the DOTS center of a tertiary care hospital. The DOTS center was under the department of community and family medicine at the time of the study.

Study population and sample size

Study population comprised adult patients visiting the DOTS center at the tertiary care hospital. The DOTS center is visited by 5–10 TB patients each day. A convenience sample of all patients who were willing to participate were interviewed on all working days from Monday to Friday from May 20, 2015, to July 7, 2015, to achieve a total of at least 100 patients. The revised 2013 definitions of TB cases and treatments[1] were used to define and classify the study cases.

Data collection

Data were collected through administration of a questionnaire-cum-case record form by the investigator. The questionnaire was developed and pilot tested in 10 patients visiting the DOTS center. It included 10 questions regarding the presence or history of concomitant diseases as well as drug intake during the past 3 months (or less in case patient has been on DOTS for <3 months). Patients were also questioned if they had at any time discontinued their TB drugs. In case of concomitant drug intake, information was collected regarding whether the drugs were prescribed or self-administered. In case of self-administered drugs, the source of drug information and drug procurement were asked.

Selection criteria

TB patients registered with DOTS center aged ≥18 years and willing to participate were included in this study.

Statistical analysis

The results have been expressed as percentages. Chi-square test was used to determine the association between concomitant drug intake along with anti-TB drugs and age, gender, or education status. $P < 0.05$ was considered statistically significant.

Results

A total of 105 patients participated in the study including 60 (57.14%) men. The mean age of the participants was 35.43 years. Majority of the patients (77 [73.3%]) had pulmonary TB, while 28 (26.6%) patients were diagnosed with extrapulmonary disease. In addition, a majority of the patients (78 or 74.28%) were new cases, while 13 (12.3%) were relapsed cases, 4 (3.8%) were treatment after default, 1 (0.9%) each were transfer-in and treatment after failure, and 8 (7.6%) were classified as other previously treated cases.

Out of a total of 105 patients, 61 (58.1%) reported suffering from one or the other concurrent illnesses or symptoms while on DOTS [Table 1]. Many of these patients complained of

Table 1: Concurrent illnesses or symptoms reported while on directly observed treatment short course

Concomitant diseases/symptoms	Number of patients (*n*=105) (%)
Disease	
Anemia	8 (7.6)
Diabetes	8 (7.6)
Hypertension	2 (1.9)
Upper respiratory tract infection	2 (1.9)
Asthma	1 (0.9)
AIDS	1 (0.9)
Trigeminal neuralgia	1 (0.9)
Symptom	
Fever	18 (17.1)
Body pain and weakness	12 (11.4)
Cough	8 (7.6)
Nausea, vomiting	4 (3.8)
Diarrhea	3 (2.8)
Adverse effects to ATT	3 (2.8)
Total	75* (71.4)

*One patient could be suffering from more than one concurrent illness/symptoms.
ATT: Antituberculosis therapy

symptoms such as cough (7.6%), fever (17.1%), body pain, and weakness (11.4%), which may have been due to TB itself. Some of these symptoms such as nausea and vomiting (3.8%) and itching (0.9%) could also be adverse effects of ATT but were not recorded as adverse effects by the treating physician. On the other hand, 3 (2.8%) patients were reported as suffering from adverse drug reactions with ATT by the treating physician. These included one patient each with rash due to ATT, isoniazid-induced neuropathy, and pyrazinamide-induced joint pain.

Diabetes and anemia (eight patients each) were the most frequent concurrent illnesses in our patients undergoing DOTS. None of the patients stopped taking their anti-TB medicines due to a concurrent illness or symptom.

A total of 66 (62.9%) patients reported having taken a non-ATT drug in the last 3 months [Table 2]. The most frequently used concomitant drugs were acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) (41.9%), minerals, proteins or vitamin supplements (25.7%), and antidiabetic drugs (15.2%). Antibacterials (10.4%) and anti-ulcer drugs (9.5%) were the other commonly used drugs.

Out of a total of 66 patients who reported taking concomitant drugs, 46 (43.8%) had taken one or more drugs which have a potential for clinically significant interactions with ATT. These included anticonvulsants, antidiabetics, acetaminophen, antihypertensives, aspirin, opioid analgesics, and proton-pump inhibitors [Table 2].

