Antituberculosis drugs: Drug interactions, adverse effects, and use in special situations. Part 2: Second-line drugs*

Drogas antituberculose: Interações medicamentosas, efeitos adversos e utilização em situações especiais. Parte 2: Fármacos de segunda linha

Marcos Abdo Arbex, Marília de Castro Lima Varella, Hélio Ribeiro de Siqueira, Fernando Augusto Fiúza de Mello

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 describe the general mechanism of action, absorption, metabolization, and excretion of the drugs used to treat multidrug resistant tuberculosis (aminoglycosides, fluoroquinolones, cycloserine/terizidone, ethionamide, capreomycin, and para-aminosalicylic acid). 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.

Keywords: Tuberculosis; Drug interactions; Antibiotics, antitubercular; Pharmacologic actions; Drug toxicity, Tuberculosis, multidrug-resistant.

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. Descrevemos os mecanismos gerais de ação, absorção, metabolização e excreção dos medicamentos utilizados no tratamento da tuberculose multidroga resistente (aminoglicosídeos, fluoroquinolonas, cicloserina/terizidona, etionamida, capreomicina e ácido para-aminossalicílico). 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.

Descritores: Tuberculose; Interações de medicamentos; Antibióticos antituberculose; Ações farmacológicas; Toxicidade de drogas; Tuberculose resistente a múltiplos medicamentos.

Introduction

In Brazil, tuberculosis treatment regimens have been standardized by the Brazilian National Ministry of Health (NMH) since 1979. According to the latest technical norms published by the NMH (in October of 2009),[1] and to the guidelines issued by the World Health Organization (WHO),[2] patients with bacilli resistant to the rifampin-isoniazid combination or to the rifampin-isoniazid combination and at least one other first-line drug, as well as patients in whom the basic regimen fails, are classified as having multidrug-resistant tuberculosis. It has been proposed that a combination regimen of streptomycin, ethambutol, terizidone, pyrazinamide, and one fluoroquinolone (levofloxacin or ofloxacin) be used in cases such as these.[1,3] If streptomycin cannot be used, it should be replaced with amikacin.[1,2] 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.[3]

In this review article, we describe the principal characteristics of each of the drugs

* Study carried out at the Nestor Goulart Reis Hospital, São Paulo State Department of Health, Américo Brasiliense, Brazil.
Correspondence to: Marcos Abdo Arbex. Rua Voluntários da Pátria, 2104, CEP 14801-320, Araraquara, SP, Brasil.
Tel 55 16 9714-2882. E-mail: arbexma@techs.com.br ou arbex@unifesp.br
Financial support: None.
Submitted: 8 April 2010. Accepted, after review: 1 June 2010.

that constitute the alternative regimen for tuberculosis treatment proposed by the Brazilian National Ministry of Health and the Brazilian Thoracic Association,[1,3] as well as the relevant aspects of the pharmacokinetics of the drugs in order to understand the mechanisms of interaction and possible adverse effects.

Aminoglycosides (streptomycin, amikacin, and kanamycin)

Streptomycin, which was discovered in 1944, was the first drug that was effective in treating tuberculosis.[4] Kanamycin was synthesized in 1957. Amikacin is a semi-synthetic compound derived from kanamycin and has been used since 1972. Aminoglycosides act on extracellular bacilli, and their intracellular activity is therefore irrelevant. The minimum inhibitory concentrations (MICs) of streptomycin, kanamycin, and amikacin for *Mycobacterium tuberculosis* are 4-8 μg/mL, 1-8 μg/mL, and 0.5-1.0 μg/mL, respectively. These drugs are bactericidal, and their effects are concentration-dependent and residual, which means that they have a bactericidal effect even when their serum concentrations are below the MICs.[5-8] Although there have been reports of cross-resistance between amikacin and kanamycin, there have been no reports of such cross-resistance between streptomycin and amikacin or kanamycin.[8,9]

Mechanism of action

Aminoglycosides inhibit protein synthesis by irreversibly binding to the 30S ribosomal subunit of *M. tuberculosis*, interfering with the integrity of the cell membrane. Resistance is due to mutations in the *rrs* gene, which encodes 16S ribosomal RNA, and in the *rpsL* gene, which encodes the S12 ribosomal protein gene.[5,9]

Metabolization and excretion

Oral absorption of aminoglycosides is minimal, and the drugs are administered parenterally. Absorption is complete when aminoglycosides are administered i.m., and the serum levels of the drugs peak within 30-90 min after their administration; however i.m. absorption can be slower, requiring successive injections at the same site.[2] It is recommended that i.v. administration of aminoglycosides be carried out over a period of 15-30 min in order to reduce the risk of adverse effects, such as neuromuscular blockade (see also Adverse effects). The binding of aminoglycosides to plasma proteins is low (approximately 10%). Over a 24-h period, 80-98% of the drug is excreted, unaltered, by the kidneys (glomerular filtration), 1% is excreted in bile, and 1% is excreted in feces. The half-life of streptomycin is 2-3 h, and the half-life of amikacin is 2 h, although the latter can be as long as 86 h in patients with kidney failure.[2,10,11]

Central nervous system

The penetration of aminoglycosides into the cerebrospinal fluid (CSF) is low, except in cases of meningitis.[2,10,11]

Adverse effects

Ototoxicity

The most severe adverse reaction caused by aminoglycosides is ototoxicity due to damage to cranial nerve VIII, including vestibular damage (vertigo, ataxia, and nystagmus) and cochlear damage that can lead to hearing loss. The risk increases with age, prolonged duration of treatment, and high total accumulated dose. The risk also increases in patients who use aminoglycosides in association with diuretics (furosemide and ethacrynic acid), in dehydrated patients, and in patients with a history of hearing impairment. Vestibular damage is more common than is cochlear damage and occurs earlier. In addition, vestibular damage is more common in patients using streptomycin than in those using amikacin. Ototoxicity requires immediate discontinuation of the drug.[2,10-13]

Neurotoxicity

Aminoglycosides can cause perioral paresthesia immediately after their administration. This adverse effect is benign.[2,10,11]

Nephrotoxicity

Aminoglycosides produce renal toxic effects due to their accumulation in the renal tubules. Such effects are more common in elderly individuals and in patients with a history of kidney disease. Clinical and laboratory manifestations of nephrotoxicity include oliguria, urinary casts, proteinuria, and decreased creatinine clearance, as well as increased serum levels of urea and creatinine. Patients who receive

more than one daily dose of the drug, patients under long-term treatment, and patients with high total accumulated dose are more likely to develop nephrotoxicity. Nephrotoxicity is more common in patients using amikacin (occurring in 3.4-8.7%) than in those using streptomycin (occurring in 2%). Discontinuation of the drug is recommended.[2,10,14-16]

Neuromuscular blockade

Aminoglycosides can cause neuromuscular blockade, leading to respiratory failure. Neuromuscular blockade can occur due to rapid i.v. injection of the drug in patients who concomitantly use anesthetics or neuromuscular blocking agents (curare or succinylcholine) or in those who have received massive blood transfusions in which citrate is used as an anticoagulant. Although calcium salts can reduce this effect, mechanical ventilation might be necessary.[2,10]

Hypersensitivity

Hypersensitivity is rare in patients treated with aminoglycosides. However, there are hypersensitivity cross-reactions among the different aminoglycosides.[2,10,11]

Use during pregnancy

Aminoglycosides are category D drugs. They rapidly cross the placental barrier and are contraindicated during pregnancy because they can induce ototoxicity and nephrotoxicity in neonates.[2,10,11]

