MALAYSIAN Journal *of* Pharmacy

Original Research Article

Systematic Review of Population Pharmacokinetic Models of Isoniazid in Children and Adults with Tuberculosis

Wen Rui Tan[1], Siti Maisharah Sheikh Ghadzi[1], Irfhan Ali Hyder Ali [2], Sabariah Noor Harun[1]*

Article Info

Received date: 07 Jun 2022
Accepted date: 19 Oct 2022
Published date: 31 Dec 2022

Keywords: *Population Pharmacokinetics, Isoniazid, Tuberculosis, Pharmacokinetic.*

ABSTRACT

Introduction: Isoniazid (INH) is one of the first-line anti-tuberculosis (anti-TB) drugs that have both bactericidal and bacteriostatic properties depending on the rate of mycobacterial growth. Several population pharmacokinetic (PPK) models of INH were established. This systemic review aims to summarise published PPK parameters of INH in the models and to identify covariates influencing the INH pharmacokinetic parameters of models. **Method:** A search of publications for PPK analyses of INH in volunteers or TB patients from 2011 to 2021 was conducted in PubMed and Scopus databases. Reviews, methodology articles, non-compartmental analysis, *in vitro*, and animal studies were excluded. **Result:** Twelve studies were included in this review. Most of the included studies described the pharmacokinetics of INH as two-compartmental with first-order absorption and elimination in most of the included studies. Eleven studies reported N-acetyltransferase 2 (NAT2) genotype polymorphism as the most common significant covariate affecting the pharmacokinetic parameters of INH. Other common significant covariates reported include body weight (n = 2) and body mass index (BMI) (n = 1). **Conclusion:** The variability of population clearance parameters of INH was explained mainly by the NAT2 genotype polymorphism. This indicates that to optimise and rationalise the dosing regimen of INH, a patient's NAT2 genotype should be considered. At the same time, body weight and BMI values should be considered when making dosing adjustments for INH to achieve the therapeutic range.

INTRODUCTION

Isoniazid (INH) is a prodrug that kills the mycobacterial cell via a passive diffusion mechanism [1]. Isoniazid is activated by the mycobacterial catalase-peroxidase enzyme (KatG) [2], a multifunctional catalase-peroxidase that has other activities, including peroxynitrite and nicotinamide adenine dinucleotide (NADH) oxidase [3]. Due to its high effectiveness and affordability, INH is one of the two primary, first-line TB drugs, along with rifampicin (RIF).

Multidrug-resistant TB (MDR-TB) is simultaneous resistance to INH and RIF. Despite, proven drug susceptibility at baseline, MDR-TB is still not uncommon. Non-compliance to anti-TB therapy is believed to be associated with MDR-TB and treatment failure emergence, which led to the implementation of the directly observed therapy-short-course strategy (DOTs), or currently, video observed therapy (VOT). The World Health Organization (WHO) has called the DOTs the most essential health breakthrough of past decades [4,5]. In addition, the development of a fixed-dose combination (FDC) regimen was also reported to enhance drug compliance among patients with TB [4]. However, a study by Srivastava et al. [4] reported a surprising finding which showed that acquired MDR-TB was related to variability in drug exposure and not to non-compliance. Previous studies have shown that low plasma anti-TB drug concentrations may result in treatment failure [6-8] and low plasma concentrations of RIF and INH have been associated with MDR-TB [8]. High variability in pharmacokinetic (PK) parameters of the first-line anti-TB drugs have been reported with factors such as age, sex, human immunodeficiency virus (HIV) co-infection, and antiretroviral treatment (ART) possibly affecting TB drug concentrations [9]. Reduced blood concentrations of anti-TBs were demonstrated

*Correspondence: sabariahnoor@usm.my
DOI:10.52494/DJIQ7058

[1]School of Pharmaceutical Sciences, Universiti Sains Malaysia, 11800 USM, Penang, Malaysia.
[2]Respiratory Department, Penang General Hospital, 10990 George Town, Penang.

in HIV-infected men or HIV-infected patients who are underweight [9]. Other factors such as diabetes and drug-drug interaction have been shown to affect the PK parameters of first-line anti-TB agents [10]. Malnutrition is also reported to affect drug exposure by decreasing total clearance and increasing the plasma half-life of anti-TBs [11]. Thus, therapeutic drug monitoring of INH is clinically relevant due to the high variability of INH concentrations [12] and incorporating the significant covariates influencing the PK of INH to achieve an optimal INH concentration is paramount.

