Original Article

Adverse effects of tuberculosis treatment: experience at an outpatient clinic of a teaching hospital in the city of São Paulo, Brazil*

Efeitos adversos no tratamento da tuberculose: experiência em serviço ambulatorial de um hospital-escola na cidade de São Paulo

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Abstract

Objectives: To determine the frequency of adverse effects related to the use of the tuberculosis treatment regimen designated Regimen I and the need for regimen alterations due to these effects. **Methods:** A retrospective analysis of 329 medical charts of patients who were treated with Regimen I and discharged after cure between March 2000 and April 2006 was carried out at the Tuberculosis Outpatient Clinic, Department of Pulmonology of the *Santa Casa de Misericórdia de São Paulo* Hospital in the city of São Paulo, Brazil. Adverse effects and the timing of their appearance, as well as subsequent modifications in the treatment regimen, were investigated. **Results:** We included 297 patients, 146 (49.1%) of whom presented one or more adverse effects related to antituberculosis medications. The frequency of minor side effects was 41.1%, and that of major side effects was 12.8%. The most common reactions were those involving the gastrointestinal tract (40.3%) and the skin (22.1%). Adverse effects were more common in the first and second months of treatment (58.4%). Modification of the treatment regimen was necessary in 11 cases (3.7% of the total sample). Drug-induced hepatitis was the adverse effect that demanded the most regimen changes. **Conclusions:** In this group of patients, the frequency of adverse effects related to treatment with Regimen I was 49.1%. However, in most of the cases, it was not necessary to modify the treatment regimen due to side effects.

Keywords: Tuberculosis/therapy; Antitubercular agents/adverse effects; Hepatitis, toxic.

Resumo

Objetivos: Verificar a freqüência de efeitos adversos com o uso do Esquema I para tratamento da tuberculose e a necessidade de alterações no tratamento devido a esses efeitos. **Métodos:** Foi feita uma análise retrospectiva de 329 prontuários de pacientes que foram tratados com o Esquema I e receberam alta por cura entre março de 2000 e abril de 2006 no Ambulatório de Tuberculose da Clínica de Pneumologia da Santa Casa de Misericórdia de São Paulo. Foram analisados os dados referentes aos efeitos adversos, época de seu aparecimento e modificações do esquema de tratamento subseqüentes. **Resultados:** Foram incluídos 297 pacientes, e 146 (49,1%) apresentaram um ou mais efeitos adversos relacionados às drogas antituberculose. A freqüência dos efeitos colaterais menores foi de 41,1%, e a dos efeitos maiores foi de 12,8%. Os efeitos relacionados ao trato gastrointestinal (40,3%) e pele (22,1%) foram os mais freqüentes. Os efeitos adversos foram mais freqüentes nos primeiros dois meses de tratamento (58,4%). Houve necessidade de modificação do esquema de tratamento em 11 casos (3,7% do total). A hepatite induzida por medicamentos foi o efeito colateral que mais exigiu modificações. **Conclusões:** A freqüência de efeitos adversos relacionados ao tratamento da tuberculose com o Esquema I foi de 49,1% neste grupo de pacientes. Entretanto, na maioria dos casos, não houve necessidade da modificação do esquema de tratamento devido aos efeitos adversos.

Descritores: Tuberculose/terapia; Antituberculosos/efeitos adversos; Hepatite tóxica.

Introduction

Tuberculosis, caused by the infectious agent *Mycobacterium tuberculosis*, has plagued humankind since the beginning of recorded history. Despite sufficient technological resources to promote its control, it is unlikely that it will be eradicated in the near future. Data from the World Health Organization support this supposition, showing that Brazil ranks 15th among the 22 countries that are responsible for 80% of the total number of tuberculosis cases worldwide, with an estimated prevalence of 50 million infected individuals. According to data from the Brazilian National Ministry of Health, Department of Health Surveillance, 85,000 new cases are diagnosed per year (corresponding

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to an incidence rate of 47/100,000 population) and there are 6,000 tuberculosis-related deaths annually. These cases constitute the 9th leading cause of hospitalization for infectious disease and the 4th leading cause of death from infectious diseases, as well as accounting for the 7th largest share of Unified Health Care System hospitalization costs related to infectious diseases.[1] In this context, therefore, the treatment regimens for this disease play a fundamental role.

