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

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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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