BENEFITS OF THERAPEUTIC DRUG MONITORING OF FIRST LINE ANTITUBERCULOSIS DRUGS

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Abstract

Tuberculosis is an airborne infectious disease that remains a huge global health-related issue nowadays. Despite constant approvals of newly developed drugs, the use of first-line antituberculosis medicines seems reasonable in drug-susceptible *Mycobacterium tuberculosis* strains. Therapeutic drug monitoring presents a useful technique for the determination of plasma drug concentration to adjust appropriate dose regimes. In tuberculosis treatment, therapeutic drug monitoring is aiding clinicians in selecting an optimal therapeutic level, which is essential for the personalisation of therapy. This review is aimed at clarifying the use of therapeutic drug monitoring of the first-line antituberculosis drugs in routine clinical practice.

Key words: first-line antituberculosis drugs, therapeutic drug monitoring, isoniazid, rifampicin, ethambutol, pyrazinamide

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by rod-shaped, aerobic, intracellular tubercle bacilli *Mycobacterium (M.) tuberculosis* (1). The expansion of this airborne disease is based on the transfer of pathogen containing drops through the air, mostly by coughing. TB might affect pulmonary or other tissue causing a pulmonary or extrapulmonary form of the disease, respectively. In the global scale, TB remains on the world's top-ten *Causa Mortis* list. Approximately 10 million people around the world are diagnosed with TB every year. Estimation of nearly one-quarter of the world's population being infected with tubercle bacilli points on the number of people in a latent state of the disease who are at risk of active tuberculosis development. The most threatened are patients with health-related risk factors such as smoking, HIV infection, or diabetes mellitus. Nevertheless, those who live in poverty, low housing quality, and suffer from malnutrition tend more to become ill. The 2019 Global Tuberculosis Report issued by the World Health Organisation (WHO) reveals that 1.5 million people worldwide died in 2018 due to TB (2).

The situation gets even more dangerous for people being infected by resistant strains of *M. tuberculosis*. Multidrug-resistant (MDR) TB is typically resistant to isoniazid (INH), and rifampicin (RMP) and tubercle bacilli are likely incurables by the first-line anti-TB treatment. On the other side, infection caused by extensively drug-resistant (XDR) strains

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appears more critical. These include MDR strains further resistant to fluoroquinolones (FQs) and to second-line parenteral anti-TB agents. Several molecular mechanisms cause resistance and its development can be enhanced by insufficient health-care system, non-adherence of the patient, and incorrect or not rationalised therapy (3, 4). Since antimicrobial agents were introduced in antibacterial treatment, the efficacy of treatment but also the incidence of side effects have arisen (5). However, TB treatment outcomes can be improved by evaluation of drug plasma concentration, allowing to perform dose adjustment when the patient is under- or over-dosed and thus cannot respond to treatment appropriately (6). Results from analyses and the systematic reviews of quantitative determination of anti-TB drugs plasma concentrations have shown a high proportion of first-line agents' plasma levels below the recommended range. Lack of reaching the recommended therapeutic concentrations represents more than 66% and 43% for RMP and INH, respectively. However, according to this study, a clear association between low plasma concentration and cure failure was not detected (7). Contrary, other authors (e.g., in INH containing regimen) found an association between low plasma concentration and therapy failure or relapses (8). However, it seems legitimate to determine TB agents' plasma concentrations in high-risk patients. The most endangered are patients suffering from diabetes mellitus (DM), HIV infection, renal or hepatic dysfunction, cancer, or taking immunosuppressive drugs. Clinicians should also be observant in possible drug-drug interactions in polypragmasy (7).

This review is focused on the standard of the first-line anti-TB drugs (INH, RMP, PZA, EMB) and the application of therapeutic drug monitoring (TDM) in anti-TB treatment in routine clinical practice. However, dose-dependant undesired drug reactions and low drug susceptibility in sensitive pathogen strain can occur, patients' care improvement is then the main reason for the implementation of TDM. Low treatment outcomes and adverse drug effects can be eliminated during hospitalisation in individual TB treatment facilities (9–11). By default, TDM of anti-TB drugs is not performed in Slovakia. In the group of anti-infectious agents only a few aminoglycosides' and vancomycin's plasma concentrations are kept under surveillance (12,13). Despite the low incidence of tuberculosis cases in Slovakia we still face certain issues (migration, social changes, vaccination regression) potentially worsening this condition (14). Therefore, we expect a significant benefit in the introduction of this procedure in our country, especially in non-responding patients, in polypragmasy, and specific groups of patients described in chapters below more in detail.

