Adverse effects of the new tuberculosis treatment regimen recommended by the Brazilian National Ministry of Health*

Efeitos adversos causados pelo novo esquema de tratamento da tuberculose preconizado pelo Ministério da Saúde do Brasil

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Abstract

Objective: To determine the principal adverse effects of the tuberculosis treatment regimen recommended by the Brazilian Ministry of Health. **Methods:** A prospective descriptive study involving 79 tuberculosis patients treated at the Clinical Research Center of the Cassiano Antonio Moraes University Hospital, in the city of Vitória, Brazil, between 2003 and 2006. The treatment regimen consisted of isoniazid, rifampicin, pyrazinamide and ethambutol for four months, followed by rifampicin and isoniazid for two months. During the treatment period, the patients were clinically evaluated every week and had a monthly medical visit. **Results:** The overall incidence of adverse effects was 83.54%. Articular/bone/muscle involvement was the most common, followed by skin involvement (24.94% and 22.09%, respectively). Adverse effects were more common in the second month of treatment (41.59%). Modification of the treatment regimen was unnecessary. One patient required concomitant medication to counter the adverse effects. The cure rate was 100%. **Conclusions:** The overall incidence of adverse effects related to the new treatment regimen recommended by the Brazilian Ministry of Health was high. However, none of those effects demanded a change in the regimen, which was effective in the patients evaluated.

Keywords: Treatment outcome; Tuberculosis; Antitubercular agents; Adverse drug reaction reporting systems.

Resumo

Objetivo: Determinar os principais efeitos adversos causados pelo esquema de tratamento da tuberculose preconizado pelo Ministério da Saúde. **Métodos:** Estudo descritivo e prospectivo envolvendo 79 pacientes com tuberculose tratados no Centro de Pesquisa Clínica do Hospital Universitário Cassiano Antônio Moraes, no município de Vitória, ES, entre 2003 e 2006. O regime de tratamento consistiu em isoniazida, rifampicina, pirazinamida e etambutol por quatro meses, seguido de rifampicina e isoniazida por dois meses. Durante o tratamento, os pacientes foram clinicamente avaliados todas as semanas e tinham uma visita médica mensal. **Resultados:** A incidência geral de efeitos adversos foi de 83,54%. O envolvimento articular/ósseo/muscular e o envolvimento cutâneo foram mais frequentes (24,94% e 22,09%, respectivamente). Os eventos adversos foram mais comuns no segundo mês de tratamento (41,59%). Não houve necessidade de modificação do esquema de tratamento. Apenas 1 paciente necessitou de medicação para amenizar os efeitos adversos. A taxa de cura foi de 100%. **Conclusões:** Apesar de alta, a incidência de efeitos adversos com o novo esquema de tratamento preconizado pelo Ministério da Saúde não exigiu a modificação do esquema de tratamento, que foi eficaz.

Descritores: Resultado de tratamento; Tuberculose; Antituberculosos; Sistemas de notificação de reações adversas a medicamentos.

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Introduction

In patients under treatment with first-line antituberculous drugs, treatment discontinuation due to adverse drug effects has serious implications for tuberculosis (TB) control. These effects can substantially increase treatment costs by increasing the number of patient visits to health care facilities and the number of complementary tests required to diagnose these effects, as well as, in cases that are more severe, by requiring patient hospitalization.[1-3]

The risk of morbidity and mortality as a result of isoniazid-related adverse effects, particularly hepatotoxicity, is well documented in the literature,[4,5] as are the adverse effects of rifampin, pyrazinamide and ethambutol.[6-9]

Most patients undergoing TB treatment, however, are able to complete the treatment without relevant side effects. Adverse reactions are related to various factors, and the principal determinants of such reactions are the dose and time of day at which the medication is administered, as well as age, nutritional status, alcoholism, pregnancy, liver function, kidney function and HIV infection status.[10]

The principal adverse reactions include irritating reactions, allergic reactions and toxic reactions. Gastrointestinal intolerance occurs due to the irritating effect of the drugs. Allergic reactions can be mild (urticaria, rash, itching or cholestatic jaundice) or severe (anaphylactic shock, bleeding disorders, vasculitides or interstitial nephritis).[11]

In Brazil, the treatment regimen consisting of the rifampin-isoniazid-pyrazinamide (RHZ) combination has been used for the treatment of TB for over 30 years, and the adverse effects of these drugs have previously been demonstrated.[11] The Brazilian National Ministry of Health (NMH) has recently recommended that TB be treated with four antituberculous drugs—RHZ + ethambutol (RHZE)—in accordance with the recommendation of the World Health Organization (WHO).[12] However, data regarding the toxicity of this combination remain unavailable in studies conducted in Brazil.

