Adverse Reactions to Antituberculosis Drugs

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I dedicate this book to my family for their patience and support and our patients, who have taught us the best way to take care of them through their suffering.

Tijuana, Mexico. April 2022

TABLE OF CONTENTS

List of Figures

LIST OF TABLES

FOREWORD

The idea to write this book was born out of necessity. A frequent reason for consultation during the care of patients undergoing treatment for tuberculosis is the presence of adverse drug reactions. Since the treatment of tuberculosis, even in pansensitive cases, involves the use of multiple drugs simultaneously for prolonged periods, practically all patients undergoing therapy will experience drug-associated adverse effects at some point.

These adverse reactions range from mild and self-limited to so severe that they endanger the patient's life and constitute a challenge for the treating physician and the health system since they frequently impact treatment adherence, being a frequent reason for loss to follow-up. Therefore, it is essential that the treating physician promptly identify these adverse reactions and initiates management in a timely manner.

This work offers the practicing physician, nurse, or medical student the opportunity to find in a single source the necessary information to establish the diagnosis, either by the affected organ or body system, by the clinical manifestation of the adverse reaction, or by the drug or drugs involved. The book includes the adverse reactions of all current medications used to treat this condition. Likewise, the clinician will find detailed, updated therapeutic recommendations for each case in it.

Rafael Laniado-Laborín MD, MPH. April 2022.

INTRODUCTION

GLOBAL ACTIVE PHARMACOVIGILANCE OF ADVERSE REACTIONS TO ANTITUBERCULOSIS DRUGS

Nothing is poison; everything is poison: the difference is in the dose.
Paracelsus, 1493-1541.

Multiple systematic reviews have summarized information on adverse drug reactions (ADR) for specific drugs (e.g., prothionamide, isoniazid, rifampin, etc.); however, these reviews do not analyze drug-associated ADR in the context of treatment regimens that includes multiple drugs.

The World Health Organization (WHO) recommends active pharmacovigilance (aDSM), inviting national tuberculosis programs to implement an "*active and systematic clinical and laboratory evaluation of patients being treated with new tuberculosis drugs or new regimens for multidrug-resistant tuberculosis (MDR-TB) for the purpose of detecting and reporting potential or confirmed drug toxicities*" (WHO, 2015).

A systematic review was carried out in September 2015 to determine the effectiveness of the various therapeutic regimens in multidrug-resistant tuberculosis; studies published between January 2009 and September 2015 on MDR-TB treatment and what was defined as extensively drug-resistant tuberculosis (XDR-TB) at the time were included in the review. A Collaborative Group for the Meta-analysis of Data of Individual Patients in the Treatment of MDR-TB with the participation of researchers from 25 countries, updated this systematic review in April 2016, using the same search terms in MEDLINE, Embase, and the Cochrane Library. The search was also extended to the list of bibliographic references of articles published since 2009.

The PRISMA protocol (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) was implemented for the meta-analysis. The only eligible studies were original reports that included treatment outcomes (i.e.,

success, failure or relapse and death) of 25 or more adults with bacteriologically confirmed multidrug-resistant tuberculosis.

Investigators from potentially eligible studies were invited to share patient data at the individual level. Studies were included if investigators provided information on clinical characteristics, diagnosis (including confirmation of rifampicin resistance by phenotypic tests), treatment regimen, and treatment results.

Eighty-seven individual studies were identified, of which 50 provided adequate data for patients with MDR-TB and XDR-TB, with a total of 12,030 patients (Ahmad N, 2017). Thirty-five of the fifty studies (with 9,178 patients) provided information on adverse effects (WHO, 2019). The meta-analysis of individual patient data estimated the absolute and relative frequency of adverse effects leading to definitive discontinuation of a drug. The overall goal is to provide useful information for tuberculosis clinicians and programs when selecting optimal treatment regimens. The risk of bias in selecting studies was considered as low because there were no important differences between the studies included and those excluded from the analysis. Drugs with a low risk of adverse effects that led to drug discontinuation included levofloxacin (1-3%; 95%CI: 0.3–5.0), clofazimine (1.6%; 95%CI: 0.5–5.3), bedaquiline (1.7%; 95%CI: 0.7–4.2) and moxifloxacin (2.9%; 95% CI 1.6–5.0). In contrast, a relatively high incidence of adverse events leading to drug discontinuation was observed with the three second-line injectable drugs, kanamycin (7.5%; 95%CI 4.6–11.9), capreomycin: (8.2%; 95%CI 6.3–10.7) and amikacin: (10.2%; CI95% 6.3–16.0), para-aminosalicylic acid (PAS): (11.6%; IC95% 7.1–18.3) and linezolid 14.1% (95%CI 9.9-19.6) (Lan Z, 2020). The WHO Guideline Development Group used this information as evidence for its 2019 guide for treating drug-resistant tuberculosis (WHO, 2019).

Another research group prospectively recorded and attributed adverse effects to a specific drug (Borisov S, 2019). The objective of this prospective study was to evaluate the frequency and severity of adverse effects in a cohort of patients with drug-resistant TB treated with new (bedaquiline, delamanid) and repurposed drugs (clofazimine, linezolid), according to the WHO aDSM project, as there was not enough information on these drugs. This project was the first effort to document the active pharmacovigilance approach's feasibility and collect quality scientific evidence on AEs in patients treated with new and repurposed drugs under field conditions in countries from all continents. Worldwide, 45 centers in 26 countries/regions reported 658 patients (68.7% men, 4.4% coinfected

with HIV) treated with the following drugs: bedaquiline (87.7%), delamanid (18.4%; 6.1% with both), linezolid (12.9%), and clofazimine (32.4%). In total, 504 ADRs episodes were reported: 447 (447/504, 88.7%) were classified as mild (grade 1-2) and 57 (57/504, 11.3%) as severe (grade 3-5). Most of the 57 serious adverse effects reported by 55 patients (51/57; 89.5%) eventually resolved. The rates of serious effects that led to the discontinuation of the drug were 0.35% (2/577) for bedaquiline, 0.8% (1/121) for delamanid, 1.9% (10/536) for linezolid, and 1.4% (3/213) for clofazimine.

Table 0.1 Serious adverse events in patients on longer MDR-TB regimens*

Drug	Absolute risk of serious adverse effects (median)
Bedaquiline	2.4%
Moxifloxacin	2.9%
Amoxicillin/clavulanate	3.0%
Clofazimine	3.6%
Ethambutol	4.0%
Levofloxacin	4.1%
Streptomycin	4.5%
Imipenem/Meropenem**	4.9%
Cycloserine/Terizidone	7.8%
Pyrazinamide	8.8%
Ethionamide/Prothionamide	9.5%
Amikacin	10,3%
p-aminosalicylic acid	14.3%
Linezolid	17.2%

*modified from WHO, 2019; ** Lanz, 2020)

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CHAPTER 1

ADVERSE REACTIONS TO ANTITUBERCULOSIS DRUGS: GENERAL ASPECTS

Abstract

Treatment of tuberculosis (TB) requires the use of multiple drugs for long periods. Most patients will experience some difficulty tolerating them at some point.

Primary antituberculosis drugs are generally well-tolerated, but there is certainly an underestimation in the reported frequency of adverse effects. The treatment of multidrug-resistant tuberculosis requires so-called "second-line" drugs associated with a greater frequency and severity of adverse drug reactions. Adverse reactions are even more frequent in patients with extensively drug-resistant tuberculosis; these adverse reactions frequently require the interruption of therapy, negatively impacting culture conversion and treatment outcome. According to their severity, adverse reactions are either minor, reported in up to 20% of cases, or severe adverse drug reactions. Fortunately, severe adverse drug reactions are less frequent and reported in less than 10% of cases. However, severe adverse reactions require, in addition to symptomatic treatment, modification, or even interruption of therapy. Some factors influence the development of adverse drug reactions, including errors in the dosage of drugs, genetic factors, age of the subject, consumption of alcohol or illicit substances, kidney or liver failure, and co-infection with HIV.

Introduction

Treatment of tuberculosis (TB) requires the use of multiple drugs for long periods, and most patients will experience some difficulty tolerating them at some point (Prasad R, 2019).

The World Health Organization (WHO) defines an adverse reaction to a drug as “any unintended harmful reaction that appears at doses normally used in humans for prophylaxis, diagnosis or treatment or to modify physiological functions” (WHO, 2012).

Primary antituberculosis drugs (isoniazid, ethambutol, rifampicin, and pyrazinamide) are generally well tolerated (Nagarajana S, 2018); nevertheless, there is an underestimation in the reported frequency of adverse effects during the treatment of tuberculosis. Most of the reports on adverse effects in patients under treatment for tuberculosis consist of retrospective studies, therefore not explicitly designed to evaluate the incidence of these events. Adverse reactions to antituberculosis drugs (ADR) are even more frequent in patients infected with drug-resistant *Mycobacterium tuberculosis* (MTB) (Borisov S, 2019; Lan Z, 2020). The treatment of multidrug-resistant tuberculosis (MDR-TB) requires so-called “second-line” drugs associated with a greater frequency and severity of ADR. Adverse reactions are even more frequent in patients with extensively drug-resistant tuberculosis (XDR-TB). These ADR frequently require the interruption of therapy, negatively impacting culture conversion and treatment outcome (Shean K, 2013). Most patients with MDR-TB, preXDR-TB, or XDR-TB live in countries with limited resources, without access to adequate monitoring, making it challenging to detect adverse effects (e.g., auditory and renal toxicity, hypothyroidism, QT interval prolongation, etc.).

Adverse drug reactions are classified into two large groups. Type A reactions are the most frequent, predictable, and dose-dependent. Type B reactions are unpredictable, dose-independent, and include 15-20% of all ADR. The latter include immunologically mediated hypersensitivity reactions to drugs and idiosyncratic non-immunological reactions (Coster A, 2019).

According to their severity, adverse reactions are either minor ADR, reported in up to 20% of cases, and only require symptomatic treatment without modifying the drug regimen or severe ADR. Fortunately, severe ADRs are less frequent and reported in less than 10% of cases. However, a severe ADR requires, in addition to symptomatic treatment, modification, or even interruption of treatment (Prasad R, 2019).

Since it is impossible to predict the response to a given drug of a particular patient, the inclusion of a drug in the regimen must not be avoided in advance for fear of an adverse reaction. Most patients can tolerate complex regimens for the treatment of drug-resistant TB despite the presence of

ADR. In contrast, some patients will have severe difficulties accepting even relatively simple regimens with first-line drugs (Curry, 2016).

Some factors influence the development of ADR, including errors in the dosage of drugs, genetic factors (e.g., slow or fast acetylators), age of the subject (more frequent in patients over 60 years of age), consumption of alcohol and illicit substances, kidney or liver failure, and co-infection with HIV (Chamorro JG, 2013).

Before starting treatment, it is essential to discuss the benefits and risks with the patient since they must be fully aware of the risks and benefits of treatment. The patients must understand that they must receive the complete treatment regimen, the importance of each drug that makes up the regimen, and their possible side and toxic effects. Patients must be mentally prepared to tolerate the side effects of such a lengthy treatment. However, health personnel must do everything possible to facilitate drug tolerance; patients must be sure that while side effects are unavoidable, they will be dealt with as quickly and vigorously as possible. The patient must rationalize that if there were a need for retreatment in the future due to having stopped the current regimen, this regimen would surely be even more toxic and less effective (Laniado-Laborín R, 2015).

The patient should be encouraged to report the appearance of ADR to health personnel as soon as possible. Healthcare personnel must respond quickly to the ADR; a careful history will sometimes determine that these symptoms are attributable to other causes and not a manifestation of side effects or toxicity of the TB drugs.

Most patients will agree to continue with the regimen despite the ADR if they understand the benefits of therapy. They should be aware that tolerance to most of these effects develops after a few weeks and that their caretakers will do whatever is necessary to evaluate and treat them if ADR occur.

Table 2.1: Classification of ADR according to their severity

Grade	Type of adverse reaction
Grade 1	they are mild adverse events. (e.g., a minor event requiring no intervention; asymptomatic laboratory data only; marginal clinical relevance)
Grade 2	moderate adverse effects
Grade 3	serious and undesirable adverse events (for example, significant symptoms requiring hospitalization or invasive intervention)
Grade 4	life-threatening or disabling adverse effects
Grade 5	adverse events that result in the death of the patient

Antituberculosis drugs pharmacokinetics

Isoniazid

Although isoniazid (H) is an essential drug for TB given its significant bactericidal effect, it occasionally causes ADR, some of which can be serious. Isoniazid is a low molecular weight, water-soluble compound that is rapidly absorbed from the digestive tract. Its pharmacokinetic properties are affected by several factors specific to each patient, including age, genetics, comorbidities, food intake, or certain medications. Meals rich in fat decrease H absorption (Wang P, 2016; Ramachandran G, 2013).

After absorption, H rapidly diffuses into all body tissues and fluids, including cerebrospinal fluid, saliva, pleural and peritoneal fluid, as well as the airway and lung parenchyma; it can even be excreted in breast milk. Isoniazid inhibits a series of enzymes that mycobacteria need to synthesize mycolic acid, preventing the formation of the bacterial wall and thus killing the mycobacteria due loss of acid resistance and hydrophobicity (Su Q, 2021).

The major metabolic pathways for H include acetylation and hydrolysis. AcINH is produced by N-acetyltransferase during acetylation, while isonicotinic acid (INA) and Hz are produced through hydrolysis. AcINH can also be hydrolyzed to produce INA and AcHz. In turn, Hz can also be

acetylated, generating AcHz and diacetylhydrazine. Hz and AcHz are thought to be involved in the hepatic toxic effects of H through microsomal P450, especially CYP2E (Delaney J, 1995).

Rifampicin

Rifampin (R) is a semi-synthetic, fat-soluble antibiotic derivative of rifamycin that inhibits the synthesis of ribonucleic acid. It is bactericidal and highly sterilizing at both intracellular and extracellular levels. Rifampin is widely distributed in all body tissues and fluids. When there is meningeal inflammation, R reaches good concentration in the cerebrospinal fluid. After intestinal absorption, R reaches the liver, is metabolized in the hepatocyte, and excreted in the bile to the intestine. Then, the metabolites can be reabsorbed in an enterohepatic cycle; when deacetylated, the metabolites are finally eliminated in the feces (Acocella G, 1983).

Ethambutol

Ethambutol is a bacteriostatic drug that inhibits cell wall synthesis; It is considered a bacteriostatic drug which mechanism of action is to interfere with the biosynthesis of arabinogalactan in the cell wall, stopping the multiplication of the bacilli. Ethambutol acts synergistically with H against *Mycobacterium tuberculosis* through transcriptional repression of the inhA gene, resulting in an increased bactericidal effect.

Ethambutol penetrates the meninges poorly. The kidneys clear it; dose adjustment is required in patients with renal failure, and daily dosing in patients with renal insufficiency increases the risk of toxicity (Lee N, 2021).

Pyrazinamide

Pyrazinamide (PZA) is a prodrug converted to its bioactive form pyrazinoic acid (POA) by the bacterial pyrazinamidase PncA and host enzymes. Most drugs do not penetrate all compartments or all lesions. In contrast, PZA is rapidly and homogeneously distributed in all types of lesions, both cellular and caseous, where the larger and more hydrophobic drugs diffuse less efficiently. PZA shows bactericidal activity in caseum (albeit in high concentrations), suggesting that it kills not only metabolically active bacilli but also non-growing persistent bacilli that reside in caseum.

Pyrazinamide is well absorbed from the gastrointestinal tract and excreted by glomerular filtration. Cerebrospinal fluid penetration is good with concentrations equivalent to serum. (Gopal P, 2019).

Levofloxacin

Levofloxacin is a broad-spectrum bactericidal and sterilizing antibiotic, belonging to the class of third generation fluoroquinolones. It works by directly inhibiting the synthesis of bacterial DNA; it promotes DNA strand breakage by inhibiting DNA gyrase in susceptible organisms, which inhibits the relaxation of supercoiled DNA. The elimination half-life of levofloxacin ranges from 27 to 35 hours in adults with renal impairment, depending on the severity compared to eight hours in healthy adults. This long half-life indicates that dose adjustment is necessary for these patients. Clinical data suggest that breast milk has a low concentration of levofloxacin, so it is unlikely to cause ADR in breastfed babies. Still, children should be monitored for possible gastrointestinal adverse effects such as diarrhea or yeast infection. Levofloxacin is poorly metabolized, and most of it is excreted unchanged in the urine (87% of the dose). Renal clearance occurs through active tubular secretion (Podder V, 2021).

Moxifloxacin

Moxifloxacin is a fluoroquinolone with bactericidal and sterilizing action against *Mycobacterium tuberculosis.* The bactericidal action occurs by binding to the DNA gyrase, thus preventing the replication, transcription, and repair of mycobacterial DNA. The bactericidal activity of fluoroquinolones, including moxifloxacin, requires two steps: the formation of bacteriostatic quinolone-gyrase-DNA complexes, followed by chromosomal fragmentation. A central feature of tuberculosis is the ability of *M. tuberculosis* to enter a latent state in which the mycobacteria display a low susceptibility to chemotherapeutic agents. Moxifloxacin has been shown to have a unique ability to kill mycobacteria even in the absence of active protein synthesis while in a latent state, an effect that is essential for the eradication of tuberculosis infection and the prevention of relapses.

Moxifloxacin is rapidly and easily absorbed after oral administration. The bioavailability of moxifloxacin after oral administration exceeds 90%. The drug is widely distributed, with some tissue concentrations above plasma levels. Concentrations in the lung epithelial lining fluid, lung tissue, alveolar

macrophages, and bronchial mucosa exceed their minimum inhibitory concentration (MIC) values.

Moxifloxacin is metabolized through glucuronide and sulfate conjugation. Cytochrome P450 enzymes are not involved in the metabolism of moxifloxacin, nor are they affected by this drug. The excretion of unchanged moxifloxacin in the urine is approximately 20%, while 25% is excreted in the feces. The glucuronide metabolite is excreted exclusively in the urine, and the sulfate metabolite is excreted mainly in the feces (Naido A, 2019).

Gatifloxacin

Gatifloxacin is an 8-methoxy fluoroquinolone that is rapidly absorbed after oral administration. The bioavailability of gatifloxacin is not affected by the presence of food. The effect of cations on gatifloxacin for chelation potential is more significant with aluminum and less with calcium and iron supplements, provided the calcium and iron are administered at least two hours before or two hours after the gatifloxacin dose. Aluminum-containing preparations should be administered at least four hours after ingestion of gatifloxacin.

Gatifloxacin is well distributed in tissues and often reaches concentrations that exceed serum concentrations. The mean concentration in the respiratory tract (bronchial mucosa, lung epithelial lining) is two times higher than the mean serum concentration. Gatifloxacin concentration is exceptionally high in alveolar macrophages and lung parenchyma, indicating good intracellular penetration.

Gatifloxacin is a metabolically stable compound; more than 80% of the drug is excreted unchanged in the urine, mainly through glomerular filtration. In patients with renal failure, the clearance of gatifloxacin is lower than in patients with normal renal function. Dose adjustment is suggested for patients with creatinine clearance <40 ml/min.

Gatifloxacin has no deleterious effect on glucose tolerance in people with diabetes with adequate metabolic control (Grasela DM, 2000).

Linezolid

Linezolid is a synthetic oxazolidinone. It is the first oxazolidinone available that inhibits bacterial protein synthesis by interfering with translation. Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S

subunit; this activity essentially inhibits protein production and prevents bacteria from multiplying.

Linezolid is a reversible non-selective monoamine oxidase (MAO) inhibitor. Monoamine oxidase inhibition leads to increased concentration of epinephrine, norepinephrine, dopamine, and serotonin in the central nervous system and the sympathetic nervous system. MAO inhibition in the gastrointestinal tract and liver can result in the systemic absorption of large amounts of tyramine from the diet and potentially cause life-threatening hypertension.

Linezolid can be administered with food; diet slows down the speed, but not the degree of oral absorption. Absorption is rapid and extensive. Linezolid has excellent tissue penetration into the lung parenchyma and the CNS, exhibiting 100% oral bioavailability. Linezolid is metabolized by non-microsomal oxidation in the liver resulting in two inactive carboxylic acid metabolites predominantly excreted in the urine. The oxidative metabolism of linezolid is not enzymatic and does not involve the hepatic microsomal oxidative system (CYP450). About 30% of the dose is excreted unchanged in the urine (Azzouz A, 2021).

Bedaquiline

Bedaquiline (BDQ) is a bactericidal diarylquinoline very active against *Mycobacterium tuberculosis* (MTB). It has potent in vitro activity against both drug-sensitive and drug-resistant strains of MTB. BDQ has also demonstrated sterilizing activity due to its bactericidal effect against latent MTB.

BDQ exerts its antimycobacterial activity by inhibiting ATP synthesis, a process that is crucial to the multiplication of MTB and its survival in a latent state. Inhibition of ATP synthesis occurs through drug interference with mycobacterial F-ATP synthetase activity, leading to depletion of bacterial ATP.

