Review Article

Pharmacokinetic profile of Antitubercular drugs and their clinical applications in therapeutic drug monitoring

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Received: 30 August 2017 Revised: 21 September 2017 Accepted: 23 September 2017

Abstract

Concomitant food, drug and disease states play a dramatic role on the pharmacokinetics of first-line anti-tuberculosis drugs. Food has enormous effect on physico-chemical properties, site, rate, and extent of absorption and first pass metabolism of the drugs. Concomitant drugs may sometimes produce sub-therapeutic level while illicit toxicity on the other hand like hepatotoxicity. Drugs with antacids in empty stomach or with food also alter pharmacokinetics. Different types of drugs in HIV and diabetes have huge alteration in pharmacokinetic parameters like C_{max}, $T_{max,}$ AUC and clearance. In tuberculosis treatment with HIV, the decrease in CD_4 cell count and compromised immunity directly alter therapeutics. The applications of Therapeutic drug monitoring (TDM) is based on the measurement of drug concentrations in blood samples collected at appropriate times and subsequent dose adjustment according to the target concentration. Appropriate dosing through individualization by TDM may lower the treatment costs and optimize the dosage regimen to achieve the optimal response with minimal toxicity. This review aims to consider the effect of food, concomitant drugs and co-morbidities in patients of tuberculosis by monitoring therapeutic drug concentration in the patient's blood plasma.

Keywords: Tuberculosis, pharmacokinetics, Therapeutic drug monitoring

Introduction

Tuberculosis (TB) is a major public health problem worldwide (Jin et al., 2015). In 1993, World Health Organization declared tuberculosis a global public health emergency (Zumla et al., 2014). Tuberculosis control depends critically on the effective treatment of patients (Heisen et al., 2014) .Standard treatment for TB is a six months regimen that includes two months of isoniazid (INH), rifampin, ethambutol, and pyrazinamide, followed by four months of INH and rifampin with or without ethambutol. Despite the rather successful therapeutic effects of this regimen, there are still treatment failures and unmanageable adverse events that lead to discontinuation of therapy. Although the concurrent administration of antituberculosis medication with food items is believed to relieve drug- induced nausea and vomiting, this regimen may decrease the bioavailability of drugs, thereby decreasing therapeutic efficacy and increasing the risk of drug resistance (Zent et al., 1995). The major adverse event induced by this multidrug regimen is liver injury. The incidence of anti-TB drug-induced hepatotoxicity ranges from 1% to 36%, and mortality is not rare. Among these medications, isoniazid is the major contributor to drug-induced hepatotoxicity (Jin et al., 2015). In addition to liver toxicity with many of the anti-tuberculosis drugs poor appetite and abdominal pain appeared, particularly in the first few weeks of treatment (Lin at al 2010)**.** Tuberculosis is commonly associated with HIV. Worldwide, of the 8.6 million people who developed TB in 2012, 13% of them were HIV positive. Drugs should be administered as fixed-dose combination under the "directly observed treatment short course" (DOTS) protocol, applying strategies to avoid unfavorable treatment results. The pharmacokinetics of the most effective anti- TB drugs is highly variable and has in some studies been shown to be affected by HIV and/or poor nutritional status (Kidola et al., 2014). Drug-related adverse events are critical public health problems (Ayako et al., 2015). Tuberculosis patients in general are at risk of nutritional deficiencies, especially in countries with high burdens of TB. Daily micronutrient supplementation given together with tuberculosis treatment considerably increases weight gain and reduces mortality treatment and is therefore considered an option for managing malnourished TB patients (Kidola et al., 2014).

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An additional factor that could negatively affect the efficacy of the antitubercular treatment is a deficiency in cellular immunity, which in turn can be influenced by nutritional status (Carlos et al., 2005). Concomitant treatment is the corner stone of TB treatment. The pharmacokinetics of co- administered drugs, lead to the lack of efficiency or adverse drug reactions of the victim drug. Therefore, when administered concomitantly, these drugs may either increase or decrease the plasma concentrations of other co-administered drugs and their metabolites. It is important to understand the pharmacokinetic and metabolic profiles for new drugs in animals and humans so that the impact on efficacy and safety can be interpreted or predicted (Katsunori et al., 2015).