The present study was designed to evaluate treatment regimens of shorter duration. The treatment adopted (in accordance with the recommendations of the WHO) consisted of the RHZE regimen, used for 6 months, and the participating patients were monitored weekly by means of an instrument for the evaluation of adverse effects.

The objective of this study was to determine the adverse effects of TB treatment with the RHZE regimen.

Methods

This was a prospective descriptive study. The study was conducted at the *Centro de Pesquisa Clinica* (CPC, Clinical Research Center) of the Federal University of Espírito Santo Cassiano Antonio Moraes University Hospital, located in the city of Vitória, Brazil. The CPC is one of the Brazilian Tuberculosis Research Network centers for clinical trials. The participants were selected from among the patients treated at the CPC between 2003 and 2006. The TB treatment protocol was that previously employed in the study entitled "Shortening treatment in adults with noncavitary tuberculosis and 2-month culture conversion".[13] The data were obtained from the medical charts.

The protocol includes HIV-negative patients ranging in age from 18 to 60 years who have recently been diagnosed with noncavitary pulmonary TB and who present with positive or negative sputum smear microscopy and positive sputum culture. After the initial diagnosis, patients underwent daily treatment with the RHZE regimen for 2 months, followed by daily use of the rifampin-isoniazid (RH) regimen for another 4 months. At least five of the seven weekly doses were administered through supervised treatment.

The usual doses were as follows: 10 mg • kg^{-1} • day^{-1} of rifampin (maximum, 600 mg/day); 5-10 mg • kg^{-1} • day^{-1} of isoniazid (maximum, 300 mg/day); 15 mg • kg^{-1} • day^{-1} of ethambutol (maximum, 1,200 mg/day); and 15-30 mg • kg^{-1} • day^{-1} of pyrazinamide (maximum, 2,000 mg/day). Throughout the treatment period, all of the patients received pyridoxine supplementation (50 mg/day, p.o.), in order to avoid isoniazid-related neurotoxicity.

In the month 4 of treatment, patients with negative sputum culture in month 2 were randomly selected to discontinue treatment (a total of 4 months of treatment) or continue treatment with the RH regimen for another 2 months (a total of 6 months of treatment). All patients were monitored for 30 months, as in the model study.[13] Only patients who received

TB treatment for 6 months between 2003 and 2006 were included in the present study.

Any drug-related adverse event was considered to be an adverse effect. Only the signs and symptoms that were not identified during the initial evaluation of patients were considered to be adverse effects.

Radiological analysis results were considered suspicious when there was an image (heterogeneous opacity, cavities, consolidations, reticulonodular pattern, nodules or parenchymal band) that was suggestive of active TB, as defined in the II Brazilian Consensus on Tuberculosis.[14]

Cavitary disease was defined as follows: transparent space of at least 1 cm in diameter, containing air in the lung parenchyma and surrounded by an infiltrate or fibrotic wall of > 1 mm in thickness. The differential diagnosis included pulmonary cysts, which present as well-demarcated lesions with walls that are generally thinner. The principal researchers or the researchers in charge were trained in order to guarantee that the evaluation of cavitary disease was standardized and monitored in accordance with the protocol.[13]

Clinical evaluations were performed weekly by the nurse of the study group and monthly by the physician, on scheduled days, throughout the period during which the patient received specific treatment. There was a specific form on which the adverse effects observed throughout the treatment were carefully recorded on a weekly basis. Any effects observed were immediately reported to the physician of the study group, and an intervention was conducted whenever necessary.

Laboratory data (results of sputum smear microscopy and mycobacterial culture) were obtained directly from the Mycobacteriology Laboratory of the Infectious Disease Center of the Federal University of Espírito Santo.

The variables used for the analysis of the data were as follows: age; gender; level of education; principal complaint; sputum smear microscopy result; culture result; chest X-ray findings; BCG status; adverse effects observed during the 6 months of treatment; duration of the adverse effect; use of support therapy; and treatment outcome.

The information obtained with the research instrument was used in order to construct a database, which was stored and analyzed using the program Microsoft Excel. The data were subsequently transferred to the STATA statistical program, version 9.0 (Stata Corp., College Station, TX, USA), in order to calculate absolute and relative frequency, mean and standard deviation.

The study design was approved by the Human Research Ethics Committee of the Federal University of Espírito Santo Health Sciences Center (protocol no. 25000.141501/2001-65).

