



PHARMACOKINETICS OF INH AND PZA IN MDR-TB: A REVIEW

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ABSTRACT

Tuberculosis remains a leading cause of morbidity and mortality in developing countries, including India. Isoniazid and pyrazinamide are powerful drugs administered as the first line and second line anti-TB drugs in tuberculosis affected patients. It plays a key role in shortening the TB therapy. Isoniazid (INH), and pyrazinamide (PZA) are the main drugs for the treatment of tuberculosis (TB). Mycobacterium tuberculosis is responsible for causing tuberculosis and can acquire multiple drug resistance (MDR) by not responding to the most powerful anti-TB agents. The complications of drug resistance in TB elevate some of the risk factors like inadequate treatment compliance, non-compliance of the patients to the treatment. Pharmacokinetics provides a basic time course of drugs and their effects in the body. These pharmacokinetic processes are referred to as ADME.

Key words Isoniazid, Pyrazinamide, MDR, ADME, TB

INTRODUCTION

Tuberculosis is an infectious disease caused by Mycobacterium species (*M. tuberculosis* in humans and *M. bovis* in cattle). The mortality rate is more higher. Tuberculosis is next to AIDS. Pharmacokinetics gives a mathematical basis to assess the time of drug interaction and their effects in the body. It enables the following processes: Absorption, Distribution, Metabolism, and Excretion. These pharmacokinetic processes are referred to as ADME [1]; determine the drug concentration in the body when medicines are recommended. A fundamental understanding of these parameters is required to design an appropriate drug regimen for a patient [2,3]. Tuberculosis (TB) is one of the increasing causes of death worldwide [4]. The number of reported MDR-TB cases has been leading in recent years [5].

Absorption: Absorption is the process of a substance entering the blood circulation. Drug substances can enter the body via gastrointestinal tract, lung or skin, and they are absorbed. The gastrointestinal tract is the most important site of absorption, it is affected by several factors such as physicochemical parameters of the drug, gastrointestinal motility, drug concentration at the site of absorption [6].

Distribution: Distribution describes the reversible transfer of drug from location to location within the body. The distribution of a drug is involved by factors such as lipid-solubility [7], concentration in plasma and in various tissues are binding to plasma, transport the proteins and tissues.

Metabolism: Metabolism is the process of irreversible transformation of parent compounds into daughter metabolites. The major site of metabolism in the body is the liver [8]. There are many factors that influence drug metabolism including route of administration, dose, genetics, disease state, and metabolic activity [9].

Excretion: Excretion is the process of eliminating the drug and other toxic substances from the body. Most of the drugs in the body are eliminated through the urine. Substances with low lipid solubility such as polar metabolites are excreted efficiently [10].

Isoniazid: Isoniazid (also, Nicotinic Acid Hydrazide, INH or H) is one of the drugs for first-line treatment of tuberculosis along with Rifampicin and Pyrazinamide. It functions to block the production of Mycolic Acid, an essential cell wall component in the tuberculosis bacterium [11] [12]. Mycolic acid confers the bacterium with resistance to chemical damage and dehydration, and prevents the effective activity of hydrophobic antibiotics. In

addition, mycolic acid allows the bacterium to grow on macrophages, effectively hiding it from the host's immune system. These are the reasons vital for the selection of mycolic acid as a drug target. They circulate in the bloodstream, the isoniazid prodrug is activated via a bacterial catalase-peroxidase enzyme, encoded by KatG gene [13]. Action of isoniazid is most significant in the first week of drug administration as it acts on rapidly multiplying bacteria. On slow growing bacteria, it acts as a bacteriostatic agent. The adverse effects of Isoniazid may result in discontinuation of treatment in some cases. The side effects can be listed astoxic, idiosyncratic and hypersensitivity reactions. Many toxic reactions are peripheral neuropathies at conventional dosage and seizures from overdosage. Idiosyncratic reactions are INH-induced lupus erythematosus, rheumatic-like syndromes and other hematologic disorders. Hypersensitivity reactions to isoniazid include hepatitis, dermatitis, fever, and haemolytic anaemia [14]. If the Mycobacterial strain is resistant to low dosage of INH (300 mg/day) in primary therapy, then a higher dosage (1 - 1.5 g/day) is administered to overcome the resistance. This high dosage of INH in the re-treatment of drug-resistant tuberculosis has been calculated in clinical trials [15].