Use during breastfeeding

Aminoglycosides should be avoided during breastfeeding. Although aminoglycosides are poorly absorbed when administered orally, changes in the intestinal flora of neonates can occur.[2,10,11]

Use in patients with liver failure

Aminoglycosides can be administered at full doses. However, patients with severe liver failure should be screened for concomitant hepatorenal syndrome.[2,10,11]

Use in patients with kidney failure

Aminoglycosides are almost exclusively eliminated by the kidney. Therefore, in patients with a creatinine clearance < 30 mL/min, the dose of the drug should be adjusted to 12-15 mg • kg^{-1} • day^{-1}, administered two to three times a week. The drug is removed by peritoneal dialysis and hemodialysis. In patients on peritoneal dialysis or hemodialysis, the dose should be adjusted and administered after the procedure.[2,10,11]

Interactions

Other drugs

The ototoxicity and nephrotoxicity of aminoglycosides can be potentiated by concomitant administration of amphotericin B, vancomycin, cephalosporin, cisplatin, and loop diuretics (ethacrynic acid and furosemide). Aminoglycosides can themselves potentiate the effects of neuromuscular blocking agents. Concomitant administration of aminoglycosides and neuromuscular blocking agents can cause respiratory depression due to respiratory muscle weakness. Patients with myasthenia gravis, botulism, hypocalcemia, severe hypokalemia, or hypomagnesemia are particularly susceptible to such adverse effects. The interaction between aminoglycosides and neuromuscular blocking agents is independent of the order of their administration. Patients using aminoglycosides should be monitored for the occurrence of respiratory depression in the perioperative and postoperative periods.[2,4,10,11,17,18]

Fluoroquinolones

Fluoroquinolones have been used as salvage drugs in the treatment of tuberculosis since 1985.[19] However, recent studies involving third-generation and fourth-generation fluoroquinolones (levofloxacin, moxifloxacin, and gatifloxacin) have demonstrated the enormous potential of these drugs and, consequently, the great interest of the scientific community in using these drugs for the treatment of tuberculosis. After their administration, fluoroquinolones are widely distributed to the body and have the remarkable property of reaching the interior of the cells, including macrophages, which explains the strong effect of these drugs on intracellular mycobacteria.[20-22] There is no cross-resistance between fluoroquinolones and other antituberculosis drugs, and, although in vitro studies have reported cross-reactions among the different fluoroquinolones,[20-22]

levofloxacin and moxifloxacin have been used even in cases of previous *M. tuberculosis* resistance to ofloxacin.[23,24] Fluoroquinolones are bactericidal and show different degrees of effectiveness against *M. tuberculosis*. The most effective fluoroquinolones are moxifloxacin and gatifloxacin, followed by levofloxacin, ofloxacin, and ciprofloxacin.[20,23,25] In vitro, the MICs of ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin for *M. tuberculosis* are 0.5-4.0 µg/mL, 1.0-2.0 µg/mL, 1.0 µg/mL, 0.20-0.25 µg/mL, and 0.12-0.50 µg/mL, respectively.[21,26] Recent studies have shown that ciprofloxacin should not be included in the antituberculosis regimen.[27] In regions where the prevalence of tuberculosis is high, fluoroquinolones have been administered as monotherapy for the empirical treatment of patients under clinical and radiological suspicion of having bacterial pneumonia; however, the respiratory symptoms can temporarily improve in patients with unsuspected or undiagnosed pulmonary tuberculosis, thus delaying the diagnosis of tuberculosis and selecting fluoroquinolone-resistant bacilli.[28-30]

Mechanism of action

Fluoroquinolones inhibit *M. tuberculosis* DNA gyrase activity or topoisomerase II activity, which regulates DNA topology and is essential to the survival of *M. tuberculosis*. The DNA molecule of *M. tuberculosis* is compacted by DNA gyrase and becomes biologically active. When fluoroquinolones inhibit this enzyme, the DNA molecule stops supercoiling in order to occupy a small cellular space for its expression, recombination, and replication. Free DNA ends induce uncontrolled mRNA synthesis, protein synthesis, exonuclease production, and chromosome degradation. These factors lead to cell death. In vitro, fluoroquinolones also inhibit topoisomerase IV; however, this does not contribute to the bactericidal effect on *M. tuberculosis*, since this enzyme is absent in the bacillus.[20,21] Bacterial resistance occurs rapidly when a fluoroquinolone is used as monotherapy or when it is included in regimens that failed. Three principal mechanisms explain resistance: mutations in the DNA gyrase enzyme, which becomes immune to the effect of the antibiotic; changes in the bacterial cell membrane, which becomes impermeable to fluoroquinolones, decreasing the diffusion of the drug to the interior of the cell; and the existence of an efflux mechanism that removes the drug from the interior of the bacterial cell.[20]

Metabolization and excretion

Fluoroquinolones are rapidly absorbed after oral administration, and their serum levels peak within 1-3 h. The bioavailability of fluoroquinolones ranges from 90% for moxifloxacin to 99% for levofloxacin. Only a small proportion is metabolized in the liver into d-ofloxacin, which has a limited bactericidal effect. Fluoroquinolones are excreted principally by the kidney through tubular secretion or glomerular filtration, and 65-80% of the drug is eliminated unaltered. A small proportion (4-8%) is excreted in bile and feces. Moxifloxacin, however, is metabolized in the liver, and 60% of the drug is excreted in bile, 45% being excreted unaltered (25% in urine and 20% in feces). The half-life of fluoroquinolones ranges from 4 h for ciprofloxacin to 10-13 h for moxifloxacin.[20-22]

Central nervous system

The penetration of fluoroquinolones into the CSF is poor. The CSF concentration of levofloxacin is at 16-20% of the serum concentration of the drug. However, in cases of meningitis, the CSF levels of ciprofloxacin and ofloxacin can be as high as 40-90% of the plasma levels of these drugs.[10,31]

Adverse effects[10,20,32-36]

Gastrointestinal effects

The most common side effects of fluoroquinolones are gastrointestinal. Patients can present with nausea, vomiting, aerophagy, anorexia, abdominal discomfort, and diarrhea. Gastrointestinal effects occur in 3-17% of the patients. Pseudomembranous colitis is rare.

Central nervous system effects

Dizziness, headache, insomnia, tremors, and mood disorders occur in 0.9-11% of patients treated with fluoroquinolones. Hallucinations, delusions, and convulsions are rare. Greater attention should be paid to these effects in elderly patients and in those using theophylline or nonsteroidal anti-inflammatory drugs (NSAIDS).

Skin reactions and allergies

Erythema, pruritus, and skin rash occur in 0.4-2.2% of patients treated with fluoroquinolones. Phototoxicity can occur when patients are exposed to ultraviolet light. Urticaria, angioedema, anaphylactic reactions, and vasculitis are uncommon.

Musculoskeletal effects

Arthropathy and cartilage erosion have been observed in young animals treated with fluoroquinolones (especially for prolonged periods or at high doses), and the use of fluoroquinolones in children is therefore restricted. However, the use of fluoroquinolones in special situations (e.g., in children with cystic fibrosis) has increased. Arthralgia has been observed in only 2% of such cases and has always been reported to be reversible. Achilles tendinopathy and Achilles tendon rupture have been reported to occur. These are rare and bilateral, occurring in 50% of the cases. These are often associated with predisposing factors such as previous corticosteroid use, rheumatoid arthritis, kidney failure, and hemodialysis.