Although antituberculosis drugs efficiently combat the microorganism, they can result in undesirable side effects, either due to the active principle itself or to its metabolites. Side effects, principally the most severe, are related to higher rates of treatment abandonment,[2] since they require therapy regimens of longer duration and a greater number of hospitalizations, as well as outpatient and home visits.[3] In addition, changes in treatment regimen resulting from these adverse effects have led to the inclusion of one or more less powerful and yet more toxic drugs, increased risk of treatment failure, recurrence of the disease[4,5] and, in some cases, increased treatment duration, with consequent decreased compliance.[4,6]

The objective of the present study was to determine the frequency of adverse effects related to the use of the tuberculosis treatment regimen designated Regimen I and the need for regimen alterations due to these effects.

Methods

This was a retrospective, descriptive study based on the analysis of 329 medical charts of patients who were discharged from tuberculosis treatment after confirmed cure, between March of 2000 and April of 2006, at the Tuberculosis Outpatient Clinic of the Pulmonology Department of the São Paulo Santa Casa Sisters of Mercy Hospital, located in the city of São Paulo, Brazil.

All patients in whom Regimen I was initiated for the treatment of tuberculosis and who were discharged during this period were included. Patients receiving other treatment regimens were excluded, as were those who were HIV-positive, those who were transferred, those who abandoned treatment and those whose diagnosis was changed during the course of the treatment.

Adverse effects and the timing of their appearance during treatment, as well as subsequent modifications in the treatment regimen, were investigated.

Patients were monitored through monthly outpatient visits in which they were asked in a guided way about possible drug-induced side effects.

The classification of adverse effects into major and minor effects was established based on the Brazilian National Ministry of Health 2004 Guide to Epidemiological Surveillance.[7] Minor adverse effects comprise the following: gastric irritation (nausea, vomiting, epigastric pain); abdominal pain; arthralgia or arthritis; peripheral neuropathy; cutaneous pruritus; headache; and changes in behavior (insomnia, anxiety, decreased libido and euphoria).

Major adverse effects comprise exanthema, vertigo, psychosis and effects related to hepatotoxicity (vomiting, alteration in liver function tests and hepatitis).

Liver function tests included aspartate aminotransferase (AST) and alanine aminotransferase (ALT) before treatment initiation and after the first month of treatment. Subsequently, patients were tested only if they presented signs or symptoms of hepatotoxicity. Elevated AST and ALT levels of over three times the upper limit of normality were considered hepatotoxicity, with or without the presence of symptoms such as nausea, vomiting, abdominal pain and jaundice.

The study protocol was analyzed and approved by the Ethics in Human Research Committee of the São Paulo Santa Casa Sisters of Mercy Hospital.

Table 1 - Distribution of adverse effects observed in the treatment of tuberculosis by systems of the organism.

Group of side effects	n	Frequency, %
Gastrointestinal	91	40.3
Cutaneous	50	22.1
Articular	42	18.6
Neurologic	26	11.5
General symptoms	10	4.4
Psychiatric/behavioral	3	1.3
Ocular	3	1.3
Cardiovascular	1	0.5
Total	226	100

Source: Tuberculosis Outpatient Clinic, Pulmonology Department, São Paulo Santa Casa Sisters of Mercy Hospital (2000-2006).

Results

Based on the study criteria 32 of the 329 patients were excluded. A total of 297 patients were included. Ages ranged from 16 to 79 years, with a mean of 40.4 years and a median of 38.5 years; 23 (15.8%) were 60 or older; 76 (52%) were male and 70 (48%) were female; 73 (50%) were white, 72 (49.3%) were nonwhite, and 1 (0.7%) was not classified by race.

