

## Antituberculosis drugs: Drug interactions, adverse effects, and use in special situations. Part 1: First-line drugs\*

Drogas antituberculose: Interações medicamentosas, efeitos adversos e utilização em situações especiais. Parte 1: Fármacos de primeira linha

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### Abstract

The main objectives of tuberculosis therapy are to cure the patients and to minimize the possibility of transmission of the bacillus to healthy subjects. Adverse effects of antituberculosis drugs or drug interactions (among antituberculosis drugs or between antituberculosis drugs and other drugs) can make it necessary to modify or discontinue treatment. We briefly review the new guidelines for the pharmacological treatment of tuberculosis, introduced by the Brazilian National Ministry of Health in 2009, and describe the general mechanism of action, absorption, metabolization, and excretion of the first-line drugs used in the basic regimen. We describe adverse drug reactions and interactions (with other drugs, food, and antacids), as well as the most appropriate approach to special situations, such as pregnancy, breastfeeding, liver failure, and kidney failure. We also describe the mechanisms by which the interactions among the antituberculosis drugs used in the basic regimen can cause drug-induced hepatitis, and we discuss the alternatives in this situation.

**Keywords:** Tuberculosis; Drug interactions; Antibiotics, antitubercular; Pharmacologic actions; Drug toxicity; Drug-induced liver injury.

### Resumo

Os objetivos principais do tratamento da tuberculose são curar o paciente e minimizar a possibilidade de transmissão do bacilo para indivíduos saudáveis. Reações adversas ou interações das drogas antituberculose entre si e com outros fármacos podem causar modificação ou descontinuação da terapêutica. Revisamos sucintamente o novo tratamento farmacológico da tuberculose introduzido pelo Ministério da Saúde do Brasil em 2009 e mostramos os mecanismos gerais de ação, absorção, metabolização e excreção dos medicamentos utilizados no esquema básico. Descrevemos as reações adversas e as interações (com medicamentos, alimentos e antiácidos) assim como a abordagem mais adequada para situações especiais, como gravidez, amamentação, insuficiência hepática e renal. Também descrevemos os mecanismos pelos quais as interações das drogas antituberculose do esquema básico podem causar hepatite medicamentosa e as possíveis alternativas nessa situação.

**Descritores:** Tuberculose; Interações de medicamentos; Antibióticos antituberculose; Ações farmacológicas; Toxicidade de drogas; Doença hepática induzida por drogas.

### Introduction

In Brazil, tuberculosis treatment regimens have been standardized by the Brazilian National Ministry of Health since 1979. According to the latest technical norms, published in October of 2009, the treatment recommended for all new cases of pulmonary and extrapulmonary tuberculosis, as well as for all cases of recurrence and retreatment due to noncompliance, is the use of a fixed-dose, single-tablet combination

of rifampin, isoniazid, pyrazinamide, and ethambutol for two months and, in the second phase, a combination of isoniazid and rifampin for another four months (2RHZE/4RH regimen).<sup>(1,2)</sup> In cases of meningoencephalitis due to tuberculosis, the same initial regimen, with the addition of a corticosteroid in the first month of treatment, is recommended. The second phase extends for seven months.

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A number of treatments have been proposed for cases of intolerance to one of the first-line drugs and for other clinical situations, such as liver disease.<sup>(1,2)</sup>

Patients with bacilli that are resistant to isoniazid and rifampin, patients with bacilli that are resistant to isoniazid, rifampin, and another first-line drug, and patients in whom the basic regimen fails constitute a group of patients classified as having multidrug-resistant tuberculosis. For cases such as these, a combination regimen of streptomycin, ethambutol, terizidone, pyrazinamide, and one quinolone (levofloxacin or ofloxacin) has been proposed.<sup>(1,2)</sup> If streptomycin cannot be used, it should be replaced with amikacin.<sup>(1,2)</sup> Patients with extensively drug-resistant tuberculosis should be referred to a tertiary referral center, and individualized salvage drug regimens (which include capreomycin, moxifloxacin, para-aminosalicylic acid, and ethionamide) should be used.<sup>(2)</sup>

Chart 1 shows the recommended doses of the aforementioned drugs according to the Brazilian National Ministry of Health/Brazilian Thoracic Association,<sup>(1,2)</sup> the American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC)/Infectious Diseases Society of America (IDSA),<sup>(3)</sup> and the World Health Organization (WHO).<sup>(4,5)</sup>

Although the therapeutic regimens are extremely effective, studies have shown that undesirable drug interactions (among the antituberculosis drugs or between the antituberculosis drugs and other drugs used by patients) can occur, as can adverse reactions of varying degrees of severity.<sup>(3)</sup>

Drug interactions can be defined as reciprocal reactions among drugs, resulting in undesirable or unexpected effects. Drug interactions can alter the serum concentrations of the drugs involved, thereby reducing their effectiveness.<sup>(6)</sup>

Adverse reactions to antituberculosis drugs 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 patient age and nutritional status, together with the presence of preexisting diseases or dysfunctions, such as alcoholism, impaired liver function, impaired kidney function, and HIV coinfection.<sup>(7)</sup>

Adverse reactions that are more severe contribute to changes in the therapeutic regimen and lead to the use of drugs that are less active and occasionally more toxic,<sup>(8,9)</sup> substantially increasing treatment costs, as well as the number of home visits, outpatient visits, and hospitalizations.<sup>(10)</sup> These reactions can lead patients to interrupt or abandon treatment,<sup>(11)</sup> resulting in higher rates of treatment failure and acquired resistance, as well as an increase in the number of tuberculosis cases<sup>(12)</sup> and, more rarely, in the number of deaths.<sup>(13)</sup>

According to the Brazilian National Ministry of Health, the incidence of minor or mild adverse reactions in patients treated with the former regimen 1 (2RHZ/4RH) ranged from 5% to 20% and did not result in immediate change in the standard regimen. Major or severe adverse reactions were less common (occurring in approximately 2% of the cases, reaching 8% in specialized clinics) and led to the discontinuation or alteration of the treatment. Minor adverse effects include nausea, vomiting, epigastric pain, abdominal pain, arthralgia, arthritis, peripheral neuropathy, cutaneous pruritus, headache, and changes in behavior (insomnia, anxiety, decreased libido, and euphoria). Major adverse effects include exanthema, vertigo, psychosis, and hepatotoxicity (vomiting, alteration in liver function tests, and hepatitis). However, a recent study investigating 329 medical charts of patients from a teaching hospital reported that 41.1% of the patients presented with minor adverse reactions and 12.8% presented with major adverse reactions.<sup>(14)</sup> The difference between the results suggests that, during the everyday monitoring in clinical practice, not all possible side effects are investigated. Perhaps these effects occur in such a mild or even transitory way that patients do not consider them relevant enough to be reported to the physicians.<sup>(14)</sup> In addition, it is often difficult to evaluate the effectiveness or toxicity of a given drug, since antituberculosis drugs are usually administered as a combination regimen of various drugs, which requires that health care workers have a thorough knowledge of the pharmacodynamics and possible side effects of the drugs used in combination, as well as of the interactions among those drugs.