PRINCIPLES OF THERAPEUTIC DRUG MONITORING IN TB TREATMENT

TDM allows for determining many pharmacokinetic (PK) parameters. Using TDM, the clinicians can resolve drug absorption extent, maximum plasma concentration (peak concentration – C_{max}), time to reach peak concentration (T_{max}), area under the curve (AUC), and many others (15). This approach enables the individualisation and personalisation of drug therapy. Additional benefits of TDM are described in previously published papers; e.g. therapy cost-effectiveness. In case of clinical dose adjustment, the most effective appears to check peak concentrations. For the vast of anti-TB drugs, this is usually determined by 2-hour post-dose plasma sampling. However, the interindividual oral absorption rate can cause peak concentration detection impossible. This is a reason for a second blood draw generally collected 6-hour post-dose. The second sample provides additional details about the oral absorption rate and its completeness. There is likewise a possibility to approximate elimination processes information for short half-lives drugs; e.g., INH. Delayed or disturbed absorption is likely to be considered when the 6-hour post-dose sample reaches higher or nearly the same plasma level as 2-hour post-dose draw. In those situations, the peak concentration presumably appeared within the 4-hour time gap. Furthermore, potential malabsorption might occur when both plasma concentrations reach values below the recommended range. Drugs plasma concentrations should not reach out of the recommended ranges. In general, values above the desired interval could be associated with a higher risk of adverse effects. In every case, when the dose is increased, clinicians should be conscious

for specific side effects; e.g. development of central and peripheral neuropathy after INH, hepatotoxicity after pyrazinamide (PZA), and ocular toxicity after ethambutol (EMB) (16, 17).

Many analytical methods have been used to determine drug plasma concentrations. The most common are high-performance liquid chromatography coupled with ultra-violet detection (HPLC-UV), liquid chromatography coupled with mass spectrometry (LC-MS), or liquid chromatography with tandem mass spectrometry (LC-MS/MS) (18, 19).

An innovative process of blood sample acquiring appears dried blood spot (DBS) method (more comfortable and cheaper in comparison with whole blood sampling). On the other hand, as a possible limiting factor drug stability on DBS card is recognised. Despite further scientific evidence requirements, DBS might be implemented also in low-income countries (20, 21).

FIRST LINE ANTI-TB DRUGS

There are two different lines of drugs presented in TB treatment. The first one is typical of peroral administered drugs INH, PZA, EMB, RMP and its derivatives rifabutin and rifapentine. The dosage and selected pharmacokinetic properties of selected first-line anti-TB drugs are shown in Table 1. It is highly recommended to use the first-line anti-TB drugs for TB patients infected by drug-susceptible strains. For the first two months (intensive phase) of the therapy regimens the combination of INH, RMP, PZA, and EMB is used. In the continuation phase (next four months) INH and RMP are administered. A different but possible scenario for strains resistant to first-line anti-TB agents may emerge. This fact is considered to be an intention for the second-line drug administration. The second-line anti-TB drugs is a group with various types of antibacterial compounds, including parenteral agents (streptomycin, kanamycin, amikacin, capreomycin), FQs (levofloxacin, moxifloxacin, ofloxacin, gatifloxacin), oral bacteriostatic drugs (ethionamide, prothionamide, cycloserine, tetrizidone, p-aminosalicylic acid and its sodium salt), and others (delamanid, bedaquiline, linezolid, clofazimine, amoxicillin/clavulanate, imipenem/cilastatin, meropenem, thioacetazone, clarithromycin) (9, 22). The first line anti-TB agents RMP and EMB are substrates for P-glycoprotein (P-gp) transporter. The phagocytosed intracellular *M. tuberculosis* bacilli were significantly better eliminated by these drugs in the presence of co-administered tariquidar, a P-gp inhibitor in P-gp overexpressing macrophages (23)

Table 1 Dosage and selected pharmacokinetic parameters of first-line antituberculous drugs (6,24–28)