Pyrazinamide: Pyrazinamide is a prodrug converted to its active form, pyrazinoic acid, by hepatic microsomal deamidase [16] and is active against dormant and semi-dormant Mycobacterium tuberculosis bacilli, especially in acidic environments [17][18]. It is currently part of a four-drug fixed-dose combination (FDC), which includes isoniazid, ethambutol, and rifampin, an inducer of a number of cytochrome P450 enzymes via the pregnane X receptor (PXR) [19]. Pyrazinamide is currently being considered as a drug in tuberculosis (TB) treatment regimens [20-22], including for multidrug-resistant tuberculosis (MDR-TB).

Interest in the drug derives from its potent sterilizing activity, which confers the ability to shorten treatment duration. Pyrazinamide exposures have been correlated with favorable treatment outcomes in patients on standard doses[20],[23-28]. A pyrazinamide area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) of at least 363 mg · h/liter has been associated with long-term TB treatment outcomes among patients with drug-susceptible TB and could be targeted for treatment optimization[20]. The current

recommended weight-adjusted daily dose of pyrazinamide for treatment of drug-susceptible TB is approximately 25 (range, 20 to 30) mg/kg of body weight[29], while that for treatment of MDR-TB is about 35 (range, 30 to 40) mg/kg [30]. Doses higher than those currently recommended may result in high levels of 5-hydroxypyrazinoic acid, which is responsible for pyrazinamide induced hepatotoxicity [31]. On the other hand, there exist discrepancies in exposure between the weight bands; patients in the lower weight bands achieve lower drug exposures [32,33].

Despite interest in pyrazinamide, relatively few studies have described its pharmacokinetics (PK) longitudinally [34-37]. We previously reported PK exposures of pyrazinamide in this cohort of HIV/TB-coinfected patients [32]. Here, we use a population modeling approach to describe changes in PK parameters during the first month of treatment and identify other factors affecting the PK. We then used parameter estimates of the final model to simulate exposures associated with a range of feasible doses for treatment of drug-susceptible TB and MDR-TB.

MDR-TB: It is a condition in which mycobacterium tuberculi develops resistance to Isoniazid and Rifampicin, the two most effective first line anti-TB medicines. Patients with Multi Drug-Resistant Tuberculosis (MDR-TB) require treatment with second-line treatment, these are more complex than those used to treat patients without drug-resistant TB [38]. The diagnosis of MDR-TB is by performing drug sensitivity tests (DST) on the isolates. DST data can also be used to identify the drug regimen. Second-line anti-tuberculosis drugs are less effective than first-line drugs and are known to cause adverse reactions more frequently. This class of anti-tuberculosis drugs includes para-aminosalicylic acid (PAS), amikacin, capreomycin, thionamide and cycloserine. New drugs such as rifapentine, levofloxacin, gatifloxacin and moxifloxacin have not yet been categorized. A retrospective study in Hong Kong compared the efficacy of two fluoroquinolones- Levofloxacin and Ofloxacin in the treatment of MDR-TB. They administered these drugs along with accompanying second-line drugs and found that Levofloxacin had a 90.0% overall success rate as compared to 79.7% success rate of Ofloxacin [39].

Conclusion:

It is necessary to obtain human pharmacokinetic information about the drug of isoniazid and

pyrazinamide in MDR-TB. Clinical pharmacokinetic studies are performed to examine the absorption, distribution, metabolism, and excretion of an investigational drug. This study will provide information on the pharmacokinetics profile INH&PZA drugs in MDR-TB patients. Not only regarding tuberculosis, but also in relation to other microbial and infectious diseases, resistance towards antibiotics results in treatment failures, advancing of disease and infections. So, treatment should be directed towards using drugs which either overwhelm the resistance of organisms towards antibiotics or improve the benefits of other anti-TB drugs. Resistance repression is explained as one medication involve the resistance to another, but not one drug involve the resistance to itself. By taking appropriate measures and strictly following the therapy, the MDR-TB might be suppressed to a greater area.

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