Cardiovascular effects

In patients treated with fluoroquinolones, prolongation of the electrocardiographic QT interval can occur, leading to ventricular tachycardia, including polymorphic ventricular tachycardia (torsades de pointes). This is a rare event. Electrocardiographic QT interval prolongation is dose-dependent. Patients with kidney failure, liver failure, cardiomyopathy, hypomagnesemia, or hypokalemia, as well as those using class IA antiarrhythmic drugs (procainamide and quinidine) or class III antiarrhythmic drugs (amiodarone and sotalol), together with those using terfenadine, erythromycin, cisapride, or tricyclic antidepressants, should receive special attention.

Urinary tract effects

Interstitial nephritis, characterized by the presence of eosinophils and crystals in urine, can occur in patients treated with fluoroquinolones. These are rare events. However, patients using fluoroquinolones who present with dehydration, diarrhea, and vomiting should receive appropriate fluid supplementation.

Endocrine effects

Changes in glycemia levels, including symptomatic hypoglycemia and, less commonly, hyperglycemia, have been reported to occur in patients with diabetes who use fluoroquinolones in conjunction with oral hypoglycemic agents or insulin.

Biochemical effects

Leukopenia and eosinophilia occur in less than 1% of the cases, and increased transaminase levels occur in 1-3% of the patients. Therapy is rarely discontinued due to these changes.

Use during pregnancy

Fluoroquinolones are category C drugs. In principle, fluoroquinolones should not be used during pregnancy. There is no evidence that the incidence of abnormalities is higher in children treated with fluoroquinolones. However, studies involving animals and ciprofloxacin have suggested that there are risks of damage to the articular cartilages of the fetus and, consequently, of juvenile arthritis and joint lesions. Fluoroquinolones should be used during pregnancy only when the benefits of the treatment outweigh the potential risks. The decision to use a fluoroquinolone can be made only after clinicians who have considerable experience in managing tuberculosis have been consulted.[2,10]

Use during breastfeeding

Ofloxacin is excreted in breast milk.[37] There are no data regarding breastfeeding and the use of levofloxacin or moxifloxacin. Considering the potential adverse effects of the drugs on infants, the WHO suggests that fluoroquinolones be used only in cases in which they are vital to the health of the mother.[2,10]

Use in patients with liver failure

Fluoroquinolones can be used without restrictions in patients with mild or moderate liver failure (Child-Pugh classes A and B). However, in cases of severe liver disease (Child-Pugh class C), as occurs with any other drug, patients should be closely monitored, through clinical evaluation and laboratory testing.[2,10]

Use in patients with kidney failure

The dose of any given fluoroquinolone should be adjusted in patients with kidney

failure. The WHO suggests that, in patients with kidney failure and creatinine clearance < 30 mL/min, the dose of ofloxacin be adjusted to 600-800 mg, administered three times a week, and the dose of levofloxacin be adjusted to 750-1,000 mg, administered three times a week. It is not necessary to adjust the dose of moxifloxacin. Fluoroquinolones are not removed by peritoneal dialysis or hemodialysis.[33]

Interactions[2,34,35,38,39]

Foods

Foods, with the exception of dairy products with a high concentration of calcium, do not interfere with the absorption of ofloxacin, levofloxacin, or moxifloxacin, as they do with the absorption of other fluoroquinolones. Patients using ciprofloxacin should be instructed to avoid excessive use of foods with high caffeine content, since ciprofloxacin inhibits the cytochrome P450 system, thereby reducing caffeine clearance.

Antacids

Antacids containing calcium, aluminum, or magnesium interfere with the absorption and concentration of fluoroquinolones. Sucralfate inhibits the absorption of the drugs. Fluoroquinolones should not be administered until 2 h after the use of antacids. The administration of H_2 receptor blockers does not interfere with the absorption of fluoroquinolones.

Other drugs

Vitamin supplements containing zinc or iron interfere with the gastrointestinal absorption of fluoroquinolones. Fluoroquinolones can inhibit numerous cytochrome P450 subfamilies, which increases the plasma concentrations of drugs that are metabolized via the cytochrome P450 system. Fluoroquinolones increase the serum levels of theophylline, glibenclamide, and cyclosporine, as well as increasing the effect of oral anticoagulants. Third-generation and fourth-generation fluoroquinolones (levofloxacin and moxifloxacin) do not inhibit the cytochrome P450 enzyme system and therefore do not interact with the aforementioned drugs. However, when a fluoroquinolone is concomitantly administered with oral anticoagulants, the international normalized ratio should be closely monitored. Probenecid and cimetidine can increase the serum levels of fluoroquinolones. Concomitant administration of fluoroquinolones and NSAIDS can increase central nervous system stimulation and the possibility of convulsions.

Cycloserine/terizidone

Cycloserine/terizidone, synthesized in 1952, is a structural analogue of D-alanine amino acid, a component that is important to the formation of the bacterial cell wall. Terizidone results from the combination of two cycloserine molecules. There is no cross-reaction between cycloserine/terizidone and other antituberculosis drugs. The MIC of cycloserine/terizidone for *M. tuberculosis* is 5-20 mg/mL. At the usual doses, cycloserine/terizidone has a bacteriostatic effect.[2,5,40,41]

Mechanism of action

Cycloserine/terizidone acts by competition, inhibiting the enzymes D-alanyl-D-alanine synthetase, alanine racemase, and alanine permease, which are indispensable for the synthesis of the peptidoglycan that confers rigidity and stability to the *M. tuberculosis* cell membrane. Although the mechanisms of *M. tuberculosis* resistance to cycloserine/terizidone have yet to be fully clarified, it is presumably due to genetic mutations in the aforementioned enzymes.[2,5,41]

Metabolization and excretion

Cycloserine/terizidone is rapidly absorbed after oral administration, and the bioavailability of the drug ranges from 70% to 90%. Plasma levels of the drug peak within 3-4 after ingestion. The half-life of cycloserine/terizidone is 10 h. The drug does not bind to plasma proteins. Only a small proportion of cycloserine/terizidone is metabolized in the liver. Most of the dose (70%) is excreted by the kidney, unaltered, within 72 h. A small proportion of the drug is excreted in feces.[2,10,41]

Central nervous system

The CSF and serum concentrations of cycloserine/terizidone are similar.[10]

Adverse effects

Central nervous system effects

Cycloserine/terizidone has neurological adverse effects (headache, vertigo, dysarthria,

somnolence, convulsion, mental confusion, and memory deficit) and psychiatric adverse effects (psychotic states with catatonic, paranoid, and depressive reactions, with a risk of suicide) that occur especially when the daily dose is higher than 500 mg or when cycloserine/terizidone is concomitantly administered with other neurotoxic drugs, such as isoniazid and ethionamide. Cases of peripheral neuropathy and changes in the pressure and quantity of proteins in the CSF have been described. The administration of pyridoxine can aid in preventing the neurotoxic effects, the recommended dose being 100-200 mg/day. Patients with a history of epilepsy, severe mental disturbances, suicidal tendencies, or alcoholism should be closely monitored when receiving cycloserine/terizidone. In cases of convulsive seizures caused by cycloserine/terizidone, the drug should be temporarily discontinued, anticonvulsant therapy should be initiated, and cycloserine/terizidone should be reinitiated at lower doses. In cases of psychotic symptoms, cycloserine/terizidone should be discontinued for one to four weeks, and antipsychotic drugs should be given until the symptoms have been controlled. If necessary, the dose of cycloserine/terizidone can be reduced, provided that this does not interfere with the therapeutic regimen. Occasionally, it is necessary to use antipsychotic drugs concomitantly with the therapeutic regimen for the duration of the treatment. Family members and health care workers should be on the alert to detect, in a timely manner, personality changes or signs and symptoms of depression.[2,10,42,43]

Skin effects

Although rare, skin rash and Stevens-Johnson syndrome can occur in patients treated with cycloserine/terizidone.[2,42,43]