The CYP3A4 isoenzyme metabolizes BDQ, and consequently, its systemic exposure and therapeutic effect may decrease during concomitant administration with CYP3A4 inducers. Most of the administered BDQ dose is eliminated in the feces. The urinary excretion of BDQ is <0.001% of the dose, indicating that the renal clearance of the intact active substance is negligible (Sarathy JP, 2019).

Clofazimine

Clofazimine (CFZ) is a hydrophobic riminophenazine. Although the mechanisms of action are not entirely understood yet, it has been suggested that MTB's respiratory chain and ion transporters are the CFZ putative targets. CFZ needs some time to cause a shortage of the stored intracellular energy and the development of reactive oxygen species to cause lethal damage to the mycobacteria.

CFZ oral bioavailability is approximately 70%, and co-administration with food increases bioavailability and absorption rate (Nix DE, 2004). If CFZ is administered with a fatty meal, there is a 60% increase in the mean area under the curve (AUC) and a 30% increase in the mean maximum concentration (Cmax). Clofazimine is highly lipophilic with an extensive protein binding and tends to be deposited in fatty tissue and the cells of the reticuloendothelial system. Another CFZ pharmacological characteristic is the slow and progressive accumulation in tissues (lungs, liver, and spleen), although plasmatic levels of the drugs remain low. Clofazimine can be considered a moderate-to-strong CYP3A4/5 inhibitor and weak CYP2C8 and CYP2D6 inhibitor.

Clofazimine is excreted unchanged via the bile, mainly in the feces. A minimal amount of the drug is found in the urine as unchanged clofazimine (RiccARDsi N, 2020).

Cycloserine

Cycloserine (Cs) is an analog of the amino acid d-alanine. Cycloserine exerts its bacteriostatic effect by inhibiting enzymes essential in synthesizing peptidoglycan and, therefore, in the biosynthesis and maintenance of the cell wall.

Cycloserine can be bactericidal or bacteriostatic, depending on the local concentration and the efficacy against a particular strain.

Cycloserine is rapidly and almost entirely (70-90%) absorbed from the intestine after oral administration and is widely distributed in most body fluids and tissues, including cerebrospinal fluid; Cs crosses the placenta. Approximately one-third of Cs is metabolized in plasma. The remainder is excreted in the urine, where it reaches high therapeutic concentrations; it accumulates and requires dose adjustment in kidney failure. Its half-life is

8-12 h. Excretion is mainly renal; 50% is excreted unchanged within 12 hours, and 70% is excreted within 24 hours (Cycloserine, 2008).

Ethionamide/Prothionamide (ETA/PTR)

Ethionamide and prothionamide are prodrugs activated by the enzyme ethA, a monooxygenase in *Mycobacterium tuberculosis* that binds to NAD+ to form an adduct that inhibits inhA in the same way as isoniazid. The mechanism of action is believed to be through alteration of mycolic acid; both are weakly bactericidal.

Ethionamide and prothionamide are widely distributed in tissues and body fluids. Extensive metabolism occurs mainly in the liver; ETA/PTR are metabolized to various inactive metabolites. Less than 1% appears in the urine as an unchanged drug; the remainder is excreted through the kidney as inactive metabolites (LiverTox, 2012; Ethionamide, 2008).

Imipenem/cilastatine

Imipenem is a β-lactam antibiotic belonging to the subgroup of carbapenems, effective in treating drug-resistant tuberculosis. Like all other β-lactams, imipenem inhibits bacterial cell wall synthesis by binding and inactivating the relevant transpeptidases, known as penicillin-binding proteins (PBPs).

It must be administered intravenously or intramuscularly because it is not effectively absorbed from the digestive tract.

Imipenem is widely distributed in tissues and fluids. Approximately 10-20% of imipenem is bound to human serum proteins. The drug is excreted through the kidney, and 70% of it is recovered in the urine within 10 hours. Imipenem is marketed in association with cilastatin sodium (1: 1 ratio), a competitive, reversible, and specific inhibitor of dehydropeptidase-I, the renal enzyme that metabolizes and inactivates imipenem. Cilastatin lacks intrinsic antibacterial activity and does not affect the antibacterial activity of imipenem. Patients with creatinine clearance <70 ml/ min or bodyweight <70 kg require dose reductions (Rodloff AC 2006).

Meropenem

Meropenem is a broad-spectrum β-lactam antibiotic that belongs to the subgroup of carbapenems. It exerts its bactericidal action by inhibiting the synthesis of the bacterial cell wall. It is minimally metabolized, producing

an inactive metabolite. Approximately 70% of the dose is excreted in the urine in 12 hours. In patients with normal renal function, the elimination half-life is 1.2 hours, increasing to 10 hours in patients with renal failure.

Unlike imipenem, it is not inactivated by the human kidney enzyme dehydropeptidase-1 and does not require cilastatin co-administration (Breilh D, 2013).

Amikacin

Amikacin is a broad-spectrum aminoglycoside antibiotic. It binds to the bacterial 30 S ribosome subunit, causing interference with reading the genetic code and, consequently, inhibition of protein synthesis. Amikacin has a moderate bactericidal effect against MTB depending on the concentration of the drug, also exerting a post-antibiotic effect.

Amikacin can be administered parenterally or by nebulization. There is no oral formulation of the drug available because the drug is not absorbed from the gastrointestinal tract. Amikacin can be administered intramuscularly when intravenous access is not available. It can be administered intrathecally in patients with meningitis and reach high concentrations in the cerebrospinal fluid immediately.

Amikacin is excreted unchanged by glomerular filtration; 94% of the administered dose is excreted in the urine in 24 hours. The elimination half-life in adults with normal kidney function is 2 to 3 hours (Sizar O, 2021).

Para-aminosalicylic Acid

Para-aminosalicylic acid (PAS) is a bacteriostatic antituberculosis drug. The mechanism of action of PAS is similar to that of sulfonamides since it competes with para-aminosalicylic acid (PABA) for dihydropteroate synthetase (DHP), a key enzyme in folate biosynthesis. Absorption of para-aminosalicylic acid in delayed-release granules is rapid and complete after oral administration. The administration of PAS in granules is associated with a higher serum concentration than when it is administered in the fasted state.

After oral administration, PAS is metabolized in the intestine to acetyl-PAS and the liver to acetyl-PAS and glycine-PAS. Approximately 80-90% of the administered dose is excreted in the urine after glomerular filtration and

tubular secretion as PAS, glycine-PAS, and acetyl-PAS (Abulfathi AA, 2020).

Streptomycin

Streptomycin cannot be administered orally; it is fully and rapidly absorbed after intramuscular administration. It is distributed mainly in the extracellular fluid in all tissues except the brain and sparingly in the cerebrospinal fluid and bronchial secretions; it has been found in bile, pleural, and ascitic fluids. It does not penetrate cells and exerts its effect exclusively on extracellular bacilli. It reaches high concentrations in the urine; it also crosses the placenta.

Streptomycin is not metabolized, and it is mainly excreted unchanged through the kidneys (it can be removed by hemodialysis); it passes through the placenta with serum levels in the cord blood similar to maternal levels. Small amounts are excreted in milk, saliva, and sweat (Streptomycin, 2008; Piepersberg W, 1995).

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CHAPTER 2

ANTITUBERCULOSIS DRUGS AND ADVERSE GASTROINTESTINAL REACTIONS

Abstract

The most annoying and frequent adverse drug reactions at the beginning of treatment are usually related to gastrointestinal symptoms. Nausea and vomiting are frequently reported when the regimen contains ethionamide, clofazimine, or PAS. Ethionamide and prothionamide are more related to upper tract digestive symptoms (nausea, vomiting), while PAS causes more large bowel symptoms (colic, diarrhea). In addition to explaining to the patient that these symptoms tend to decrease with time, it is necessary to start treatment as soon as possible to mitigate these adverse effects. Antiemetic options include dopamine antagonists such as metoclopramide or prochlorperazine and serotonin antagonists such as ondansetron. Proton pump inhibitors can be helpful, but they should be used at night, as distanced as possible from administering the antituberculosis regimen. By modifying the gastric pH they can reduce the absorption of the drugs. Ethionamide, clofazimine, and PAS frequently cause diarrhea.

Introduction

The most annoying and frequent adverse drug reactions (ADR) at the beginning of treatment are usually related to gastrointestinal symptoms (El Hamdouni, 2020). They are extremely common when the regimen contains ethionamide, prothionamide, clofazimine, or PAS. Gastrointestinal upset is frequent with rifampin, ethambutol, pyrazinamide, and fluoroquinolones; they are infrequent with isoniazid, cycloserine, and injectables drugs.

Gastrointestinal ADR are more frequent when first-line drugs are in individual presentations than with combined fixed-dose tablets. A recent meta-analysis that included more than 3,500 patients reported a 65% increased chance of gastrointestinal adverse effects with a regimen with

drugs in an individual presentation compared to the four-drug fixed-dose combination treatment. (Lima GC, 2017).

Gastritis

Nausea and vomiting are frequently reported (Emrani Z, 2016); for this reason, ethionamide, prothionamide, and PAS can be initiated with a gradual increase over 1 to 2 weeks ("ramping up") to help avoid nausea and vomiting. The metallic taste caused by ethionamide can cause anorexia and prevent the patient from gaining weight. It is important to remember that nausea and vomiting can also be due to hepatotoxicity, a much more severe ADR than gastritis secondary to drugs, so the presence of these symptoms always requires liver function evaluation.

In the presence of gastrointestinal ADR, it is essential to consider other causes of digestive symptoms not associated with antituberculosis drugs, such as irritable bowel syndrome, lactose intolerance, diabetic gastroparesis, or pregnancy (Scorza K, 2007).

Occasionally, when using individual drugs, the patient may associate nausea/vomiting with a particular medicine. Ethionamide and prothionamide are more related to upper tract digestive symptoms (nausea, vomiting), while PAS causes more large bowel symptoms (colic, diarrhea). It is convenient to divide the dose with both drugs, even when it represents a significant complication for the direct supervision of treatment. Linezolid, clofazimine, and the fluoroquinolones (levofloxacin and moxifloxacin) can also be associated with nausea/vomiting. Still, since linezolid and fluoroquinolones constitute crucial elements in MDR-TB treatment, the dose of these drugs **MUST NOT BE REDUCED** to control these non life-treathening side effects (Curry International Tuberculosis Center, 2016).

In addition to explaining to the patient that these symptoms tend to decrease with time, it is necessary to start treatment as soon as possible to mitigate these adverse effects. Therapeutic options include dopamine antagonists such as metoclopramide or prochlorperazine and serotonin antagonists such as ondansetron (Metz A, 2007). Antiemetic drugs can be recommended 30 minutes before taking the antituberculosis drugs.

It is essential to consider the risk of prolonging the QT interval when prescribing antiemetic medications. Although the effect may not be significant in isolation, the risk of arrhythmia increases with other risk factors that affect the QT interval, such as medications, hypokalemia, and

hypocalcemia. Dopamine antagonists, such as metoclopramide, chlorpromazine, and prochlorperazine, are associated with QT interval prolongation (Aronow WS, 2018). Serotonin antagonists cause a dose-dependent, reversible prolongation of the QT interval. Ondansetron prolongs the QT interval when administered intravenously in doses greater than 8 mg. However, there have been no reports of QT prolongation after oral administration (Keefe DL, 2002). Antituberculosis drugs, including fluoroquinolones, bedaquiline, delamanid, pretomanid, and clofazimine, can prolong the QT interval and cause serious cardiac arrhythmias when given simultaneously. If this is the case, patients should be monitored electrocardiographically (Hernandez-Arroyo, 2015).

If present, gastritis and gastroesophageal reflux must be treated. Proton pump inhibitors can be helpful, but they should be used at night, as distanced as possible from the administration of the antituberculosis regimen. By modifying the gastric pH they can reduce the absorption of the drugs. Antacids and sucralfate (as well as dairy products) must be avoided at least two hours before and two hours after the ingestion of fluoroquinolones, as they interfere with their absorption (McIlleron H, 2019).

Isoniazid and rifampicin should be administered in the fasting state, as food delays their absorption. Carbohydrates reduce the absorption of isoniazid; food also reduces the absorption of rifampicin. However, if the patient cannot tolerate taking the drugs while fasting, a small serving of non-fatty food (e.g., toast or crackers) may be useful before taking the medication to alleviate nausea (Lomaestro BM, 1995). It is essential to evaluate the effect of these measures on nausea/vomiting. Vomiting shortly after taking the medication will prevent their absorption.

If vomiting persists, it may be necessary to stop the specific drug causing the symptoms if the regimen is strong enough to allow it or if it can be substituted with another effective drug. Treatment regimen must include at least four effective drugs to be successful (Laniado-Laborin R, 2012).

A recommended strategy to determine which drug is causing nausea and vomiting is to stop medication for two to three days and gradually add it back in increasing doses until the therapeutic dose is reached. Ethionamide/prothionamide or PAS should be discontinued first as these drugs are more likely to cause nausea and vomiting.

Colitis

After prolonged administration of high doses, clofazimine can accumulate in tissues, e.g., in the small intestine wall, and precipitate. Enteropathy can develop if the crystals are deposited in the lamina propria of the jejunal mucosa and mesenteric lymph nodes, sometimes producing intestinal obstruction. If gastrointestinal symptoms develop during treatment, the dose should be reduced or the interval between doses prolonged. Symptoms may slowly subside when the drug is withdrawn.

Ethionamide, clofazimine, and PAS frequently cause diarrhea (rifampin to a lesser extent). PAS is a bacteriostatic drug that contributes little to the regimen's effectiveness and can cause diarrhea, abdominal cramps, and flatulence more frequently than other antituberculosis drugs. If its use is considered essential, it is recommended to progressively increase the dose in the first two weeks of treatment until the total dosage is attained. Symptoms usually subside over weeks; if not, since PAS is rarely essential, it is recommended to discontinue it. Linezolid can also cause diarrhea, but it should not be stopped since this is a critical drug for the regimen. Reducing the dose from 600 mg to 300 mg is usually sufficient, but it is necessary to monitor the serum values of the drug to ensure that therapeutic levels are reached (Felix-Ponce M, 2018).

Treatment should be discontinued while diarrhea persists (drug absorption decreases and will lead to subtherapeutic serum levels). In case of persistent diarrhea, an antidiarrheal agent (e.g., loperamide 2-4 mg PO) can be used in patients with very frequent bowel movements; the administration of lactobacilli may be helpful to replenish the intestinal flora (Lin S, 2020).

If diarrhea persists, other causes of diarrhea such as *Clostridium difficile* colitis (treatment with fluoroquinolones has been associated with *C. difficile* diarrhea) or other infectious or parasitic causes of diarrhea should be ruled out (Kruszka PS, 2002).

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CHAPTER 3

ANTITUBERCULOSIS DRUGS AND HEPATOTOXICITY

Abstract

Several of the antituberculosis drugs can cause hepatitis, including isoniazid, pyrazinamide, rifampin, and ethionamide. Drug-induced hepatotoxicity constitutes a diagnosis of exclusion, and other causes of liver damage should be investigated methodically, such as acute viral hepatitis. Rechallenge with the suspect drug followed by a rise of more than twice of the liver enzymes or a decrease in the levels of the enzymes after stopping the medication is considered a strong confirmation of the diagnosis of drug-induced hepatitis. Factors such as advanced age, chronic liver disease, alcoholism, HIV, and illicit intravenous drugs increase the risk of hepatotoxicity. Any gastrointestinal symptom can be a manifestation of liver toxicity. If liver enzymes are normal, we can continue with the regimen using the strategies already described to mitigate nausea and vomiting. All potentially hepatotoxic medications should be withdrawn immediately while obtaining liver function test results if liver damage is suspected. When total bilirubin is ≥3 mg/dL, it is advisable to suspend hepatotoxic drugs. If enzymes are higher than three times the upper limit of normal in the presence of symptoms consistent with hepatotoxicity or ≥five times the upper limit of normal even in the absence of symptoms, all hepatotoxic drugs should be stopped.

Introduction

Exposure to antituberculosis drugs can elicit an adaptive physiological response (Williams GM, 2002). Several of the antituberculosis drugs can cause hepatitis, including isoniazid, pyrazinamide, rifampin, and ethionamide. The induction of specific genes, including those that regulate antioxidant, anti-inflammatory, and anti-apoptotic pathways, can prevent liver damage; this adaptive response can also stimulate hepatocyte proliferation. This physiological response is reflected by a transient and

asymptomatic elevation of alanine aminotransferase due to mild and non-progressive damage to the mitochondria of hepatocytes. Exposure to other hepatoxic substances (e.g., ethanol) can interfere with this protective adaptive response (Saukkonen JJ, 2006).

Drug-induced hepatotoxicity constitutes a diagnosis of exclusion, and other causes of liver damage should be investigated methodically, such as acute viral hepatitis. Liver damage secondary to antituberculosis drugs can range from an asymptomatic and transient increase of liver enzymes to fulminant hepatitis with liver failure. Rechallenge with the suspect drug followed by a rise of more than twice of the liver enzymes or a decrease in the levels of the enzymes after stopping the medication is considered a strong confirmation of the diagnosis of drug-induced hepatitis (Benichou C, 1990)

Drug-induced liver injury: general concepts

The frequency of hepatotoxicity during tuberculosis treatment varies from 2% to 39% in different countries. Antituberculosis drug-induced hepatotoxicity is unpredictable, although certain patients are at relatively higher risk. The incidence of liver disease is higher in developing countries. Factors such as advanced age, chronic liver disease, alcoholism, HIV, and illicit intravenous drugs increase the risk of hepatotoxicity (Prasad R, 2019).

The liver is the pathway through which the absorbed nutrients from the digestive tract reach the systemic circulations. It also acts as a filter to minimize the exposure of the rest of the body to toxins and other harmful substances. It, therefore, is exposed to a high concentration of potentially toxic substances and their metabolites.

The splanchnic circulation carries ingested drugs directly to the liver. Liver enzymes metabolize these drugs initially through oxidation, reduction, or hydrolysis, which are carried out mainly by enzymes of the cytochrome P450 class. Subsequently, the drugs are subjected to glucuronidation, sulfation, acetylation, glutathione conjugation, deacetylation, and deamination, to generate compounds excreted by transport proteins into the bile or the systemic circulation. These liver metabolic functions are influenced by host factors such as circadian rhythm, hormone levels, comorbidities, genetic factors, age, sex, ethnicity, and nutritional status. The main excretory pathway for hepatic metabolites is through the bile, where excreted compounds can be reabsorbed in the small intestine, returning to the portal circulation (enterohepatic circulation). (Saukkonen JJ, 2006).

Liver damage secondary to antituberculosis drugs can result from direct toxicity, from a drug metabolite, or an immunologically mediated response, affecting hepatocytes, biliary epithelial cells, and the liver vasculature (Ramappa V, 2013).

Studies in rats and human hepatocytes show that treatment with antituberculosis drugs causes significant liver damage, inducing an inflammatory response and oxidative stress, activating the NLRP3 inflammasome, reducing the activity of drug-metabolizing enzymes, and altering the antioxidant defense (Su Q, 2021).

Clinical aspects of hepatotoxicity

Any gastrointestinal symptom can be a manifestation of liver toxicity. If liver enzymes are normal, we can continue using the strategies already described to mitigate nausea and vomiting (Chapter 2). ***IF LIVER DAMAGE IS SUSPECTED, ALL POTENTIALLY HEPATOTOXIC MEDICATIONS SHOULD BE WITHDRAWN IMMEDIATELY*** while obtaining liver function test results. Stopping hepatotoxic drugs usually means temporarily halting the entire regimen. If pyrazinamide was part of the original regimen, it should be permanently discontinued given its high hepatotoxic potential (Kameda K, 1995).

Liver function tests should be obtained before starting antituberculosis treatment; the panel must include alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic dehydrogenase (LD), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGTP), and total bilirubin (TB). Furthermore, in patients with drug-resistant TB receiving second-line drugs, periodic monitoring of liver function is recommended (Yew WW, 2018).

Alanine aminotransferase originates from the hepatocyte cytoplasm, while aspartase aminotransferase can originate from the hepatocyte cytoplasm, the hepatocyte mitochondria, and muscle (both skeletal and cardiac). Alkaline phosphatase originates from the hepatocyte's biliary canalicular surface and bone (produced during bone formation), intestine, and placenta. Gamma-glutamyl transpeptidase likewise originates from the biliary canalicular surface of the hepatocyte. Lactic dehydrogenase (LD) is found in many tissues of the body, but it is most significant in the heart, liver, kidneys, muscles, red blood cells, brain, and lungs. Bilirubin is a hemoglobin metabolite conjugated in the liver.