Of the total, 146 (49.1%) presented one or more adverse effects related to antituberculosis drugs, with a total of 226 occurrences, of which 183 (81.0%) involved minor effects and 43 (19.0%) involved major effects. The relative frequency of minor and major side effects, in relation to the total number of patients, was 41.1% and 12.8%, respectively. Grouped by systems, the side effects related to the gastrointestinal tract (40.3%) and to the skin (22.1%) were the most common (Tables 1 and 2). We observed greater occurrence of adverse effects (58.4%) in the first two months of treatment (Table 3).

Hepatotoxicity occurred in 24 patients (8.1%). Of those 24, 17 (70.8%; 5.7% of the total population studied) were asymptomatic, presenting an asymptomatic increase in hepatic enzyme levels to three times the upper limit of normality.

Modification of the treatment regimen was necessary in 11 patients (3.7%). In most of those cases, Regimen I was changed during the first two months of treatment (18.2% and 45.4%, respectively, in the 1st and 2nd month). In 36.4%, change occurred in the remaining months (18.2%, 9.1% and 9.1%, respectively, in the 3rd, 4th and 5th month). The side effect that demanded the most change was hepatotoxicity (63.7% of the cases of change in treatment; Table 4). Except for 3 patients in this situation, all of the other patients presented signs and symptoms (nausea, vomiting, abdominal pain or jaundice). In 3 cases of hepatotoxicity in which there was an increase in liver function enzymes accompanied by symptoms, there was no need to change the treatment regimen, and clinical improvement occurred immediately after temporary suspension of medication and subsequent reintroduction. No patient died due to drug-induced side effects of antituberculosis medication.

Table 2 - Distribution of adverse effects observed in the treatment of tuberculosis by severity.

Side effects	n	Frequency, %
Minor side effects		
Epigastric pain and/or abdominal pain	46	20.4
Arthralgia	37	16.4
Nausea and/or vomiting	21	9.3
Pruritus	18	8.0
Peripheral neuropathy	13	5.8
Acne	11	4.9
Dizziness	7	3.1
Myalgia	6	2.7
Swelling and/or arthritis	5	2.2
Weakness and/or asthenia	4	1.8
Decreased visual acuity	3	1.3
Headache	3	1.3
Motor deficit	2	0.9
Insomnia	2	0.9
Decreased libido	1	0.4
Tachycardia and/or palpitation	1	0.4
Alopecia	1	0.4
Skin hyperpigmentation	1	0.4
Memory loss	1	0.4
Total minor side effects	183	81.0
Major side effects		
Drug-induced liver disease	24	10.6
Exanthema	19	8.4
Total major side effects	43	19.0
Total side effects	226	100

Source: Tuberculosis Outpatient Clinic, Pulmonology Department, São Paulo Santa Casa Sisters of Mercy Hospital (2000-2006).

Table 3 - Distribution of adverse effects observed in the treatment of tuberculosis by the month it occurred.

Month of treatment	Side effects, n	Frequency, %
1st	66	29.2
2nd	66	29.2
3rd	32	14.2
4th	33	14.6
5th	14	6.2
6th	15	6.6
Total	226	100

Source: Tuberculosis Outpatient Clinic, Pulmonology Department, São Paulo Santa Casa Sisters of Mercy Hospital (2000-2006).

Table 4 - Distribution of adverse effects observed in the treatment of tuberculosis by need to change the treatment regimen.

Side effect	Patients, n (%)
Drug-induced liver disease	7 (63.7)
Exanthema	3 (27.3)
Peripheral neuropathy	1 (9.0)
Total	11 (100)

Source: Tuberculosis Outpatient Clinic, Pulmonology Department, São Paulo Santa Casa Sisters of Mercy Hospital (2000-2006).

Discussion

Approximately half of the patients treated for tuberculosis with Regimen I at our clinic presented drug-induced adverse effects. However, modification of the treatment regimen due to side effects was necessary in only 3.7%.