Use during pregnancy

Cycloserine/terizidone is a category C drug. It has no teratogenic effects in laboratory animals. Although it is known that cycloserine/terizidone crosses the placental barrier, there are no data as to whether the drug is safe for the fetus. Cycloserine/terizidone should be used only when there is no therapeutic alternative.[2,10,42]

Use during breastfeeding

The American Academy of Pediatrics considers cycloserine/terizidone to be compatible with breastfeeding. Infants exposed to cycloserine/terizidone must receive supplemental doses of pyridoxine.[2,10,42,44]

Use in patients with liver failure

In patients with liver failure, cycloserine/terizidone can be used without precautions, except in patients with hepatitis due to alcoholism or in those at a high risk for convulsions.[2,10]

Use in patients with kidney failure

The dose of cycloserine/terizidone should be adjusted in patients with kidney failure. In patients with creatinine clearance < 30 mL/min, the recommended dose is 250 mg/day or 500 mg three times a week. These doses are not well-established. Patients should be closely monitored for signs of neurotoxicity.[2,10,42] Hemodialysis removes 56% of the drug, and patients on hemodialysis should receive cycloserine/terizidone after the procedure, at a dose of 500 mg administered three times a week.[45]

Interactions

Foods

Foods increase the time required for cycloserine/terizidone to be absorbed by 3.5 times, and there can be a 35% reduction in the maximum concentration of the drug. Orange juice (and probably other acidic beverages) reduces the maximum concentration of the drug by 15%. Whenever possible, the drug should be ingested with water, well before or after meals.[46]

Antacids

Antacids do not significantly interfere with the absorption and concentration of cycloserine/terizidone.[46]

Other drugs

There is evidence that combining cycloserine/terizidone with ethionamide and isoniazid can potentiate the neurotoxic effects. Cycloserine/terizidone can increase the serum levels of phenytoin and oral anticoagulants, as well as decreasing those of pyridoxine. In patients using anticonvulsants and neuroleptics, the dose of cycloserine/terizidone should be adjusted.

Chart 1 - Approach to the secondary effects of the most common antituberculosis drugs, according to the symptoms.[57,58,59]

Secondary effects	Probable causative drug	Control
Minor		Continue the treatment and reevaluate the doses.
Anorexia, nausea, and abdominal pain	Rifampin, pyrazinamide, and isoniazid	Instruct patients to take the tablets at bedtime or after a light meal. Advise patients to take the drug slowly, taking small sips of water. If the symptoms persist or worsen, or if signs of vomiting or bleeding appear, these should be considered major effects.
Arthralgia	Pyrazinamide	Prescribe acetylsalicylic acid, nonsteroidal anti-inflammatory drug, or paracetamol.
Burning sensation, hypesthesia, or tingling in the hands and feet	Isoniazid	Prescribe a daily dose of 50-75 mg of pyridoxine.
Somnolence	Isoniazid	Tranquilize patients. Advise patients to take the drug at bedtime.
Orange or red urine	Rifampin	At the initiation of the treatment, patients should be told that this often occurs and is to be expected.
Flu-like syndrome (fever, chills, headache, indisposition, and arthralgia)	Rifampin at intermittent doses	Patients should be instructed to use rifampin daily.
Cutaneous pruritus	Isoniazid and rifampin	Instruct patients. Prescribe antihistamines.
Hyperuricemia (with or without symptoms)	Pyrazinamide	Instruct patients to go on a low purine diet and prescribe acetylsalicylic acid.
Major		Discontinue the causative drug and perform another clinical evaluation.
Skin rash with or without pruritus	Streptomycin, isoniazid, rifampin, and pyrazinamide	Discontinue the drugs.
Hearing loss (if the possibility of cerumen impaction has been ruled out by otoscopy)	Streptomycin	Discontinue streptomycin.
Vertigo and nystagmus	Streptomycin	Discontinue streptomycin.
Jaundice (if other causes have been ruled out) and hepatitis	Rifampin, isoniazid, and pyrazinamide	Discontinue the antituberculosis drugs. Reinitiate the drugs in sequence.
Confusion (suspect drug-induced acute liver failure if there is jaundice)	Most antituberculosis drugs	Discontinue the drugs and do not reinitiate them until the symptoms have disappeared. Request liver function tests and a prothrombin time test. Reinitiate the drugs in sequence.
Visual disorders (if other causes have been ruled out)	Ethambutol	Discontinue ethambutol.
Shock, purpura, and acute kidney injury	Rifampin	Discontinue rifampin.
Oliguria	Streptomycin	Discontinue streptomycin.
Rhabdomyolysis with myoglobinuria and kidney failure	Pyrazinamide	Discontinue pyrazinamide.

However, due to the potential effect that cycloserine/terizidone has on the central nervous system, patients should be closely monitored for side effects of this drug combination. Concomitant use of cycloserine/terizidone and fluoroquinolones can worsen the effects on the central nervous system. Concomitant use of cycloserine/terizidone and alcohol increases the risk of convulsions.[2,10,42]

Ethionamide

Ethionamide has been used as a second-line drug in the treatment of tuberculosis since 1956. It is an inactive prodrug, the structure of which is analogous to that of isoniazid. However, there is no cross-resistance to ethionamide and isoniazid. Ethionamide needs to be activated by the bacterial enzyme EthA (a monooxygenase containing flavin adenine dinucleotide, and it is NADPH-specific. Ethionamide acts on intracellular and extracellular bacilli. The MIC of ethionamide for *M. tuberculosis* is 0.6-2.5 µg/mL. At the usual doses, ethionamide is bacteriostatic.[5,47]

Mechanism of action

Although ethionamide is similar to isoniazid, the former inhibits the activity of the *inhA* gene of *M. tuberculosis*. Although the mechanisms of action are different, the result is the same: the two drugs inhibit protein synthesis, preventing mycolic acid biosynthesis and affecting the bacterial cell membrane. Resistance to ethionamide is due to genetic alterations in EthA. *M. tuberculosis* strains that are resistant to isoniazid due to alterations in the *katG* gene (catalase/peroxidase enzyme) remain sensitive to ethionamide, which indicates that the enzymes that are responsible for the activation of isoniazid and ethionamide are different.[5,21,47]

Metabolization and excretion

Ethionamide is rapidly and completely absorbed when administered orally, and serum levels of the drug peak within approximately 1 h after its administration. Approximately 30% of the drug binds to plasma proteins, and the bioavailability of the drug is 80%. Ethionamide is metabolized in the liver and excreted in urine, 1-5% being excreted as active drug (unaltered) and the remainder being excreted as metabolites. The half-life of ethionamide is 2 h.[2,47]

Central nervous system

The CSF and plasma levels of ethionamide are similar.[2,10,47]

Adverse effects

Gastrointestinal effects

Ethionamide produces intense gastrointestinal effects, including a metallic taste in the mouth, excessive salivation, nausea, vomiting (commonly severe), loss of appetite, and abdominal pain. The symptoms improve if the drug is taken at mealtime or at bedtime. In some cases, it might be necessary to increase the doses progressively until the full dose is reached or to use antiemetics (or to do both).[2,10,39,42]

Hepatotoxicity

Ethionamide and isoniazid have a similar structure. Therefore, the two drugs can cause similar side effects. Hepatotoxicity (toxic hepatitis) occurs in approximately 4.3% of the patients, especially in those with a history of liver disease or alcoholism. Liver changes can occur up to five months after the initiation of treatment with the drug, and it remains unclear whether these changes are due to direct toxicity or to hypersensitivity. Hepatotoxicity habitually resolves when the drug is discontinued.[2,10,39]