In this review article, we describe the principal characteristics of each of the drugs that constitute the basic regimen for tuberculosis treatment proposed by the Brazilian National Ministry of Health and the Brazilian Thoracic

**Chart 1** – Drug doses recommended by the Brazilian National Ministry of Health/Brazilian National Tuberculosis Control Program/Brazilian Thoracic Association, American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America, and World Health Organization.

Drug	Type of patient	Daily dose		
		NMH/NTCP/BTA <sup>(1,2)</sup>	ATS/CDC/IDSA <sup>(3)</sup>	WHO <sup>(4,5)</sup>
Rifampin	Adults	35-50 kg: 450 mg >50 kg: 600 mg	10 mg/kg (maximum of 600 mg)	10 mg/kg (8-12 mg/kg; maximum of 600 mg)
	Children and adolescents	10 mg • kg <sup>-1</sup> • day <sup>-1</sup> 20-35 kg: 300 mg	10-20 mg/kg (maximum of 600 mg)	10 mg/kg (8-12 mg/kg; maximum of 600 mg)
Isoniazid	Adults	35-50 kg: 225 mg >50 kg: 300 mg	5 mg/kg (maximum of 300 mg)	5 mg/kg (4-6 mg/kg; maximum of 300 mg)
	Children and adolescents	10 mg • kg <sup>-1</sup> • day <sup>-1</sup> 20-35 kg: 150 mg	10-15 mg/day (maximum of 300 mg)	5 mg/kg (4-6 mg/kg; maximum of 300 mg)
Pyrazinamide	Adults	36-50 kg: 1,200 mg >50 kg: 1,600 mg	20-25 mg/kg (maximum of 2,000 mg)	25 mg/kg (20-30 mg/kg)
	Children and adolescents	35 mg • kg <sup>-1</sup> • day <sup>-1</sup> 20-35 kg: 800 mg	15-30 mg/kg (maximum of 2,000 mg)	25 mg/kg (20-30 mg/kg)
Ethambutol <sup>a</sup>	Adults	36-50 kg: 825 mg (800 mg for MDR-TB) > 50 kg: 1,100 mg (1,200 mg for MDR-TB)	15-20 mg/kg (maximum of 1,600 mg)	15 mg/kg (15-20 mg/kg)
	Children and adolescents	Up to 20 kg: 7.5-10 mg/kg 21-35 kg: 550 mg (400-800 mg for MDR-TB)	15-20 mg/kg (maximum of 1,000 mg)	15 mg/kg
Streptomycin	Adults	36-50 kg: 750-1,000 mg  > 50 kg: 1,000 mg	15 mg/kg (maximum of 1,000 mg)  > 60 years of age: maximum of 750 mg/day	15-20 mg/kg (maximum of 1,000 mg)  > 60 years of age: < 50 kg: maximum of 500-750 mg/day 20-40 mg/kg
	Children and adolescents	Up to 20 kg: 15-20 mg/kg 21-35 kg: 500 mg/day	20-40 mg/kg (maximum of 1,000 mg)	20-40 mg/kg
Amikacin / Kanamycin	Adults		15 mg/kg (maximum of 1,000 mg)  > 60 years of age: maximum of 750 mg	15-20 mg/kg (maximum of 1,000 mg)  Usually 750-1,000 mg/day
	Children and adolescents		15-30 mg/kg (maximum of 1,000 mg/day)	15-30 mg/kg
Ofloxacin <sup>a</sup>	Adults	20-50 kg: 400 mg > 50 kg: 800 mg		15-20 mg/kg. Usually 800 mg/day
	Children and adolescents	10 mg/kg		15-20 mg/kg
Levofloxacin <sup>a</sup>	Adults	36-50 kg: 500-750 mg > 50 kg: 750 mg	500-1,000 mg/day	7.5-10 mg/kg Usually 750 mg/day
	Children and adolescents	Up to 20 kg: 7.5-10 mg/kg 21-35 kg: 250-500 mg		7.5-10 mg/kg
Moxifloxacin <sup>a</sup>	Adults		400 mg/day	7.5-10 mg/kg Usually 400 mg/day
	Children and adolescents			7.5-10 mg/kg
Cycloserine / Terizidone	Adults	36-50 kg: 750 mg  > 50 kg: 750 mg	10-15 mg/kg (maximum of 1,000 mg) Usually 500-750 mg/day	10-15 mg/kg (maximum of 1,000 mg) Usually 500-750 mg/day
	Children and adolescents	Up to 20 kg: 15-20 mg/kg 21-35 kg: 500 mg	10-15 mg/kg (maximum of 1,000 mg)	10-20 mg/kg

NMH: (Brazilian) National Ministry of Health; NTCP: (Brazilian) National Tuberculosis Control Program; BTA: Brazilian Thoracic Association; ATS: American Thoracic Society; CDC: Centers for Disease Control and Prevention; IDSA: Infectious Diseases Society of America; WHO: World Health Organization; and MDR-TB: multidrug-resistant tuberculosis. <sup>a</sup>Drugs that should be used with caution in children.