Drug	log P	pKa	Recommended daily dose	Alternative dosing schedules	C _{max} (µg/mL)	T _{max} (h)
Isoniazid	-0.64	1.8	4 – 6 mg/kg (max. 300 mg)	8 – 12 mg/kg (bw/tw)	3 – 6 (d) 9 – 15 (bw)	1 – 2
Rifampicin	1.09	5.0	10 mg/kg (max. 600 mg)	10 mg/kg (bw/tw)	8 – 24 (d/bw)	1 – 3
Ethambutol	-0.14	pKa ₁ = 6.4 pKa ₂ = 9.4	15 – 20 mg/kg	25 – 35 mg/kg (tw) 50 mg/kg (bw)	2 – 6 (d) 4 – 12 (bw)	2 – 3
Pyrazinamide	-1.88	2.9	20 – 30 mg/kg	30 – 40 mg/kg (tw) 50 mg/kg (bw)	20 – 60 (d) 60 – 90 (bw)	1 – 2

d – daily; bw – biweekly; tw – three time per week

ISONIAZID

INH (Fig. 1) given on an empty stomach is quickly and almost completely absorbed from the gastrointestinal tract. Absorption is delayed and reduced with concomitant food ingestion and high-fat meal may reduce $C_{\max}$ to 51%. Gastroduodenal surgical interventions (e.g. resections) has usually only a non-significant impact on INH mucosa penetration. Rich carbohydrate diet causes decreased bioavailability by hydrazine-sugar complex formation (29, 30). Despite the fact that pyridoxine (vitamin B6) and INH undergo competitive intestine permeability and the INH absorption rate constant is decreased, no significant pharmacokinetic impact was observed – probably due to its rapid absorption (31).

Fig. 1. Chemical structures of selected first-line anti-TB drugs.

INH is well distributed to all tissues and fluids with poor plasma proteins binding ability. It is easily detectable in cerebrospinal fluid (CSF), peripheral nerves, red blood cells, pleural effusion, breast milk, placenta, saliva, skin, lungs, and faeces. Its volume of distribution (V_d) represents on average 0.6 L/kg (30, 32).

The main pathway in the process of INH inactivation is acetylation. N-acetyltransferase 2 (NAT-2; EC 2.3.1.5) transposes the acetyl residue to the free, non-acetylated amino functional group to form N-acetylisoniazid. Mycobacterial NAT carries out the same process in order to expel the drug out and, thus, protect maternal bacilli from cytotoxic effect. Based on genotype, there are three types of acetylators, namely slow, intermediate, and rapid ones. Rapid acetylators should be at risk of resistance development. Contrary, slow acetylators should be in a potential hepatotoxicity hazard and, thus, employing of TDM enables

clinicians to prevent both complications. Metabolites of INH are expelled preferentially by urine (33). INH biological half-life depends on acetylation speed and varies from 1.5 to 4 hours (25).

Blood sampling should be performed 2 and 6 hours post-dose. After subsequent centrifugation it is necessary to freeze the sample in case of delayed analysis, as isoniazid is stable neither in serum nor in whole blood (6,24). A daily dose of 300 mg should lead to reaching the plasma concentration range from 3 to 6 µg/mL. Biweekly doses of 900 mg should achieve the plasma concentration range from 9 to 15 µg/mL. In general, INH dose adjustment should be considered in case of plasma concentration less than 2 µg/mL and less than 7 µg/mL in daily and biweekly dosage scheme, respectively. Peak concentration appearing later than 2 hours post-dose suggests a malabsorption or rapid pre-systemic elimination of INH (6).

RIFAMPICIN

Oral absorption of RMP (Fig. 1) administered in the non-fasting state is slower (higher T_{max} value) and, thus, is linked with decreased C_{max} values. However, the total extent of absorption is unchanged. Mean C_{max} value of RMP administered with a high-fat meal is reduced by approximately 30% in comparison with the fasting state. Therefore, the pre-meal administration of RMP is recommended. Fixed drugs combinations (FDC) of RMP and INH or pyrazinamide (PZA) modestly decrease its absorption. This issue might be overcome by an increased amount of RMP in FDC (34).

The RMP plasma bound range is 80–90% and, thus, about 10–20% is available for antibacterial effects (35). The drug is well distributed into body fluids and tissues such as liver, bile, CSF, ureter, skin, muscles, and lungs (32).

Absorbed RMP is metabolised by esterases to 25-desacetylrifampicin, the main metabolite that has about 25–50% of antibacterial activity of RMP. Approximately 15% of RMP can be found in urine. It is rapidly excreted to bile and undergoes enterohepatic cycling (25). The biological half-life of RMP ranges from 1.1 to 3.8 hours (36). Rifampicin is a potent inducer of CYP 3A4 isoform and also induces expression of isoforms CYP 2B6, CYP 2C8, CYP 2C9, and CYP 2C19 (34). Autoinduction of metabolism of RMP is the main reason for a single-dose versus steady-state plasma concentration variance. Also, the pregnane X receptor (PXR) was reported to be responsible for rifampicin drug-drug interactions. This nuclear factor is involved in the regulation of transcription of genes encoding microsomal CYP450 enzymes, aldehyde dehydrogenases, and enzymes of second bioelimination phase such as UDP-glucuronosyltransferases (UGTs) or glutathione-S-transferases (GSTs) (37). Due to the above-mentioned autoinduction and extensive first-pass metabolism, RMP reaches steady-state after seven-days of administration (34).