Neurotoxicity

Peripheral neuritis, optic neuritis, diplopia, irritability, anxiety, depression, hallucinations, convulsions, and psychosis have been reported to occur in 1-2% of the patients. In patients with a history of mental instability, ethionamide should be administered with caution. The neurological effects can be minimized by administering 50-100 mg/day of pyridoxine.[2,10,47]

Cardiovascular effects

Postural hypotension can occur in patients treated with ethionamide.[43,48]

Endocrine effects

Patients receiving ethionamide can develop gynecomastia, alopecia, hypothyroidism, impotence, or menorrhagia. Ethionamide makes

glycemic control difficult in patients with diabetes mellitus.[2,10,49]

Skin reactions

Acne, photosensitivity, and exanthema can occur in patients treated with ethionamide. Thrombocytopenia and purpura have been reported to occur sporadically.[2,10,49]

Use during pregnancy

Ethionamide is a category C drug. It crosses the placental barrier. The use of ethionamide during pregnancy is controversial. In rodents, high doses of ethionamide have been associated with teratogenic effects. In humans, two studies reviewing 47 cases showed no deleterious effects; however, one study reported malformations in 7 of 23 neonates born to mothers who used the drug.[50,51] Ethionamide should be used during pregnancy only when the benefits of the treatment outweigh the potential risks. The decision to use the drug can be made only after clinicians who have considerable experience in managing tuberculosis have been consulted.[2,10,47,49]

Use during breastfeeding

There are no data regarding the concentration of ethionamide in breast milk. It is advisable to avoid the use of ethionamide during breastfeeding.[2,39,51]

Use in patients with liver failure

Ethionamide should be used with caution and under continuous monitoring in patients with liver disease.[2,10]

Use in patients with kidney failure

In patients with creatinine clearance lower than 30 mL/min or in those who are on hemodialysis, the dose of ethionamide should be reduced to 250-500 mg/day. The drug is not removed by hemodialysis.[2,10,45]

Interactions

Foods

The effects of foods on the bioavailability of ethionamide are minimal.[34]

Antacids

Antacids do not interfere with the absorption of ethionamide.[34]

Other drugs

Concomitant use of ethionamide and terizidone or isoniazid can potentiate the neurotoxic effects (hallucinations, irritability, tremors, depression, convulsions, psychosis, and peripheral neuropathy). Concomitant use of ethionamide and para-aminosalicylic acid can increase hepatotoxicity and the possibility of hypothyroidism. Concomitant use of ethionamide and alcohol can produce psychotic reactions.[2,44]

Capreomycin

Capreomycin is a polypeptide antibiotic that is obtained from *Streptomyces capreolus* and has been used as an antituberculosis drug since 1959. The MIC of capreomycin for *M. tuberculosis* is 10 µg/mL. The chemical structure of capreomycin is different from that of aminoglycosides. However, capreomycin and aminoglycosides are quite similar in terms of their antibacterial activity and adverse effects. There is no cross-reaction between capreomycin and streptomycin; however, there might be a cross-reaction between capreomycin and certain strains resistant to amikacin and kanamycin.[8,52,52]

Mechanism of action

The mechanism of action of capreomycin has yet to be fully understood. It is believed that the drug is active because it interferes with bacterial protein synthesis.[52]

Metabolization and excretion

Capreomycin is not absorbed when taken orally. Capreomycin is administered i.m., and absorption can be delayed in cases in which the same site of application is used repeatedly. Tissue distribution has yet to be fully understood. The serum levels of capreomycin peak within 1-2 h after the administration of the drug. The plasma half-life of capreomycin is 4-6 h in patients with normal renal function, and it can be as long as 55 h in patients with kidney failure. Most of the dose (50-60%) is excreted through glomerular filtration 12 h after administration, and a small proportion is excreted via the biliary tract.[2,52]

Central nervous system

Capreomycin reaches the CSF only in patients with meningitis.[2]

Adverse effects

In patients treated with capreomycin, common side effects include nephrotoxicity (in 20-25% of the patients), renal tubular damage, proteinuria, electrolyte disturbances, urticaria, and maculopapular rash.[2,10]

Ototoxicity (especially vestibular), electrolyte changes (decreased serum levels of calcium, magnesium, and potassium), pain, edema, and abscess at the site of application occasionally occur.[2,10]

Use during pregnancy

Capreomycin is a category C drug. In adults, capreomycin is less ototoxic than are aminoglycosides. However, capreomycin should be avoided during pregnancy, since it is unknown whether this can be extrapolated to the health of the fetus. If it is essential to use any given injectable antituberculosis agent during pregnancy, capreomycin should be the drug of choice.[2,10]

Use during breastfeeding

The concentrations of capreomycin in breast milk are unknown. Capreomycin should therefore be avoided during pregnancy.[2,10]

Use in patients with liver failure

It is not necessary to adjust the doses of capreomycin in patients with liver failure.[10]

Use in patients with kidney failure

Capreomycin should be used with extreme caution in patients with creatinine clearance < 30 mL/min and in those on hemodialysis. In these situations, the dose should be adjusted to 12-15 mg/kg, administered twice or three times a week. The drug is removed by dialysis and should be administered after the procedure.[2,10]

Interactions

Other drugs

Capreomycin should not be administered concomitantly with neuromuscular blocking agents, aminoglycosides, or polymyxin B due to the possibility of additive toxic effects.[2,10]

Para-aminosalicylic acid

Para-aminosalicylic acid has been used as an antituberculosis drug since 1946. Beginning in 1955 and for nearly 15 years, para-aminosalicylic acid was considered a first-line drug in a combination regimen with isoniazid and streptomycin. Para-aminosalicylic acid is used as an acid or as a sodium salt. Para-aminosalicylic acid is bacteriostatic, and the MIC of the drug for *M. tuberculosis* is 1 µg/mL. Para-aminosalicylic acid acts preferentially on extracellular bacilli. The drug can currently be administered in granules stored in 4-mg envelopes, replacing the former 500-mg capsules.[2,5,8,54]

Mechanism of action

The mechanism of action of para-aminosalicylic acid has yet to be elucidated, and it is believed that the mechanism is related to interference with bacterial folic acid synthesis and inhibition of iron uptake.[2,54]

Metabolization and excretion

Para-aminosalicylic acid is administered orally. Para-aminosalicylic acid granules are better tolerated than are para-aminosalicylic acid capsules. The ingestion of 4 g of para-aminosalicylic acid granules leads to a maximum serum concentration of 20-60 µg/mL after 4-6 h. The serum levels of para-aminosalicylic acid peak within 90-120 min after the ingestion of para-aminosalicylic acid capsules. The half-life of para-aminosalicylic acid is 1 h, and the plasma concentrations of the drug after 4-5 h are minimal, which justifies the need for doses of 10-12 g in order to maintain the bacteriostatic activity. Para-aminosalicylic acid is metabolized in the intestines and liver, via acetylation, into N-acetyl-para-aminosalicylic acid. More than 80% of the drug is excreted by the kidney through glomerular filtration and tubular secretion.[2,54-56]

Central nervous system

In the presence of meningitis, the CSF concentration of para-aminosalicylic acid is 10-50% of the plasma concentration of the drug.[2,10]

Adverse effects

In patients treated with para-aminosalicylic acid, gastrointestinal effects (anorexia, diarrhea, nausea, and vomiting) and hypothyroidism, the latter occurring especially when para-aminosalicylic acid is administered concomitantly with ethionamide, are common. Thyroid function returns to normal when the drug is discontinued.[2,10]