Drug Food Interaction

***In vivo* Effect of food quality on drug pharmacokinetics**

In an experimental study the diets were designed as the high carbohydrate diet comprised 250 ml of cooked maize meal, 125 ml of 2% fat milk, 2 slices (60 g) of brown bread, 40 g of jam and 15 g sugar. This provides 530 kcal with the source of energy, being 81% carbohydrate, 10% protein and 9% fat and the high protein high fat diet comprised 250 ml soup (Protol), 2 slices of brown bread, 20 g margarine and 40 g Cheddar cheese. This provides 520 kcal with the source of energy being 28% carbohydrate, 15% protein and 57% fat. This study was conducted in tuberculosis patients, and showed that the carbohydrate diet significantly decreased the bioavailability of isoniazid (C_{max} and AUC_{0-8}) and marginally decreased the AUC_{0-8} for rifampicin in males. The lipid diet decreased the C_{max} of isoniazid and increased the T_{max} for rifampicin. Pyrazinamide bioavailability was not affected by food. The C_{max} or AUC_{0-8} values were decreased by more than 20% by food for between 15% and 54% of rifampicin and isoniazid and between 4 and 12% of pyrazinamide. There is evidence to suggest that C_m may be an important determinant of effect for both rifampicin and isoniazid (Zent et al., 1995). Dietary components were also seen to effect serum drug concentrations. A high-fat meal as recommended by the Food and Drug Administration in the USA reduced the Isoniazid C_{max} by 32-51% and AUC by 12-13%. A carbohydrate-based diet reduced the Isoniazid C_{max} and AUC to levels lower than those of high-fat meals. The T_{max} of Rifampicin was increased more by carbohydrate than by lipid (Hsein Chun et al., 2014). In the last few decades, cholesterol has received huge attention, mainly because of its harmful effect on the cardiovascular system, and current recommendations are all directed to achieving low serum levels. However, taking into account the above-mentioned clinical observations and in vitro studies, it was evident that in the case of pulmonary tuberculosis, a low-cholesterol level might have a detrimental effect. Thus, it is important to investigate whether a cholesterol-rich diet could have a beneficial effect on the bacteriologic sterilization of sputum cultures in newly diagnosed cases of pulmonary tuberculosis in patients receiving the antitubercular drugs regimen. A cholesterol-rich diet accelerated the bacteriologic sterilization of the sputum culture in patients with newly diagnosed pulmonary tuberculosis during the intensive phase with four antitubercular drugs. These preliminary findings suggest that cholesterol should be used as a complementary measure in antitubercular treatment, the reduction of the infectious period for tuberculosis patients decreases the risk of the dissemination of bacilli to others (Carlos et al., 2005). The test meal followed the FDA guidance on high-fat (ca. 50% of total caloric content of the meal) and high-calorie (800 to 1000 cal) content and consisted of two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes, and eight ounces of whole milk was used. The effect of a high-fat, high-calorie meal on PA-824 (novel nitroimidazo-oxazine) exposure after oral administration was assessed across a wide range of doses (50, 200, and 1,000 mg). The PA-824 C_{max} and AUC increased less than dose proportionally in the fasted state. The highest dose of PA-824 had the greatest relative increase in C_{max} and AUC after the high-fat, high-calorie meal, with more modest increases in C_{max} and AUC being observed for the 50mg and 200 mg doses compared to the fasted state. After a high-fat, high calorie meal, the median T_{max} occurred ~1.5 h sooner after administration of 1,000 mg PA-824 and~1 h later after administration of 200 mg compared to the fasted state. No significant difference in T_{max} was observed at the 50mg or 1,000mg doses. This meant that $t_{½}$ of PA-824 at all doses was marginally longer in the fed state than in the fasted state. No significant difference $t_{½}$ was observed at the 50mg or 200mg doses (Helen et al., 2013). The nutritional supplement was in the form of high-energy and vitamin/mineral-enriched biscuits that contained approximately 1,000 kcal and additional vitamins and minerals, including zinc and selenium .The supplements were given during the first 2 months of TB treatment, and the intake was monitored. It was concluded that among HIV coinfected TB patients, the use of nutritional supplementation resulted in higher rifampin exposure, mitigating the detrimental effect of HIV co-infection on rifampin drug levels (Kidola et al., 2014).