Most of the patients who reported non-TB-related drug intake were prescribed these drugs by a medical practitioner (57, 54.3%), while 10 (9.5%) took medicines on their own. Self-administered drugs were acetaminophen or NSAIDs in eight patients and Ayurvedic medicines (Trikut and a combination product of tulsi, aloe vera, and avla) in two patients. The major source of self-administered drugs was a chemist shop (6.6%).

There was no association between concomitant drug intake along with anti-TB drugs and age, gender, or education status [Table 3].

Regarding patients' awareness about concomitant drug intake, a large percentage (78.1%) of the patients thought they should inform that they are on ATT when consulting a doctor for non-TB ailment [Table 4]. Similarly, 87 (82.9%) patients thought they should inform DOTS staff about concomitant drug use while on ATT. A somewhat smaller proportion (61.9% of patients) were also aware they should avoid self-administration of drugs while on ATT.

Discussion

More than half of the multidrug-resistant TB (MDR-TB) patients notified in 2014 were in India, China, and the Russian Federation. Nonadherence of patients is a well-known cause of emergence of MDR-TB,[19] which has a prevalence of ≤3% in new cases of smear-positive pulmonary TB and 12%–17% among smear-positive previously treated PTB cases.[20] In recent years, the role of pharmacokinetic drug interactions has been reemphasized in the emergence of TB drug resistance. Drug–drug or drug–disease interactions causing suboptimal plasma concentration of antimicrobials can lead to emergence of drug-resistant strains. Hence, it is important to recognize such interactions so that suitable measures can be taken to maintain the adequate plasma levels of anti-TB drugs such as dose adjustment or selection of alternate non-TB drugs.

Our study highlights the occurrence of concomitant drug intake in patients on ATT, with 43.8% patients reporting intake of at least one drug with a potential for clinically significant interactions with ATT, over the past 3 months. These included anticonvulsants, antidiabetics, acetaminophen, antihypertensives, aspirin, opioid analgesics, and proton-pump inhibitors. Our study also revealed the frequent use of acetaminophen along with ATT. This finding is of particular concern as isoniazid may decrease the metabolism of acetaminophen and lead to hepatotoxicity.[4,11] Moreover, many first-line anti-TB drugs such as rifampin, isoniazid, and pyrazinamide are hepatotoxic. Therefore, patients on isoniazid should be advised caution when taking acetaminophen since the hepatotoxic effects of isoniazid, acetaminophen as well as other hepatotoxic antitubercular drugs may add up to cause clinically significant hepatic damage.

Besides potential pharmacokinetic interactions, the use of concurrent medications has another important implication for a TB patient. Use of second-line antimicrobials such as fluoroquinolones may encourage the emergence of MDR and make the drug useless for the treatment of MDR-TB. They are, therefore, not recommended in TB patients. However, we found

Table 2: Concomitant drugs taken by patients on directly observed treatment short-course

Drug group	Drug	Number of patients (*n*=105) (%)	Potential for interaction with ATT	Reference number
Acetaminophen and NSAIDs	Total	44 (41.9)		
	Acetaminophen	29	Yes	[2-4,11]
	Aspirin	3	Yes	[12]
	Other NSAIDs*	12		
Nutrient supplements	Total	27 (25.7)		
	Multivitamins	15		
	Iron supplements	8		
	Calcium/protein supplements	4		
Antidiabetics	Total	16 (15.2)	Yes	[2,3,9,10,13-16]
	Insulin	3		
	Metformin	6		
	Sulfonylureas	4		
	Other	3		
Anti-ulcer drugs	Total	10 (9.5)		
	Proton-pump inhibitors**	6	Yes	[4]
	Histamine H_2 blockers	4		
Antiemetics	Total	6 (5.7)		
	Domperidone	5		
Antibacterials	Total	11 (10.4)		
	Fluoroquinolones***	4		
	Other[#]	7		
Antiretroviral therapy	Tenofovir, lamivudine, efavirenz	1 each (2.8)		
Antihistamines	Total	7 (6.6)		
	Cetirizine	5		
	Other	2		
Other	Total	19 (18)		
	Phenytoin	1	Yes	[2-4,16,17]
	Carbamazepine	1	Yes	[2-4,16,17]
	Amlodipine	1	Yes	[2]
	Other antihypertensives[##]	3		
	Opioids	4	Yes	[2,18]
	Miscellaneous	9		
Total		143[¥]	61[¥]	