**Chart 1** – Continued...

Drug	Type of patient	NMH/NTCP/BTA <sup>(1,2)</sup>	Daily dose	
			ATS/CDC/IDSA <sup>(3)</sup>	WHO <sup>(4,5)</sup>
Ethionamide	Adults		15-20 mg/day (maximum of 1,000 mg/day) Usually 500-750 mg/day	15-20 mg/kg (maximum of 1,000 mg) Usually 500-750 mg/day
	Children and adolescents		15-20 mg/day (maximum of 1,000 mg/day)	15-20 mg/kg
Capreomycin	Adults		15 mg/kg (maximum of 1,000 g/day). > 60 years of age: maximum of 750 mg/day	15-20 mg/kg  Usually 1,000 mg/day
	Children and adolescents		15-30 mg/day (maximum of 1,000 mg/day)	15-30 mg/kg
Para-aminosalicylic acid	Adults		8-12 g/day	150 mg/kg Usually 10-12 g/day
	Children and adolescents		200-300 mg/kg	150 mg/kg

NMH: (Brazilian) National Ministry of Health; NTCP: (Brazilian) National Tuberculosis Control Program; BTA: Brazilian Thoracic Association; ATS: American Thoracic Society; CDC: Centers for Disease Control and Prevention; IDSA: Infectious Diseases Society of America; WHO: World Health Organization; and MDR-TB: multidrug-resistant tuberculosis. \*Drugs that should be used with caution in children.

Association,<sup>(1,2)</sup> as well as the relevant aspects of the pharmacokinetics of the drugs in order to understand the mechanisms of interaction and possible adverse effects.

## Isoniazid

Isoniazid is one of the most important drugs in the treatment of tuberculosis. It has been used since 1952. The structure of isoniazid is simple. It comprises a pyridine ring and a hydrazine group. The minimum inhibitory concentration (MIC) of isoniazid for *Mycobacterium tuberculosis* is 0.02-0.20 µg/mL. Although isoniazid has a bactericidal effect on rapidly growing bacilli, it has a limited effect on slow-growing (generally intracellular) and intermittently growing (generally extracellular) bacilli.<sup>(15,16)</sup>

### Mechanism of action

Isoniazid is a prodrug and must be activated by the *M. tuberculosis* catalase-peroxidase enzyme KatG; the activation of isoniazid produces oxygen-derived free radicals (superoxide, hydrogen peroxide, and peroxydinitrite) and organic free radicals that inhibit the formation of mycolic acids of the bacterial cell wall, causing DNA damage and, subsequently, the death of the bacillus. The most common mechanism of resistance to isoniazid consists of KatG mutations, which decrease the activity of isoniazid and prevent the prodrug from being converted into its active metabolite.<sup>(15,17)</sup>

### Metabolization and excretion

Isoniazid is metabolized in the liver through acetylation by N-acetyltransferase, which produces acetylisoniazid and isonicotinic acid. The acetylation rate is a genetic characteristic and therefore varies from patient to patient. Certain patients present the rapid acetylator phenotype, whereas others present the slow acetylator phenotype. There is controversy as to whether the latter are more likely to develop manifestations of hepatotoxicity than are the former, there being no differences between these phenotypes in terms of antimicrobial activity. Isoniazid is excreted by the kidney (70-96%), generating, for the most part, inactive metabolites. In patients with the rapid acetylator phenotype, 70% of the isoniazid excreted in urine can appear as free isoniazid, whereas 37% can appear as conjugated isoniazid in patients with the slow acetylator phenotype. A small proportion is excreted in feces. The half-life of isoniazid is approximately 1 h (range: 0.5-1.6 h) in patients with the rapid acetylator phenotype and 2-5 h in those with the slow acetylator phenotype; in patients with liver disease or kidney failure, the half-life of isoniazid can be even longer.<sup>(16,18)</sup>

### Central nervous system

The cerebrospinal fluid (CSF) and plasma concentrations of isoniazid are similar.<sup>(3)</sup>

## Adverse effects

Isoniazid, when used in isolation for tuberculosis prophylaxis (at a dose of  $10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ , up to 300 mg), rarely causes side effects in individuals without liver disease or kidney failure.<sup>(3)</sup> If isoniazid is used in combination with other drugs for the treatment of tuberculosis, this is the dose that is currently recommended in Brazil.<sup>(1,2)</sup>

### Minor adverse effects

- Nausea, vomiting, and epigastric pain: Although uncommon, nausea, vomiting, and epigastric pain can occur at the initiation of treatment with isoniazid when the drug is used in isolation for tuberculosis chemoprophylaxis. Taking the drug 2 h after the first meal and using symptomatic medication (metoclopramide, ranitidine, or omeprazole) can relieve the symptoms.<sup>(7)</sup>
- Transitory and asymptomatic increase in hepatic enzyme levels: In 10-20% of the patients who use isoniazid in isolation, there is an up to three-fold increase over the normal serum levels of the enzyme alanine aminotransferase (formerly known as glutamic-pyruvic transaminase), which is more specific for liver damage than is aspartate aminotransferase (formerly known as glutamic-oxaloacetic transaminase). Those levels normalize as the treatment continues.<sup>(3,19-22)</sup>
- Arthralgia: Arthralgia is a rare complication of isoniazid administration and responds to treatment with nonsteroidal anti-inflammatory drugs.<sup>(7,23)</sup>
- Changes in behavior: Headache, insomnia, euphoria, agitation, anxiety, and somnolence can occur in patients receiving isoniazid.<sup>(7,23)</sup>
- Acne: Acne on the face and torso is a common manifestation that disappears when isoniazid is discontinued.<sup>(23)</sup>
- Cutaneous pruritus or fever: Patients report developing cutaneous pruritus or fever after taking isoniazid.<sup>(23)</sup>

### Major adverse effects

- Psychosis, convulsive seizures, mental confusion, and coma: In patients receiving isoniazid, neurological and psychiatric

manifestations are less common, more severe, and often difficult to diagnose. The differential diagnosis with tuberculous meningitis and hepatic encephalopathy should be established. Attempted suicides have been reported to occur among patients using isoniazid.<sup>(24-26)</sup>