***In vitro* evaluation of food effect on the bioavailability**

In vitro, effect of food on the bioavailability was studied by simulating in vivo conditions in dissolution fluid, to understand the variable effect of food on rifampicin release. Dissolution studies were done by simulating in vivo

conditions after meal intake. Here, we assessed the effect of hydrodynamic stress in presence of food and meal composition on two rifampicin containing fixed dose combination formulations by carrying out dissolution at different agitation rates (simulation of fasted and fed state) as well as in the presence of different percentage of oil (fatty food). Agitation intensity as well as presence of oil did not have any influence on rifampicin release from first formulation. This formulation had shown excellent release characteristics at all the conditions. Whereas, second formulation showed agitation rate dependent release and also release was affected in presence of oil. Hence, it is concluded that food may not have any effect on the release of rifampicin and subsequently on its bioavailability. Further, effect of food on the rifampicin release was a function of dosage form such as disintegration time and dissolution rate, which will subsequently affect the release behavior of a formulation in presence of food (Ramesh et al., 2003). In another study, Oleanolic acid (OA), a triterpenoid, exists widely in food, medicinal herbs and other plants and that it has antimycobacterial activity against the *Mycobacterium tuberculosis*. It was found that OA had antimycobacterial properties against eight clinical isolates of *M. tuberculosis* and that the minimum inhibitory concentrations of OA against drug-sensitive and drug-resistant isolates were 50–100 and 100–200 µg /ml, respectively. The combination of OA with isoniazid (INH), rifampicin (RMP) or ethambutol (EMB) showed favorable synergistic antimycobacterial effects against six drug-resistant strains, with fractional inhibitory concentrations. The combination treatments of OA/INH, OA/RMP and OA/EMB displayed either a synergistic interaction or did not show any interaction against two drug-sensitive strains. No antagonism resulting from the OA/ INH, OA/RMP or OA/EMB combination was observed for any of the strains (Fa et al., 2010).

Effect of fasting Conditions, food, and antacids on pharmacokinetics

Ethambutol (EMB)

In an experimental study the pharmacokinetics of EMB in serum was studied. EMB is the most frequently used for the empiric treatment of *Mycobacterium tuberculosis* and used drug for infections caused by *Mycobacterium avium* complex. The pharmacokinetics of EMB in serum was studied with 14 healthy males and females in a randomized, four-period crossover study. Subjects ingested a single dose of EMB of 25 mg/kg of body weight under fasting conditions twice, with a high-fat meal, and with aluminum-magnesium antacid. Serum was collected for 48 h and assayed by gas chromatography-mass spectrometry. Data were analyzed by non-compartmental methods and by at pharmacokinetic model with zero-order absorption and first-order elimination. Both fasting conditions produced similar results i.e. a mean (6 standard deviation) EMB maximum concentration of drug in serum (C_{max}) of 4.5 ± 1.0 µg/ml, time to maximum concentration of drug in serum (T_{max}) of 2.5 ± 0.9 h, and area under the concentration-time curve from 0 h to infinity ($AUC_{0-\infty}$) of 28.9 ± 4.7 µg. h/ml. In the presence of antacids, subjects had a mean C_{max} of 3.3 ± 0.5 µg /ml, T_{max} of 2.9 ± 1.2 h, and $AUC_{0-\infty}$ of 27.5 ± 5.9 4.7 µg. h/ml.In the presence of the Food and Drug Administration high-fat meal, subjects had a mean C_{max} of 3.8 ± 0.8 µg /ml, T_{max} of 3.2 ± 1.3 h, and $AUC_{0-\infty}$ of 29.6 ± 4.7 µg. h/ml. These reductions in C_{max}, delays in T_{max}, and modest reductions in $AUC_{0-\infty}$ can be avoided by giving EMB on an empty stomach whenever possible (Peloquin et al., 1999).