Sampling strategy of 2 and 6 hours post-dose fits perfectly for RMP. RMP is slightly more stable in human plasma than INH or ethionamide. Samples of RMP and most of the other anti-TB drugs remain stable 24 hours at room temperature in human plasma conditions. The peak concentration is within the range of 8 to 24 µg/mL after daily administration of 600 mg RMP. Clinicians should consider a dose adjustment when plasma concentration of RMP drops under 4 µg/mL (6).

ETHAMBUTOL

Most of the orally administered EMB (Fig. 1) enters the systemic circulation and its bioavailability is up to 80% (38). Interindividual absorption variability of EMB under fasting conditions is only limited. In case of concomitant food administration, the C_{max} may be reduced by 17% and T_{max} may increase by 29% (39). EMB has a low ability to bound to plasma proteins and, thus, free (unbound fraction) represents nearly 80% of dose absorbed from the intestine (38). EMB might deposit in erythrocytes that serve as a depot from which small portions are released continuously (40). EMB is distributed into many tissues and fluids of the body, including the lungs and alveolar lymph node macrophages (32).

Only 8–15% of EMB is metabolised by oxidation to a carboxylic acid with derivatives of butyraldehyde as oxidation intermediates (40). Approximately 54–67% of a single orally administered dose of EMB is excreted unchanged in urine by active renal secretion (41). Its bioelimination half-life is within the range from 6.9 to 13.5 hours (36).

The blood drawing between 2 to 3 hours post-dose to measure $C_{\max}$ is suitable for most patients, therefore sampling together with other anti-TB drugs at 2 and 6 hours post-dose is also adequate (39). The 3 and 6 to 7 hours post-dose sampling has an advantage in case of simultaneous rifabutin or clarithromycin intake (6,16). In usual dosage schemes EMB dose varies daily from 15 to 25 mg/kg and biweekly about 50 mg/kg. Dosage modification should be considered when plasma concentrations are less than the lower limit of 2 to 6 µg/mL and 4 to 12 µg/mL range in daily and biweekly administration strategy, respectively (6,39).

PYRAZINAMIDE

PZA (Fig. 1) is quickly and reliably absorbed from the intestine and its $T_{\max}$ is about 1 hour. With its relatively broad biological half-life range of 4.1 – 15.7 hours and rapid absorption, the detection of $C_{\max}$ of PZA is possible from 0.5 to 3.0 hours post-dose. However, the most appropriate $C_{\max}$ can be obtained with blood collection at approximately 1 hour post-dose (36,42). As the food rich in carbohydrates or fat does not significantly affect its absorption, PZA administration is not limited by food intake (42).

Protein binding range of PZA is very low, about 15 to 40%. A recent study has shown only less than 1% of protein binding (43). Thus, PZA is easily distributed into blood, bronchial alveoli cells and fluids, CSF and other tissues (44, 45).

PZA undergoes hepatic enzymes metabolism with the formation of metabolites such as pyrazinoic acid (POA) and 5-hydroxypyrazinoic acid (46). As PZA is a prodrug, the first-mentioned metabolite (POA) is an active substance of PZA with antimicrobial effect (47). Only about 3% of absorbed dose is excreted unchanged in the urine, whereas 30% is eliminated as POA (46).

Despite fast absorption and rapid plasma concentration increase, it seems sufficient to provide blood sampling at 2 and 6 hours post-dose. The daily dosing of 25 mg/kg usually leads to the concentration in plasma from 20 to 50 µg/mL. When PZA is administered at the dose of 50 mg/kg biweekly, the expected plasma concentrations are between 60 to 90 µg/mL. Generally, the dose adjustment is appropriate if plasma concentration reaches less than 75% of its lower range (6, 24).

SPECIFIC GROUPS OF PATIENTS WITH SIMULTANEOUS TB DIABETES MELLITUS

Patients with DM are likely to develop an active form of *M. tuberculosis* infection. Besides, this metabolic disorder might have a negative impact on an active TB treatment efficacy (48). Neuropathy as a typical DM complication is responsible also for the degeneration of *n. vagus* and, thus, for gastroparesis. Reduced motility and decreased digestive ability can lead to medicine malabsorption and the delayed absorption (49). Furthermore, DM induced nephropathy should be taken into consideration, especially in cases of renal drug elimination or its substantial nephrotoxic side effect (50). The overview of drugs used in the treatment of DM and their potential of drug-drug interactions is summarised in Table 2.