Conventional clinical practice guidelines recommend dosing anti-TB drugs according to ideal body weight and providing dosing caps for most first-line agents [13]. However, this recommendation may be placing obese patients with TB at risk as increased total body weight is associated with an increased risk of clinical failure [12].

Population pharmacokinetic (PPK) modelling is broadly used to distinguish the pharmacokinetic parameters of a population and investigate the covariates that contribute to pharmacokinetic variability [14]. Nonlinear mixed-effects modelling is viewed by many as the optimum population modelling method currently. The "effects" are factors that contribute to the variability of the measured observations and are of two types: fixed and random. Fixed effects are the parameters that define the structural PK model while the random effects are described as random interpatient variability (covariates) and residual random error [15].

Extensive reviews elucidating the PK characteristics of INH have been reported elsewhere [16, 17]. However, a systematic review of the PPK models of INH is still lacking. Analysing and understanding the significant covariates and their relationship in different patient populations is critical for appropriate regimens for individualised therapy. This review aims to compare published population pharmacokinetic (PPK) models of INH and to summarise and explore identified covariates influencing the INH PK models.

METHOD

Search Strategy

Data for this review were identified by a systematic review of publications listed in PubMed databases from inception to September 2021 following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [22]. The search terms used include the following: "isoniazid" AND ("population pharmacokinetics" OR "pharmacometrics" OR "pharmacokinetic model" OR "PopPK" OR "pop PK" OR "PPK" OR "nonlinear mixed effects model" OR "NONMEM" OR "MONOLIX" OR "Pmetrics" OR "NLME"). Additional publications were identified by reviewing study reference lists and consulting expert review articles identified through the search.

Inclusion/Exclusion Criteria

All relevant articles selected from the databases and reference lists were screened to evaluate their eligibility for inclusion according to specific criteria. The inclusion of studies was based on original studies describing PPK models for INH in healthy volunteers or patients from infants to adults and the target population was human. Extrapulmonary TB like tuberculous meningitis is also included in the study, but only the recorded plasma concentrations of INH were included in this review and not the concentrations at the other site. Reviews, methodology articles, *in vitro* and animal studies, and studies that used a previously described PK model and those that involved noncompartmental analysis were excluded. PPK analysis was performed in the study, and only the study published in English was selected.

Data Extraction

The variables that were retrieved from the identified studies include first author, publication year, country, number of subjects, subject characteristics (age, sex, weight, and pathology), INH dose, INH, and AcINH levels, sampling schedule, and assay method, number of observations, observations per patient, data source, software used for modelling, structural and statistical model, tested and statistically significant covariates, and model validation which was further classified based on the increasing order of quality into three types: basic internal, advanced internal, and external model validation.

RESULT

Study Identification

The initial search strategy identified 107 potentially relevant articles, of which 106 remained after duplicates, and review-type articles were removed. After abstract and title scanning for 106 articles, 14 articles were retained for final evaluation. A total of 12 studies published between 2013 and 2021 were included in this review in the final decision, as demonstrated in **Figure I**. Study characteristics of the included publications, samples, and concentrations are summarised in **Table I**. The number of study participants varied from 33 to 466, totalling 1,444 patients in all 12 publications with reported ages ranging from 0 to 72 years. Only four of the studies included subjects aged less than 18 years old. Seven studies present data on adult patients with pulmonary TB and one study was conducted on adult volunteers.

The assay used to measure INH concentrations

Liquid chromatography with tandem mass spectrometry (LC-MS/MS) or high-performance liquid chromatography (HPLC) was used to determine the serum levels of INH and AcINH in all studies except one study [18] where spectrocolorimetric was used instead. The number of concentration readings ranged from 195 to 2546. The daily dose was reported in 11 studies. 4 studies were reported in mg/kg, 7 studies reported the dosing in mg, and one reported in mg/dose.