Table 3.1. Blood test results for liver function tests

Test	Lower and upper normal limits
Alanine aminotransferase (ALT)	7 to 55 units per liter (U/L)
Aspartate aminotransferase (AST)	8 to 48 U/L
Alkaline phosphatase	40 to 129 U/L
Gamma-glutamyl transpeptidase (GGTP)	8 to 61 U/L
Lactic dehydrogenase (LD)	122 to 222 U/L.
Bilirrubin	0.1 to 1.2 milligrams per deciliter (mg/dL)

Antituberculosis drugs and hepatotoxicity

Isoniazid is eliminated mainly via the liver by acetylation to N-acetyl transferase 2 (NAT-2). Fast acetylators excrete more than 90% of the drug as acetyl-isoniazid. In contrast, in slow acetylators, 67% of the drug is excreted as acetyl-isoniazid, and a more significant percentage is excreted unchanged through the urine. Preliminary studies suggested that rapid acetylators had a higher risk of liver damage because they generate more acetyl-isoniazid that can be metabolized to toxic intermediates (Huang YS, 2014). However, fast acetylators clear mono-acetyl hydrazine (MAH) more quickly than slow acetylators, who may have greater exposure to MAH. The reactive metabolites of MAH are probably toxic to the liver through the generation of free radicals. Slow acetylators present elevation of transaminases up to three times the standard upper limit more frequently than rapid acetylators (Chamorro JG, 2013). Up to 20% of subjects receiving isoniazid monotherapy for latent tuberculosis infection experience mild and transient increases in liver enzymes due to hepatic adaptation. Isoniazid hepatotoxicity is related to age; the older the patient, the higher the frequency of hepatitis (Hosford JD, 2015). Hepatotoxicity due to direct drug damage generally occurs in weeks to months, unlike hypersensitivity hepatitis that occurs days to weeks after starting treatment (Preziosi P, 2007).

Rifampin may interfere with bilirubin uptake in a dose-dependent manner, resulting in subclinical unconjugated hyperbilirubinemia or jaundice without hepatocellular damage. Rifampicin-conjugated hyperbilirubinemia is due to the inhibition of bile-exporting pumps. It can also occur (dose-

dependent effect) by competition with bilirubin clearance through the sinusoidal membrane or by preventing bile secretion at the canalicular level.

Rifampin can occasionally cause hepatocellular damage and potentiate the hepatotoxic effect of the other antituberculosis drugs; rifampin infrequent liver damage appears to be due to a hypersensitivity reaction, being more common when higher doses are used intermittently. Rifampin hypersensitivity hepatitis has been reported in combination with renal dysfunction, hemolytic anemia or "flu-like" syndrome (Baskaran UL, 2017).

Pyrazinamide, a derivative of nicotinic acid, can exhibit both dose-dependent and idiosyncratic hepatotoxicity. The half-life of pyrazinamide is longer than that of either isoniazid or rifampin, approximately 10 hours, and increases up to 15 hours in patients with preexisting hepatic disease. Pyrazinamide is de-amidated to pyrazinoic acid in the liver, and it can share damage pathways with isoniazid due to its similar molecular structure. Pyrazinamide can also induce hypersensitivity reactions with eosinophilia and liver damage (Steele MA, 1988, Knobel B, 1997).

Hepatotoxicity has similarly been reported with second-line antituberculosis drugs but less frequently compared to first-line medications. The incidence of hepatotoxicity is 2 to 3% with fluoroquinolones (with fulminant hepatitis in less than 1%), 1-2% with ethionamide/prothionamide, and 0.3% with para-aminosalicylic acid. Hepatotoxicity is uncommon with linezolid, clofazimine, and the new drugs bedaquiline and delamanid (Prasad R, 2019).

Fluoroquinolones can cause hepatitis, probably due to a hypersensitivity reaction, which frequently manifests as eosinophilia. Moxifloxacin is partially metabolized by the liver, while levofloxacin and gatifloxacin are excreted unchanged, mainly by the kidney. Between 2-3% of patients treated with fluoroquinolones experience mild and self-limited transaminasemia. Moxifloxacin can cause severe hepatitis in approximately 1% of treated patients, while for levofloxacin, a rate of 1 in a million cases is reported (Wolfson JS, 1991; Liver Tox, 2020).

Diagnosis of hepatotoxicity

An increase in serum ALT is more specific for hepatocellular injury than an increase in AST, which can also be increased in muscle, cardiac, and kidney damage. Increases in alkaline phosphatase and bilirubin with little or no elevation in ALT indicate cholestasis (alkaline phosphatase levels can also

be abnormally high in bone, intestinal, or placental inflammatory processes). An increase in GGTP, an inducible enzyme of hepatic cholangioli, is helpful to distinguish whether the increase in AF is due to liver disease or has another etiology (Baskaran UL, 2017). ALT and AST elevation may also occur after exercise, hemolysis, or muscle injury (Saukkonen JJ, 2006).

If hepatocellular enzymes are increased, but under three times the upper limit of normal, and there is no jaundice (total bilirubin <2.0 mg/dL), treatment should be continued using strategies to control nausea and vomiting. Nonetheless, liver function should be carefully monitored, initially at least once a week. If bilirubin is elevated but with normal or only slightly elevated hepatocellular enzymes, then hepatobiliary obstruction (e.g., due to choledocholithiasis) should be ruled out, and causes of direct hyperbilirubinemia (e.g., cirrhosis of the liver) and indirect hyperbilirubinemia should be investigated. (e.g., hemolysis). When total bilirubin is ≥3 mg/dL, it is advisable to suspend hepatotoxic drugs.

If both bilirubin and alkaline phosphatase are increased (known as a cholestatic pattern) without elevated liver enzymes, rifampicin is the most likely cause of liver damage. When liver damage is primarily manifested by transaminasemia, pyrazinamide and isoniazid are the most likely cause. In asymptomatic patients under treatment with a regimen containing rifampicin and who present elevated total bilirrubin ≤3 mg/dL with normal AST/ALT, is not necessary to stop treatment. As mentioned, rifampicin competes with bilirubin for its elimination, causing the latter's elevation; hyperbilirubinemia usually resolves spontaneously even though treatment is not discontinued (Nagarajan S, 2018).

If enzymes are higher than three times the upper limit of normal in the presence of symptoms consistent with hepatotoxicity or ≥five times the upper limit of normal even in the absence of symptoms, **ALL HEPATOTOXIC DRUGS SHOULD BE STOPPED**. If a regimen with at least four effective non-hepatotoxic drugs can be sustained (e.g., linezolid, ethambutol, a second-line injectable, levofloxacin, or cycloserine), treatment can continue. Otherwise, the regimen will have to be stopped (Curry International Tuberculosis, 2016).

Once the enzymes decrease to a value below twice the upper limit of normal (although some experts recommend waiting for the enzymes to normalize), the reintroduction of one of the potentially hepatotoxic drugs may be accompanied by non-hepatotoxic drugs. If the reintroduction is successful, the rest of the potentially hepatotoxic drugs can be added one at a time

(Sonika U, 2012). Even when a particular drug is found to be responsible for the adverse reaction, the rest of the medications must be reintroduced individually, since occasionally, more than one drug may be accountable for hepatotoxicity. Clinical follow-up and frequent monitoring of liver function tests are essential, at least once a week until the last drug has been reintroduced to the regimen and liver function tests have remained stable. If one of the drugs alters the enzymes during reintroduction, the drug must be eliminated from the regimen. Once the case has stabilized, liver function should be monitored monthly (Chamorro JG, 2013). Rechallenge, however, can, in some cases, endanger the patient and is usually limited to essential drugs or used when multiple potentially hepatotoxic drugs have been administered simultaneously (Chiturri S, 2002).

Patients with prior liver disease are at increased risk of hepatotoxicity with antituberculosis treatment. Patients with hepatitis B and C have a higher risk of hepatotoxicity when they present with active chronic infection than those who are only seropositive (Kumar N, 2014).

Likewise, it has been reported that HIV-positive patients, especially those receiving antiretroviral treatment (ART), have an increased risk of developing hepatotoxicity. In a study conducted in Brazil, logistic regression analysis showed that a CD4+ count of fewer than 200 cells/mm3 increased the risk of hepatotoxicity by 23% and co-infection with hepatitis B or C increased the risk 18:1. Patients with HIV and hepatitis C co-infection receiving antituberculosis treatment develop hepatotoxicity in up to 20% of cases. The immune reconstitution syndrome can include granulomatous hepatitis in patients with disseminated TB at the start of ART (Silva de Lima, 2012).

The use of hepatoprotective treatment is controversial. A clinical trial in Iran compared the benefits of carnitine as a hepatoprotector vs. placebo, finding a significant reduction in the rate of hepatic adverse effects (Hatamkhani S, 20149. A study conducted in Thailand showed a lower risk of hepatotoxicity in patients who received antituberculosis treatment plus the herb *Silybum marianum* (milk thistle) compared to placebo. In contrast, a study conducted in China with the same herb reported no benefit but a risk of hepatotoxicity (Zhang S, 2016; Jiménez-Arellanes, 2016).

N-acetylcysteine (NAC) has been studied as a hepatoprotector; in theory, it can attenuate antituberculosis drug-induced liver disease by scavenging free radicals formed during the drug's metabolism (Ejigu DA, 2020). However, a randomized clinical trial testing the antimycobacterial properties of NAC

reported no significant differences in the rate of drug-induced liver disease vs. placebo (Safe IP, 2020).

To date, there is not enough evidence to recommend the use of this type of hepatoprotective agents.

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CHAPTER 4

ANTITUBERCULOSIS DRUGS AND DERMATOLOGICAL ADVERSE EFFECTS

Abstract

Cutaneous adverse drug reactions (ADR) are those secondary reactions to their systemic administration. Antituberculosis drugs are the leading cause of dermatological ADR. Antituberculosis drugs are associated with diverse clinical patterns of cutaneous ADR, ranging from mild and moderate, such as pruritus, maculopapular rashes, lichenoid rashes, and urticaria, to severe and even life-threatening adverse reactions such as the Stevens-Johnson Syndrome and toxic epidermal necrolysis. A single drug can cause multiple skin ADR, and a specific skin ADR can occur with different antituberculosis drugs. Facial redness or itching reactions without a rash are generally associated with rifampin and pyrazinamide. All antituberculosis drugs can cause urticaria ("hives"). Photosensitivity has been described in patients receiving isoniazid, ethambutol, pyrazinamide, clofazimine, PAS or fluoroquinolones (levofloxacin, gatifloxacin or moxifloxacin). Clofazimine treatment is associated with a red-brown or a violaceous-brown cutaneous and conjunctival discoloration. Stevens-Johnson Syndrome and Toxic Epidermal Necrosis are infrequently associated with the use of antituberculosis drugs; however, due to its severity, antituberculosis treatment must be interrupted immediately. If a drug is identified as causing this reaction, it must not ever be used again. The drug hypersensitivity syndrome known as DRESS has been described with several antituberculosis drugs. In addition to the skin reaction, patients suffering from this syndrome present eosinophilia, lymphadenopathy and liver, lung, and kidney involvement.

Introduction

Cutaneous adverse drug reactions (ADR) are secondary reactions to their systemic administration (oral, subcutaneous, intravenous, muscular, inhalation). Antituberculosis drugs are the leading cause of dermatological ADR. ADR can be confined exclusively to the skin or part of a multisystemic

reaction associated with first and second-line antituberculosis drugs (Lehloenya RJ, 2012).

Antituberculosis treatment regimen is associated with diverse clinical patterns of cutaneous ADR, ranging from mild and moderate, such as pruritus, maculopapular rashes, lichenoid rashes, and urticaria, to severe and even life-threatening adverse reactions such as the Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). These ADR are more frequent in high HIV prevalence settings and developing countries, where tuberculosis is a common infection, resulting in a higher frequency of these reactions. Skin ADR can cause significant treatment interruptions or modifications, increasing the risk of failure, acquisition or extension of drug resistance, relapse, increased risk of complications, and even a fatal outcome. It is essential to identify the best possible treatment and preventive regimens to allow the continuity of antituberculosis therapy in its entirety (Rezakovic S, 2014).

Skin ADR must be included in the differential diagnosis of a sudden onset symmetric skin rash, especially in patients with a higher risk of adverse reactions such as the elderly, patients with organ failure, patients receiving other drugs in addition to antituberculosis medication (e.g., patients with antiretrovirals, treatment for diabetes or hypertension), malignant neoplasms and genetic susceptibility (Rezakovic S, 2014).

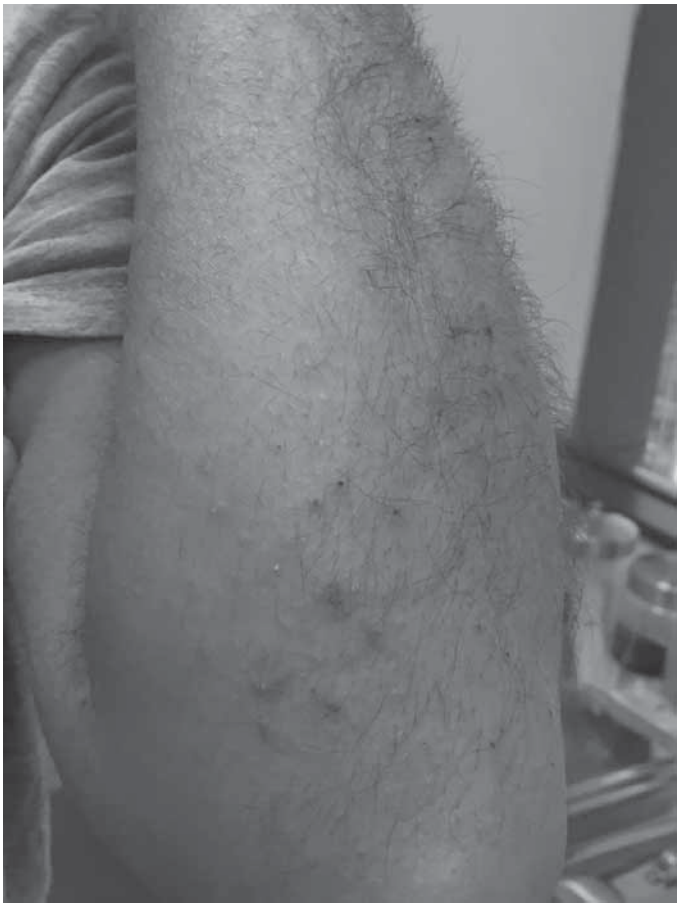
A single drug can cause multiple skin ADR, and a specific skin ADR can occur with different antituberculosis drugs. Dermatologic ADR are typically present in the first weeks of treatment; in most cases, they constitute a self-limited reaction with minimal clinical consequences (for example, acne on the face and torso commonly associated with isoniazid). However, cutaneous ADR can occasionally be associated with significant morbidity and mortality (up to 30% in toxic epidermal necrolysis), requiring interruption or changes in the treatment regimen (Collado-Chagoya R, 2018).

HIV co-infected patients have a higher incidence of ADR in general and skin ADR in particular, including skin hypersensitivity reactions. Highly active antiretroviral therapy (HAART) and prophylactic treatment for *Pneumocystis jirovecii* pneumonia, which is often started concurrently with tuberculosis therapy, complicate identifying the causative agent of ADR (Swami A, 2012).

Itching reactions

Facial redness or itching reactions without a rash usually involve the face and scalp and occur 2-3 hours after taking the medications. They are generally associated with rifampin and pyrazinamide (Forget EJ, 2006), typically mild and self-limited. It is necessary to rule out other etiologies as the cause of the dermal adverse reaction, including scabies, phototoxicity, contact dermatitis (ask about lotions, creams, perfumes, etc.), and other dermatoses such as psoriasis or atopic dermatitis (Tan WC, 2007).

Figure 4.1. Itching reaction without a rash in the forearm. See centerfold for this image in color.



In diabetic patients, dry skin can cause itching. Of the second-line antituberculosis drugs, clofazimine can cause dry skin and itching. PAS and ethionamide can cause hypothyroidism, which, in turn, cause dry and itchy skin (Curry International Tuberculosis Center, 2016).

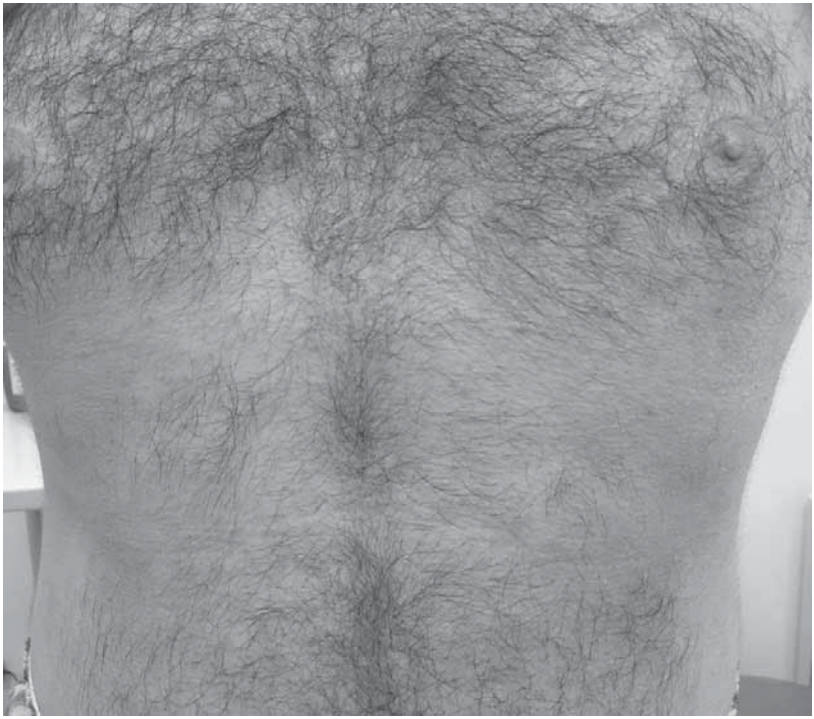
Since isoniazid is a monoamine oxidase inhibitor, patients receiving isoniazid may experience redness and itching without a skin rash, as well as palpitations, hypertensive crisis, and headache 2-3 hours after consuming tyramine-rich foods or beverages (liver and fermented products such as cheeses and alcoholic beverages, as well as sardines, tuna, and soy sauce). Patients should be advised to avoid these products while receiving isoniazid (Hauser MJ, 1982).

Morbiliform eruptions

Morbilliform (exanthematous) drug eruptions are among the most common cutaneous ARD, representing 80% in adults and 35% in children. They are thought to be a form of type IV or delayed T-cell hypersensitivity reaction (Nguyen E, 2020). Morbiliform eruptions consist of red macular lesions, usually 2–10 mm in diameter, coalescing into patches and plaques.

In most cases, morbilliform eruptions are self-limited and resolve with only superficial desquamation; treatment can continue without interruption or modification of the regimen. However, occasionally the maculopapular rash can be the initial manifestation of more serious reactions such as Stevens-Johnson syndrome or the drug hypersensitivity syndrome. The increase in the severity of the cutaneous lesions, accompanied by systemic symptoms and mucositis, is an indicator of severe ADR and requires treatment interruption (Collado-Chagoya R, 2018).

Figure 4.2 Morbilliform (exanthematous) drug eruption. See centerfold for this image in color.



Urticaria

All antituberculosis drugs can cause urticaria ("hives"). It consists of transient (less than 24 hours) pruriginous, blanchable, generalized, edematous papules that range from 1 mm to various centimeters. It has been described mainly with first-line drugs, with isoniazid being the most common antituberculosis causative agent, followed by rifampin and pyrazinamide. Still, it can occur with the use of ethionamide, cycloserine, and fluoroquinolones, and there are reports of urticaria with linezolid and bedaquiline. Drug-induced urticaria can result from either an IgE-mediated mechanism or direct mast cell degranulation by a non–IgE-mediated mechanism (Nguyen E, 2020). Antituberculosis treatment should be withheld until the ADR resolves. If the initial reaction is not severe and there is no evidence of anaphylaxis, an attempt should be made to identify the

causative agent by restarting the regimen with one drug at a time and sequentially adding the remaining drugs if there is no adverse reaction. If the initial ADR was severe, reintroducing the drugs should be carried out in a hospital to treat any severe ADR. Once the regimen has been reinstated, it should be administered seven days a week since intermittent treatments are more frequently associated with this type of reaction (El Hamdouni M, 2020).

Photosensitivity

Photosensitizing drugs are exogenous chromophores that absorb photons, commonly from solar radiation, leading to their activation and consequent chemical reactions (Hofmann, 2021). Patients receiving isoniazid, ethambutol, pyrazinamide, clofazimine, PAS, or fluoroquinolones (levofloxacin, gatifloxacin, and moxifloxacin) should be warned that the possibility of photosensitivity exists and should therefore limit their sun exposure and use sunscreen and ultraviolet light-blocking clothing. Photosensitivity can persist for long periods even after the responsible drug is discontinued. Dermal hyperpigmentation can occur in a high proportion (75-100%) of patients during treatment with clofazimine. It is more severe in dark-skinned individuals, and it gets worst by exposure to sunlight; It usually gets better when the drug is stopped, but it can take up to 6 to 12 months for this to happen.