- Hematological alterations or vasculitis: Hematological alterations and vasculitis are rare complications of isoniazid administration and occur due to hypersensitivity.<sup>(23)</sup>
- Peripheral neuropathy: Peripheral neuropathy occurs in approximately 20% of patients treated with isoniazid. It is dose-dependent and uncommon at a dose of  $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ . It is more common at doses higher than 300 mg/day. The risk of polyneuritis increases in the presence of associated conditions, such as advanced age, diabetes mellitus, alcoholism, nutritional deficiency, slow acetylator phenotype, HIV infection, kidney failure, pregnancy, and breastfeeding. Patients can be treated prophylactically with pyridoxine, at a dose of 25-50 mg/day. Patients who develop polyneuritis should be treated with 100-200 mg/day of pyridoxine.<sup>(3,5,27,28)</sup>
- Clinical hepatitis: Recent studies have shown that the incidence of clinical hepatitis in patients receiving isoniazid is lower than previously thought. A meta-analysis of six studies investigating the use of isoniazid in isolation reported that the incidence of hepatitis was 0.6%. When isoniazid was used in combination with rifampin, the incidence of hepatitis was 2.7%. In patients using isoniazid in isolation, the risk of developing hepatitis increases with age. The disease is rare in individuals under 20 years of age. However, in patients in the 50-64 year age bracket, the risk of developing hepatitis can be as high as 2%. The risk also increases in individuals with previous liver disease, in individuals who drink alcohol daily or who are heavy drinkers, and in women in the immediate postpartum period. Fatal hepatitis is extremely rare and occurs in less than 0.023% of the cases. The treatment must be discontinued, and, in patients using multiple-drug regimens, the

causative drug must be identified (see also Hepatotoxicity).<sup>(3,7,19-22)</sup>

- Lupus-like syndrome: Patients receiving isoniazid can develop antinuclear antibodies during the use of the drug. Less than 1% develop systemic lupus erythematosus, the incidence of which is the same in both genders. Isoniazid administration can also worsen preexisting lupus.<sup>(3,29,30)</sup>

### ***Use during pregnancy***

Isoniazid is a category C drug. Isoniazid use during pregnancy is considered safe. However, there is a risk of developing hepatitis in the postpartum period. The WHO recommends that all pregnant women receiving isoniazid also take pyridoxine (25-50 mg/day). Neonates born to mothers who have been under treatment with isoniazid are at risk of developing convulsive seizures.<sup>(3,5,31)</sup>

### ***Use during breastfeeding***

Although isoniazid is considered compatible with breastfeeding, the infant should be monitored for jaundice.<sup>(32)</sup>

### ***Use in patients with liver failure***

Isoniazid is a hepatotoxic drug, the effect of which becomes more evident in individuals with liver disease, in alcoholic individuals, and in individuals over 50 years of age. In such patients, the half-life of isoniazid is longer, and the serum levels of the drug are higher. These patients should be closely monitored and should undergo clinical examination and laboratory tests more frequently than is necessary for patients without liver disease.<sup>(3,33)</sup>

### ***Use in patients with kidney failure***

Adjustments to the doses of isoniazid are not required in patients with kidney failure or in those on hemodialysis.<sup>(3,4,34)</sup>

### ***Interactions***

#### ***Foods***

Isoniazid should be taken on an empty stomach because it requires an acid medium in order to be absorbed. Foods, particularly

carbohydrates, can decrease the absorption of the drug by as much as 57% and the plasma concentration of the drug by as much as 30%. The drug should not be taken with fluids containing excess glucose or lactose. Isoniazid inhibits the monoamine oxidase enzyme, which is why the drug should not be taken concomitantly with foods rich in tyramine and histamine, such as certain types of cheese (Swiss and Cheshire), fish (tuna and herring), and alcohol, especially red wine. The symptoms of these interactions include palpitation, sweating, flushing of the face, chills, headache, diarrhea, erythema, and pruritus.<sup>(35)</sup>

#### ***Antacids***

Drugs that increase the gastric pH delay the absorption of isoniazid. Antacids containing aluminum hydroxide or ranitidine should be administered 1 h after the administration of isoniazid.<sup>(35)</sup>

#### ***Other drugs***

Isoniazid is an inhibitor of the cytochrome P450 (CYP450) system families CYP2C9, CYP2C19, and CYP2E1, but its effect on the CYP3A family is minimal. This inhibitory effect of isoniazid can increase the plasma concentrations of certain drugs to toxic levels.<sup>(3,36)</sup> The plasma concentrations of anticonvulsants, such as phenytoin and carbamazepine, can increase when these drugs are used in combination with isoniazid.<sup>(37)</sup> The same occurs with the benzodiazepines that are metabolized by oxidation (e.g., diazepam and triazolam), as well as with theophylline, valproic acid, disulfiram, acetaminophen, and oral anticoagulants. The combination of isoniazid and levodopa can cause hypertension, palpitation, and flushing of the face.<sup>(3,5,6,38)</sup>

### ***Rifampin***

Rifampin is the most important drug in the treatment of tuberculosis. The drug has been used since 1966 and the MIC of rifampin for *M. tuberculosis* is 0.05-0.50 µg/mL.<sup>(15)</sup> Rifampin is a bactericidal drug that kills growing, metabolically active bacilli, as well as bacilli in the stationary phase, during which metabolism is reduced. When rifampin is used in combination with pyrazinamide, tuberculosis treatment duration can be reduced to six months.<sup>(3)</sup>

### ***Mechanism of action***

Rifampin inhibits the gene transcription of mycobacteria by blocking the DNA-dependent RNA polymerase, which prevents the bacillus from synthesizing messenger RNA and protein, causing cell death.<sup>(39)</sup> Resistance to rifampin occurs due to mutations in the *rpoB* gene, which encodes the RNA polymerase beta chain.<sup>(15,39)</sup>

### ***Metabolization and excretion***

The serum and plasma levels of rifampin peak at 5-10 µg/mL within 2-4 h after the oral ingestion of a 600-mg dose of the drug. Approximately 85% of the drug is metabolized in the liver through microsomal enzymes of the CYP450 system. The drug is excreted via the biliary tract (60-65%). Part of rifampin (6-15%) is excreted in unmetabolized form and is reabsorbed in the intestine, progressively increasing the serum levels of the drug. After approximately 14 days, enzymes that increase the metabolism of the drug are produced (autoinduction of metabolism), and the half-life of rifampin is reduced from 3-5 h to 2-3 h. A smaller proportion of the drug is excreted in urine.<sup>(40,41)</sup>

### ***Central nervous system***

The concentration of rifampin in the central nervous system is only 10-20% of the serum concentration of the drug. However, it is enough for the drug to be clinically effective. The concentration increases during meningitis.<sup>(3)</sup>

### ***Adverse effects<sup>(3-5,7)</sup>***

#### ***Minor adverse effects***

- **Gastrointestinal reactions:** Nausea, anorexia, and abdominal pain can occur in patients treated with rifampin. The incidence of gastrointestinal reactions varies. However, the symptoms are rarely severe enough to warrant discontinuation of the drug. Gastrointestinal reactions can be treated as previously described for isoniazid.
- **Orange-colored tears, sweat, and urine:** Patients should be alerted to the possibility that rifampin administration can cause

discoloration of body fluids. Orange-colored tears can stain contact lenses.