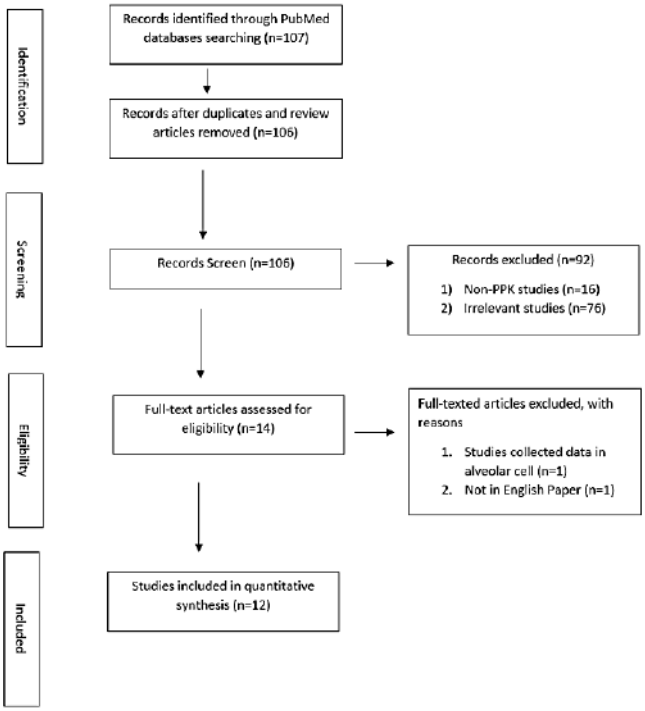

Figure I: The selection process of the studies included in the systematic review

Study Design

Most PPK studies were performed on patients with pulmonary TB, and only one study by Seng et al. [19] engaged healthy adults. Four studies included infants and children or paediatrics [20-23], and eight studies only enrolled adults [18,19,24-29]. Subjects in all included studies were administered INH orally; 1-12 samples were collected per individual. The sampling time points ranged from 0 (pre-dose) to 24 h post-dosing. The detailed characteristics of all studies are listed in **Table I**.

Modelling Approach

All twelve PPK analyses were conducted using population modelling software, including NONMEM (Icon plc, Dublin, Ireland), Phoenix NLME, Monolix (Lixoft, Antony, France), and Pmetrics. The most used algorithm was first-order conditional estimation with interaction.

Structural Model

The final PK parameter estimates in each study are summarised in **Table II**. A study by Fredj et al. [18] and Aruldhas et al. [23] described the INH structural model as a one-compartment model disposition model with first-order absorption and transit time (MTT) absorption model, respectively. Of the twelve studies, ten studies described PPK of INH as a two-compartment model, with five studies [19,20,25,28] describing first-order absorption and elimination. Three studies described the absorption model with MTT [21,22,29]. While the study by Rao et al. [24] and Naidoo et al. [26] described the absorption model with a lag time (**Table II**).

The reported mean clearance (CL) from all the studies was 20.55 L/h (SD = 16.60), and the range of the CL was between 5.19 to 28.77 L/h. The reported mean central volume of distribution ($V_{central}$) was 26.63 L (SD = 23.53), with a range from 1.5 to 73.4 L. The reported mean MTT was 0.66 h (SD = 0.34), with a range from 0.179 to 0.924 h (**Table II**).

Children vs Adults

There were four PPK studies conducted on children, and the other eight articles were conducted on adults. Three studies involved HIV children [22,24,29]. The estimated median CL for children was 6.5 (range = 4.44-11.3) L/h and was lower than CL in adults at 22.8 L/h (range = 11.4-40.5 L/h). Moreover, the median $V_{central}$ in children was lower than that in adults. The determined median V_d was 16.69 (range = 3.78-29.7) L/kg for children and 29.7 (range = 1.5-73.4) L/kg for adults.

Covariates model

The covariates investigated and identified in each study are shown in **Figure III**. Twenty-nine covariates have been investigated in the twelve studies, and five significant covariates have been identified using a stepwise covariate modelling approach. There were three covariates reported significantly affecting the CL of INH in the included studies, which include NAT2 polymorphism (n = 11), creatinine clearance (n = 1), and body mass index (BMI) (n = 1). Creatinine clearance in the study, where it was the significant covariate was estimated by using the Cockcroft and Gault equation with total body weight [19]. While middle-upper arm circumference (MUAC) (n = 1), body weight (n = 2) and body mass index (BMI) (n = 1) significantly explained the variability in Vcentral. Figure IV shows a comparison of mean CL as an effect of NAT2 polymorphism between studies.