Hepatitis (in 0.3-0.5% of the cases), allergic reactions (fever, rash, and pruritus), hemolytic anemia, agranulocytosis, leukopenia, thrombocytopenia, malabsorption syndrome, and increased thyroid volume are rare, as are cardiovascular adverse effects (pericarditis), neurological adverse effects (encephalopathy), respiratory adverse effects (eosinophilic pneumonia), and ocular adverse effects (optic neuritis). Para-aminosalicylic acid should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency and in those who are allergic to aspirin.[2,10,55]

Use during pregnancy

Para-aminosalicylic acid is a category C drug. There have been reports of congenital anomalies associated with the administration of the drug in the first trimester of pregnancy. Therefore, the drug should be used in pregnant women only when there is no therapeutic alternative.[2,10]

Use during breastfeeding

Para-aminosalicylic acid is secreted in breast milk (at 1.4% of the maternal plasma concentration of the drug). Para-aminosalicylic acid can be used during breastfeeding.[44]

Use in patients with liver failure

Para-aminosalicylic acid should be used with caution in patients with liver failure. Hepatic enzyme levels should be monitored.[10]

Use in patients with kidney failure

It is not necessary to adjust the doses of para-aminosalicylic acid in patients with kidney failure. However, the drug can exacerbate acidosis and crystalluria in patients with severe kidney failure. Sodium para-aminosalicylate can also increase blood volume in this situation.[2,10]

Interactions

Foods

Foods increase the absorption of para-aminosalicylic acid. The drug can be administered with water, orange juice, or fatty foods.[46]

Antacids

Antacids do not interfere with the absorption of para-aminosalicylic acid.[46]

Other drugs

Digoxin can reduce the absorption of para-aminosalicylic acid. Ethionamide can increase hepatotoxicity and hypothyroidism in patients treated with para-aminosalicylic acid. Isoniazid increases acetylation, which results in an increase in the serum levels of para-aminosalicylic acid. Concomitant use of angiotensin-converting enzyme inhibitors and para-aminosalicylic acid can reduce the antihypertensive effect of the latter, and the use of calcium channel blockers can increase the anticoagulant effect of para-aminosalicylic acid. Concomitant use of para-aminosalicylic acid and carbonic anhydrase inhibitors potentiate the adverse effects of both drugs, and concomitant use of para-aminosalicylic acid and systemic corticosteroids can also increase the number and severity of adverse effects, especially gastrointestinal effects. Para-aminosalicylic acid can reduce the effect of loop diuretics, and, conversely, loop diuretics can increase the serum levels of para-aminosalicylic acid. With the exception of diclofenac, nonselective NSAIDS can increase the adverse effects of para-aminosalicylic acid. Para-aminosalicylic acid can increase the hypoglycemic effects of sulfonylurea, as well as increasing the risk of bleeding when administered in conjunction with oral anticoagulants, thrombolytics, or salicylates.[2,10]

Chart 1 shows the most common adverse effects of the principal antituberculosis drugs, as well as the recommended practices according to the symptoms.[57-59]

Appendix 1 summarizes the interactions among antituberculosis drugs.[10,17,38,39,60]

Final considerations

The drugs used for the treatment of multidrug-resistant tuberculosis are generally less

effective, more toxic, and more expensive than are the drugs that constitute the basic regimen. These characteristics prolong the treatment and increase its cost (which can be up to one hundred times higher), as well as increasing the possibility of adverse events. In addition, these characteristics reduce treatment adherence and increase treatment failure rates. The relationship between the patient and the health care team, the early recognition of adverse effects, and the knowledge of the pharmacological properties of the drugs involved allow professionals to tailor their approach to each individual case, thus avoiding potentially fatal reactions.

References

1. Ministério da Saúde. Secretária de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Programa Nacional de Controle da Tuberculose. Nota técnica sobre as mudanças no tratamento da tuberculose no Brasil para adultos e adolescentes - versão 2. Brasília: Ministério da Saúde; 2009.
2. World Health Organization. Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis: Emergency Update 2008. Geneva: World Health Organization, Stop TB Department; 2008.
3. Conde MB, Melo FA, Marques AM, Cardoso NC, Pinheiro VG, Dalcin Pde T, et al. III Brazilian Thoracic Association Guidelines on tuberculosis. J Bras Pneumol. 2009;35(10):1018-48.
4. STREPTOMYCIN treatment of pulmonary tuberculosis. Br Med J. 1948;2(4582):769-82.
5. Zhang Y. The magic bullets and tuberculosis drug targets. Annu Rev Pharmacol Toxicol. 2005;45:529-64.
6. Rieder HL. Intervenciones para el control y la eliminación de la tuberculosis. Paris; Unión internacional contra la tuberculosis y enfermedades respiratorias. 2007; p. 32-5.
7. Chen LF, Kaye D. Current use for old antibacterial agents: polymyxins, rifamycins, and aminoglycosides. Infect Dis Clin North Am. 2009;23(4):1053-75, x.
8. Coll P. Active drugs against Mycobacterium tuberculosis [Article in Spanish]. Enferm Infecc Microbiol Clin. 2009;27(8):474-80.
9. Ramaswamy S, Musser JM. Molecular genetic basis of antimicrobial agent resistance in Mycobacterium tuberculosis: 1998 update. Tuber Lung Dis. 1998;79(1):3-29.
10. Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med. 2003;167(4):603-62.
11. World Health Organization. The Treatment of Tuberculosis Guidelines. Geneva: World Health Organization; 2010.
12. Peloquin CA, Berning SE, Nitta AT, Simone PM, Goble M, Huitt GA, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infect Dis. 2004;38(11):1538-44.
13. Guthrie OW. Aminoglycoside induced ototoxicity. Toxicology. 2008;249(2-3):91-6.
14. Rybak MJ, Abate BJ, Kang SL, Ruffing MJ, Lerner SA, Drusano GL. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. Antimicrob Agents Chemother. 1999;43(7):1549-55.
15. Rougier F, Claude D, Maurin M, Sedoglavic A, Ducher M, Corvaisier S, et al. Aminoglycoside nephrotoxicity: modeling, simulation, and control. Antimicrob Agents Chemother. 2003;47(3):1010-6.
16. de Jager P, van Altena R. Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis. Int J Tuberc Lung Dis. 2002;6(7):622-7.
17. Pai MP, Momary KM, Rodvold KA. Antibiotic drug interactions. Med Clin North Am. 2006;90(6):1223-55.
18. Gilbert DN, Leggett JE. Aminoglycosides. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Churchill Livingstone/Elsevier; 2009. p. 359-84.
19. Tsukamura M, Nakamura E, Yoshii S, Amano H. Therapeutic effect of a new antibacterial substance ofloxacin (DL8280) on pulmonary tuberculosis. Am Rev Respir Dis. 1985;131(3):352-6.
20. Ginsburg AS, Grosset JH, Bishai WR. Fluoroquinolones, tuberculosis, and resistance. Lancet Infect Dis. 2003;3(7):432-42.
21. Di Perri G, Bonora S. Which agents should we use for the treatment of multidrug-resistant Mycobacterium tuberculosis? J Antimicrob Chemother. 2004;54(3):593-602.
22. van den Boogaard J, Kibiki GS, Kisanga ER, Boeree MJ, Aarnoutse RE. New drugs against tuberculosis: problems, progress, and evaluation of agents in clinical development. Antimicrob Agents Chemother. 2009;53(3):849-62.
23. Yew WW, Chan CK, Leung CC, Chau CH, Tam CM, Wong PC, et al. Comparative roles of levofloxacin and ofloxacin in the treatment of multidrug-resistant tuberculosis: preliminary results of a retrospective study from Hong Kong. Chest. 2003;124(4):1476-81.
24. Mitnick CD, Shin SS, Seung KJ, Rich ML, Atwood SS, Furin JJ, et al. Comprehensive treatment of extensively drug-resistant tuberculosis. N Engl J Med. 2008;359(6):563-74.
25. Chan ED, Laurel V, Strand MJ, Chan JF, Huynh ML, Goble M, et al. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2004;169(10):1103-9.
26. Davies GR, Nuermberger EL. Pharmacokinetics and pharmacodynamics in the development of anti-tuberculosis drugs. Tuberculosis (Edinb). 2008;88 Suppl 1:S65-S74.
27. Ziganshina LE, Squire SB. Fluoroquinolones for treating tuberculosis. Cochrane Database Syst Rev. 2008;(1):CD004795.
28. Yoon YS, Lee HJ, Yoon HI, Yoo CG, Kim YW, Han SK, et al. Impact of fluoroquinolones on the diagnosis of pulmonary tuberculosis initially treated as bacterial pneumonia. Int J Tuberc Lung Dis. 2005;9(11):1215-9.
29. Devasia RA, Blackman A, Gebretsadik T, Griffin M, Shintani A, May C, et al. Fluoroquinolone resistance in Mycobacterium tuberculosis: the effect of duration and timing of fluoroquinolone exposure. Am J Respir Crit Care Med. 2009;180(4):365-70.
30. Chang KC, Leung CC, Yew WW, Lau TY, Leung WM, Tam CM, et al. Newer fluoroquinolones for treating respiratory infection: do they mask tuberculosis? Eur Respir J. 2010;35(3):606-13.
31. Suh B, Lorber B. Quinolones. Med Clin North Am. 1995;79(4):869-94.
32. Handbook of Anti-Tuberculosis Agents. Tuberculosis (Edinb). 2008;88(2):119-21.