Pyrazinamide (PZA)

In this pharmacokinetic study the subjects ingested single doses of PZA 30 mg/kg under fasting conditions twice, without a high-fat meal and with an aluminum magnesium antacid. They also received standard dosages of isoniazid, rifampin, and ethambutol. Serum was collected for 48 hours and assayed by gas chromatography with mass selective detector. Data were analyzed by non compartmental methods and a compartmental analysis using nonparametric expectation maximization. Both fasting conditions produced similar results that are mean PZA C_{max} 53.4 ±10.4 µg/ml, T_{max} 1.43± 1.06 hours, and $AUC_{0-\infty}$ 673 ± 79.7 µg.hr/ml. Fasting results are similar to those in previous reports. In the presence of antacids, subjects had a mean C_{max} of 55.6± 9.0 µg/ml, T_{max} of 1.43 ±1.23 hours and $AUC_{0-\infty}$ 628 ± 88.4 µg.hr/ml. In the presence of the high-fat meal, mean C_{max} was 45.6± 9.44 µg/ml, T_{max} 3.09 ± 1.74 hours and $AUC_{0-\infty}$ 687 ± 116µg.hr/ml. It was concluded that these small changes in C_{max} T_{max} and $AUC_{0-\infty}$ can be avoided by giving PZA on an empty stomach whenever possible (Peloquin et al., 1998).

Rifampin (RIF)

In this pharmacokinetic study the subjects ingested single doses of RIF, 600 mg, under fasting conditions twice, with a high-fat meal, and with aluminum-magnesium antacid. They also received standard doses of isoniazid, pyrazinamide, and ethambutol. Serum was collected for 48 h and assayed by high-pressure liquid chromatography. Data were analyzed using non-compartmental methods and a compartmental analysis using nonparametric expectation maximization. Both fasting conditions produced similar results that are a mean RIF maximal serum concentration (C_{max}) of 10.54 ±3.18 µg/ml, the time at which it occurred (T_{max}) of 2.42±1.32 h, and the area under the curve from time zero to infinity ($AUC_{0-\infty}$) of 57.15±13.41 µg.h/ml. These findings are similar to those reported previously. Antacids

Table 1. Effect of Food on the pharmacokinetics of antitubercular drugs

Food item	Pharmacokinetic parameters	Outcomes	References
Fatty food	Bioavailability	Disintegration time and dissolution rate vary with fatty food	Ramesh et al., 2003
Carbohydrate and lipid	C_{max} and T_{max}	C_{max} reduced and T_{max} increased by carbohydrate than by lipid	Hsien-Chun et al., 2014
Oleanolic acid	Minimum inhibitory concentrations (MICs)	synergistic anti-mycobacterial effects	Fa et al., 2010
Cholesterol-rich diet	Minimum inhibitory concentrations (MICs)	Cholesterol should be used as a complementary measure in antitubercular treatment	Carlos et al., 2005
High-fat meal, and with aluminum-magnesium antacid	C_{max}, T_{max} and $AUC_{0-\infty}$	Reductions in C_{max}, delays in T_{max}, and modest reductions in $AUC_{0-\infty}$ can be avoided by giving ethambutol on an empty stomach whenever possible	Peloquin et al, 1999
High-calorie and high-fat meal	C_{max}, T_{max} and $AUC_{0-\infty}$	Increase in C_{max}, and $AUC_{0-\infty}$ and decrease in T_{max}	Helen et al., 2013
Vitamins and minerals, including zinc and selenium enriched biscuits	C_{max}, T_{max} and $AUC_{0-\infty}$	Increase in C_{max} and $AUC_{0-\infty}$, use of defined nutritional supplementation in HIV-co-infected TB patients should be considered in TB control programs	Kidola et al., 2014
High-fat meal and with an aluminum magnesium antacid	C_{max}, T_{max} and $AUC_{0-\infty}$	Small changes in C_{max} T_{max} and $AUC_{0-\infty}$can be avoided by giving Pyrazinamide on an empty stomach whenever possible	Anthony et al., 2015
High-fat meal and with an aluminum magnesium antacid	C_{max}, T_{max} and $AUC_{0-\infty}$	Small changes in C_{max} T_{max} and $AUC_{0-\infty}$can be avoided by giving Pyrazinamide on an empty stomach whenever possible	Peloquin et al., 1999
High-fat meal and with an aluminum magnesium antacid Efavirenz	C_{max}, T_{max} , $AUC_{0-\infty}$ and clearance	Changes in C_{max}, T_{max}, and $AUC_{0-\infty}$ can be avoided by giving INH on an empty stomach whenever possible	Peloquin et al., 1999

did not alter these parameters (C_{max} of 10.89 ±5.22 µg/ml, T_{max} of 2.36 ±1.28 hand $AUC_{0-\infty}$ of 58.37 ±18.49 µg.h/ml). In contrast, the Food and Drug Administration high-fat meal reduced RIF C_{max} by 36% (7.27 ±2.29 µg/ml), nearly doubled T_{max} (4.43 ±1.09 h), but reduced $AUC_{0-\infty}$ by only 6% (55.20±14.48 µg.h/ml). These changes in C_{max}, T_{max}, and $AUC_{0-\infty}$can be avoided by giving RIF on an empty stomach whenever possible (Peloquin et al., 1999).