- **Skin reaction:** Pruritus, with or without erythema, occurs in 6% of patients receiving rifampin. This reaction is generally mild and, in most cases, does not warrant treatment discontinuation. It might be necessary to use topical or systemic medication (moisturizers, antihistamines, or even corticosteroids).
- **Flu-like syndrome:** Flu-like syndrome is rare and occurs in patients who use intermittent regimens that include rifampin.
- **Fatigue, dizziness, headache, dyspnea, and ataxia** can also occur in patients treated with rifampin.

### ***Major adverse effects***

- **Exanthema:** Exanthema can occur due to the use of rifampin or of another drug administered in combination with rifampin. If exanthema occurs, treatment should be discontinued, and the drugs should be subsequently reintroduced, one by one, in order to identify the causative drug.
- **Hepatotoxicity:** Transitory and asymptomatic increases in the serum levels of bilirubin and hepatic enzymes occur in 5% of patients treated with rifampin. Those levels subsequently normalize, without the need to discontinue the treatment. However, cholestatic hepatitis occurs in 2.7% of the patients receiving rifampin in combination with isoniazid and in up to 1.1% of those receiving rifampin in combination with antituberculosis drugs other than isoniazid.
- **Immunological reactions:** Thrombocytopenia, leukopenia, eosinophilia, hemolytic anemia, agranulocytosis, vasculitis, acute interstitial nephritis, and septic shock can occur after rifampin administration. These reactions are rare and occur in less than 0.1% of the patients. However, these reactions are severe and call for a change in the therapeutic regimen.

### ***Use during pregnancy***

Rifampin is a category C drug. Rifampin has been used during pregnancy, and no teratogenic effects have been reported.<sup>(3,5,31)</sup> As a precaution,

neonates born to mothers who have been under treatment with isoniazid should be given vitamin K, in order to avoid postpartum hemorrhage.<sup>(42)</sup>

### ***Use during breastfeeding***

Although rifampin is compatible with breastfeeding, the infant should be monitored for jaundice.<sup>(5,32)</sup>

### ***Use in patients with liver failure***

Liver failure can impair rifampin clearance, increasing the serum levels of the drug. However, due to the important role that rifampin plays in tuberculosis treatment regimens, the drug is generally included, with the proviso that the patients be closely monitored through frequent clinical evaluations and laboratory tests (see also Drug-induced hepatitis).<sup>(3)</sup>

### ***Use in patients with kidney failure***

Because rifampin is metabolized in the liver, the drug can be used at full doses in patients with kidney failure.<sup>(3-5)</sup>

## ***Interactions***

### ***Foods***

Rifampin should be taken on an empty stomach. Foods decrease the absorption of the drug by as much as 26%, as well as increasing the time required for the drug to reach maximum concentration and decreasing that concentration by 15-36%.<sup>(35)</sup>

### ***Antacids***

Antacids containing aluminum hydroxide delay the absorption of rifampin.<sup>(35)</sup>

### ***Other drugs***

A large number of interactions can occur between rifampin and other drugs. The drug is a potent inducer of the CYP450 system, including the CYP3A and CYP2C subfamilies, which account for more than 80% of the CYP450 isoenzymes. Therefore, rifampin can increase the metabolism of numerous drugs that are partially or completely metabolized by CYP450 when these drugs are administered concomitantly with rifampin. In addition, rifampin induces

uridine diphosphate-glucuronosyltransferase, an enzyme that has also been implicated in the metabolism of various drugs, the plasma levels of which can be reduced when such drugs are administered in combination with rifampin.<sup>(43,44)</sup>

The possibility of interaction between rifampin and other drugs calls for a thorough history taking that focuses on the drugs currently used by patients. There is a decrease in the plasma concentrations of the following drugs when administered concomitantly with rifampin: oral hypoglycemic agents, the doses of which might have to be increased, and which might sometimes have to be replaced with insulin<sup>(45)</sup>; protease inhibitors and non-nucleoside reverse transcriptase inhibitors, although efavirenz or a combination of saquinavir and ritonavir can be used without the need for discontinuing rifampin<sup>(46)</sup>; oral anticoagulants, the doses of which should be carefully monitored, as should their international normalized ratios; and other drugs, such as valproic acid, antidepressants (nortriptyline and sertraline), barbiturates, benzodiazepines, beta-adrenergic blocking agents, ketoconazole, chloramphenicol, contraceptives, corticosteroids, cyclosporine, dapsone, digoxin, diltiazem, enalapril, phenytoin, fluconazole, haloperidol, itraconazole, macrolides, nifedipine, quinidine, rapamycin, simvastatin, theophylline, and verapamil.<sup>(3,6,7,47)</sup> The administration of rifampin in combination with ketoconazole or para-aminosalicylic acid decreases the serum levels of rifampin. The drugs should be administered separately, at least 12 h apart.<sup>(48,49)</sup>