Skin discoloration

Clofazimine treatment is associated with a red-brown or a violaceous-brown cutaneous and conjunctival discoloration. The initial red coloration is thought to be due to the deposit of clofazimine in the macrophages and subcutaneous fat. At the same time, the more prolonged dark pigmentation is related to melanin accumulation in the epidermis and upper dermis (Dereure O, 2001).

Physicians should be aware that skin coloration due to clofazimine can cause depression. Patients should be warned that it can cause discoloration of the conjunctiva, tear fluid, sweat, sputum, urine, feces, nasal secretions, semen, milk, and reddish to dark brown discoloration of the skin. Most patients accept skin hyperpigmentation but feel stigmatized by ichthyosis (Nguyen K, 2019). Although this skin coloration is reversible, the patient must be aware that it may take a few months or years to disappear after finishing treatment with clofazimine.

Lichenoid eruptions

Lichenoid eruptions are initially present as small, itchy macules that gradually progress to firm, flat, purplish, polygonal papules. The mucosa, mainly the oral and genital, are the most frequently affected sites with a string-like pattern known as Wickham's striae.

These lichenoid reactions usually occur after a few months of treatment. When the causative agent is discontinued, the lesions resolve spontaneously, sometimes with persistent hyperpigmentation. If the administration of the responsible drug continues, the lesions may worsen with an increase in hyperpigmentation and painful cracking of the skin.

Lichenoid lesions have been reported with treatment with isoniazid, pyrazinamide, PAS, streptomycin, or ethambutol (Forget EJ, 2006; Halevy S, 1993).

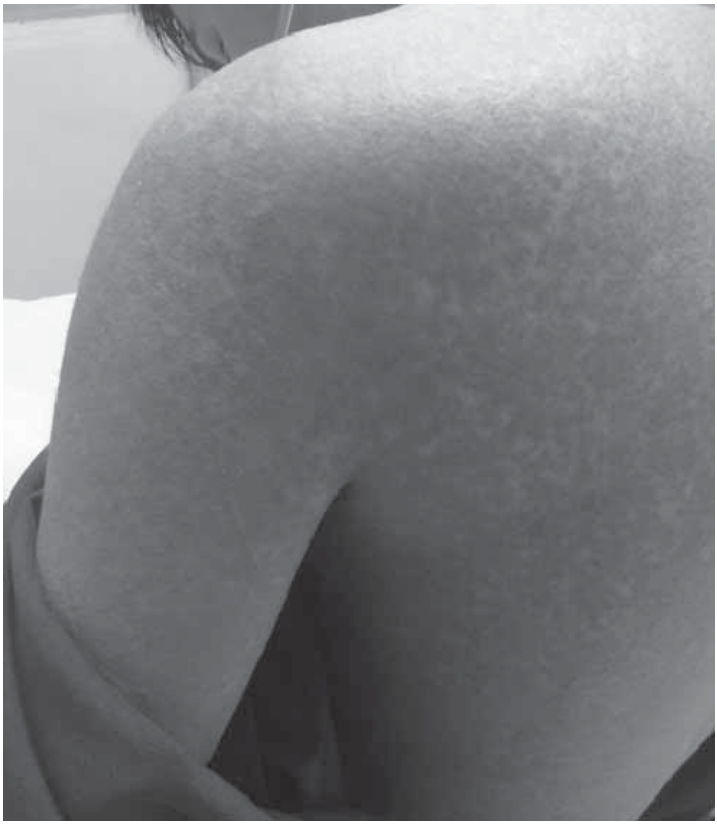
Cutaneous vasculitis

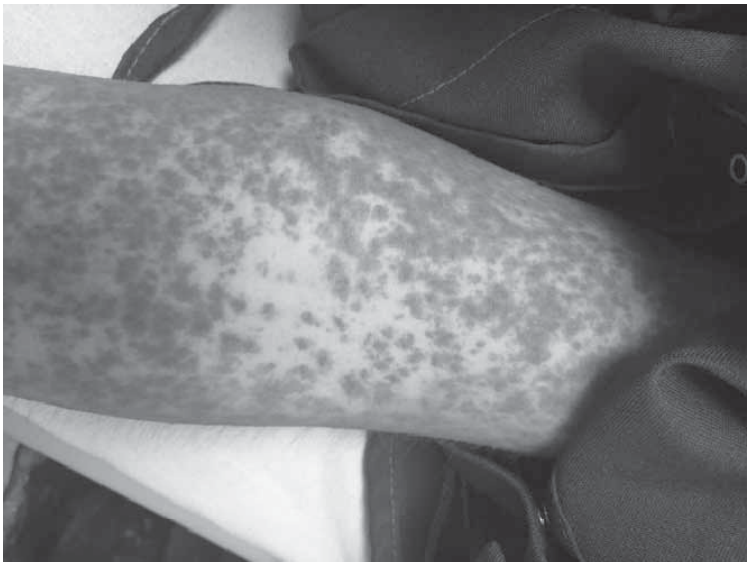
The diagnosis of drug-induced cutaneous vasculitis should be suspected when palpable purpura develops, especially in the pelvic limbs. Depending on the severity of the reaction, purpura can progress with the appearance of hemorrhagic blisters and skin ulcers. As with any immune complex-mediated vasculitis, the involvement of internal organs, especially the kidney, should be investigated. It is not a frequent ADR and has been reported when treatment includes rifampin and pyrazinamide (Lehloenya RJ, 2012).

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrosis (TEN) are characterized by extensive erythematous, erosive, and painful skin lesions, conjunctiva, and mucous membranes secondary to massive apoptosis of epithelial cells. They are considered two extremes of a spectrum of cutaneous severe adverse drug reactions, differing only by the extent of skin shedding (Harr T, 2012).

Figure 4.1 A & B. Early erythematous lesions in a patient with Stevens-Johnson syndrome. See centerfold for these images in color.





This syndrome is infrequently associated with the use of antituberculosis drugs (0.96% of cases). In SJS, TEN is observed in 10% of cases, while in TEN, epidermal involvement is present in more than 30% of patients (Hsu DY, 2016).

Initial symptoms of fever, malaise, cough, burning eyes, and odynophagia are often mistaken for a viral infection of the upper respiratory tract. However, the clinical picture rapidly progresses to epidermal necrolysis and mucositis. Painful erythema and blisters on the palms and soles are early features of SJS/ NET (Minor DR, 2012).

It has been described during treatment with rifampin, pyrazinamide, isoniazid, ethambutol, streptomycin, cycloserine, linezolid, and fluoroquinolones.

This reaction requires urgent hospital treatment with systemic steroids. **ANTITUBERCULOSIS TREATMENT MUST BE INTERRUPTED IMMEDIATELY. IF A DRUG IS IDENTIFIED AS CAUSING THE CONDITION, IT SHOULD NOT BE USED AGAIN.**

The induction of tolerance and desensitization in SJS or TEN have been described as an absolute contraindication by some authors (Thong BY, 2014). Still, there are cases in which there is no alternative treatment. Severe

drug reactions such as SJS and NET are life-threatening; given that alternative therapies for tuberculosis are limited, the role of desensitization and reintroduction becomes essential (Collado-Chagoya R, 2018), and there are multiple reports in the literature of cases of successful desensitization (Minor DR, 2012; Thong BY, 2014; Siripassorn K, 2018).

Drug hypersensitivity syndrome (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS; also known as drug-induced hypersensitivity syndrome or drug-induced delayed multiorgan hypersensitivity syndrome) is a delayed, potentially fatal multiorgan systemic idiosyncratic drug reaction (Sharifzadeh S, 2021).

DRESS has been described with several of the antituberculosis drugs (Martínez-Cabriales SA, 2019). It has been associated with the use of rifampicin, isoniazid, and ethambutol, and especially if they are receiving allopurinol to treat hyperuricemia secondary to the use of pyrazinamide. In addition to the skin reaction, the patients present lymphadenopathy and liver, lung, and kidney involvement. The laboratory usually reveals elevated alanine aminotransferase and alkaline phosphatase, leukocytosis with eosinophilia (>700/mm3), renal involvement, and nitrogen retention. Treatment of DRESS syndrome consists of stopping treatment until the condition resolves (Palmero D, 2013).

Identifying the causal agent

A drug challenge test is defined as the controlled administration of a drug to diagnose a hypersensitivity reaction and is considered the gold standard for establishing causality. The sequence in which the drugs are reintroduced is controversial. Some experts suggest starting the sequence with the drug least likely to cause the ADR; on the contrary, others suggest initiating reintroduction with the most effective drug (rifampicin, isoniazid, fluoroquinolone) to reduce the risk of a suboptimal regimen. The drug challenge should not be performed after a severe reaction, as the ADR can be even more severe (Lehloenya RJ, 2012; Rezakovic S, 2014).

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Figure 4.1. Itching reaction without a rash in the forearm

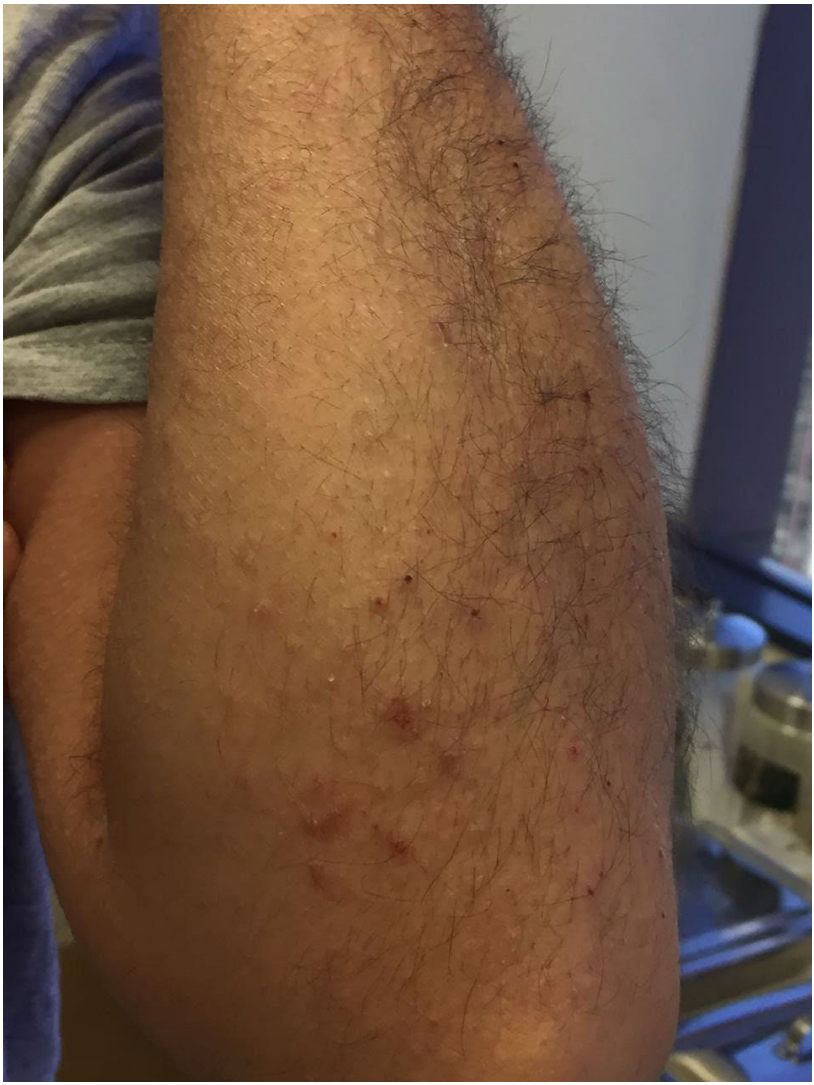


Figure 4.2 Morbilliform (exanthematous) drug eruption.

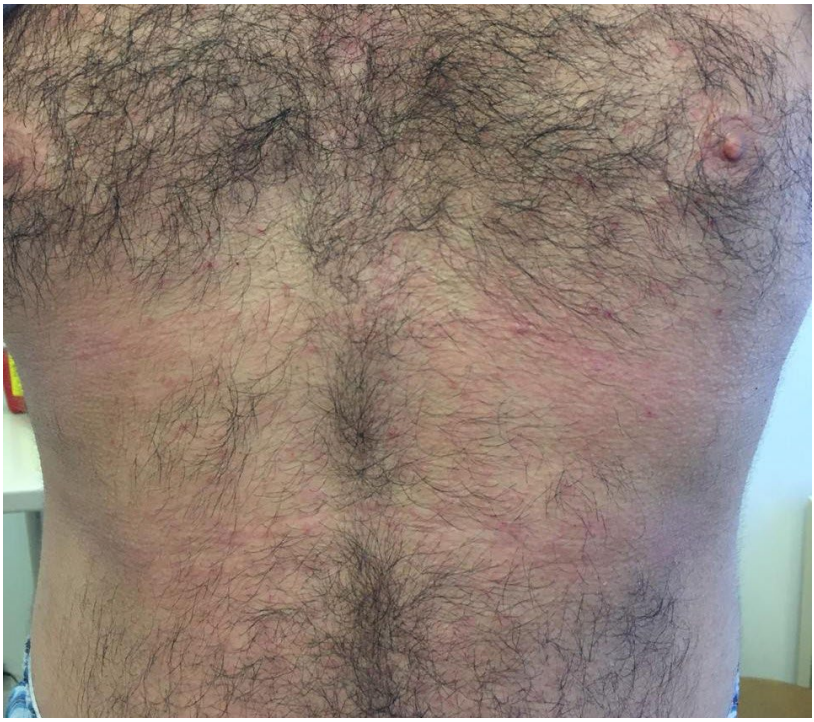
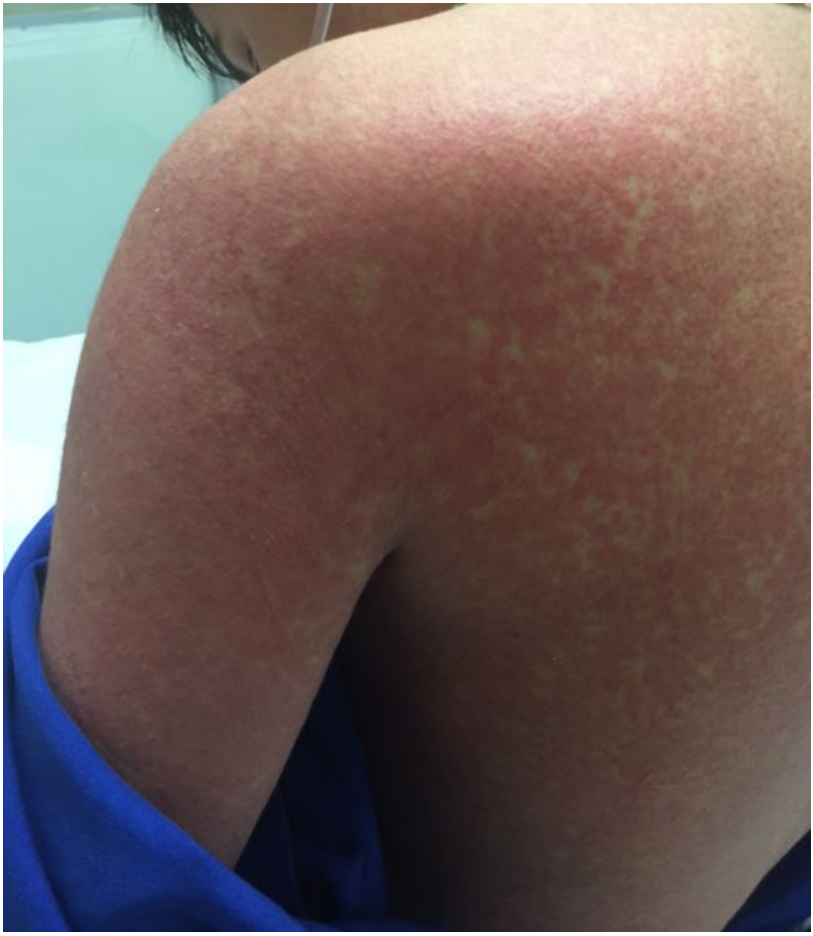


Figure 4.1 A & B. Early erythematous lesions in a patient with Stevens-Johnson syndrome



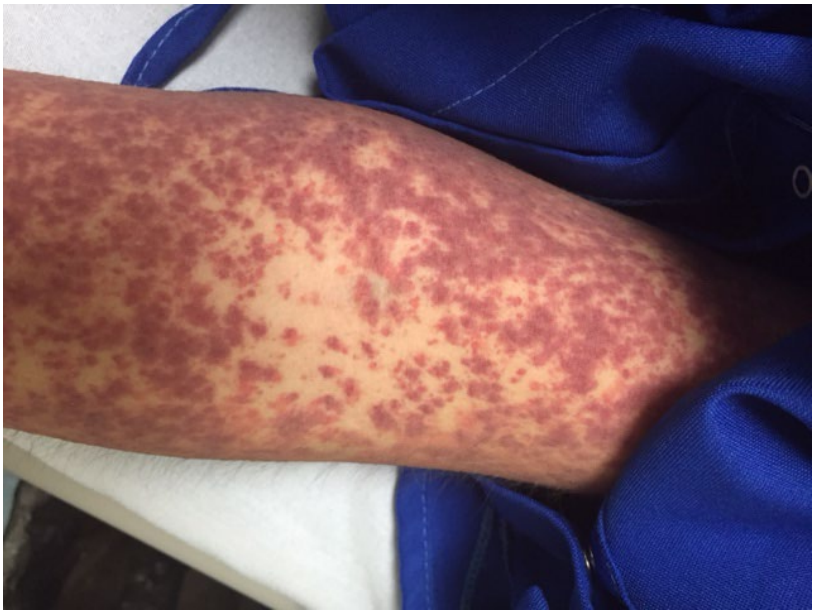
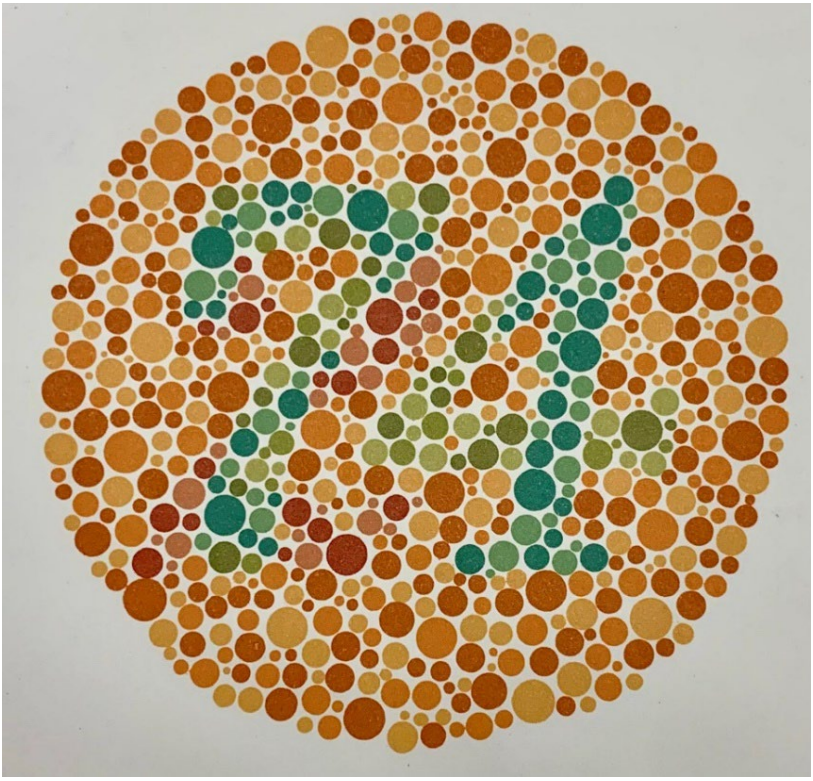


Figure 8.1 Ishihara plate for color perception testing



CHAPTER 5

ANTITUBERCULOSIS DRUGS AND NEUROTOXICITY

Abstract

Antituberculosis drugs, especially isoniazid, ethionamide, and cycloserine, can cause peripheral sensory-predominant neuropathy. Peripheral neuropathy is characterized by symmetric polyneuropathy with tingling, itching, and burning in the extremities. This may be followed by paresthesias, loss of ankle reflexes, and muscle weakness. Neurological examination reveals loss of sensation (to touch, pain, position, and vibration), areflexia, muscle weakness, and atrophy. Linezolid neuropathy usually occurs after a few months of treatment and is dose-dependent. It usually manifests with paresthesias and distal numbness in the extremities ("sock and glove" distribution). Neuropathy prevention is carried out with pyridoxine and is generally very effective. Neuropathy associated to linezolid is frequently NOT reversible when the drug is stopped and does not respond to pyridoxine treatment. Antituberculosis medicines can also cause depression, especially cycloserine and ethionamide. Depression associated with cycloserine can be severe and associated with suicidal ideas. Isoniazid, cycloserine, fluoroquinolones, and carbapenems (especially imipenem) can cause seizures.