Isoniazid (INH)

In this pharmacokinetic study the subjects ingested single doses of INH 300 mg under fasting conditions twice, with a high-fat meal, and with aluminum magnesium antacid. They also received standard doses of rifampin, pyrazinamide, and ethambutol. Serum was collected for 48 hours, and assayed by high performance liquid chromatography (HPLC). Data were analyzed using non compartmental methods and a compartmental analysis using nonparametric expectation maximization. Both fasting conditions produced similar results: a mean INH C_{max} of 5.53 ±2.92 µg/ml, T_{max} of 1.02 ±1.10 hours and $AUC_{0-\infty}$ of 20.16 ±12.45 µg.hr/ml. These findings are similar to those reported previously. Antacids did not alter these parameters significantly (C_{max} of 5.62±2.53 µg/ml, T_{max} of 0.71 ± 0.56 hours, and $AUC_{0-\infty}$ of 20.27 ± 11.39 µg.hr/ml). In contrast, the high-fat meal recommended by the Food and Drug Administration reduced INH C_{max} by 51% (2.73 ±1.70 µg/ml), nearly doubled T_{max} (1.93±1.61 hours), and reduced $AUC_{0-\infty}$ by 12% (17.72±10.32 µg.hr/ml).These changes in C_{max}, T_{max}, and $AUC_{0-\infty}$ can be avoided by giving INH on an empty stomach whenever possible (Peloquin et al., 1999). Different Pharmacokinetic alternations of Food and drugs, are given in **Table 1.**

Drug-Drug Interaction

The Purpose of drug interaction is concern when treating patients co-infected with human immunodeficiency virus (HIV) and tuberculosis. Safe, effective concomitant treatment regimens for tuberculosis and HIV infection are urgently needed. Bedaquiline is a novel anti-TB drug, and efavirenz is a commonly used antiretroviral. Due to efavirenz's induction of cytochrome P450 3A4, the metabolic enzyme responsible for Bedaquiline biotransformation, the drugs are expected to interact. Impact of induction was described as an instantaneous change in clearance one week after initialization of efavirenz treatment (Elin et al., 2013). Concomitant use of

efavirenz with the enzyme inducer rifampicin might be expected to increase efavirenz clearance. Overall there was a 29.5% reduction in efavirenz clearance during tuberculosis treatment. Unexpectedly, concomitant treatment of rifampicin and efavirenz reduced apparent efavirenz clearance with a corresponding decrease in efavirenz clearance exposure (Tanuja et al., 2012). The steady-state concentrations of indinavir and ritonavir before and after administration of rifampin were evaluated. An 87% reduction in median indinavir and a 94% reduction in median ritonavir concentrations were seen 12 h after the last dose of rifampin was administered. These results strongly indicate that the administration of rifampin with a combination of indinavir (800 mg) and ritonavir (100 mg) could lead to sub-therapeutic concentrations of indinavir (Justesen et al., 2004). A pharmacokinetic evaluation of the steady-state concentrations of atazanavir and ritonavir were performed. More than 50% of the time the atazanavir level was below the minimum recommended trough plasma level. These results strongly indicate that the administration of rifampicin with a combination of atazanavir 300 mg qd plus ritonavir 100 mg qd must be avoided because sub therapeutic concentrations of atazanavir are produced (Mallolas et al., 2007). Rifampicin-based anti-TB co-treatment has no significant influence on long-term efavirenz plasma exposure and efficacy. Hence, there is no need to increase the dose of efavirenz during concomitant rifampicin-based anti-TB co-treatment in the sub-Saharan African population (Requena et al., 2014). Co-administration of rifampin with edoxaban decreased edoxaban exposure but increased active metabolite exposure. Rifampin increased apparent oral clearance of edoxaban by 33 % and decreased its half-life by 50 % (Jeanne et al., 2015). There was a substantial proportion of patients having comorbidities that 56% with diabetes mellitus, 31% with cardiovascular disease, and 19% with hepatitis B virus carrier. Drug interactions should be considered in the pharmacokinetic study and all medication for these comorbidities should be reviewed. The effects of some drugs may be interfered by INH and/or RIF, such as sulfonylurea, metformin, acarbose, calcium channel blockers, angiotensin receptor blockers, β-blockers, α-blockers, and clopidogrel (Hsien et al., 2014). Different Pharmacokinetic alternations of drug-drug are given in **Table 2.**