*Diclofenac, 6; aceclofenac, 3; ibuprofen, 2; piroxicam, 1; **Rabeprazole, esomeprazole, 2 each; omeprazole, pantoprazole, 1 each; ***ofloxacin, norfloxacin, ciprofloxacin; [#]doxycycline, amoxicillin, 2 each; azithromycin, metronidazole, cotrimoxazole, 1 each; [##]clonidine, cilnidipine, torsemide, 1 each; [¥]One patient may have taken more than one drug. ATT: Antitubercular therapy; NSAIDs: Nonsteroidal anti-inflammatory drug

Table 3: Association between concomitant drug intake during the laCst 3 months with age, gender, and educational status of tuberculosis patients

Variable	Concomitant drug intake during the last 3 months		χ^2, df, *P*
	Yes (*n*=66)	No (*n*=39)	
Age group			
18-35	42 (63.6)	21 (53.8)	0.99, 2, 0.60
36-60	19 (28.8)	14 (35.9)	
>60	5 (7.6)	4 (10.3)	
Gender			
Male	40 (60.6)	20 (51.3)	0.87, 1, 0.35
Female	26 (39.4)	19 (48.7)	
Educational status			
Illiterate	11 (16.7)	15 (38.5)	6.7, 3, 0.08
Till 5th class or below	7 (10.6)	4 (10.3)	
Class 6th-12th	30 (45.5)	11 (28.2)	
College and above	18 (27.3)	9 (23.1)	

that four patients had been prescribed fluoroquinolones. These were ciprofloxacin, ofloxacin, and a fixed-dose combination of norfloxacin plus tinidazole.

Although we found no association between concomitant drug intake along with anti-TB drugs and age, gender, or education status, this could be due to our small sample size. We have not come across any study which has evaluated such an association.

Even though the majority of the patients were aware that both the DOTS staff and the physician treating non-TB disorders should be informed about the drugs they were getting, there were a considerable number of patients who were not aware about this issue – 13% regarding informing the DOTS staff and 22% regarding informing other physicians. Similarly, 38% of the patients were not aware that they should avoid self-administration of drugs while on ATT.

Table 4: Patient awareness regarding the use of concomitant drugs while on antituberculosis medications (*n*=105)

Question	Yes (%)	No (%)	Do not know (%)	Total (%)
Do you think you need to inform that you are on medication for tuberculosis when consulting a doctor for another illness?	82 (78.1)	17 (16.2)	6 (5.7)	105 (100)
Do you think you need to inform the DOTS staff if you are taking any other medications?	87 (82.9)	13 (12.4)	5 (4.7)	105 (100)
Are you aware that you should avoid taking any drugs without a prescription while you are on medication for tuberculosis?	65 (61.9)	40 (38.1)	-	105 (100)

DOTS: Directly observed therapy, short course

Limitations of the study

The small sample size is a major limitation of our study. The study was carried out at a newly established tertiary health-care institute, and hence, the number of registered TB patients at the DOTS center is small. A larger study prospective is required to give more conclusive data.

Conclusion

In view of the prevalence of concomitant intake of potentially interacting drugs with ATT, the authors feel that there should be a greater awareness among all stakeholders which include patients, caregivers, DOTS staff, and policymakers about the possible influence of concurrent disease and concomitant drugs in patients on ATT. A list of commonly used interacting drugs could be made available at the DOTS centers and to patients and included in the DOTS literature. In addition, patient treatment cards should include information about concomitant drugs or diseases which a TB patient may be taking or suffering from, respectively.

Further studies may be done to evaluate any difference in outcomes of patients with TB on chronic treatment for diabetes, hypertension, or other chronic disorders.

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Conflicts of interest

There are no conflicts of interest.

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