Peripheral neuropathy

Peripheral neuropathy is characterized by symmetric polyneuropathy with tingling, itching, and burning in the extremities. This may be followed by paresthesias, loss of ankle reflexes, and muscle weakness; ataxia may even develop due to loss of proprioception (Arsalan R, 2015). The drugs most frequently involved are isoniazid, ethionamide, cycloserine, and linezolid. Neuropathy occurs more frequently in patients with diabetes, alcoholism, HIV infection, hypothyroidism, pregnancy, and malnutrition (Sekaggya-Wiltshire C, 2017; van der Watt JJ, 2015).

Isoniazid is associated with peripheral neuropathy in up to 20% of cases (Prasad R, 2019). Isoniazid binds to pyridoxine and depletes the stores of this vitamin. Pyridoxine is required to synthesize gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system, whose primary role is to reduce neuronal excitability. The decrease in GABA levels caused by pyridoxine deficiency has been implicated in seizures associated with the use of isoniazid (Watkins RC, 1990).

Isoniazid-associated peripheral neuropathy is a sensory-predominant axonal neuropathy that usually begins in the feet and ascends to the hands and arms, accompanied by muscle weakness and pain, and can progress to more severe symptoms of cerebellar ataxia. Neurological examination reveals loss of sensation (to touch, pain, position, and vibration), areflexia, muscle weakness, and atrophy (Arsalan R, 2015).

Linezolid neuropathy usually occurs after a few months of treatment and is dose-dependent (Kishor K, 2015). It usually manifests with paresthesias and distal numbness in the extremities with “sock and glove” distribution (Wilson HJ, 2003).

Ethambutol, ethionamide, cycloserine, and fluoroquinolones can also cause predominant sensory neuropathy (Staff NP, 2014).

Neuropathy prevention is carried out with pyridoxine and is usually very effective. Prophylactic treatment with 100 mg of pyridoxine should be instituted in all patients with risk factors for neuropathy and those under treatment for MDR-TB with ethionamide, cycloserine, or linezolid (Choudhary CR, 2018). Very large doses of vitamin B6 (greater than two g/d) can also cause sensory neuropathy. However, sensory neuropathy has even been reported in patients taking much lower doses (such as 50 mg/d) during long periods, as in patients with drug-resistant TB on prolonged treatment with linezolid (Staff NP, 2014). If neuropathy develops despite B6 prophylaxis, antineuritic therapy with gabapentin, pregabalin, or carbamazepine can be added.

Neuropathy associated with linezolid is frequently NOT reversible when the drug is stopped and does not respond to pyridoxine treatment. The initial dose of 600 mg of linezolid can be reduced to 300 or 450 mg daily, which generally makes it possible to continue with linezolid in the treatment regimen despite neuropathy (Swaminathan A, 2017).

Effects on the central nervous system (CNS)

Like any chronic disease, MDR-TB can cause depression; this can be mild and does not require specific treatment outside of family support and health personnel.

However, antituberculosis drugs can also cause depression, especially cycloserine and ethionamide. Depression associated with cycloserine can be severe and associated with suicidal ideas (Kass JS, 2010; Intini E, 2019). In these cases, cycloserine and ethionamide should be discontinued, and psychological support requested. In cases with severe depression, an antidepressant can be used, avoiding tricyclic antidepressants in patients receiving linezolid due to the risk of serotonin syndrome. In patients with pre-existing depressive disorder, cycloserine should not be included in the regimen if other effective drugs are available. Assess for concomitant abuse of illicit substances and seek counseling support in these cases.

Cycloserine (and to a lesser extent, fluoroquinolones, and isoniazid) can cause psychotic outbreaks (Singanamala B, 2019). If the patient presents a psychotic episode, all the antituberculosis drugs must be stopped and the patient hospitalized in a psychiatric ward for continuous surveillance and psychiatry consultation. Treatment consists of vitamin B6 and antipsychotic medication (e.g., haloperidol).

Antituberculosis drugs, especially isoniazid (Aiwale AS, 2015), cycloserine, fluoroquinolones, and carbapenems (especially imipenem), can cause seizures. In the presence of seizures, the patient should be immediately hospitalized for treatment in an intensive care unit.

Table 5.1: Central nervous system toxicity associated with antituberculosis drugs

Drug	Adverse drug reaction
Frequent (>10%)	
Aminoglycosides	hearing loss
Cycloserine	psychosis
Ethionamide	peripheral neuritis
Isoniazid	headache, psychosis with higher doses
Linezolid	headache, optic and peripheral neuritis
Meropenem	headache

Occasional (1-10%)	
Aminoglycosides	vestibular damage (especially whit streptomycin)
Cycloserine	headache, anxiety, seizures
Ethambutol	optic neuritis
Ethionamide	headache, dizziness
Isoniazid	peripheral neuritis
Linezolid	dizziness, insomnia, serotonin syndrome
Fluoroquinolones	dizziness, headache, insomnia, drowsiness
Infrequent (<1%)	
Aminoglycosides	neuromuscular block
Cycloserine	agitation, bipolar exacerbation, dizziness, insomnia, dyslalia, tremor, suicide
Ethambutol	dizziness, confusion, peripheral neuropathy, headache
Ethionamide	agitation, confusion
Isoniazid	agitation, confusion, ataxia, dizziness, insomnia, psychosis
Linezolid	optic neuropathy, peripheral neuropathy
Meropenem	agitation, confusion, delirium, seizures, insomnia
Fluoroquinolones	agitation, confusion, delirium, fasciculations, myoclonus, psychosis, seizures, Tourette-like syndrome
Rifampin	ataxia, dizziness, drowsiness, headache

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CHAPTER 6

ANTITUBERCULOSIS DRUGS AND OTOTOXICITY

Abstract

Ototoxicity is defined as a transient or definitive disturbance of auditory and vestibular function induced by substances of therapeutic use. Cochlear toxicity refers to the damage that affects the auditory system causing tinnitus and sensorineural hearing damage. The selective destruction of sensory cells of the inner ear is the main cause of ototoxicity; hair cells are vulnerable to various stresses, such as aging, acoustic trauma, genetic disorders, infection, and exposure to ototoxic drugs. Vestibular drug toxicity is secondary to injury to the vestibular system and manifests as dizziness, vertigo, and loss of balance. Although the use of second-line injectables in drug-resistant tuberculosis is being phased out in favor of more potent and less toxic oral drugs, they still will be needed occasionally in patients with extensive drug resistance.

All aminoglycosides used to treat tuberculosis are toxic to the 8th cranial nerve and cause hearing and vestibular damage. Aminoglycosides hearing loss is caused by apoptosis of sensory hair cells in the inner ear; these cells transform sound waves into electric signals. Cochlear toxicity of aminoglycosides is difficult to detect during the clinical interview or physical examination. Hearing damage appears first in the high frequencies (4,000-8,000 Hz), eventually progressing to the lower frequencies. Hearing damage secondary to prolonged use of aminoglycosides is irreversible. Clinicians should quickly rule out other etiologies, and if they are not detected, the injectable should be discontinued immediately.

Introduction

Ototoxicity is defined as a transient or definitive disturbance of auditory and vestibular function induced by substances of therapeutic use (Mercado M, 2007).

The ear contains hearing, balance, and spatial orientation receptors, located in the inner ear at the cochlea and vestibular apparatus. Cochlear toxicity refers to the damage that affects the auditory system causing tinnitus and sensorineural hearing damage. The selective destruction of sensory cells of the inner ear is the main cause of ototoxicity; hair cells are vulnerable to various stresses, such as aging, acoustic trauma, genetic disorders, infection, and exposure to ototoxic drugs. Unfortunately, humans have minimal hair cell regeneration ability, and their death is irreparable, leading to permanent hearing loss. Hearing loss might not be a life-threatening disease, but it will affect the quality of life, especially in children (Wu P, 2021).

Vestibular drug toxicity is secondary to injury to the vestibular system and manifests as dizziness, vertigo, and loss of balance. These manifestations can appear during treatment or after it has ended, and they can be bilateral and symmetrical or asymmetric with a more unilateral involvement (Lanvers-Kaminsky C, 2017).

Aminoglycosides and ototoxicity

Although the use of second-line injectables in drug-resistant tuberculosis is being phased out in favor of more potent and less toxic oral drugs, they still will be needed occasionally in patients with extensive drug resistance.

All aminoglycosides (and capreomycin) used to treat tuberculosis are toxic to the 8th cranial nerve and cause hearing and/or vestibular damage. Amikacin and kanamycin tend to cause hearing loss more often than streptomycin; on the contrary, streptomycin is associated with vestibular impairment more frequently than the other injectables (Sánchez-Sellero I, 2016). Capreomycin can also cause hearing loss, but less frequently than that of the other injectables. Toxicity is related to the total cumulative dose of the drug, so it must be calculated strictly according to body weight (Sagwa EL, 2017).

Aminoglycosides distribute freely in most tissues' vascular and interstitial space due to their poor attachment to proteins and high level of solubility. Aminoglycosides have difficulty traversing cell membranes except for the renal tubular cells and the inner ear; they are slowly removed from the internal ear fluids; after multiple doses, the half-life increases up to 30 days (Mercado M, 2007).

Aminoglycosides hearing loss is caused by apoptosis of sensory hair cells in the inner ear; typically, these cells transform sound waves into electric

signals. Initially, they affect the cells at the base of the cochlea, which affects hearing at high frequencies; if the exposure continues, the hair cells in the upper part of the cochlea are affected, affecting hearing in the frequencies of conversation. Vestibular damage is due to the involvement of the sensory vestibular cells of the crista ampullaris. In both cases, it is due to the generation by the antibiotic of reactive oxygen species, such as hydrogen radicals and peroxynitrites. Another mechanism implicated in ototoxicity is at least partially inhibiting potassium channels induced by the depletion of phosphoinositides (Jiang M, 2017; Guo J, 2019).

The cochlear toxicity of aminoglycosides is difficult to detect clinically. Hearing damage appears first in the high frequencies (4,000-8,000 Hz), eventually progressing to the lower frequencies, and the hearing range for speech is not initially affected. A trial in South Africa demonstrated poor clinical sensitivity (41%) for detecting mild to moderate hearing loss whit audiometry as the gold standard. Therefore, it is necessary to perform periodic audiometry (at least every two months) during the injectable drug's use (Ramma LD, 2012).

HEARING DAMAGE SECONDARY TO PROLONGED USE OF AMINOGLYCOSIDES IS IRREVERSIBLE. In patients with complex resistance patterns and few therapeutic options, a certain degree of hearing loss may have to be tolerated and discussed with the patient; it is necessary in these cases to obtain specific written informed consent.

The presence of tinnitus, dizziness, nystagmus, or instability suggests vestibular damage (Sánchez-Sellero I, 2016). Clinicians should quickly rule out other etiologies, and if they are not detected, the injectable should be **STOPPED IMMEDIATELY**, since if continued, it can progress to irreversible ataxia. Persistent tinnitus is associated with anxiety, depression, and poor quality of life; vestibular disorders frequently cause panic attacks, agoraphobia, and depression (Voogt GR, 1996).

Once culture conversion occurs, the injectable can be spaced three times a week and suspend as soon as possible to reduce its impact on the eighth cranial nerve. The bactericidal activity of aminoglycosides depends on their serum concentration, and intermittent dosing overcomes adaptive bacterial resistance. Because mycobacteria replicate very slowly compared to other bacteria, some experts recommend administering aminoglycosides three times a week instead of daily, with a higher dose per application (25 mg/kg instead of 15 mg/kg). However, a clinical trial designed to determine the ototoxicity of intermittent vs. daily administration, showed that the

frequency of administration is not the determining factor of ototoxicity. Ototoxicity is mainly associated with the patient's age (more severe in older patients) and the total dose of the injectable (Peloquin CA, 2004).

There is little evidence of the advantages of one injectable over another; streptomycin is less ototoxic than other second-line injectables. However, given the frequent resistance to this drug, its use will only be considered in cases with a strain resistant to all other injectables.

Exposure of the human embryo to aminoglycosides must be avoided during the treatment of pregnant women since it is associated with irreversible ototoxicity in the fetus (Snider DE Jr, 1980).

Prevention of aminoglycoside ototoxicity

Aspirin has been shown in clinical studies to reduce hearing damage by 75% compared to placebo. The mechanism of action can be multifaceted. Aspirin is a weak chelator and scavenger of free radicals; likewise, it can influence the expression of genes related to cell survival and apoptosis (Chen Y, 2007). Another antioxidant is N-acetylcysteine, which has shown in studies with a limited number of patients a significant reduction in hearing loss secondary to aminoglycosides (Kranzer K, 2015). On the contrary, vitamin E did not show a significant protective effect.

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CHAPTER 7

ANTITUBERCULOSIS DRUGS AND NEPHROTOXICITY

Abstract

All aminoglycosides (and capreomycin) used to treat tuberculosis are nephrotoxic, requiring frequent and constant evaluation of renal function. Up to 25% of patients treated with aminoglycosides develop nephrotoxicity. Aminoglycosides cause kidney damage through three mechanisms: renal tubular toxicity, decreased glomerular filtration, and reduced renal blood flow. The most important mechanism is renal tubular toxicity. The early signs of damage are increased urinary excretion of calcium, magnesium, proteins, and other organic anions, resulting in hypocalcemia, hypomagnesemia, and proteinuria. As the damage progresses, potassium and sodium excretion and creatinine levels increase. Several patient-specific factors increase the risk of aminoglycoside nephrotoxicity, including advanced age, previous kidney damage, pregnancy, dehydration, renal atrophy, hypothyroidism, liver dysfunction, metabolic acidosis, and sodium depletion. Aminoglycosides should be administered as a single daily dose; nephrotoxicity at this dosage is much lower than when multiple doses are given per day.

Introduction

Since 2019, the World Health Organization has recommended in its treatment guideline for RR-TB/MDR the all-oral regimen with bedaquiline, eliminating the use of injectables whenever possible (WHO, 2018). A recent meta-analysis (Ahmad N, 2018) demonstrated the lack of efficacy of kanamycin and capreomycin, and these two injectables are not included now in the list of essential antituberculosis drugs. The 2019 guideline also includes a recommendation ***against*** the use of amikacin, except for cases when it is not possible to use bedaquiline, linezolid, fluoroquinolones or clofazimine. Later, an analysis of this and another database demonstrated second-line injectables' significant toxicity (Lan Z, 2020; Borisov S, 2019). Up to 25% of patients treated with aminoglycosides develop nephrotoxicity.

Nephrotoxic mechanisms

Aminoglycosides cause kidney damage through three mechanisms:

1. Renal tubular toxicity

2. Decreased glomerular filtration

3. Reduction in renal blood flow

The most important mechanism is renal tubular toxicity. At the level of the proximal tubule of the nephron, aminoglycosides are concentrated by endocytosis in the lysosomes, the Golgi apparatus, and the endoplasmic reticulum. Once a specific concentration is reached, the aminoglycosides empty into the cytoplasm and act on the mitochondria, causing apoptosis and cell necrosis. They also inhibit proximal tubule transport mechanisms, which affect reabsorption and compromises cell viability. The early signs of damage are increased urinary excretion of calcium, magnesium, proteins, and other organic anions, resulting in hypocalcemia, hypomagnesemia, and proteinuria. As the damage progresses, potassium and creatinine levels increase (Jospe-Kaufman M, 2020).

Finally, aminoglycosides cause kidney damage by reducing renal blood flow by increasing the kidney's vascular bed resistance. This increase in vascular resistance occurs after the proximal tubule has been damaged as a compensatory mechanism to prevent fluid and electrolyte loss. Subsequently, the release of endothelin-1 and thromboxane A2 further reduces the glomerular filtration rate (Perazella MA, 2019).

Risk factors for nephrotoxicity

Several patient-specific factors increase the risk of aminoglycoside nephrotoxicity, including advanced age, previous kidney damage, pregnancy, dehydration, renal atrophy, hypothyroidism, liver dysfunction, metabolic acidosis, and sodium depletion. There are also drug-related risk factors, including prolonged duration of treatment and high cumulative doses. Concomitant use of other drugs also increases the risk, including non-steroidal anti-inflammatory drugs, loop diuretics, amphotericin B, cisplatin, cyclosporine, iodinated contrast medium, vancomycin, and cephalosporins (Appel GB, 1990).

Aminoglycosides and nephrotoxicity

All aminoglycosides (and capreomycin) used to treat tuberculosis are nephrotoxic, requiring frequent and constant evaluation of renal function. They usually cause non-oliguric renal failure secondary to renal tubular necrosis. Amikacin is more nephrotoxic than streptomycin; a maximum dose of 750 mg/day of amikacin and streptomycin is recommended in elderly patients (Sales GTM, 2020).

Calculation of injectable drug doses is calculated based on (ideal) body weight. If available, it is advisable to measure injectable serum levels (ideal peak level: 25 mcg/mL one hour after IV administration or two hours after intramuscular administration).

Strategies to reduce risk of nephrotoxicity

Aminoglycosides should be administered as a single daily dose; nephrotoxicity at this dosage is much lower than when multiple doses are given per day.

The daily dosage recommendation is based on four central concepts (Bland CM, 2018):

1. The bactericidal activity of aminoglycosides depends on the drug's concentration and correlates with its peak concentration.
2. The aminoglycosides post-antibiotic effect, defined as the capacity to inhibit bacterial growth after the drug concentration falls below the minimum inhibitory concentration (MIC).
3. The reduction of adaptive resistance. Adaptive resistance constitutes a form of reversible resistance that occurs when the bacteria can decrease the amount of the actively transported drug into the cell. This type of resistance can develop within 1-2 hours of initial exposure to the aminoglycoside and will disappear after several hours when no antibiotic is available. This type of resistance is associated with reduced antibiotic activity when extra doses are administered when there are still detectable aminoglycoside concentrations. For this reason, the single dose can improve antibacterial efficiency by allowing the deactivation of adaptive resistance.
4. Saturation by accumulation of the aminoglycoside at the tubular level. One of the mechanisms of nephrotoxicity of aminoglycosides is directly related to the accumulation of the drug in the cells of the

proximal tubules of the kidney. Administration of multiple doses perpetuates the saturation of the renal tubules with the antibiotic; single doses reduce the accumulation of aminoglycoside and reduce the nephrotoxic potential of the treatment (Wargo KA, 2014).

Due to its nephrotoxic effect, the use of injectables is associated with alterations in serum electrolyte levels that must be monitored monthly (potassium, chloride, sodium, calcium, magnesium). Since some antituberculosis medications can prolong the QT interval of the cardiac cycle (levofloxacin, moxifloxacin, clofazimine, delamanid, pretomanid, and bedaquiline), special care must be taken to maintain electrolyte levels within normal limits (Curry International Tuberculosis Center, 2016).

In patients with renal failure (creatinine clearance <30 ml/minute), adjustment of some antituberculosis drugs is required (Peloquin CA, 2004).

Table 7.1. Dosage recommendations for adult patients with non-critical reduced renal function.

FIRST LINE DRUGS	**Change in frequency**	**Recommended dose in renal failure**
Isoniazid	not needed	
Rifampin	not needed	
Ethambutol	yes	20 mg/kg three times per week
Pyrazinamide	yes	30 mg/kg three times per week
SECOND-LINE DRUGS		
Bedaquiline	not needed	
Linezolid	not needed	
Levofloxacin	yes	750 mg-1 gr. three times per week
Moxifloxacin	not needed	
Clofazimine	not needed	
Cycloserine	yes	500-750 mg three times per week
Amikacin	yes	15 mg/kg three times per week
Ethionamide	not needed	
Meropenem	yes	750 mg every 12 hours for creatinine clearance of 20–40 ml/min; 500 mg every 12 hours for creatinine clearance <20 ml/min.

Imipenem	yes	patients with creatinine clearance less than 15 mL/min should not receive imipenem
Delamanid	not needed	
PAS	yes	CrCl 10-50 mL/min: Decrease dose by 25-50% CrCl <10 mL/min: Decrease dose by 50%

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CHAPTER 8

ANTITUBERCULOSIS DRUGS AND OPHTHALMOLOGICAL TOXICITY

Abstract

Toxic optic neuropathy refers to an adverse reaction to a drug that causes vision loss due to damage to the optic nerve. It involves a pattern of painless bilateral visual acuity loss with gradual onset, central scotomas, dyschromatopsia (alteration in color perception), and atrophy of the optic nerve. Ethambutol is the antituberculosis drug most frequently associated with ophthalmic toxicity. If not detected early, the damage can be irreversible, so monitoring for its early detection should be emphasized, even in the subclinical stage. Upon detection, the drug should be discontinued immediately to prevent the progression of neuropathy and allow recovery of function. Linezolid optical neuritis is characterized by a progressive decrease in visual acuity and sudden onset central scotomas with gradual loss of visual acuity and color discrimination. Vision loss can occur a couple of months after starting therapy but usually occurs between 4 and 12 months of treatment. Other antituberculosis drugs, including ethionamide, isoniazid, rifabutin, and clofazimine, can occasionally cause ophthalmological toxicity

Visual acuity (Snellen test) and color discrimination (Ishihara plates) must be monitored monthly, and request an ophthalmology consultation when detecting any alteration.