Drug- Disease Interaction

For drug-compliant patients, poor responses to tuberculosis (TB) treatment might be attributable to sub-therapeutic drug concentrations. An impaired absorption of rifampin was reported for patients with diabetes mellitus (DM) or HIV (Requena et al., 2014). The objective of this report was to study the pharmacokinetics of rifampin (RMP), isoniazid (INH), and pyrazinamide (PZA) in HIV-infected children

Table 2. Effect of drugs on the pharmacokinetics of antitubercular drugs

Drugs	Pharmacokinetic parameters	Outcomes	References
Efavirenz	Plasma clearance	change in clearance	Elin et al., 2013
Efavirenz	Plasma clearance	Overall there was a 29.5% reduction in EFV clearance during tuberculosis treatment	Tanuja et al., 2012
Efavirenz	Clearance	CYP2B6*6 and *18 variant alleles, weight and sex were the most significant covariates explaining 55% of inter-individual variability in efavirenz clearance	Milcah et al., 2015
MofIndinavir, Ritonavir	C_{max}, T_{max} and $AUC_{0-\infty}$	Administration of rifampin with a combination of indinavir (800 mg) and ritonavir (100 mg) lead to sub-therapeutic concentrations of indinavir	Justesen et al., 2004
Efavirenz	Clearance	Change in clearance	Anthony et al., 2015
Nevirapine	C_{max}, T_{max} and $AUC_{0-\infty}$	Sub-therapeutic nevirapine concentration	Mohammed et al., 2011
Azanavir	C_{max}, T_{max} and $AUC_{0-\infty}$	sub-therapeutic concentrations of azanavir	Mallolas et al., 2007
Lopinavir/Ritonavir	C_{max}, T_{max} and $AUC_{0-\infty}$	The administration of isoniazid may cause higher lopinavir concentrations, which may increase lopinavir toxicity	Decloedt et al., 2015
Efavirenz	C_{max}, T_{max} and $AUC_{0-\infty}$	There is no need to increase the dose of efavirenz during concomitant rifampicin-based anti-TB cotreatment in the sub-Saharan African population	Habtewold et al., 2015
Colistin	C_{max}, T_{max} and $AUC_{0-\infty}$	combinations resulted in substantially greater killing at the low inoculums	Hee et al., 2013
Efavirenz	C_{max}, T_{max} , $AUC_{0-\infty}$ and Clearance	Increase in Para amino-salicylic acid(PAS) clearance and reduction in mean PAS area under the concentration curve	Lizanne et al., 2014
Nevirapine	C_{max}, T_{max} , $AUC_{0-\infty}$ and Clearance	Rifampicin reduced the nevirapine concentration below subtherapeutic level	Elsherbiny et al., 2009
Edoxaban	Clearance and T_{max}	Rifampin increased apparent oral clearance of edoxaban by 33 % and decreased its half-life by 50 %	Jeanne et al., 2015
Fixed-dose Combinations	C_{max}, T_{max} , $AUC_{0-\infty}$, and bioequivalence	Two drugs displayed inferior rifampin bioavailability compared with the reference	Hui et al., 2015
Moxifloxacin	C_{max}, T_{max} and $AUC_{0-\infty}$	The large variability observed in moxifloxacin pharmacokinetics	Manika et al., 2015
Drug-drug interaction	C_{max}, T_{max} and $AUC_{0-\infty}$	According to the results of the bioequivalence analysis carried out in this study, rifampin formulations A, B, C and D were not within the acceptable range	Hao et al., 2015