Although the factors related to adverse effects in the treatment of tuberculosis are multiple, the principal determinants of these reactions are the dose administered and time of day at which the medication is administered, as well as patient age, nutritional status, alcoholism, liver function, kidney function and HIV co-infection.[6,8] These reactions can be divided into two groups:

a) minor, or mild: occur in 5% and 20% of the cases and do not result in immediate change in the standard regimen.[7,9] These effects can be controlled using relatively simple measures, such as additional explanation and encouraging the patient, as well as changing the method or time of administration of medications and using symptomatic medications.[6]
b) major, or severe: are less frequent (occurring in approximately 2%, reaching 8% in specialized clinics) and imply the discontinuation of or a change in the treatment.[7,9]

Our study demonstrated a 41.1% rate of minor adverse reactions and a 12.8% rate of major adverse reactions. This difference observed between our findings and those in the literature might be explained by the fact that, at our outpatient clinic, which is affiliated with a medical school, we routinely question all possible side effects. Therefore, it is possible that, during the everyday monitoring in clinical practice, not all possible side effects are questioned, or maybe such effects occur in such a mild or even transitory way that patients do not consider them relevant enough to be reported to the physicians.

It is known that most reactions occur during the first three months of treatment.[6] In a study involving 511 patients under antituberculosis treatment in Buenos Aires, Argentina, a 63.6% incidence of adverse effects was observed in the first month of treatment.[10] In our study, 58.4% of the side effects occurred within the first two months of treatment.

Gastric intolerance, various skin manifestations and joint pain are the most frequently described adverse reactions during treatment with Regimen I. Gastrointestinal effects (nausea, vomiting, epigastric pain and abdominal pain) constitute the most common group of reactions and can be attributed to any antituberculosis drug.[6,11] In our sample, gastric effects, cutaneous effects and joint manifestations were the most common adverse side effects, representing, respectively, 40.3%, 22.1% and 18.6% of the total.

Arthralgia is a common symptom, usually related to treatment with pyrazinamide, and can be attributed to hyperuricemia. The mechanism is related to pyrazinoic acid, the principal metabolite of pyrazinamide, which inhibits the renal tubular secretion of uric acid, resulting in its increased concentration in serum and, consequently, joint pain. One group of authors found that 83% of the patients studied presented an increase in the serum concentration of uric acid.[12] Although the majority of the patients using pyrazinamide presented increased uric acid levels, few manifested arthralgia. Of the 76 patients treated with pyrazinamide at our clinic, 61 (80.3%) developed hyperuricemia by the end of the first month of treatment, and only 8 (13.1%) of those 61 were symptomatic (unpublished data). In a study involving 40 patients with tuberculosis under treatment with pyrazinamide, it was observed that the clinical significance of hyperuricemia related to pyrazinamide is unclear, since there is an evident association between joint profiles and hyperuricemia.[13]

The medications included in regimens employed in the treatment of tuberculosis present interactions with one another that increase the risk of hepatotoxicity. The incidence of isoniazid- or rifampin-induced hepatitis is low (0.6% and near

zero, respectively). However, it reaches 2.7% when the two medications are combined.[14,15]

In a study conducted in Brazil, clinical and laboratory signs of liver injury were observed in 6.0% of the 1,096 patients treated for tuberculosis with Regimen I.[16] In a retrospective study carried out in Porto Alegre, Brazil, a 4.2%[17] incidence of hepatotoxicity caused by Regimen I was observed, which is in contrast with the 8.1% incidence found in our sample. This apparent difference might be explained by the different methodology applied in the two studies. We defined hepatotoxicity as an increase in hepatic enzyme levels with or without the presence of symptoms, whereas, in that study, it was defined only as the laboratory alteration accompanied by symptoms.

In a previous study,[18] we found an 8.0% incidence of hepatotoxicity in 210 patients treated at our clinic with the drugs used in Regimen I, and this adverse reaction predominated in the 2nd month of treatment. Pyrazinamide was the principal drug responsible for hepatotoxicity (76%, 18% and 6% of the cases were due to pyrazinamide, rifampin and isoniazid, respectively), and alcoholism was the factor related to the side effect. In a study on the incidence of severe side effects due to first-line antituberculosis medications, other authors also observed that the toxicity of pyrazinamide is greater than is that of rifampin and isoniazid.[3] The authors concluded that the incidence of major side effects (hepatotoxicity and exanthema) was three times greater among patients receiving pyrazinamide than among those receiving rifampin or isoniazid (1.48/100 patients/month using pyrazinamide vs. 0.43/100 patients/month using rifampin and 0.49/100 patients/month using isoniazid).