Introduction

Toxic optic neuropathy is a well-known side effect of some systemic medications (McKinley SH, 2005). Toxic optic neuropathy refers to an adverse reaction to a drug that causes vision loss due to damage to the optic nerve. It involves a pattern of painless bilateral visual acuity loss with gradual onset, central scotomas, dyschromatopsia (alteration in color perception), and atrophy of the optic nerve (Kerrison JB, 2004).

Ethambutol

Ethambutol is the antituberculosis drug most frequently associated with ophthalmic toxicity. Ethambutol is a component in the initial regimen for the treatment of tuberculosis. It can cause toxic optic neuropathy, with an incidence ranging from <1% at doses of 15 mg/kg to 5-6% at 25 mg/kg (Melamud A, 2003).

If not detected early, the damage can be irreversible, so monitoring for its early detection should be emphasized, even in the subclinical stage. Optic neuritis can occur even after a few days of treatment, although on average has been reported after 3.5 months of treatment. Upon detection, the drug should be discontinued immediately to prevent the progression of neuropathy and allow recovery of function. Fortunately, in most patients, the adverse effect reverses after discontinuation of the drug (Chan RY, 2006).

Doses of 25 mg/kg are more frequently associated with optic damage. It causes a retrobulbar affection of the ophthalmic nerve; the central fibers of the optic nerve are the most affected, producing blurred vision, central scotoma, and the ability to distinguish red and green colors. As the neuritis is retrobulbar, the fundus is normal (Donald PR, 2006).

Since ethambutol is excreted through renal tubular secretion, patients with renal failure are at increased risk of optic neuritis during treatment with this drug. In patients with renal failure, the drug should be spaced, administered three times a week instead of daily, and the dose adjusted to their glomerular filtration rate (Fang JT, 2004).

Linezolid

Linezolid can cause optic neuritis, reversible when the drug is stopped (Spellberg B, 2004). The mechanism for linezolid-induced optic neuropathy is unknown. Linezolid and ethambutol cause mitochondrial damage that is dose and duration-dependent. Linezolid optical neuritis is characterized by a progressive decrease in visual acuity and sudden onset central scotomas with gradual loss of visual acuity and color discrimination. Vision loss usually can occur after a couple of months of therapy but usually occurs between 4 and 12 months of treatment. (Lee E, 2003).

Other drugs

Other drugs (ethionamide, isoniazid, and clofazimine) can occasionally cause ophthalmological toxicity (Rana P, 2018). Up to half of the patients treated with clofazimine may present a reddish coloration of the conjunctiva, which is dose-dependent (more noticeable at higher doses); it usually disappears after a few months after stopping the medicine. In addition, clofazimine can cause pigmentary maculopathy and generalized degeneration of the retina (Kokkada SB, 2005).

Rifabutin, especially in doses >300 mg daily or administered together with drugs that reduce its clearance, such as protease inhibitors, azoles, and macrolides can cause pan-uveitis (Petrowski JT 3rd, 1996). Pan-uveitis is manifested by conjunctival redness, eye pain, and blurred vision. Rifabutin should be withheld until symptoms subside; if it is necessary to reinstall it, it should be administered at a lower dose, ensuring that its serum levels are within the therapeutic range (Tseng AL, 1995). The patient should be evaluated by ophthalmology to rule out other possible etiologies of uveitis such as HIV, bacterial and other viral infections.

Some comorbidities can affect visual acuity (e.g., diabetes) and should receive specific treatment. The recommended conduct is to suspend the causative agent and request urgent ophthalmology consultation.

Management of optical neuritis

Health personnel in charge of cases receiving long-term antituberculosis treatment with the drugs previously mentioned should assess visual acuity (using Snellen tables) and color vision (using Ishihara charts) during the monthly visit and request an ophthalmology consultation when detecting any alteration.

Figure 8.1 Ishihara plate for color perception testing. See centerfold for this image in color.

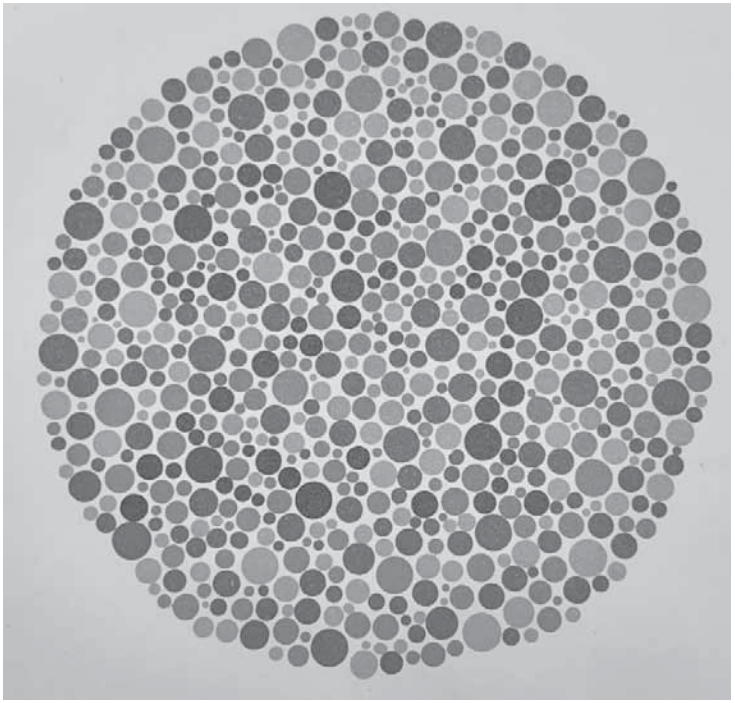
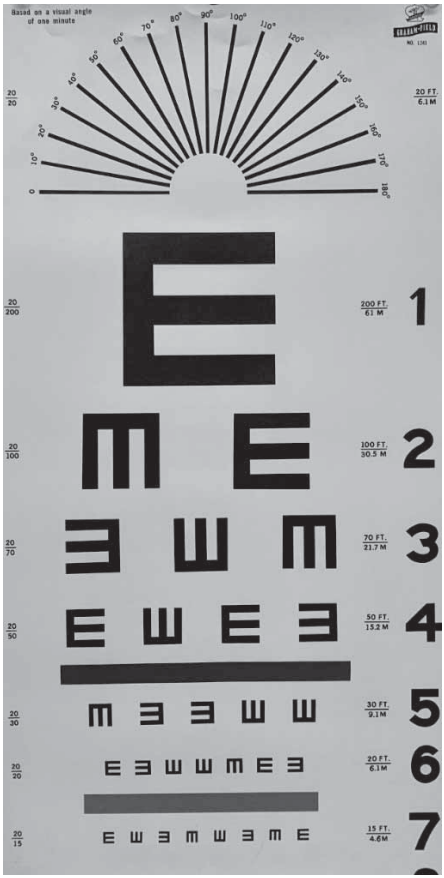


Figure 8.2. Snellen chart for visual acuity testing



Likewise, the patient must be informed about the symptoms associated with loss of visual acuity and dyschromatopsia and the need to report them immediately if they occur.

If discontinuation of linezolid due to toxicity jeopardizes the regimen's effectiveness, the dose can be reduced from 600 mg to 300 mg (Sotgiu G, 2012).

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CHAPTER 9

ANTITUBERCULOSIS DRUGS AND MUSCULAR, ARTICULAR, AND TENDON TOXICITY

Abstract

Myalgias and arthralgias are common during tuberculosis treatment and can be caused by multiple medications, including pyrazinamide, ethambutol, fluoroquinolones, isoniazid, ethionamide, and bedaquiline. Treatment discontinuation is not usually required, and pain is treated with non-steroidal anti-inflammatory drugs; it is, however, convenient to rule out other causes of myalgia and arthralgia. If gouty arthritis develops secondary to hyperuricemia (usually due to pyrazinamide and less frequently to ethambutol), treatment does not need to be discontinued. This adverse reaction is usually treated with non-steroidal anti-inflammatory drugs (e.g., indomethacin, ibuprofen, or colchicine).

The main risk factor for tendinopathy is age, being more frequent after age 60. Other risk factors include high-dose quinolones, pre-existing tendinopathies, diabetes, and concomitant use of glucocorticoids. Quinolones toxicity on tendons is a class effect; it is observed with all family members of these synthetic antimicrobials, regardless of their administration route and the dose used. As levofloxacin is primarily eliminated via the kidneys, patients with renal failure are at increased risk of tendinopathy when receiving this drug. The tendons of the lower extremities are more frequently affected, the Achilles tendon being the most commonly affected site. Tendon rupture (especially of the Achilles tendon) has been described predominantly in elderly patients. Up to 40% of quinolone tendinopathy cases experience tendon rupture. Tendinopathy is typically treated with rest and non-steroidal anti-inflammatory drugs; it generally has a favorable prognosis within the first two months after stopping treatment, although recovery may take several months, and residual damage may persist in 10% of cases.

Introduction

Muscle pain is also known as myalgia. It is a nonspecific symptom related to systemic diseases, secondary to a wide variety of drugs, or associated with primary muscle diseases such as metabolic and inflammatory myopathies. Arthralgia is a pain in one or more joints but without inflammation. Frequently the terms tendinopathy and tendonitis are used interchangeably. While the two conditions have very similar symptoms, they are different entities. Tendinopathy is a degeneration of the collagen protein that forms the tendon; tendonitis, on the other hand, is just inflammation of the tendon.

Myalgias and arthralgias

Myalgias and arthralgias are common during tuberculosis treatment and can be caused by multiple medications, including pyrazinamide, ethambutol, fluoroquinolones, isoniazid, ethionamide, and bedaquiline (Curry International Tuberculosis Center, 2016). The pyrazinamide metabolite (pyrazinoic acid) inhibits the renal tubular secretion of uric acid, increasing its concentration, causing arthralgias.

Although rare, rhabdomyolysis has been reported with isoniazid (Komai T, 2018).

Treatment discontinuation is not usually required for myalgias and arthralgias, and pain is treated with non-steroidal anti-inflammatory drugs. It is convenient to rule out other causes of myalgia and arthralgia (including hypothyroidism secondary to treatment with ethionamide).

If gouty arthritis develops secondary to hyperuricemia (usually due to pyrazinamide and less frequently to ethambutol), treatment does not need to be discontinued. This adverse reaction is generally treated with non-steroidal anti-inflammatory drugs, e.g., indomethacin, ibuprofen, or colchicine (Curry International Tuberculosis Center, 2016).

Tendinopathy

The main risk factor for tendinopathy is age, being more frequent after age 60 (more than eight times higher risk of Achilles tendinopathy after age 60 compared to 1.6 times higher risk for young subjects when treated with quinolones). Other risk factors include high dose quinolones, pre-existing tendinopathies, diabetes, and concomitant use of glucocorticoids; the risk of

Achilles tendinopathy is 9.1 times higher than in the general population if quinolones and steroids are combined vs. 3.2 times when only quinolones are used (Bolon B, 2017; Baombe JP, 2016; Stephenson AL, 2013).

In 2016, the US Food and Drug Administration (FDA) published a black box warning. It introduced significant restrictions for oral and injectable fluoroquinolones on their use, particularly in children and in people aged 65 years (Michalak K, 2017).

Tendons are composed mainly of collagen fibers that constitute 70-80% of the dry weight of the tendon. The extracellular matrix found between collagen fibers is composed of glycosaminoglycans, glycoproteins, and proteoglycans. In tendinitis (or tendonitis), there is no degeneration of the collagen protein within the tendon. In tendinopathies, histological findings show fiber disorganization, tenocyte apoptosis, neovascularization, and increased glycosaminoglycans. It is considered that this adverse drug reaction (ADR) is due to the production and accumulation of reactive oxygen species that favor apoptosis and also to a direct cytotoxic effect on the components of the extracellular matrix, which would explain the presence of this ADR after only a few days of treatment (Kirchgesnera T, 2014).

The toxicity of quinolones on tendons is a class effect; it is observed with all family members of these synthetic antimicrobials, regardless of their route of administration and regardless of the dose used (Bidell MR, 2016). Quinolones tendinopathy is a rare ADR with an estimated incidence of 0.5-2% in patients receiving these drugs. The tendons of the lower extremities are more affected. The Achilles tendon is the most affected site (90% of cases) (Budny AM, 2015) and is affected bilaterally in more than 40% of cases. Tendon rupture (especially the Achilles tendon) has been described predominantly in elderly patients. Other less frequently affected sites are the rotator cuff tendon (Eyer-Silva Wde A, 2012), the extensor carpi radialis, the flexor tendons of the fingers, and the quadriceps tendon; Tendinopathy of the eyeball muscles causing diplopia has also been described. Up to 40% of quinolone tendinopathy cases are complicated by tendon rupture. Signs of tendinopathy can occur as early as 2 or 3 days of therapy (Godoy-Santos AL, 2017), and there are reports of rupture up to six months after discontinuing quinolones (Rosa B, 2016). Achilles tendinopathy after fluoroquinolone treatment in individuals as young as 20 years old, with no predisposing conditions, has also been reported (Durey A, 2010).

Tendinopathy is treated with rest and non-steroidal anti-inflammatory drugs. This adverse effect is more frequent with levofloxacin than with moxifloxacin (Bidell MR, 2016; Eyer-Silva W de A, 2012); levofloxacin reaches higher systemic concentrations than moxifloxacin and produces more toxic metabolites. As levofloxacin is eliminated via the kidneys, patients with renal failure are at increased risk of tendinopathy when receiving this drug. In patients with renal failure, it is recommended to space the levofloxacin dose to every third day; administration of moxifloxacin does not require dose modification. Since fluoroquinolones are a vital element of the treatment regimen, it is unlikely that they can be discontinued (Kim GK, 2010). Tendinopathy generally has a favorable prognosis within the first two months after stopping treatment, although recovery may take several months, and residual damage may persist in 10% of cases.

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CHAPTER 10

ANTITUBERCULOSIS DRUGS AND THYROID TOXICITY

Abstract

Para-aminosalicylic acid (PAS) and thioamides (ethionamide and prothionamide) are more frequently associated with hypothyroidism. The thioamides are derivatives of nicotinic acid; both drugs inhibit thyroid hormone synthesis, causing hypothyroidism. This effect is related to their chemical structure, which is very similar to propylthiouracil and methimazole. Para-amino salicylic acid (PAS) is another second-line drug that can induce hypothyroidism. The mechanism by which it causes hypothyroidism is also considered to be the inhibition of iodine organification. Rifampin does not usually affect thyroid function in subjects without thyroid disease, but hypothyroidism has been reported in patients with thyroid disease (e.g., Hashimoto´s thyroiditis) while receiving rifampin. Treatment of MDR/XDR-TB in HIV co-infected patients is challenging; patients receiving antiretroviral therapy with stavudine, efavirenz, amprenavir, lopinavir, and ritonavir may develop hypothyroidism. If ethionamide/prothionamide or PAS are used simultaneously with the antiretroviral drugs, the risk of hypothyroidism is theoretically greater. Thyroid function tests are required before starting treatment with thioamides o PAS and, after that, every two months. When the TSH value increases to 1.5 times the upper limit of normal (4.0 mlU / L), that is, ≥10 mlU/L, thyroid hormone should be added to the regimen.

Introduction

Since the publication of the 2019 consolidated guideline of the World Health Organization (WHO) for the treatment of drug-resistant tuberculosis (WHO, 2019), the use of para-aminosalicylic acid (PAS) and thioamides (ethionamide and prothionamide), the two drugs more frequently associated with hypothyroidism (Matveyeva SL; Tola HH, 2019), are now seldom used due to their poor effectiveness and significant toxicity.

Ethionamide and prothionamide

Ethionamide and prothionamide are thionamide derivatives of nicotinic acid that have been used for decades in the treatment of drug-resistant tuberculosis. Both drugs inhibit thyroid hormone synthesis causing hypothyroidism, so thyroid function tests must be monitored periodically (Dutta BS, 2012). This effect is related to their chemical structure, which is very similar to propylthiouracil and methimazole, drugs that inhibit thyroid hormone synthesis by impeding the organification of iodine (McDonnell ME, 2005).

Para-amino salicylic acid

Para-amino salicylic acid (PAS) is another second-line drug that can induce hypothyroidism. The mechanism by which it causes hypothyroidism is also considered to be the inhibition of iodine organification (Satti H, 2012).

When both PAS and ethionamide/prothionamide are used simultaneously in the regimen, the risk of hypothyroidism increases considerably; rates have been reported ranging between 3.5% and 28.7% (Tola HH, 2019).

Rifampin

Rifampicin (RIF) increases the metabolic clearance of thyroxine (T4) and triiodothyronine (T3), by inducing hepatic metabolism and increasing biliary excretion of iodothyronine conjugates. Although there is a reported case of hypothyroidism due to rifampin in a patient without thyroid disease, rifampin does not usually affect thyroid function in subjects without thyroid disease. Three cases of hypothyroidism have been reported in euthyroid patients with Hashimoto's thyroiditis who were treated with rifampin. The adverse reaction reversed by suspending rifampicin (Takasu N, 2006; Kim DL, 2007).

HIV and hypothyroidism

Treatment of MDR/XDR-TB in HIV co-infected patients is challenging. Patients with HIV/AIDS and low CD4 counts are at increased risk of hypothyroidism, perhaps because 1) HIV infection causes thyroid dysfunction, 2) the presence of opportunistic infections that affect thyroid function, or 3) thyroid infiltration due to Kaposi's sarcoma. Additionally, patients receiving antiretroviral therapy with stavudine, efavirenz,

amprenavir, lopinavir, and ritonavir may develop hypothyroidism. If ethionamide/prothionamide and PAS are used simultaneously with the antiretroviral drugs, the risk of hypothyroidism is theoretically greater (Andries A, 2013).

Management of hypothyroidism during treatment of drug-resistant tuberculosis

Thyroid function tests should be requested before starting treatment with thioamides o PAS and every two months while the patient receives any of these medications. If the diagnosis of hypothyroidism is based on clinical data only, this adverse drug reaction will be detected late. Hypothyroidism has nonspecific and vague symptoms and may easily go undetected by the clinician, especially given the wide range of common side effects in patients on second-line antituberculosis drugs.

When the TSH value increases to 1.5 times the upper limit of normal (4.0 mlU / L), that is, 10 mlU/L, thyroid hormone should be added to the regimen. The usual dose ranges from 75 to 150 mcg and should be adjusted according to the results of a new thyroid profile after two months of treatment. The goal is to normalize TSH levels (Laniado-Laborín R, 2015).

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CHAPTER 11

ANTITUBERCULOSIS DRUGS AND HEMATOLOGICAL ADVERSE EFFECTS

Abstract

Drug toxicity can affect any cell line due to virtually any antituberculosis drug; the most involved drugs in hematological toxicity are isoniazid, rifampin, and linezolid.

Hematological reactions to isoniazid include anemia, agranulocytosis, neutropenia, hemolytic anemia, disseminated intravascular coagulation, and hemophagocytic syndrome. Thrombocytopenia is the most common hematological adverse effect associated with the use of rifampin. Thrombocytopenia associated with rifampin is an immunologically mediated adverse drug reaction associated with antibodies vs. rifampicin. Prolonged courses of linezolid (>28 days) and high drug doses are associated with anemia, leukopenia, thrombocytopenia, and even pancytopenia. Linezolid inhibits both bacterial and mitochondrial protein synthesis, and this inhibition is responsible for the adverse events associated with its use.

Introduction

Hematological abnormalities during antituberculosis treatment may be due to comorbidity (e.g., renal failure, malnutrition), disseminated tuberculosis disease involving the bone marrow, or the effect of antituberculosis drugs (Forget EJ, 2006; Nicolini A, 2016; Colucci G, 2012). Drug toxicity can affect any cell line due to virtually any antituberculosis drug; the most involved drugs in hematological toxicity are isoniazid, rifampin, and linezolid.

Isoniazid

Hematological reactions to isoniazid include anemia, which responds to pyridoxine treatment, agranulocytosis, neutropenia, hemolytic anemia,

disseminated intravascular coagulation, and hemophagocytic syndrome (Menzies D, 2008). The hemophagocytic syndrome is a rare, life-threatening immune disease characterized by a cytokine storm and severe inflammation that causes fever, hepatosplenomegaly, cytopenia, hypertriglyceridemia, hyperferritinemia, and hemophagocytosis in the bone marrow, liver, spleen, or lymph nodes.

Rifampin

Thrombocytopenia can occur as an idiosyncratic reaction to certain medications that stimulate the production and binding of platelet antibodies (Arnold DM, 2013).

Thrombocytopenia is the most common hematological adverse effect associated with the use of rifampin; figures as low as 35,000 platelets are reported. Thrombocytopenia is observed more frequently with intermittent treatment (1-6%) than with the daily regimen (0.08%); it usually reverses when the drug is stopped. Thrombocytopenia is an immunologically mediated adverse drug reaction associated with antibodies vs. rifampicin. Thrombocytopenia is reversible if the drug is discontinued (Burnette PK, 1989).