## ***Pyrazinamide***

Pyrazinamide is a nicotinic acid derivative, the molecular structure of which is similar to that of isoniazid. However, there is no cross-resistance of *M. tuberculosis* to pyrazinamide and isoniazid. Pyrazinamide was synthesized in 1936 and has been used as an antituberculosis drug since 1952. The MIC of pyrazinamide for *M. tuberculosis* is 6.25-50.0 µg/mL at a pH of 5.5. After oral administration, pyrazinamide is well absorbed and widely distributed throughout the body. The plasma concentration of the drug peaks within 2 h after its administration. Pyrazinamide is bactericidal and has a potent sterilizing effect, principally in the acid medium within macrophages and at sites of acute

inflammation. In patients with tuberculosis-induced lung injury, the growth of the bacilli that are phagocytosed by macrophages is inhibited by the acid environment within the phagolysosomes. Growth is also inhibited in the inflammatory zones of the cavitory wall due to the acid pH in those zones. These bacilli (designated persistent bacilli in the sporadic multiplication phase) are responsible for bacteriological relapse. Pyrazinamide is the most effective drug in eliminating this population. This sterilizing activity of pyrazinamide allows the duration of the treatment with the RHZ regimen to be reduced to six months.<sup>(3,50,51)</sup> *M. tuberculosis* is the only microorganism that is susceptible to pyrazinamide.<sup>(50,51)</sup>

### **Mechanism of action**

Pyrazinamide is a prodrug that needs to be converted into its active form, pyrazinoic acid, by bacterial enzymes (nicotinamidase/pyrazinamidase). The mechanism of action of pyrazinamide has yet to be fully understood. It is supposed that pyrazinamide enters the bacillus passively, is converted into pyrazinoic acid by pyrazinamidase, and reaches high concentrations in the bacterial cytoplasm due to an inefficient efflux system. The accumulation of pyrazinoic acid decreases the intracellular pH to levels that cause the inactivation of enzymes—such as fatty acid synthase I, which plays a fundamental role in synthesizing fatty acids—and, consequently, the impairment of mycolic acid biosynthesis. Resistance to pyrazinamide results from mutations in the *pncA* gene, which encodes the nicotinamidase/pyrazinamidase enzyme and prevents pyrazinamide from being converted into its active form.<sup>(50,52,53)</sup>

### **Metabolization and excretion**

Pyrazinamide is metabolized in the liver, and 70% of the drug is excreted in urine (3% in non-metabolized form), principally through glomerular filtration. The half-life of pyrazinamide is 9–10 h but can be as long as 26 h in patients with kidney failure if the doses are not adjusted.<sup>(3,51)</sup>

### **Central nervous system**

Pyrazinamide crosses the blood-brain barrier, and the concentrations of the drug in the CSF are similar to those in plasma.<sup>(3,51)</sup>

## **Adverse effects**

### **Minor adverse effects**

- Gastrointestinal symptoms: Nausea, vomiting, and anorexia are common in patients treated with pyrazinamide.<sup>(3,7)</sup>
- Hyperuricemia and arthralgia in non-gouty individuals: In non-gouty patients receiving pyrazinamide, hyperuricemia commonly leads to arthralgia. The mechanism is related to pyrazinoic acid, the principal metabolite of pyrazinamide, which inhibits the renal tubular secretion of uric acid. This rarely requires that pyrazinamide be discontinued or that the dose be adjusted. The hyperuricemia is typically asymptomatic, and the pain responds well to treatment with aspirin or nonsteroidal anti-inflammatory drugs.<sup>(3,7,13)</sup>
- Exanthema and pruritus: Exanthema and pruritus are relatively common effects of pyrazinamide administration. In most cases, these improve with the administration of antihistamines.<sup>(3,7)</sup>
- Dermatitis: Treatment with pyrazinamide can cause photosensitivity dermatitis.<sup>(3)</sup>

### **Major adverse effects**

- Severe exanthema and pruritus: If severe exanthema and pruritus occur, pyrazinamide should be discontinued.<sup>(3,7)</sup>
- Rhabdomyolysis with myoglobinuria and kidney failure: Rhabdomyolysis with myoglobinuria and kidney failure is a rare complication of pyrazinamide treatment and requires that the drug be discontinued.
- Acute arthritis in gouty individuals: In patients receiving pyrazinamide, acute arthritis is rare, except in those with a history of gout. The symptoms improve with the use of moisturizers and allopurinol, as well as with dietary changes.<sup>(3,7)</sup>
- Hepatotoxicity: Pyrazinamide is the most hepatotoxic of the drugs cited in the present study. Therefore, it is essential that the doses of the drug be adjusted to the weight of the patient. Liver impairment is rare if the drug is administered at a maximum dose of 35 mg • kg<sup>-1</sup> • day<sup>-1</sup>. The new guidelines for the treatment of

tuberculosis in Brazil<sup>(1,2)</sup> recommend a dose of 1,600 mg for patients who weigh more than 50 kg, which is likely to reduce the hepatic adverse effects of the drug. In patients with pyrazinamide-induced hepatitis, the drug should be temporarily discontinued or even replaced.<sup>(7)</sup>

### ***Use during pregnancy***

Pyrazinamide is a category C drug. The WHO considers it safe to use pyrazinamide during pregnancy. In Brazil, pyrazinamide has been used for more than two decades as part of regimen 1 (RHZ), and no risks have been reported.<sup>(7,30,51)</sup>

### ***Use during breastfeeding***

Although pyrazinamide is considered compatible with breastfeeding, the infant should be monitored for jaundice.<sup>(3,32,51)</sup>

### ***Use in patients with liver failure***

Pyrazinamide is a hepatotoxic drug, the effect of which is more evident in individuals with liver disease. These patients should be closely monitored and should undergo clinical examination and laboratory tests more frequently than is necessary for patients without liver disease.<sup>(3,7)</sup>

### ***Use in patients with kidney failure***

The metabolites of pyrazinamide are eliminated by the kidney and can accumulate in patients with kidney failure, which requires that the dose of the drug be decreased. The risk of developing pyrazinamide-induced hyperuricemia also increases in patients with kidney failure. The daily dose should be reduced to half when creatinine clearance is lower than 10 mL/min. Patients with creatinine clearance lower than 30 mL/min or those on hemodialysis should be given pyrazinamide at a dose of 25-35 mg/kg, three times a week.<sup>(3,4,51)</sup>

### ***Interactions***

#### ***Foods***

Foods have very little impact on the absorption of pyrazinamide. The drug can be taken at mealtime.<sup>(35)</sup>