HIV

The immune system of an HIV infected patient is not able to resist external factors as observed in healthy subjects. HIV-positive patients tend more to develop an active form of TB either from latent state or after subsequent noxious bacilli exposure. People suffering from acquired immune deficiency syndrome (AIDS) may be co-infected with other, for them life-threatening infections and may suffer from malabsorption of nutrients and medicine. Furthermore, antiretroviral therapy (ART) may influence the PK properties of other medications and, thus, several drug-drug interactions may occur (24, 50). Rifampicin, a strong

Table 2 Involvement of cytochrome P450 (CYP) in the metabolism of selected peroral antidiabetics (PAD) (51). Biguanide derivatives (BG), sulphonylurea derivatives (SU), meglitinide derivatives (MGL), thiazolidinediones (TZD), dipeptidyl-peptidase 4 inhibitors (DPP-4), sodium-glucose transport protein 2 inhibitors (SGLT-2), uridine 5'-diphospho-glucuronosyltransferase (UGT).

Group	Drug	Substrate
BG derivatives	metformin	CYP not involved
SU derivatives	glimepiride, glipizide	2C9
MGL derivatives	repaglinide	3A4; 2C8
	nateglinide	3A4; 2C9
TZD	pioglitazone	mainly 2C8, less 3A4
	rosiglitazone	mainly 2C8, less 2C9
DPP-4 inhibitors	saxagliptin	3A4
SGLT-2 inhibitors	dapagliflozin	metabolised by glucuronidation; negligible or insignificant metabolism by CYP

enzyme inducer, is the most potent first-line anti-TB drug in possible PK drug-drug interaction scenario. It accelerates the degradation of various ART drugs and, on the other hand, some of these agents can increase the concentration and toxicity of RMP. According to guidelines for concurrent TB in HIV infected patients, the replacement of RMP with rifabutin is recommended (52).

Table 3 Involvement of CYP and P-glycoprotein (P-gp) in the pharmacokinetics of selected ART drugs (50,53). Non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI), integrase inhibitors (InI).

Group	Drug	Substrate	Inducer	Inhibitor
NNRTI	delavirdine	3A4, 2D6	3A4, 2C9, 2C19	3A4; 2C9; 2C19, P-gp
	nevirapine	3A4, 2B6	3A4	P-gp
	efavirenz	3A4, 2B6	2B6	P-gp
PI	ritonavir	3A4,2D6	1A2; 2C9; 2C19	P-gp; 3A4 (very potent); 2D6
	nelfinavir	3A4, 2D6		P-gp; 3A4 (intermediate)
NRTI	zidovudine	not metabolised by CYP450		
InI	raltegravir	not metabolised by CYP450	not induce (fewer drug-drug interactions)	
	elvitegravir	3A4		weak P-gp

RENAL AND HEPATIC DYSFUNCTION

Similarly, patients undergoing haemodialysis have shown a higher predisposition of developing the active TB form both from latent state and after recent exposure (54). Renal and hepatic elimination is essential in the excretion of drugs. Each anti-TB drug demonstrates different elimination pharmacokinetic requirements and they are mentioned individually above more in detail (32).

IMMUNOSUPPRESSIVE DRUGS AND CANCER

The reduction of the efficacy of the immune system based on anticancer therapy and immunosuppressants is the main reason for the transition from a latent to an active form of TB. However, in these patients other risk factors are present and contribute to a lower anti-TB effectivity. Furthermore, there are certain cancer types (lungs cancer, haematological malignancies, head or neck cancer) and specific diseases in which suppressed immunity may contribute to the development of TB and influence the result of the therapy (55).

CONCLUSION

Tuberculosis is a deadly airborne illness threatening millions of people worldwide. Despite continuous research on new drug development, first-line antituberculosis drugs represent a valuable group of compounds still used in drug-susceptible tuberculosis treatment regimens. The first-line of anti-TB drugs represents various compounds with different pharmacokinetics and pharmacodynamics. However, the antimicrobial effect and adverse effects depending on the concentration of a drug presented in the patient's body, drug plasma concentrations under or above the desired range might negatively affect treatment efficacy. In clinical practice, TDM represents a useful technique for observing drug plasma concentration and for appropriate dose adjustment. Despite many benefits of TDM, it has not been routinely established yet in TB treatment. Finally, employing TDM might be helpful in individualisation and personalisation of drug therapy, not only in patients with high-risk of active TB form development.

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