with tuberculosis (TB). The proportions of children with subnormal peak concentrations (C_{max}) of RMP, INH, and PZA were 97%, 28%, and 33%, respectively. These findings have important clinical implications and emphasize that drug doses in HIV-infected children with TB have to be optimized**.** High mortality among patients already on ART before initiating MDR-TB treatment is a worrisome development. Management of adverse-events, opportunistic infections and co-morbidities in these patients is important if the protective benefits of being on ART are to be maximized. There is the need to intensify intervention programmes targeted at early identification of MDR-TB, treatment initiation, drug monitoring and increasing adherence among HIV co- infected MDR-TB patients (Teye et al., 2015). HIV-infected patients with a CD_4 cell count 200 cells/µl had a higher risk of poor treatment outcome (27%). After adjustment for HIV infection and CD_4 cell count, patients with low pyrazinamide C_{max} were 3 times more likely than patients with normal pyrazinamide C_{max} to have poor outcomes. Lower than expected antituberculosis drug C_{max} occurred frequently, and low pyrazinamide C_{max} was associated with poor treatment outcome. Exploring the global prevalence and significance of these findings may suggest modifications in treatment regimens that could improve tuberculosis cure rates (Sekai et al., 2009). Different Pharmacokinetic alternations of drug -diseases are given in **Table 3.**

Applications of pharmacokinetic alternations in therapeutic drug monitoring (TDM)

Worldwide, tuberculosis (TB) remains the leading cause of death from a curable infectious disease. Death is a consequence of delayed diagnosis and ineffective or incomplete treatment. Slow response to therapy can lead to prolonged infectiousness, extended treatment duration, acquired drug resistance, or recurrence of TB after treatment (Scott et al., 2010). Treatment success in multidrug-resistant (MDR) TB cases is low (62%, with 7% failing or relapsing and 9% dying) and in extensively drug-resistant (XDR) TB cases is even lower (40%, with 22% failing or relapsing and 15% dying). The treatment of drug-resistant TB is also more expensive (exceeding €50 000 for MDR-TB and €160 000 for XDR-TB) and more toxic if compared to that prescribed for drug-susceptible TB. Appropriate dosing of first- and second-line anti-TB drugs can improve the patient's prognosis and lower treatment costs. Therapeutic drug monitoring (TDM) is based on the measurement of drug concentrations in blood samples collected at appropriate times and subsequent dose adjustment according to the target concentration (Giovanni et al., 2015). The reasons for slow response are diverse, but measurement of serum anti-TB drug levels, or therapeutic drug monitoring (TDM), is a potentially useful tool for uncover the causes of slow response. Low serum levels can be a consequence of mal absorption, inaccurate dosing, altered metabolism, or drug–drug interactions, but in most instances low serum levels can be readily corrected with dose adjustment (Scott et al., 2013). Therapeutic drug monitoring (TDM) is the process of obtaining the serum concentration of a medication and modifying the dose based on the results to optimize its therapeutic benefits, while minimizing its risk for side effects or toxicity (Jiehui et al., 2004). The goal of TDM include the study and management of pharmacokinetic drug–drug and drug–disease interactions as well as the evaluation of new fixed-dose combinations developed for treatment of tuberculosis. Some drugs used for treatment of multidrug-resistant tuberculosis have low therapeutic indices and can often lead to adverse reactions. One example is the likely additive synergistic neurotoxicity resulting from the co-administration of ofloxacin and cycloserine. TDM might have a possible role to play by further optimizing therapeutic efficacy and minimizing toxicity. The liver is the principal organ for metabolizing rifampin, isoniazid and pyrazinamide. Liver dysfunction is a known complication of antituberculosis chemotherapy (Yew et al., 2001). Recent evidence suggests that some TB patients may benefit from TDM; certain comorbidities, such as human

Table 3. Effect of diseases on the pharmacokinetics of antitubercular drugs

Diseases	Pharmacokinetic parameters	Outcomes	References
Comorbidities and Food	C_{max}, T_{max} and $AUC_{0-\infty}$	Isiniazid exposure was affected by weight-adjusted dose and by food, but comorbidities did not indicate any effect on pharmacokinetics	Ana et al., 2014
Diabetes or HIV	C_{max}, T_{max} and $AUC_{0-\infty}$	Delayed absorption and low plasma concentrations	Ana et al., 2012
HIV-Patient	C_{max}, T_{max} and $AUC_{0-\infty}$	A high proportion of children with HIV and TB had a subnormal Rifampin C_{max}, The Pyrazinamide C_{max} significantly influenced in treatment outcome	Ramachandran et al., 2015
HIV-Positive and HIV-Negative	C_{max}, T_{max} and $AUC_{0-\infty}$	Variation in C_{max}, and $AUC_{0-\infty}$ and decrease in T_{max}	van et al., 2015
HIV-Patient	Hematological parameters	Variation in hematological parameters	Teye et al., 2015
HIV-Patient	C_{max}, T_{max} and $AUC_{0-\infty}$	Lower than expected antituberculosis drugs $C_{max.}$	Sekai et al., 2009