Results

We evaluated 79 patients who underwent TB treatment for 6 months. Of those 79 patients, 66 (83.54%) presented one or more adverse effects during the treatment. In the sample as a whole, the male gender predominated (59.49%). The predominant levels of education were 9 or fewer years of schooling and no schooling. Only 1 patient (1.27%) had finished college. The predominant age bracket in the study population was between 18 and 45 years. The majority of the patients were residents of the greater metropolitan area of Vitória, 28 (35.44%) residing in the city of Serra (Table 1).

All of the patients presented negative HIV serology, since this was one of the exclusion criteria of the study. All of the patients presented chest X-ray results that raised the suspicion of

Table 1 - Sociodemographic characteristics of the study population.

Characteristic	n	%
Gender		
Female	32	40.51
Male	47	59.49
Level of education		
No schooling	30	37.97
Middle school	30	37.97
High school	18	22.79
College	1	1.27
Age, years		
18-29	34	43.04
30-45	31	39.24
≥ 45	14	17.72
City of residence		
Vitória	19	24.05
Serra	28	35.44
Vila Velha	11	13.92
Cariacica	17	21.53
Other	4	5.06

Table 2 - Distribution of the patients under study according to BCG status and complementary test results.

Tests	N	%
Chest X-ray		
Suspicious	79	100
Normal	0	0
BCG		
Vaccinated	35	44.30
Not vaccinated	9	11.40
Unknown	35	44.30
Sputum smear microscopy		
Positive	61	77.21
Negative	18	22.79
Sputum culture		
Positive	79	100
Negative	0	0

TB. A large proportion of patients (44.3%) were unaware of their BCG vaccination status, and 9 patients (11.4%) had not received the BCG vaccine. All of the patients underwent sputum smear microscopy and culture. Sputum smear microscopy was positive in 61 patients (77.21%). All of the patients presented positive sputum culture (Table 2).

Table 3 shows the adverse effects according to the month of treatment and the onset of symptoms. A total of 226 adverse effects occurred during the 6 months of treatment. The patients under study presented one or more adverse effects, the onset of which occurred in specific months during the treatment. The highest proportion of adverse effects (41.59%) occurred in month 2, whereas the lowest proportion (4.87%) occurred in month 5. The number of patients presenting with some type of adverse effect was highest (n = 50) in month 2.

Table 3 - Distribution of the occurrence of adverse effects observed during the treatment of tuberculosis, by month of onset.

Onset of the adverse effect	Adverse effects	Patients with adverse effects
	(n = 226)	(n = 79)
Month 1, n (%)	46 (20.35)	21 (26.58)
Month 2, n (%)	94 (41.59)	50 (63.29)
Month 3, n (%)	34 (15.04)	21 (26.58)
Month 4, n (%)	26 (11.50)	19 (24.05)
Month 5, n (%)	11 (4.87)	10 (12.66)
Month 6, n (%)	15 (6.65)	11 (13.92)

Table 4 shows all of the adverse events (new or recurrent) that occurred during the treatment. Among the 421 types of adverse events observed, joint pain, which was seen in 61 patients (14.48%), was the adverse event that was most commonly reported by patients, followed by skin manifestations, which were seen in 36 patients (8.54%). Depression and sweats were the least common effects observed during the treatment, occurring in only 1 patient each (0.23%).

Approximately 5% of the effects, among which were lymph node enlargement and adenopathy, were not classified as being related to drug toxicity but as being related to the reconstitution of the immune response to TB.

Regarding the distribution of adverse effects according to the body systems, the musculoskeletal system was the most commonly affected, accounting for 105 of the cases (24.94%), followed by the skin, which accounted for 93 of the cases (22.09%). The following symptoms were considered general symptoms: insomnia; dysuria; somnolence; headache; petechiae or bleeding (or a combination of the two); alopecia; myalgia; loss of appetite; dizziness; anemia; fever; sweats; weakness; and depression. These symptoms were found in 92 cases (21.85%) during the treatment. Events related to the ocular system were the least common, being observed in 22 of the cases (5.24%; Table 5).

All of the patients were discharged after cure. None of the adverse effects demanded a change in the treatment regimen. Only 10% of the patients required medication to treat the adverse reactions. It is of note that, in the evaluation performed in month 30 (24 months after the end of the treatment), only 1 patient presented with recurrence (recurrence rate = 1.26). All measures were taken in accordance with the Brazilian national criteria for the initiation of treatment.[10]

Discussion

Although the drugs used in the treatment of TB are effective against *Mycobacterium tuberculosis*, they can cause adverse effects, either due to the active principle itself or to its metabolites. Adverse effects, principally the most severe, are related to higher rates of treatment noncompliance,[15] since they require therapy regimens of longer duration and a greater

Table 4 - Distribution of the types of adverse effects observed during the six months of tuberculosis treatment.