Rifampicin can also cause antibody-mediated hemolytic anemia; this adverse drug reaction can be fatal if not detected. Rifampin also interferes with vitamin K absorption and metabolism, causing hypoprothrombinemia (Sveroni D, 2018).

Linezolid

Prolonged courses of linezolid (>28 days) and high drug doses are associated with anemia, leukopenia, thrombocytopenia, and even pancytopenia (Letswee G, 2019; Gerson SL, 2002). Thrombocytopenia is seen more frequently when treatment is continued for more than two weeks; platelet count usually normalizes when linezolid is stopped. Reversible myelosuppression and immune-mediated toxicity are suggested as a mechanism.

Pure red cell aplasia can lead to anemia, decreased reticulocytes, and decreased erythroid lineage cells in various stages, especially erythroid precursor cells. The mechanism behind the hematologic toxicity of linezolid is believed to be the suppression of mitochondrial respiration by inhibiting mitochondrial protein synthesis (Luo Z, 2018). Linezolid inhibits both

bacterial and mitochondrial protein synthesis, and this inhibition is responsible for the adverse events associated with its use (Garrabou G, 2017).

The reticulocyte count can be used as a predictive marker of anemia since it reflects the erythroid function of the bone marrow (Luo Z, 2018).

Pyridoxine administration is used to prevent the hematologic toxicity of linezolid; however, there are conflicting data on its efficacy (Moraza L, 2015).

In cases with clinically significant anemia (especially with linezolid), erythrocyte levels can be increased with erythropoietin if it is considered that stopping the drug would jeopardize the regimen's effectiveness.

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CHAPTER 12

ANTITUBERCULOSIS DRUGS AND CARDIOVASCULAR ADVERSE EFFECTS

Abstract

Several of the drugs used to treat drug-resistant tuberculosis, including fluoroquinolones, bedaquiline, clofazimine, delamanid, and pretomanid, can cause adverse cardiovascular reactions. These antituberculosis drugs can prolong the QT interval of the cardiac electrical cycle favoring the development of a polymorphic ventricular tachycardia called "*Torsades de pointes*," which can manifest through syncope, dizziness, or palpitations. It usually resolves spontaneously but, in some cases, it produces ventricular fibrillation and sudden cardiac death.

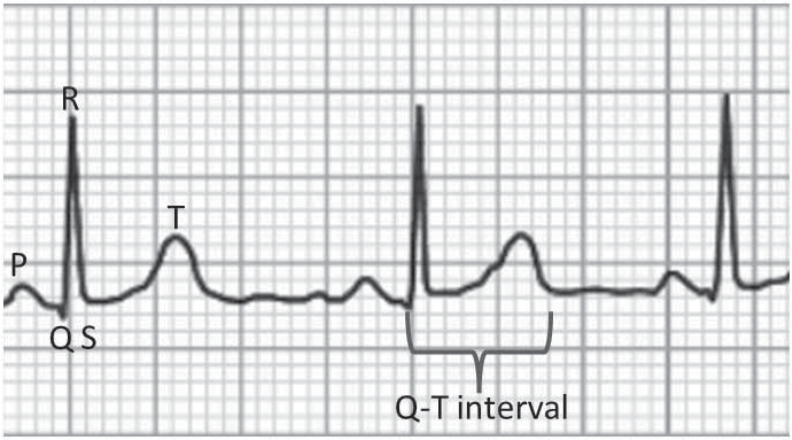
Prolongation of the QT interval can be clinically significant in the presence of other risk factors for *Torsades de pointes*, such as female sex, familial long QT syndrome, other heart diseases, kidney and liver dysfunction, and electrolyte alterations. When multiple drugs that prolong the QT interval are combined in a regimen, frequent electrocardiographic monitoring must be carried out during treatment. Treatment of *Torsades de pointes* or marked QT prolongation involves removal or correction of precipitant factors, including discontinuation of causative drugs and institution of cardiac monitoring. Electrolyte abnormalities and hypoxia should be corrected, maintaining potassium concentrations in the high normal range. The emergency treatment of *Torsades de pointes* is by intravenous administration of magnesium sulfate and ending prolonged episodes by electrical cardioversion.

Introduction

Several of the drugs used to treat drug-resistant tuberculosis, including fluoroquinolones, bedaquiline, clofazimine, delamanid, and pretomanid, can cause adverse cardiovascular reactions (Guglielmetti L, 2018).

The QT interval is measured from the beginning of the Q wave to the end of the T wave. The electrocardiogram represents the total duration of both the depolarization and repolarization phases of the electric heart cycle.

Figure 12.1. QT interval in the electrocardiogram



The QT interval is dependent on the heart rate (the higher the frequency, the shorter the interval) and has to be adjusted to this frequency for its interpretation. This value is known as the corrected QT (QTc). Its standard corrected value is accepted to be less than 440 ms. The standard upper limit of QTc in men is 450 ms, while in women, an expected value of QTc is 470 ms. There are several online free QTc calculators (e.g., https://play.google.com/store/apps/details?id=com.mdaware.mdcalc).

Some antituberculosis drugs can prolong the QT interval of the cardiac electrical cycle favoring the development of a polymorphic ventricular tachycardia called "*Torsades de pointes*," which can manifest through syncope, dizziness, or palpitations. It usually resolves spontaneously but, in some cases, it produces ventricular fibrillation and sudden cardiac death.

Fluoroquinolones

In a dose-dependent effect, fluoroquinolones cause a prolongation of the QT interval by inhibition of calcium channels. Although this effect can vary between the different agents, the prolongation is usually minimal (3-6 ms) (Briasoulis A, 2011; Chiba K, 2000; Khan F, 2018); moxifloxacin causes a more significant QT prolongation than levofloxacin and gatifloxacin, even

compared to high doses of levofloxacin of up to 1 to 1.5 grams daily. However, this effect of fluoroquinolones can be clinically significant in the presence of other risk factors for *Torsades de pointes*, such as female sex, familial long QT syndrome, other heart diseases, kidney and liver dysfunction, electrolyte alterations (Anderson ME, 2001), and interaction with numerous other drugs that prolong QT. In most of the reports of *Torsades de pointes* in patients receiving treatment with fluoroquinolones, the patient was receiving other drugs that prolong the QT interval or had hypokalemia or hypothyroidism, the latter one an entity secondary to therapy with ethionamide/prothionamide or PAS. (Stancampiano FF, 2015). Cocaine and methamphetamines prolong the QT interval, so the medical history requires that the use of these substances be investigated (Haning W, 2007; Supervía A, 2012).

Bedaquiline

Bedaquiline (BDQ), a recently introduced drug for MDR/XDR-TB treatment, can prolong the QT interval, thus constituting a risk for sudden death due to ventricular tachycardia. For this reason, the concomitant use of BDQ with non-antituberculosis drugs that prolong the QT interval (e.g., macrolides, azole antifungals, omeprazole, etc.) should be avoided. A QTc ≥500 ms is considered high risk for *Torsades de point* and is reason enough not to start or stop BDQ and all other drugs in the regimen that prolong QT. If concomitant use of other drugs that prolong the QT interval is indispensable, frequent electrocardiographic monitoring must be carried out during treatment with BDQ. Given the long half-life of BDQ, the risk of cardiac toxicity persists even after its use has stopped, especially if other drugs that prolong the QT interval are being administered (Pontali E, 2017). In general, the large-scale implementation of BDQ has shown that the risk of QTc prolongation is low compared to the benefit of this drug (Ramachandran G, 2015).

Delamanid

Delamanid (DLM), another new drug for treating MDR/XDR-TB, can cause a prolongation of the QT interval through its primary metabolite, DM-6705. Clinical studies have shown an increase in QTc of 14.6 ms with the 200 mg daily dose and 18.9 ms with the 400 mg daily dose, with QTc reaching its maximum value at the end of the second month of treatment without further increase after that. Most patients who developed increased QTc had cardiovascular risk factors (including AV and bundle branch

blocks) or hypokalemia. No cases of *Torsades de pointes* or arrhythmias have been reported to date with the use of delamanid. As in the case of BDQ, the concomitant use of other drugs that prolong QT (for example, fluoroquinolones or clofazimine) simultaneously with DLM will have an additive effect on the QT interval, so its use should be carefully monitored (Gupta R, 2015).

Clofazimine

Clofazimine, a drug used in treating resistant TB, can also prolong the QT interval, but this effect is rarely clinically significant (Zweijpfenning SMH, 2018). A clinical trial in a region with a high burden of HIV coinfection (60% of the patients had HIV coinfection) compared treatment of MDR-TB with a WHO optimized background regimen with and without clofazimine; clofazimine was significantly associated with an 18.4 ms increase in QTc; however, patients on clofazimine were not more likely to experience a QTc increase of >50 ms (p= 0.630) (Ndjeka N, 2015).

Pretomanid

Pretomanid, a new drug used to treat drug-resistant TB, is chemically related to delamanid (Conradie F, 2020), also prolongs the QT interval. QTc prolongation modeling was applied to pretomanid; data came from eight phase 2 and phase 3 studies. Pretomanid 200 mg once a day alone resulted in an increase of 9.1 ms. For the BPaL regimen (bedaquiline, pretomanid and linezolid), due to the additional impact of bedaquiline, the corresponding value was 13.6 ms (Li H, 2019).

Treatment of QT prolongation

Treatment of *Torsades de pointes* or marked QT prolongation includes removal or correction of precipitant factors, including discontinuation of causative drugs and institution of cardiac monitoring. Electrolyte abnormalities and hypoxia should be corrected, maintaining magnesium and potassium concentrations in the high normal range. The immediate treatment of *Torsades de pointes* is by intravenous administration of magnesium sulfate and ending prolonged episodes by electrical cardioversion. In refractory cases, isoproterenol (isoprenaline) or transvenous pacemakers can suppress the arrhythmia by increasing the underlying heart rate. Other interventions are rarely needed, but there are case reports of successful use of lidocaine

or phenytoin. Antiarrhythmic drugs that prolong ventricular repolarization (e.g., amiodarone and sotalol) should be avoided (Thomas SH, 2016).

Table 12.1: Commonly used drugs that prolong the QT interval*

Antibiotics azithromycin clarithromycin moxifloxacin levofloxacin ofloxacin gatifloxacin ciprofloxacin Trimethoprim-SMX metronidazole pretomanid clofazimine bedaquiline	**Antiretrovirals** nelfinavir efavirenz ritonavir atazanavir saquinavir	**Antidepressants** fluoxetine paroxetine sertraline citalopram escitalopram amitriptyline nortriptyline imipramine
Antifungals fluconazole ketoconazole itraconazole voriconazole	**Antiemetics** ondansetron granisetron dolasetron	**Antihistaminics** diphenhydramine astemizole
Antipsychotics haloperidol thioridazine clozapine risperidone quetiapine chlorpromazine	**Antiarrhythmic** sotalol amiodarone quinidine procainamide disopyramide flecainide	**Diuretic** hydrochlorothiazide furosemide
Decongestant's pseudoephedrine phenylpropanolamine	**Bronchodilators** Albuterol Salmeterol Ephedrine	**Nonsteroidal antiinflammatory** diclofenac celecoxib ketorolac

*Modified from Liu J, 2019

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CHAPTER 13

ANTITUBERCULOSIS DRUGS AND MISCELLANEOUS ADVERSE REACTIONS

Abstract

All antituberculosis drugs are capable of causing a wide variety of, although infrequent, adverse reactions. This chapter describes some of these rare reactions associated with first and second-line drugs.

Isoniazid can cause hypersensitivity reactions, with chills or fever as high as 40°C that can be sustained or intermittent, occasionally accompanied by a skin rash; adverse drug reactions can even present in the form of anaphylaxis. Rifampin produces an influenza-like syndrome with fever, chills, dizziness, bone pain, and occasionally dyspnea. It is more frequent with intermittent dosing, especially when the intervals are longer. Streptomycin can cause multiple adverse skin reactions, from hives to Stevens-Johnson Syndrome and DRESS. Aminoglycosides (including streptomycin) can cause neuromuscular blockade leading to respiratory failure. Occasionally, dizziness, headache, insomnia, and tremor can occur with the use of fluoroquinolones. Fluoroquinolones (especially gatifloxacin) can cause dysglycemia manifested by hypo or hyperglycemia in patients treated with insulin or oral hypoglycemic agents. Ethionamide/prothionamide can occasionally cause peripheral neuritis, optic neuritis, diplopia, irritability, anxiety, depression, hallucinations, seizures, and psychosis. Serotonin syndrome can occur when linezolid is co-administered with a non-selective MAO inhibitor or selective serotonin reuptake inhibitors. It is characterized by a clinical triad of behavioral and cognitive changes and neuromuscular excitability. In addition to its effect on the QT interval, the most frequently reported adverse effects with bedaquiline are nausea, myalgias, arthralgias, headache, vomiting, dizziness, diarrhea, and liver damage with elevated liver enzymes.

In addition to its effect on the QT interval, delamanid adverse drug reactions include anemia, nausea, vomiting, abdominal pain, palpitations, headache,

paresthesia, tremor, insomnia, tinnitus, asthenia, fatigue, hyperhidrosis, hyperuricemia, and hypokalemia

Introduction

All antituberculosis drugs are capable of causing a wide variety of, although infrequent, adverse reactions. Here are some of these less frequent reactions associated with first and second-line drugs.

First-line drugs

Isoniazid

Isoniazid can cause hypersensitivity reactions, with chills or fever as high as 40°C that can be sustained or intermittent, occasionally accompanied by a skin rash; adverse drug reactions can even present in the form of anaphylaxis. These reactions occur after 2-3 weeks of treatment and disappear when the drug is stopped, but they usually reappear if the drug is reintroduced. Desensitization can be successful (see Chapter 15) (Bakkum RS, 2002).

Many other rare adverse effects have been reported with isoniazid. A lupus erythematosus-like syndrome (<1%) with pleurisy and lupus-like nephritis has been reported that resolves on discontinuation of the drug—up to 20% of patients treated with isoniazid present high titers of antinuclear antibodies (Vaghela JH, 2019).

Isoniazid is a histaminase inhibitor, and adverse drug reactions have been reported when foods rich in histamine are eaten, such as Swiss or cheddar cheese, red wine, and tuna. This syndrome includes head and neck flushing, throbbing headache, tachycardia, and tremor. The only treatment is to avoid foods rich in histamine (Miki M, 2005).

Rifampicin

Rifampin produces an influenza-like syndrome with fever, chills, dizziness, bone pain, and occasionally dyspnea. The syndrome can progress to hypotension and shock. Symptoms appear 1-2 hours after taking the drug and can persist for up to 8 hours. It typically occurs after a couple of months of treatment and is dose-dependent (in 10% of patients who receive 600 mg daily vs. 22% of those who receive 900 mg daily). It is more frequent with

intermittent dosing, especially when the intervals are longer (4-16% with biweekly administration vs. 10-57% with weekly administration). It is considered an autoimmune-mediated reaction by antibodies. Only a few patients require discontinuation of treatment. The current recommendation is to switch to a daily regimen of rifampicin administration (Parking AA, 1989).

Other infrequent effects with rifampicin administration include myopathy, oligomenorrhea, amenorrhea, interstitial pneumonitis, acute respiratory distress, exudative conjunctivitis, fatigue, myalgia, and headache. Rifampin can induce hyperglycemia after a glucose load (Takasu N, 1982).

Pyrazinamide

Nausea (1-5%), fever (<1%), sideroblastic anemia, lupus erythematosus-like syndrome, seizures, photodermatitis, myoglobinuric renal failure, aseptic meningitis, and leukopenia have been described with pyrazinamide (Colucci G, 2012).

Ethambutol

Cholestasis with jaundice, aplastic anemia, and neutropenia, thrombocytopenia, pulmonary infiltrates with eosinophilia, exacerbations of lupus, hyperuricemia with gouty arthritis, tubulointerstitial nephritis with anuric renal failure have been reported infrequently (Lee N, 2020).

Streptomycin

Streptomycin can cause multiple adverse skin reactions, from hives to Stevens-Johnson Syndrome and DRESS.

Hematologic abnormalities such as neutropenia, hemolytic anemia, eosinophilia, thrombocytopenia, granulocytopenia, pancytopenia, and aplastic anemia have been described. Perioral paresthesia and dizziness have been reported after its administration (Streptomycin, 2008).

Second-line drugs

Amikacin

Aminoglycosides (including streptomycin) can cause neuromuscular blockade leading to respiratory failure. Neuromuscular blockade can occur when the drug is administered intravenously very rapidly in patients who simultaneously receive neuromuscular blockers or those who have received massive blood transfusions containing citrate as an anticoagulant (Kass JS, 2008).

Fluoroquinolones

Occasionally, dizziness, headache, insomnia, and tremor can occur with the use of fluoroquinolones. Hallucinations and seizures are extremely rare.

These drugs can cause peripheral polyneuropathy; the neurotoxic effect is believed to be due to the inhibition of γ-aminobutyric acid receptors (Etminan M, 2014).

Fluoroquinolones can occasionally cause a skin rash and itching. Exposure to sunlight can exacerbate phototoxicity.

Interstitial nephritis has been described with these drugs, characterized by eosinophils and crystals in the urine.

Fluoroquinolones (especially gatifloxacin) can cause dysglycemia manifested by hypo or hyperglycemia in patients treated with insulin or oral hypoglycemic agents (Stahlmann R, 2013).

Cycloserine (and terizidone)

In addition to its adverse effects on the central nervous system, cycloserine can occasionally cause skin adverse drug reactions from a rash to Stevens-Johnson syndrome (Protivinsky R. 1971).

Ethionamide / protionamide

Ethionamide/prothionamide occasionally (1-2%) can cause peripheral neuritis, optic neuritis, diplopia, irritability, anxiety, depression, hallucinations, seizures, and psychosis. Caution should be exercised in patients with a

history of mental illness. These neurologic adverse effects can be offset by administering vitamin B6 (50-100 mg/day).

It has also been described that these drugs can be associated with orthostatic hypotension.

Ethionamide and prothionamide can cause gynecomastia, alopecia, impotence, or menorrhagia. They can also complicate the control of diabetes mellitus.

Other adverse drug reactions include acne, photosensitivity, and rashes. Thrombocytopenic purpura is occasionally reported (Ramachandran, G2015).

Para-aminosalicylic acid (PAS).

Allergic reactions (fever, rash, pruritus), hemolytic anemia, agranulocytosis, leukopenia, thrombocytopenia, intestinal malabsorption syndrome have been reported with PAS. It is rarely associated with pericarditis or encephalopathy, eosinophilic pneumonia, and optic neuritis. Its use should be avoided in individuals allergic to aspirin (Arbex MA, 2010).

Linezolid

Oxazolidinones are weak inhibitors of monoamine oxidase A and B (MAO). These enzymes are responsible for the metabolism of neurotransmitters, including epinephrine, norepinephrine, serotonin, and dopamine. Serotonin syndrome can occur when linezolid is co-administered with a non-selective MAO inhibitor or selective serotonin reuptake inhibitors (or SSRIs). This syndrome is secondary to an excess of serotonin in the central nervous system, which can be fatal. It is characterized by a clinical triad of behavioral and cognitive changes and neuromuscular excitability. The most reliable physical sign is spontaneous clonus. Serotonin toxicity is reversible if linezolid is discontinued.

Linezolid can cause lactic acidosis that reverses with the discontinuation of the drug. Pancreatitis associated with linezolid has occasionally been reported (Huang V, 2006; Lawrence KR, 2006).

Bedaquiline

In addition to its effect on the QT interval, the most frequently reported adverse effects with bedaquiline have been nausea, myalgias, arthralgias, headache, vomiting, dizziness, diarrhea, and liver damage with elevated transaminases (Cohen K, 2019).

Delamanid

In addition to its effect on the QT interval, delamanid adverse drug reactions include anemia, nausea, vomiting, abdominal pain, palpitations, headache, paresthesia, tremor, insomnia, tinnitus, asthenia, fatigue, hyperhidrosis, hyperuricemia, and hypokalemia (Li Y, 2019).

Pretomanid

The addition of pretomanid to antituberculosis drug regimens has been associated with an increased rate of transient abnormalities in serum liver tests during treatment and with several cases of clinically apparent mild liver injury (Nat Center Biotechnol, 2021).

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CHAPTER 14

TUBERCULOSIS TREATMENT AND PREGNANCY

Abstract

Untreated tuberculosis represents a greater risk to the pregnant woman and the fetus than the potential risk of the adverse effects of antituberculosis treatment. When tuberculosis is not treated during pregnancy or is treated inadequately, complications are frequent, including pre-eclampsia, transvaginal bleeding, preterm birth, and maternal death. In addition to the possibility of congenital TB, untreated TB is associated with congenital malformations and other neonatal complications, including low birth weight, prematurity, and death. During pregnancy, there are changes in the pharmacokinetics of antituberculosis drugs, including their absorption rates, distribution, metabolism, and excretion The four primary antituberculosis drugs have an excellent and comprehensive safety record in pregnancy and are not associated with teratogenicity or neonatal complications. The current World Health Organization MDR-TB treatment guidelines endorsed an individualized approach for treating MDR-TB in pregnant women as a conditional recommendation due to the very low-quality evidence. Treating MDR-TB with drug regimens that include older drugs such as aminoglycosides, ethionamide/prothionamide, clarithromycin, and PAS has been associated with maternal complications such as spontaneous abortion, transvaginal bleeding, placenta previa and premature rupture of membranes, and neonatal adverse outcomes such as prematurity, low birth weight, meconium aspiration, and death.