Table 4. Concomitant drug interactions of antitubercular drugs

S. No	Drug	Drugs	Enzyme inhibition/Induction	Interaction
1	Isoniazid	Carbamazepine Acetaminophen Phenytoin Ketoconazole	CYP450 inhibition Induction a liver enzyme Phenytoin C_{max} increase decrease serum levels of ketoconazole	carbamazepine toxicity Acetaminophen Phenytoin toxicity Sub therapeutic effect
2	Rifampicin	Oral contraceptives Warfarin	Induction of the cytochrome P450 system Enzyme Induction	reduce the efficacy of birth control pills Inadequate anticoagulation
3	Streptomycin	Diuretics Neuromuscular blocking agents	Synergetic effect	Ototoxicity Neuro Toxicity

immunodeficiency virus (HIV), diabetes, malnutrition, renal and hepatic impairment, along with drug-resistant disease, have been associated with low drug levels (Tongeren et al., 2013). Concomitant drug interactions of antitubercular drugs are given in **Table 4.** PK-PD approach has demonstrated its relevance in contributing to the understanding of many important phenomena in the treatment of tuberculosis such as the role of isoniazid, dose size of rifamycins and potency in fluoroquinolones and promises to become a key component of the rational development of new agents (Davies et al., 2008). TDM in diabetics starting anti-TB therapy revealed that a low isoniazid or rifampin serum concentration corrected to the expected range with a single dose increase and no major reported toxicity. Diabetics with early TDM and pulmonary TB had a favorable time to sputum culture conversion and the total statewide burden of slow response appeared to be minimized during the period of the initiative. Thus, early TDM for diabetics can be considered in settings of high diabetes/TB coprevalence where slow response and prolonged treatment duration are programmatic concerns (Scott et al., 2013). Obviously, TB treatment does not fulfill all requirements for TDM, mainly because of gaps in knowledge and understanding of the pharmacokinetics and pharmacodynamics of TB drugs. Sharing clinical experience of using TDM to individualize TB treatment could help to fill parts of those gaps and TDM will play an important role in the development of safe and effective therapeutic medications and individualization of these medications (Cecile et al., 2012).

Conclusion

The research and review articles, studied for understanding the pharmacokinetic profile of antitubercular drugs and their clinical applications in therapeutic drug monitoring, are sufficient enough to conclude that hepatotoxicity and sub-therapeutic effect of antitubercular drugs have been observed due to concomitant food, drugs and diseases interactions causing alteration in pharmacokinetics of antitubercular drugs leading to drug resistance. Therefore to maintain an effective therapeutic medication the pharmacokinetic parameters for these drugs need to be monitored with accuracy and precision. Food supplements like high carbohydrate and lipid containing diet directly effect on drug plasma concentration. *e.g.* Carbohydrate reduced C_{max} and increased T_{max} while lipid had the same effect but with lesser extent. Diseases conditions like HIV and diabetes also effect on pharmacokinetics since such diseases alter the metabolism and immunity of the patients, *eg* delayed absorption and low plasma concentrations. Drugs used in HIV and diabetes also alterthe pharmacokinetics of antitubercular drugs, *eg* overall there was a 29.5% reduction in efavirenz clearance during tuberculosis treatment while rifampin considerably decreases the plasma concentration of repaglinide. Therefore all the factors mentioned above should be monitored meticulously. Further it is mandatory to make such studies a team work involving clinicians, paramedics, statisticians and the bio-analysts to harvest the benefits of TDM in clinical application by lowering drug interaction and the incidence of treatment failure through individualization of the therapy. Such a bio-analytical technique in clinical practice for sure will help in identifying the most appropriate dosage regimen to achieve the optimal response with minimal toxicity.

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