### ***Antacids***

Antacids do not interfere with the absorption of pyrazinamide.<sup>(35)</sup>

### ***Other drugs***

Probenecid, rifampin, isoniazid, and ethionamide can potentiate the toxic effects of pyrazinamide. The combination of pyrazinamide and zidovudine can reduce the effect of pyrazinamide. Pyrazinamide antagonizes the effects of probenecid and decreases the serum concentration of cyclosporine. Pyrazinamide can increase the serum concentrations of uric acid, and it might be necessary to adjust the doses of allopurinol and colchicine in patients under gout treatment.<sup>(3,47,51)</sup>

### ***Ethambutol***

Ethambutol was synthesized in 1961 and has been used in the treatment of tuberculosis since 1966. It acts on intracellular and extracellular bacilli, principally on rapidly growing bacilli. The MIC of ethambutol for *M. tuberculosis* is 1-5 µg/mL. At the usual doses, ethambutol has a bacteriostatic effect.<sup>(3,15,54)</sup>

### ***Mechanisms of action***

Ethambutol interferes with the biosynthesis of arabinogalactan, the principal polysaccharide on the mycobacterial cell wall. Ethambutol inhibits the arabinosyltransferase enzyme encoded by the *embB* gene, which mediates the polymerization of arabinose into arabinogalactan. In vitro resistance to ethambutol develops slowly and is probably due to mutations in the *embB* gene.<sup>(15,50,54)</sup>

### ***Metabolization and excretion***

After the oral administration of ethambutol, 75-80% of the dose is absorbed, and the serum levels of the drug peak within 2-4 h. A single 25-mg/kg dose produces plasma concentrations of 2-5 µg/mL. The serum half-life of ethambutol is 3-4 h, and it can be as long as 10 h in patients with severe kidney failure. Part of the drug (20-30%) binds to plasma proteins. Ethambutol is widely distributed throughout the body, with the exception of the CSF in patients without meningitis. Ethambutol is metabolized in the

liver, and the principal mechanism is oxidation to form an intermediate aldehyde, followed by conversion into dicarboxylic acid. Most of the drug (50–80%) is excreted in urine (8–15% is excreted as metabolites), and 20% is excreted in feces.<sup>(3,40,51,54)</sup>

### ***Central nervous system***

Ethambutol does not cross healthy meninges. In cases of meningitis, the CSF levels of ethambutol are at 10–50% of the plasma levels of the drug.<sup>(3,40,51)</sup>

### ***Adverse effects***

Ethambutol is generally well tolerated. Most adverse effects are dose- and time-dependent, being more common at doses higher than 15 mg/kg.

- **Retrolubar neuritis:** When retrolubar neuritis occurs in patients treated with ethambutol, it is generally reversible and depends on the dose and duration of administration. The central fibers of the optic nerve are most commonly affected, causing symptoms of blurred vision; ophthalmologic examination reveals a decrease in visual acuity, presence of scotomas, and loss of the ability to discern the color green and, in some cases, the color red. Peripheral fiber impairment is less common and manifests as a reduction in the visual field. The reaction is dose-dependent. The risk is small (1%) when ethambutol is administered at doses of 15 mg • kg<sup>-1</sup> • day<sup>-1</sup>. However, retrolubar neuritis occurs in 15–18% of patients receiving doses of 35 mg • kg<sup>-1</sup> • day<sup>-1</sup> for more than two months. In addition, the risk of developing retrolubar neuritis is greater in patients with kidney failure and in elderly individuals with impaired renal function. Retrolubar neuritis is reversible when the symptoms are detected early and the drug is immediately discontinued. The administration of ethambutol should be avoided in young children, whose visual acuity is difficult to evaluate.<sup>(3,40,51,54–56)</sup>
- **Peripheral neuritis:** In rare cases, treatment with ethambutol causes peripheral neuritis, the symptoms of which improve after administration of pyridoxine.<sup>(3,40,51)</sup>
- **Other effects:** Additional effects of ethambutol administration include gastrointestinal

symptoms (nausea, vomiting, abdominal pain, and hepatotoxicity), hematological symptoms (eosinophilia, neutropenia, and thrombocytopenia), cardiovascular symptoms (myocarditis and pericarditis), neurological symptoms (headache, dizziness, and mental confusion), hyperuricemia/gout (due to a reduction in the excretion of uric acid by the kidney), hypersensitivity (skin rash, arthralgia, and fever), and (occasionally) pulmonary infiltrates.<sup>(3,40,51,54)</sup>

### ***Use during pregnancy***

Ethambutol is a category B1 drug. Ethambutol crosses the placental barrier, and the plasma concentration of ethambutol in the fetus can be as high as 30% of the plasma concentration of the drug in the mother. The WHO considers it safe to use ethambutol during pregnancy.<sup>(3,51)</sup>

### ***Use during breastfeeding***

Ethambutol concentrations in breast milk are similar to the plasma concentrations of the drug. The American Academy of Pediatrics considers ethambutol to be compatible with breastfeeding.<sup>(32)</sup>

### ***Use in patients with liver failure***

Ethambutol can be used at full doses in patients with liver failure. It is not necessary to adjust the dose of the drug in such patients.<sup>(3,51)</sup>

### ***Use in patients with kidney failure***

Ethambutol and its metabolites can accumulate in patients with kidney failure. Patients with a creatinine clearance of 30–50 mL/min should use the drug at longer intervals between doses, usually every 36 h. In patients on hemodialysis or in those in whom creatinine clearance is lower than 30 mL/min, a dose of 15–20 mg/kg should be administered three times a week. Ethambutol is removed by peritoneal dialysis and, to a lesser degree, by hemodialysis.<sup>(3,4,57)</sup>

### ***Interactions***

#### ***Foods***

Foods have a minimal effect on the bioavailability of ethambutol.<sup>(35)</sup>

### *Antacids*

Antacids can reduce the maximum concentration of ethambutol by as much as 28%. The drugs should therefore be administered at longer intervals.<sup>(35)</sup>