33. Handbook of Anti-Tuberculosis Agents. Tuberculosis (Edinb). 2008;88(2):127-31.
34. O'Donnell JA, Gelone SP. Fluoroquinolones. Infect Dis Clin North Am. 2000;14(2):489-513, xi.
35. Zhanel GG, Ennis K, Vercaigne L, Walkty A, Gin AS, Embil J, et al. A critical review of the fluoroquinolones: focus on respiratory infections. Drugs. 2002;62(1):13-59.
36. Bolon MK. The newer fluoroquinolones. Infect Dis Clin North Am. 2009;23(4):1027-51, x.
37. Giamarellou H, Kolokythas E, Petrikkos G, Gazis J, Aravantinos D, Sfikakis P. Pharmacokinetics of three newer quinolones in pregnant and lactating women. Am J Med. 1989;87(5A):49S-51S.
38. Yew WW. Clinically significant interactions with drugs used in the treatment of tuberculosis. Drug Saf. 2002;25(2):111-33.
39. Universidade de São Paulo. Faculdade de Medicina. Hospital das Clínicas. Comissão de Controle de Infecção Hospitalar. Normas para o diagnóstico, tratamento, isolamento e prevenção da tuberculose. São Paulo: Hospital das Clínicas/FMUSP; 2009.
40. Zhang Y, Yew WW. Mechanisms of drug resistance in Mycobacterium tuberculosis. Int J Tuberc Lung Dis. 2009;13(11):1320-30.
41. Handbook of Anti-Tuberculosis Agents. Tuberculosis (Edinb). 2008;88(2):100-1.
42. Ministério da Saúde. Secretaria de Vigilância em Saúde. Centro de Referência Prof. Hélio Fraga. Tuberculose Multirresistente: Guia de Vigilância Epidemiológica. Rio de Janeiro: Centro de Referência Professor Hélio Fraga/SVS/Ministério da Saúde e Projeto MSH; 2007.
43. Seaworth BJ. Multidrug-resistant tuberculosis. Infect Dis Clin North Am. 2002;16(1):73-105.
44. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics. 2001;108(3):776-89.
45. Malone RS, Fish DN, Spiegel DM, Childs JM, Peloquin CA. The effect of hemodialysis on cycloserine, ethionamide, para-aminosalicylate, and clofazimine. Chest. 1999;116(4):984-90.
46. Caminero Luna JA. Guía de la Tuberculosis para Médicos Especialistas. Paris: Unión Internacional Contra la Tuberculosis y Enfermedades Respiratorias; 2003.
47. Morlock GP, Metchock B, Sikes D, Crawford JT, Cooksey RC. ethA, inhA, and katG loci of ethionamide-resistant clinical Mycobacterium tuberculosis isolates. Antimicrob Agents Chemother. 2003;47(12):3799-805.
48. Migliori GB, D'Arcy Richardson M, Sotgiu G, Lange C. Multidrug-resistant and extensively drug-resistant tuberculosis in the West. Europe and United States: epidemiology, surveillance, and control. Clin Chest Med. 2009;30(4):637-65, vii.
49. Handbook of Anti-Tuberculosis Agents. Tuberculosis (Edinb). 2008;88(2):106-8.
50. Ormerod P. Tuberculosis in pregnancy and the puerperium. Thorax. 2001;56(6):494-9.
51. Shin S, Guerra D, Rich M, Seung KJ, Mukherjee J, Joseph K, et al. Treatment of multidrug-resistant tuberculosis during pregnancy: a report of 7 cases. Clin Infect Dis. 2003;36(8):996-1003.
52. Handbook of Anti-Tuberculosis Agents. Tuberculosis (Edinb). 2008;88(2):89-91.
53. Wallace Jr RC, Griffith DE. Antimycobacterial agents. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Churchill Livingstone/Elsevier; 2009. p. 533-48.
54. Para-aminosalicylic acid. Tuberculosis (Edinb). 2008;88(2):137-8.
55. Petri Jr WA. Quimioterapia da tuberculose, complexo mycobacterium avium e hanseníase. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman & Gilman - As Bases Farmacológicas da Terapêutica. Rio de Janeiro: McGraw-Hill; 2006. p.1083-101.
56. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs. 2002;62(15):2169-83.
57. Silva Jr JB. Tuberculose: Guia de vigilância epidemiológica. J Bras Pneumol. 2004;30(Suppl 1):S57-S86.
58. Brasil. Ministério da Saúde. Fundação Nacional de Saúde. Centro de Referência Professor Hélio Fraga. Sociedade Brasileira de Pneumologia e Tisiologia. Controle da tuberculose: uma proposta de integração ensino-serviço. Rio de Janeiro: FUNASA/CRPHF/SBPT; 2002.
59. World Health Organization. Treatment of Tuberculosis: Guidelines. 4th ed. Geneva: World Health Organization; 2009.
60. Morrone N, Marques JF, Fazolo N, Soares LC, Macedo L. Reações adversas das drogas tuberculostáticas. J Pneumol. 1993;19:52-9.

About the authors

Marcos Abdo Arbex
Physician. Clinical Medicine Section of the Department of Internal Medicine, Federal University of São Paulo/Paulista School of Medicine, São Paulo, Brazil. Pulmonologist. Nestor Goulart Reis State Hospital, São Paulo State Department of Health, Américo Brasiliense, Brazil.

Marília de Castro Lima Varella
Assistant Professor. Department of Clinical Medicine, University of Mogi das Cruzes School of Medicine, Mogi das Cruzes, Brazil.

Hélio Ribeiro de Siqueira
Visiting Professor. Department of Pulmonology and Phthisiology, Rio de Janeiro State University School of Medical Sciences. Physician in Charge of the Tuberculosis Outpatient Clinic of the Rio de Janeiro State University Pedro Ernesto University Hospital, Rio de Janeiro, Brazil.