In our study, it was difficult to correlate side effects with the drugs used in the treatment of tuberculosis, since many of those manifested during treatment with a combination of two or more drugs and without the need to change the regimen. This made it impossible to specifically identify the drug that caused these effects in most cases. Despite the pertinent discussion of the possibilities that some adverse effects occur due to the interaction between drugs and their metabolites or to mechanisms of hypersensitivity, we drew some correlations based on clinical improvement resulting from the substitution or discontinuation of the drugs:

- Side effects related to pyrazinamide: two cases of exanthema, one of epigastric pain, one of nausea and three of drug-induced liver disease, which improved after substitution or discontinuation of the medication, or whose profile returned after reintroduction of the medication.
- Side effects related to rifampin: one case of drug-induced liver disease and one case of exanthema, due to improvement of the profile after substitution of the medication.

In previous studies,[19,20,21] the incidence of severe adverse effects related to Regimen I that led to change in treatment occurred in 0.6-3.0% of the cases. However, in a retrospective analysis of 519 patients who were treated in a university hospital in Germany, modification of the treatment due to side effects of Regimen I was necessary in 23% of the patients.[4] Risk factors for hepatotoxicity, such as alcohol abuse or use of other hepatotoxic drugs, can vary among the populations studied, which would explain the difference in the indices of modification of the regimen due to side effects. The same authors also observed that the side effects most often related to the modification of treatment were hepatotoxicity (in 11%), exanthema (in 6%) and arthralgia (in 2%). In a study involving 403 patients treated for tuberculosis in Montreal, Canada, it was reported that the most common severe side effects were cutaneous exanthema and fever (together accounting for 5.1%) and drug-induced hepatitis (in 2.9%).[3]

In our population, it was necessary to modify the treatment regimen due to adverse effects in 3.7% of the patients. In 63.7% of those cases, hepatotoxicity was responsible for the modification. It is of note that the medication was changed in only 7 (29.1%) of the 24 patients who presented hepatotoxicity, since the majority presented only a transitory increase in hepatic enzyme levels, without any symptoms, therefore not requiring modification of the treatment regimen.

Despite the considerable morbidity caused by these drugs, death due to antituberculosis therapy is an extremely rare complication.[5] However, in a study conducted in New Delhi, India,[11] involving 72 patients with drug-induced hepatitis, a 12.5% mortality rate was observed. The authors attributed

the high mortality rate in their results to the fact that the hospital where the research was conducted was a tertiary care referral center. None of the patients in our study died due to the use of antituberculosis medications.

Although the basic principles of the treatment of tuberculosis are the same worldwide, some relevant points are of note when our results are compared with international results. Treatment regimens, as well as the combination of drugs, time and strategies used in order to increase compliance, can differ among countries. There are some particularities in Brazil regarding treatment: here, three drugs are used in the initial phase, and not four, as in most other countries; and the dose of isoniazid is higher and is combined with rifampin in one single tablet, with possible pharmacokinetic consequences that have not yet been studied. The ideal thing would be if the comparison could be made only with relation to Brazilian studies or studies conducted in places where a treatment regimen similar to ours was used. However, since 1979, when the current treatment recommended by the Ministry of Health was introduced, there have not been assessments carried out with methodological and scientific rigor regarding its efficacy or in relation to its side effects.

In conclusion, we can state that the frequency of side effects related to antituberculosis treatment with Regimen I in the population of the Tuberculosis Outpatient Clinic of the Pulmonology Department of the São Paulo Santa Casa Sisters of Mercy Hospital was 49.1%. However, in the great majority of the cases, it was not necessary to modify the treatment regimen due to adverse effects. These results show the importance of the early recognition of these effects and the early initiation of the appropriate approach. It is fundamental to follow the recommendation of the National Health Foundation Guide to Epidemiological Surveillance of Tuberculosis[22] that clinical follow-up evaluations of patients be carried out by health professionals at least once a month and include an interview regarding the possible signs and symptoms related to side effects.

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