Introduction

Untreated tuberculosis represents a greater risk to the pregnant woman and the fetus than the potential risk of the adverse effects of antituberculosis treatment (Rai DK, 2016).

Pregnant women with MDR-TB are routinely denied access to new antituberculosis drugs due to the limited evidence on the safety of these

drugs during pregnancy, which is difficult to obtain since pregnancy systematically constitutes an exclusion criterion in clinical research trials. Consequently, the evidence for treatment during pregnancy is often based on observational cohorts, case reports, or case series (McKenna L, 2017; Aaquah R, 2021).

When tuberculosis is not treated during pregnancy or is treated inadequately, complications are frequent, including pre-eclampsia, transvaginal bleeding, preterm birth, and maternal death. In addition to the possibility of congenital TB (although rare, it has a 50% mortality rate; Hageman J, 1980), untreated TB is associated with congenital malformations and other neonatal complications, including low birth weight, prematurity, and death (Acqua R, 2021). Even when antituberculosis treatment is delayed for fear of teratogenicity (e.g., until the second trimester or even later), high obstetric and neonatal complications rates are reported (Figueroa-Damian R, 1998; Alene KA, 2021).

Therefore, there is no basis to deny treatment to a pregnant woman with MDR-TB or force her to decide whether or not to terminate the pregnancy.

Pharmacokinetics of antituberculosis drugs

During pregnancy, there are changes in the pharmacokinetics of antituberculosis drugs, including their absorption rates, distribution, metabolism, and excretion (Tasnif Y, 2016). These changes are due to physiological alterations typical of pregnancy, such as a reduction in gastric emptying, an increase in the transport capacity of the kidney, increased blood volume and body water, and changes in cardiac output. These changes are secondary to physiological alterations typical of pregnancy, such as a reduction in gastric emptying, an increase in the kidney's filtration capacity, increased blood volume and body water, and changes in cardiac output (Shiu JR, 2021).

Treatment of drug-susceptible TB during pregnancy

The four primary antituberculosis drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) have an excellent and comprehensive safety record in pregnancy and are not associated with teratogenicity or neonatal complications. Streptomycin has been discontinued for decades for the treatment of drug-susceptible TB as it causes fetal deafness.

By inducing microsomal liver enzymes of cytochrome P450, rifampin increases the metabolism of contraceptive hormones, which can cause

unwanted pregnancies in patients treated with this drug. In women of childbearing potential, an alternative method of contraception should be recommended (Bothamley G, 2001; Czeizel AE, 2001).

Treatment of MDR-TB during pregnancy

Although there is ample evidence of safety regarding teratogenicity of first-line drugs during pregnancy, experience with second-line drugs is limited. This lack of information on their safety rather than the proof of teratogenicity has caused clinicians to err on the side of caution and treat pregnant women with MDR-TB ineffective regimens that include older drugs for which there is a little more evidence on safety during pregnancy (Figueroa-Damian, 1998).

The current World Health Organization (WHO) MDR-TB treatment guidelines endorsed an individualized approach for treating MDR-TB in pregnant women as a conditional recommendation due to the very low-quality evidence (WHO, 2020).

Treating MDR-TB with drug regimens that include older drugs such as aminoglycosides, ethambutol, ethionamide/prothionamide, clarithromycin, and PAS has been associated with maternal complications such as spontaneous abortion, transvaginal bleeding, placenta previa and premature rupture of membranes, and neonatal adverse outcomes such as prematurity, low birth weight, meconium aspiration, and death (Palacios E, 2009). This increased risk of maternal and fetal complications should be the most potent incentive to treat tuberculosis during pregnancy appropriately. Nonetheless, there is little evidence on the safety of new drugs (bedaquiline, delamanid, and pretomanid) and repurposed drugs (linezolid and clofazimine). Currently, there is no consensus on the optimal regimen for the treatment of MDR-TB in pregnancy, and new evidence is required regarding safety and maternal-fetal outcomes (Baluku JB, 2021).

Amikacin and streptomycin are contraindicated during pregnancy (Mirzayev F, 2021). The known ototoxicity of streptomycin has been extrapolated to amikacin, and although there are no reports of teratogenicity associated with amikacin, potential risk of ototoxicity with amikacin is assumed (Korzeniowski OM. 1995).

The use of ethionamide during pregnancy has been associated with congenital malformations in experimental animals, including abortions and malformations of the central nervous system; its use during pregnancy in

humans has been associated with congenital heart disease, phocomelia, spina bifida, atresia of the digestive tract and subluxation of the hip (Holdiness MR, 1987 & Korzeniowski OM. 1995). However, a literature search found several case reports on using ethionamide or prothionamide during pregnancy without maternal o fetal adverse reactions (Laniado-Laborin R, 2018; Palacios E, 2009).

There is very little evidence on the safety of cycloserine, clofazimine, and PAS during pregnancy. Their use is decided individually on a case-by-case basis when there are no other options. (Korzeniowski OM, 1995). Infants exposed to clofazimine may acquire a dark skin color either when in utero or during breastfeeding.

Animal studies raised the possibility that ciprofloxacin might damage the articular cartilage. Although a review of 200 women exposed to ciprofloxacin during the first trimester failed to note any musculoskeletal abnormalities (Bothamley G, 2001), the experimental findings have been extrapolated to newer generation fluoroquinolones. Nonetheless, an association between the use of fluoroquinolones and musculoskeletal malformations in humans has never been demonstrated. A recent meta-analysis found no association between quinolone use and increased risk for fetal malformations, preterm delivery, stillbirth, and miscarriage. However, fluoroquinolones were administered for short periods, unlike the prolonged administration required in tuberculosis (Loveday M, 2021). The safety of fluoroquinolones administered for more extended periods during pregnancy has not yet been established, and the evidence on the safety of new fluoroquinolones is still limited.

Even though the experience with beta-lactams and amoxicillin-clavulanate during pregnancy has been on their use for relatively short periods, no teratogenicity events have ever been described with these drugs, and they are currently considered safe during pregnancy (Korzeniowski OM, 1995).

Regarding the safety of bedaquiline during pregnancy, there is a recent report on treating rifampicin-resistant TB in South Africa. Of 108 pregnant women (81% of them co-infected with HIV), 58 (53.7%) received a regimen that included bedaquiline. Treatment results for this group were compared with those of 50 women who did not receive bedaquiline. The only statistically significant difference between the groups was the higher frequency of low birth weight in the group that received bedaquiline (45% vs. 26%, $p = 0.034$). However, during follow-up, no significant difference

was found in postnatal weight gain (Loveday M, 2021; Mirzayev F, 2021, Hlangu S, 2021).

In its best-practice statement on the use of delamanid, the WHO does not recommends this drug during pregnancy (WHO, 2017).

Recommendations

1. The best treatment regimen must be decided on a case-by-case basis.
2. Patients must be informed of potential risks from each drug included in the regimen and must be involved in the decision making
3. Access to new and repurposed drugs should not be automatically denied to a pregnant MDR-TB patient. The risk-benefit ratio for each drug according to the patient characteristics and drug-resistance profile should be individualized
4. If the regimen includes isoniazid, ethionamide/prothionamide, cycloserine, and linezolid, it should be supplemented with 50-100 mg of vitamin B6 (pyridoxine)
5. In all women of childbearing age diagnosed with TB, pregnancy should be ruled out, and an effective contraceptive method should be offered (Acquah R, 2021)

Table 14.1. Recommendation of antituberculosis drugs in pregnancy/breastfeeding.

Drug	Recommendation in pregnancy/breastfeeding
Amikacin	Generally avoided in pregnancy due to congenital hearing loss seen with other aminoglycosides. Safe while breastfeeding.
Bedaquiline	According to the literature, more babies exposed to bedaquiline were of low birth weight; however, 80% had gained weight and were developing normally at one year
Clofazimine	It is not recommended due to limited data. Use if there are not better choices. Avoided while breastfeeding due to pigmentation of the infant
Cycloserine	Not well studied, but no teratogenicity documented. Use if there are not better choices. It can be used while breastfeeding. Administer B6 to the infant

Delamanid	May cause harm to a fetus. It is usually not recommended for use during pregnancy. Use if there are not better choices. Breastfeeding is not recommended during treatment with delamanid
Ethambutol	Safe in pregnancy; can be used while breastfeeding
Ethionamide/ Prothionamide	Generally avoided during pregnancy due to reports of teratogenicity; little data about use during breastfeeding (administer B6 to the infant if breastfed)
Fluoroquinolones	Fluoroquinolones are generally avoided in pregnancy and breastfeeding due to observation of arthropathy in animal models. Use if there are not better choices
Imipenem/cilastatin	Limited data regarding use in pregnancy for prolonged periods; unknown safety during breastfeeding
Isoniazid	Safe during pregnancy; safe during breastfeeding (supplement both with vitamin B6)
Linezolid	Not recommended during pregnancy or breastfeeding due to limited data. Use if there are not better choices
Meropenem	Limited data regarding use in pregnancy for prolonged periods; unknown safety during breastfeeding
Para-aminosalicylate (PAS)	Not studied, but no teratogenicity known. There is little data regarding use during breastfeeding
Pyrazinamide	In some countries, pyrazinamide is avoided in pregnancy for drug-susceptible disease due to a lack of data regarding teratogenicity. WHO recommends it for the treatment of drug-susceptible TB. It is used for drug-resistant TB when the isolate is susceptible to pyrazinamide. It can be used while breastfeeding
Rifabutin	Insufficient data in pregnancy. Unknown effects from breastfeeding
Rifampin	Recommended for use in pregnancy; can be used while breastfeeding
Rifapentine	Not recommended due to limited data. Use if there are not better choices
Streptomycin	Avoid during pregnancy due to congenital hearing loss. Safe while breastfeeding

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CHAPTER 15

MANAGEMENT PROTOCOLS FOR ALLERGIC REACTIONS TO ANTITUBERCULOSIS DRUGS

Abstract

The definition of an allergic reaction to tuberculosis drugs includes (1) the existence of a temporal relationship between drug use and the allergic reaction; (2) the improvement in the severity of the adverse reaction after stopping the drug; (3) the reappearance of the allergic reaction upon reintroducing the offending drug only; and (4) and have ruled out other causes of the adverse reaction.

Although immediate reactions (mediated by IgE) have been reported with the administration of antituberculosis drugs, these types of reactions are infrequent. Most hypersensitivity reactions do not appear immediately but are rather T-cell-mediated reactions, which usually appear 1 to 2 weeks after the start of treatment. The drug hypersensitivity syndrome is the most used term to describe a type of severe drug reaction, characterized by the triad consisting of fever, skin, and multi-organ involvement.

Desensitization to a drug is defined as a procedure consisting of the induction of clinical tolerance to a drug responsible for a previous allergic reaction. The basic principles in the treatment of hypersensitivity reactions include: (1) starting with a very low drug concentration and (2) increasing the drug dose progressively, (3) hospitalization during desensitization, and (4) close monitoring for one month after desensitization to the drug is complete. Two different approaches for the management of hypersensitivity reactions are a graded challenge with the suspected drug or a desensitization protocol.

Introduction

Treatment of tuberculosis requires the simultaneous use of multiple drugs. Most patients tolerate mild side effects and manage to complete their

treatment; however, approximately 5% of patients with antituberculosis treatment present adverse reactions that require interruption or modification of the treatment regimen (Cernadas JR, 2013).

The definition of an allergic reaction to tuberculosis drugs includes (1) the existence of a temporal relationship between drug use and the allergic reaction; (2) the improvement in the severity of the adverse reaction after stopping the drug; (3) the reappearance of the allergic reaction upon reintroducing the offending drug only; and (4) and have ruled out other causes of the adverse reaction.

Although immediate reactions (mediated by IgE) have been reported with administering antituberculosis drugs (especially with isoniazid, rifampin, and pyrazinamide), these types of reactions are infrequent. Most hypersensitivity reactions do not appear immediately but are rather T-cell-mediated reactions, which usually occur 1 to 2 weeks after the start of treatment (Nagarajan S, 2018).

The drug hypersensitivity syndrome is the most used term to describe a type of severe drug reaction, characterized by the triad consisting of fever, skin, and multi-organ involvement. Some authors extend this concept by adding lymphadenopathy and eosinophilia.

It is thought that the drugs can produce an accumulation of reactive metabolites, which behave like haptens and induce an immune response. However, exposure to the drug is not considered enough, and there must also be an individual susceptibility to develop this adverse reaction.

Immediate hypersensitivity reactions to antituberculosis drugs can occur with any medication used to treat TB; they seem to be more frequent in women. HIV seropositivity is the only well-defined risk factor for developing hypersensitivity reactions to antituberculosis drugs (Buhari GK, 2015).

Drug hypersensitivity usually develops between 2 and 6 weeks after starting the intake of the responsible drug. However, the appearance of the first symptoms is usually earlier, and it is not uncommon to observe it between 7 and 15 days. In patients previously sensitized, this period is much shorter (Fernández-Herrera J, 2007).

Immediate hypersensitivity reactions to antituberculosis drugs usually present with fever, morbilliform maculopapular eruptions, or urticaria (Holland CL, 1990).

Desensitization to the drug is defined as a "procedure consisting of the induction of clinical tolerance to a drug responsible for a previous allergic reaction." The drug desensitization process is based on modifying the patient's immune response by introducing minimal amounts of the drug to which the adverse reaction has occurred and progressively increasing the drug concentration until the optimal dose is administered (Matz J, 1994). Desensitization is an option for patients who have had allergic reactions to tuberculosis treatment but is only indicated when an effective alternative medication without cross-reaction is unavailable. Desensitization is generally contraindicated in severe reactions, such as Stevens-Johnson syndrome

Management of hypersensitivity from antituberculosis drugs

Patch testing has been recommended for the diagnosis of allergic reactions to antituberculosis drugs. However, there are reports of systemic adverse reactions with the use of this test, so most experts do not recommend its use (Siripassorn K, 2018).

Completely replacing the regimen that caused the adverse reaction with previously unused medications is one of the options for restarting treatment. However, conversion to second-line drugs is unfavorable in terms of drug efficacy and duration of therapy (Oh JH, 2021).

The basic principles in the treatment of hypersensitivity reactions include: (1) starting with a very low drug concentration and (2) increasing the drug dose progressively, (3) hospitalization during desensitization, and (4) close monitoring for one month after desensitization to the drug is complete. There is no consensus on the use of antihistamines or corticosteroids as premedication for drug desensitization (Siripassorn K, 2018).

Two different approaches for managing hypersensitivity reactions are a) a graded challenge with the suspected drug or b) a desensitization protocol.

Table 15.1. Example of a graded challenge protocol. Doses are in milligrams*

Day	Isoniazid	Rifampin	Ethambutol	Pyrazinamide
1	**100**			
2	**200**			
3	**300**			
4	**300**	**150**		
5	**300**	**300**		
6	**300**	**600**		
7	**300**	**600**	**400**	
8	**300**	**600**	**800**	
9	**300**	**600**	**1,200**	
10	**300**	**600**	**1,200**	**500**
11	**300**	**600**	**1,200**	**1,000**
12	**300**	**600**	**1,200**	**1,500**

*modified from Oh JH, 2021.

Rapid oral desensitization should be carried out using validated desensitization protocols. This process includes admission to the hospital (preferably in an intensive care unit or a ward with available resuscitation equipment), written informed consent, intravenous access, and medical personnel familiar with desensitization protocols (Holland CL, 1990).

Table 15.2. An Example of a desensitization protocol for isoniazid*

Time (hour:minute)	Isoniazid dose (mg)
0:00	0.1
0:15	0.5
0:30	1.0
0:45	2.0
1:00	4.0
1:30	8.0
2:00	16.0
2:30	32.0
3:00	50.0

*modified from Curry Center, 2016.

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APPENDIX 1

FREQUENT ADVERSE EFFECTS AND ANTITUBERCULOSIS DRUGS COMMONLY ASSOCIATED

Adverse effect	Possible drug	Suggested management	Commentary
Nausea and vomit	Ethionamide PAS Moxifloxacin Linezolid Clofazimine	Start antiemetic If the symptom persists, use a proton pump inhibitor (remember that this can affect the absorption of some drugs) If possible, reduce the dose of the drug; if the symptoms still persist, the drug will have to be discontinued	Almost all patients who receive these drugs tend to have nausea and vomiting. It usually remits spontaneously in most cases
Hepatitis	Ethionamide Isoniazid Pyrazinamide Prothionamide PAS Linezolid Clofazimine Bedaquiline	Suspend the entire regimen until the hepatitis resolves Rule out other causes of hepatitis Reintroduce drugs, one at a time with the least hepatotoxic initially, monitoring liver function weekly If identified, discontinue causative agent permanently	Investigate a history of hepatitis Hepatitis is generally reversible when the drug is stopped

Skin and hypersensitivity reactions Hyper-sensitivity Skin adverse reactions	PAS Linezolid Clofazimine Virtually all drugs can cause them	Discontinue all medications and treat symptomatically with systemic antihistamines / steroids until reaction clears If the problem reappears when the drug is reintroduced, the causative agent must be discontinued. Discontinue all medications and treat symptomatically with systemic antihistamines / steroids until reaction clears If the problem reappears when the drug is reintroduced, the causative agent must be discontinued.	Hypersensitivity reactions can range from simple itching to severe forms of exfoliative epidermal necrolysis Skin reactions can range from simple itching to blistering skin rashes (rare)
Psychiatric adverse reactions Psychosis Suicidal tendencies Anxiety	Cycloserine Linezolid	Psychiatric consultation Reduce the dose or stop the drug	Monitoring of serum levels may be helpful in adjusting the dose

Neurologic adverse reactions Peripheral neuropathy	Linezolid Isoniazid Ethionamide	Increase pyridoxine to maximum dose (200 mg / day) Initiate therapy with tricyclic antidepressants (e.g. amitriptyline), NSAIDs to relieve symptoms Reduce if possible the dose of the drug; if the problem persists, suspend the causal agent	Patients with co-morbidity (e.g. diabetes, HIV, alcoholism, etc.) are at increased risk of neuropathy Neuropathy can be irreversible
Seizures	Moxifloxacin Linezolid Cycloserine Imipenem	Treatment should be stopped immediately until the seizures resolve. Anticonvulsant treatment should be started Increase pyridoxine to maximum dose Restart the possible causative agent at a lower dose (if still effective at that dose) if the drug is essential to the regimen If the problem persists, the drug should be discontinued	The anticonvulsant should be maintained until the end of treatment (or until the possible causative agent is discontinued If the patient has a history of seizures, but these are under control, they can be treated with these drugs if they are considered useful, but it should be borne in mind that they are at increased risk of seizure during treatment

Ototoxicity	Aminoglycosides	Document hearing loss and compare with baseline audiometry if a hearing loss is available. Decrease the frequency of application of the medicine (3 times a week instead of daily). If the problem persists, stop the drug	Previous exposure to aminoglycosides increases the risk as hearing damage may have already been caused. Hearing damage is generally irreversible. The benefit of the injectable will have to be assessed vs. the risk of irreversible hearing damage
Optic Toxicity	Ethambutol Linezolid	Urgently consult ophthalmology	Monthly monitoring of visual acuity and color discrimination must be carried out
Tendinopathy / myalgia	Levofloxacin Moxifloxacin	Can be treated with non-steroidal anti-inflammatory drugs	Symptoms usually disappear over weeks. NSAIDs can aggravate gastritis secondary to antituberculosis There is rarely a tendon rupture
Hematologic adverse reactions	Linezolid Rifampicin PAS	Monthly hematological monitoring	Anemia, leukopenia, thrombocytopenia, or prolonged prothrombin times may occur

Nephrotoxicity	Aminoglycosides Linezolid	Discontinue the causative agent If it is not possible to space the dose to 2-3 times a week Kidney function monitoring monthly Adjust drug dose to creatinine clearance levels	Kidney damage can be permanent It should be considered especially in patients with co-morbidity (diabetes, hypertension, previous kidney damage)
Metabolic and electrolyte adverse reactions	Aminoglycosides Linezolid Moxifloxacin Clofazimine	Monthly glucose and electrolyte monitoring	Low levels of calcium, magnesium, and potassium may occur Linezolid can cause elevations of alkaline phosphatase and creatine phosphokinase Moxifloxacin can cause dysglycemia
Hypothyroidism	PAS, Ethionamide, Prothionamide	Suplementar con levothyroxine	Clinically assess and monitor thyroid function every 2-3 months
RAFA cardiovascular	Moxifloxacin, Clofazimine, Bedaquiline, Delamanid	Electrocardiographic monitoring	Although infrequent, they should be monitored due to their severity