Fernando Augusto Fiúza de Mello
Director. Clemente Ferreira Institute, Disease Control Committee, São Paulo State Department of Health, São Paulo, Brazil.

Appendix 1 - Interactions between antituberculosis drugs and foods, as well as between antituberculosis drugs and other drugs.[10,17,38,39,60]

Rifampin
Foods (decreased absorption of rifampin)
Para-aminosalicylic acid (decreased absorption of rifampin)
Amiodarone (decreased serum levels of amiodarone)
Oral anticoagulants (decreased serum levels of the anticoagulant)
Contraceptives (decreased serum levels of the contraceptive)
Anticonvulsants (decreased serum levels of the anticonvulsant)
Tricyclic antidepressants (decreased serum levels of the antidepressant)
Antipsychotics (decreased serum levels of the antipsychotic)
Barbiturates and benzodiazepines (decreased serum levels of the barbiturate and benzodiazepine)
Beta blockers (decreased serum levels of the beta blocker)
Cyclosporine (reduced effect of cyclosporine)
Ketoconazole (decreased serum levels of ketoconazole)
Codeine (decreased serum levels of codeine)
Corticosteroids (decreased serum levels of the corticosteroid)
Dapsone (possible decrease in the serum levels of dapsone)
Digital (decreased serum levels of digital)
Diltiazem (decreased serum levels of diltiazem)
Enalapril (decreased serum levels of enalapril)
Statins (decreased serum levels of the statin)
Fluconazole (decreased serum levels of fluconazole)
Haloperidol (decreased serum levels of haloperidol)
Oral hypoglycemic agents (decreased serum levels of the hypoglycemic agent)
Itraconazole (decreased serum levels of itraconazole)
Methadone (decreased serum levels of methadone)
Morphine (decreased serum levels of morphine)
Narcotics and analgesics (decreased serum levels of the narcotic and analgesic)
Propafenone (decreased serum levels of propafenone)
Nifedipine (decreased serum levels of nifedipine)
Quinidine (decreased serum levels of quinidine)
Theophylline (decreased serum levels of theophylline)
Verapamil (decreased serum levels of verapamil)
Isoniazid + ketoconazole (greater hepatotoxicity)
Ethionamide (greater hepatotoxicity)
Phenytoin (greater hepatotoxicity)
Isoniazid (greater hepatotoxicity)
Sulfonamides (greater hepatotoxicity)
Pyrazinamide (greater uric acid excretion)
Efavirenz (decreased serum levels of efavirenz)
Indinavir (decreased serum levels of indinavir)
Lopinavir/Ritonavir (decreased serum levels of lopinavir)
Nelfinavir (decreased serum levels of nelfinavir)
Saquinavir (decreased serum levels of saquinavir)
Zidovudine (decreased serum levels of zidovudine)
Isoniazid
Foods (decreased absorption of isoniazid)
Valproic acid (increased serum concentration of valproic acid)
Antacids/aluminum hydroxide (decreased absorption of isoniazid)
Oral anticoagulants (increased serum concentration of the anticoagulant)
Benzodiazepines (increased serum concentration of the benzodiazepine)
Enflurane (possibility of nephrotoxicity)
Carbamazepine (increased serum concentration of carbamazepine)
Corticosteroids (decreased serum levels of isoniazid)
Ketoconazole (decreased serum concentration of ketoconazole)
Cycloserine (greater neurotoxicity)
Diazepam (increased serum concentration of diazepam)
Disulfiram (possibility of psychotic events)
Phenytoin (increased serum concentration of phenytoin)
Levodopa (increased serum concentration of catecholamines)
Paracetamol (greater hepatotoxicity)
Rifampin (greater hepatotoxicity)
Theophylline (increased concentration of theophylline)
Cheese and red wine (inhibition of monoamine oxidase)
Fish (increased concentration of histamine)

Pyrazinamide
Allopurinol (decreased effect of allopurinol, pyrazinamide increases the serum levels of uric acid)
Colchicine (decreased effect of colchicine, pyrazinamide increases the serum levels of uric acid)
Cyclosporine (decreased serum concentration of cyclosporine)
Ketoconazole (greater hepatotoxicity)
Ethionamide (the adverse effects of ethionamide can increase)
Rifampin (greater hepatotoxicity)
Isoniazid (greater hepatotoxicity)
Ethambutol
Antacids (decreased absorption of ethambutol)
Ethionamide (increased possibility of neurotoxic effects of ethambutol)
Pyrazinamide (increased possibility of hepatotoxicity)
Didanosine and zalcitabine (peripheral neuritis is potentiated)
Aminoglycosides (streptomycin and amikacin)
Acyclovir (increased possibility of nephrotoxicity)
Ethacrynic acid (increased possibility of ototoxicity)
Amphotericin (increased possibility of nephrotoxicity)
Oral anticoagulants (greater effect of the anticoagulant)
Nonsteroidal anti-inflammatory drugs (increased possibility of ototoxicity and nephrotoxicity)
Capreomycin (increased possibility of ototoxicity and nephrotoxicity)
Cephalosporins (increased possibility of nephrotoxicity)
Cisplatin (increased possibility of nephrotoxicity)
Cyclosporine (increased possibility of nephrotoxicity)
Furosemide (increased possibility of ototoxicity)
Methotrexate (possible increase in the toxicity of methotrexate)
Polymyxins (greater nephrotoxicity)
Vancomycin (greater ototoxicity and nephrotoxicity)
Neuromuscular blocking agents (additive effect)
Ethionamide
Alcohol (increased possibility of psychotic reactions)
Antituberculosis drugs (greater adverse effects)
Isoniazid (temporarily increased serum concentration of isoniazid)
Para-aminosalicylic acid (increased possibility of hypothyroidism)
Terizidone (increased possibility of toxic effects on the central nervous system)
Dapsone (peripheral neuritis is potentiated)
Cycloserine (terizidone)
Alcohol (increased effects of alcohol and dizziness)
Anticoagulants (increased serum concentration of the anticoagulant)
Ethionamide (possibility of increased toxic effects on the central nervous system)
Phenytoin (increased serum concentration of phenytoin)
Isoniazid (possibility of increased toxic effects on the central nervous system)
Vitamin B6 (increased vitamin B6 clearance)
Fluoroquinolones
Antacids with cations Ca, Mg, Al, and Fe (decreased absorption of fluoroquinolones)
Sucralfate (decreased absorption of fluoroquinolones)
Drugs metabolized by cytochrome P450: cyclosporine, theophylline, warfarin, phenytoin, and sulfonylurea (increased effect of these drugs)
Nonsteroidal anti-inflammatory drugs (increased stimulation of the central nervous system and possibility of convulsions)
Probenecid (increased serum levels of the fluoroquinolone)
Theophylline (increased serum levels of theophylline)
Capreomycin
Neuromuscular blocking agents (increased adverse effects of the two drugs)
Aminoglycosides (increased adverse effects of the two drugs)
Polymyxin B (increased adverse effects of the two drugs)
Para-aminosalicylic acid
Anticoagulants (possibility of increased anticoagulant effect)
Digoxin (decreased serum levels of digoxin)
Corticosteroids (possibility of increased adverse effects of the corticosteroid)
Ethionamide (increased possibility of hypothyroidism and hepatotoxicity)
Isoniazid (possibility of increased serum levels of isoniazid)
Probenecid (increased serum concentration of para-aminosalicylic acid)
Vitamin B12 (decreased serum levels of vitamin B12)
Sulfonylurea (possibility of increasing hypoglycemic effects of sulfonylurea)