### *Other drugs*

Ethionamide can exacerbate the toxic effects of ethambutol.<sup>(58)</sup>

## **Drug-induced hepatitis due to interactions among antituberculosis drugs**

Three of the drugs that constitute the basic regimen proposed by the Brazilian National Ministry of Health (rifampin, isoniazid, and pyrazinamide) are potentially hepatotoxic. These drugs are metabolized in the liver. The three drugs interact with one another and with other drugs, which occasionally increases the risk of hepatotoxicity. The predisposing factors for hepatotoxicity include genetic causes, advanced age, extent of the disease, female gender, nutritional status, excessive doses of the drugs, use in combination with other hepatotoxic drugs, alcoholism, chronic viral hepatitis (types B and C), and HIV infection. Approximately 5% of the tuberculosis patients who use the RHZ regimen present with a three- to five-fold increase in hepatic enzyme levels, as well as with increased bilirubin levels, without clinical manifestations. These levels decrease spontaneously as the treatment progresses. According to the international literature, in patients using these medications, the mean risk of developing drug-induced hepatitis is 1-10%, depending on factors such as race, socioeconomic status, and geographic location. Drug-induced hepatitis, including hepatitis due to antituberculosis drugs, might be related to mechanisms of hypersensitivity to drugs that are intrinsically hepatotoxic or to drugs that can produce a toxic metabolite that liver tissue might not be able to clear. Antituberculosis drug-induced cholestasis can be accompanied by early clinical manifestations, such as increased bilirubin levels and increased alkaline phosphatase levels, the prognosis of the latter being better than that of the former. Most of the cases of drug-induced hepatotoxicity occur within two months after

the initiation of treatment and can be classified as mild (hepatic enzyme levels three to five times higher than normal), moderate (hepatic enzyme levels up to ten times higher than normal), or severe (hepatic enzyme levels more than ten times higher than normal).

Pyrazinamide is considered the most hepatotoxic drug of the basic regimen, and pyrazinamide-induced hepatotoxicity is dose-dependent. Because the risk increases when the dose is higher than  $30 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ , the dose must be adjusted to the weight of the patient.

The administration of isoniazid in isolation, at doses adjusted to the weight of the patient, rarely produces drug-induced hepatitis, which is practically nonexistent in children but is more common in alcoholic and elderly individuals. Hepatocyte injury caused by isoniazid seems to be more closely related to the formation of the hydrazine radical produced by direct metabolism of the drug. The histopathological characteristics of isoniazid-induced hepatitis can include acute cellular necrosis or cholestasis. In patients with cholestasis, clinical manifestations occur earlier due to sensitization mechanisms that are evidenced (through laboratory testing) by an increase in bilirubin and alkaline phosphatase levels. Patients with cholestatic hepatitis have a better prognosis. Acute cellular necrosis is indistinguishable from viral hepatitis, which is why extremely high aminotransferase levels can be found. In these cases, serology for viral hepatitis should be ordered. When administered in combination with rifampin, isoniazid can lead to acute, fatal drug-induced hepatitis, which is fortunately rare. Especially when administered in combination with rifampin, isoniazid can reactivate inapparent viral infections in asymptomatic patients and therefore cause the onset of viral hepatitis, usually hepatitis B.

The administration of rifampin in isolation rarely causes liver changes. It can, however, potentiate the hepatotoxic effect of isoniazid, since rifampin induces hepatic microsomal enzymes of CYP450 that, in turn, facilitate the conversion of isoniazid into monoacetylhydrazine and hydrazine (toxic metabolites of isoniazid). These agents are implicated in the pathogenesis of liver necrosis. There has been no statistical confirmation that the incidence of hepatotoxicity is higher in individuals with the rapid acetylator

phenotype than in those with the slow acetylator phenotype, since the quantity of final metabolites is similar in the two groups of patients. The use of rifampin in isolation can induce cholestasis, since the drug is excreted in bile after having been absorbed by the hepatocyte and having undergone partial deacetylation. The absorption of rifampin competes with the absorption and conjugation of bilirubin for the inhibition of glucuronosyltransferase. Therefore, in the first weeks of treatment, jaundice can be observed, although it disappears whether the drug is discontinued or not.

In cases of hepatotoxicity due to anti-tuberculosis drugs, the following is recommended:

- 1) Patients who present with complaints of vomiting should be carefully observed, and it should be investigated whether these patients also present with jaundice, pain in the right hypochondrium, pruritus, acholic stools, and choluria. In these cases, aminotransferase levels, as well as the levels of alkaline phosphatase and bilirubin, should be determined. Viral hepatitis and cholecystitis (principally when there is pain) should be ruled out.
- 2) Special attention should be paid to cases in patients who present with low weight, poor general health status, or a history of liver disease or chronic alcoholism, as well as in those who are over 60 years of age.
- 3) The combination of isoniazid/rifampin with hydantoins, imidazoles, carbamazepine, azathioprine, or cyclosporine requires careful monitoring, through clinical examination and laboratory testing, for the early detection of drug-induced hepatitis.
- 4) If hepatotoxicity is suspected, on the basis of clinical findings or laboratory test results (serum levels of hepatic enzymes three times higher than baseline levels, with symptoms, or serum levels of hepatic enzymes at least five times higher than baseline levels, with or without symptoms), the medication should be discontinued and patients should be referred to a specialized center.

If, after treatment discontinuation, the serum levels of hepatic enzymes decrease and the symptoms resolve, the drugs that constitute the basic regimen should be reintroduced one

by one at weekly intervals. Because rifampin (with or without ethambutol) is the most potent and least hepatotoxic drug in the regimen, the ATS/CDC/IDSA guidelines,<sup>(3)</sup> as well as the III Brazilian Thoracic Association Guidelines on Tuberculosis,<sup>(2)</sup> recommend that rifampin be the first drug to be reintroduced, followed by isoniazid and pyrazinamide. In cases of intolerance to one of the drugs, the III Brazilian Thoracic Association Guidelines on Tuberculosis recommend that the following regimens be used: a) intolerance to rifampin: 2HZES5\10HE, b) intolerance to isoniazid: 2RZES5\7RE, c) intolerance to pyrazinamide: 2RHE\7RH, d) intolerance to ethambutol: 2RHZ\4RH<sup>(1-3,10,59-63)</sup>

## Final considerations

The treatment of tuberculosis can cause adverse reactions. The management of situations that are more severe (which are, fortunately, uncommon) is generally the responsibility of referral centers and experienced professionals with knowledge of the therapeutic alternatives available.

Accurate diagnoses and knowledge of the pharmacological properties of the drugs involved allow professionals to tailor their approach to each individual case.

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