Types of adverse effects	n	%
Joint pain	61	14.48
Skin edema or irritation (or both)	36	8.54
Memory loss	30	7.12
Acne	29	6.88
Itching	28	6.65
Epigastric or abdominal pain (or both)	23	5.46
Nausea or vomiting (or both)	21	4.98
Muscle pain	19	4.41
Headache	15	3.55
Painful limbs	15	3.55
Chest pain	12	2.74
Somnolence	11	2.69
Cough/sore throat/presence of secretion	11	2.69
Pulmonary rhonchi or sounds (or both)	10	2.37
Weakness/dyspnea	9	2.22
Eye irritation	9	2.22
Decreased visual acuity	9	2.22
Dysuria	7	1.67
Swelling of joints or bone (or both)	6	1.42
Hepatomegaly	6	1.42
Insomnia	6	1.42
Petechiae or bleeding (or both)	6	1.42
Alopecia	5	1.18
Myalgia	5	1.18
Loss of appetite	5	1.18
Dizziness	5	1.18
Adenopathy	4	0.94
Intolerance to light	4	0.94
Tremors	4	0.94
Anemia	2	0.47
Confusion or lack of attention (or both)	2	0.47
Fever	2	0.47
Lymph node enlargement	2	0.47
Depression	1	0.23
Sweats	1	0.23
Total	421	100

number of hospitalizations, as well as outpatient and home visits.[9]

Antituberculous therapy with the RHZE regimen is associated with frequent side effects of little clinical significance and with predictable and idiosyncratic effects. Mild adverse effects are generally controlled symptomatically; severe reactions require temporary or permanent discontinuation of one or more drugs and the use of other agents. In the present study, the highest frequency of effects was observed during months 1 and 2 of treatment. The results of the present study are similar to those reported in other studies.[16-19] In a study conducted in the United Kingdom, the most severe effects occurred during the second month of treatment.[20] In a study conducted in Canada, adverse drug reactions in patients treated with the RHZ regimen or with the RHZE regimen were more common in the initial phase of the treatment, and few effects occurred after 150 days of treatment.[21]

The mechanisms responsible for a greater occurrence during the initial phase of the treatment have yet to be fully understood. Elevated liver transaminases have been observed in up to 20% of patients treated with the RHZE regimen, generally during the first month of treatment.[7] Exposure to certain drugs triggers adaptive physiological responses, designated hepatic adaptation.[22] This phenomenon might involve gene induction, modulating inflammation, cell proliferation and drug metabolism. Rifampin can induce the metabolism of many drugs. However, further studies are required in order to determine the moment at which adverse effects occur during the treatment.

Various skin manifestations, joint pain and gastric intolerance are the adverse effects that are most frequently described during treatment with the RHZ regimen.[16,18] In the patients who participated in the present study, adverse effects affecting the skin (edema, irritation, acne and itching), the joints and the stomach (epigastric pain, abdominal pain, nausea and vomiting) were also the most common.

In the present study, changes in the treatment regimen due to adverse effects were unnecessary. In a study in which the RHZ regimen was used, the treatment regimen had to be changed in 3.7% of the patients, due mostly to hepatotoxicity. In a retrospective analysis of 519 patients who received treatment at a university hospital in Germany, the authors reported that treatment changes due to the side effects of the RHZ regimen were necessary in 23% of the patients.[18,23]

In a study published recently, the treatment regimen in which four drugs are combined into one tablet or capsule and that in which the drugs are taken separately were compared in terms of adverse effects and patient acceptance. The study concluded that there were no differences between the two formulations with regard to

Table 5 - Distribution of the adverse effects observed during the treatment of tuberculosis, in groups, by body system.

Groups	n	%
Musculoskeletal	105	24.94
Skin	93	22.09
General symptoms	92	21.85
Gastrointestinal	44	10.45
Thoracic/respiratory	33	7.83
Neurological	32	7.60
Ocular	22	5.24
Total	421	100

adverse effects; however, combination tablets or capsules were more widely accepted by patients than were individual tablets or capsules.[24]

The results of the present study demonstrated that the drugs used for the treatment of TB with the RHZE regimen (isoniazid and rifampin in a single tablet; ethambutol and pyrazinamide taken as individual tablets) caused many adverse effects and that, although most of the effects appeared in the first 2 months, adverse effects occur during the entire treatment period and should be monitored at the treating health care facility. It is noteworthy that some of the patients in the present study received a dose of medication higher than that recommended by the NMH in the new TB treatment regimen. However, effects that required treatment interruption were few. These findings can aid in the institution of the new NMH strategy for TB control: the use of the four-drug RHZE regimen.

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