Table I: Studies population characteristics, samples, and concentrations

Study	N (male/female)	Sample/subject	Total sample	Age	Body weight (kg)	Site	Subject characteristics	Dose	Sampling time (h)	Isoniazid concentration	Acetyl isoniazid concentration
Horita et al., 2018 [20]	113 (63/59)	5	565	5 (2.17-8.25)	14.3 (9.7-20.1)	US	Tuberculosis, Children	10.99 mg/kg (9.06-12.8)	0, 1, 2, 4, 8	C_{max} = 5.70 µg/mL	NA
Rao et al., 2021 [24]	81 (52/29)	4	324	36 (30-3.5)	52.5 (45.3-58)	US	Tuberculosis with HIV	300, 450, 600, 750, 900 mg	1, 2, 4, 6	C_{max} = 3.6 (2.3-4.6) mg/kg	NA
Jing et al., 2020 [25]	89 (59/30)	1-4	195	42.9 (16-72)	60.1 (35-100)	C	Tuberculosis	300 mg/dose (300-600)	Within 0.5-6	C_{max} = 3-6 µg/mL	NA
Naidoo et al., 2019 [26]	172 (119/53)	4	573	35 (30-41)	55.7 (50.3-62.1)	A	Tuberculosis	225 mg (below 55 kg), 300 mg (above 55 kg)	2.5, 5, 6, 24	C_{max} = 4.70 (3.93-5.98) mg/L	NA
Zvada et al., 2013 [21]	76 (40/36)	Cohort 1: 0.75, 1.5, 3, 4, 6 Cohort 2: 0.5, 1.5, 3,5	715	2.17 (0.417, 10.7)	10.5 (4.9, 21.8)	A	Tuberculosis	1st PK (mg/kg): 5.03 (3.56, 12.1) 2nd PK (mg/kg): 9.77 (2.73, 13.3)	Cohort 1: 0.75, 1.5, 3, 4, 6 Cohort 2: 0.5, 1.5, 3, 5	NA	NA
Panjasatwong et al., 2021 [22]	100 (56/44)	2	523	3.0 (0.167-15)	10.9 (4-4.3)	V	Tuberculous meningitis	10 mg/kg	2 of 10 possible time points (i.e., 1, 2, 3, 4, 5, 6, 8, 12, 18, or 24 h after dose)	C_{max} = 2.41 mg/L	NA
Seng et al., 2015 [19]	33	NA	NA	33 (22-56)	62.5 (45.8-86.1)	S	Healthy	Singapore	0, 1, 2, 4, 6, 8, 10, 12, 18, and 24 h after the final dose of INH	3 mg/L < C_{max} < 6 mg/L	NA
Fredj et al., 2021 [18]	118 (39/79)	2	INH :298	36.7 (5-77)	62 (8.9-104)	T1	Tuberculosis	5, 10, 25 and 15 mg/kg	3 h post-dose	NA	NA
Van Beek et al., 2021 [27]	466	NA	2546	NA	NA	T2, I1, TN, SA	Tuberculosis	NA	NA	C_{max} = 3.03 mg/L	NA

Table I: Studies population characteristics, samples, and concentrations (continued)

Study	N (male/female)	Sample/subject	Total sample	Age	Body weight (kg)	Site	Subject characteristics	Dose	Sampling time (h)	Isoniazid concentration	Acetyl isoniazid concentration
Huerta-García et al., 2020 [28]	55 (31/24)	Hospitalised: 8-12	294	44.7 (18-72)	56.6 (30-108)	M	Tuberculosis	225 mg (below 55 kg),	Hospitalised: 0, 20 min, 40 min, 60 min, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 h Outpatient: 2, 4 h	NA	NA
Denti et al., 2015 [29]	100 (58/42)	3	574	35 (29-40)	51.9 (48.3-57.3)	T2	Tuberculosis	225 mg (below 50 kg), 300 mg (above 50 kg)	2, 4, 6 h post-dose	Slow acetylator: 3.53 mg/L Fast acetylator: 3.03 mg/L	NA
Aruldhas et al., 2019 [23]	41 (29/12)	8	290	7 (3.5-13)	19.5 (13.7-33.7)	I2	Tuberculosis	50 mg (4-7 kg), 100 mg (8-11 kg), 150 mg (12-15 kg), 200 mg (16-24 kg)	0.5, 1, 1.5, 2, 2.5, 4 and 6 h post-dose	C_{max} = 5.90 mg/L	NA

C_{max} = maximum concentration; NA=Not applicable
A = Africa; C = China; I1= Indonesia; I2 = India; M = Mexico; SA = South Africa; S = Singapore; T1 = Tunisia; T2 = Tanzania; TN = The Netherlands; US = United State; V = Vietnam

Table II: Model structure, pharmacokinetic parameters, and tested and retained covariates

Study	Assay	Software/Algorithm	Structure	Final population pharmacokinetic parameters for Isoniazid	Acetylisoniazid	Covariates tested	Retained covariates in the final model
Horita et al., 2018 [20]	LC-MS/MS	MonolixSuite2016R1/ FOCE-INTER	Two-compartment model with first-order absorption and linear elimination	K_a (h^{-1}) = 4.23 CL/F_{slow} (L/h) = 4.44 $CL/F_{nonslow}$ (L/h) = 8.08 V_1/F (L) = 16.6 Q/F (L/h) = 8.46 V_2/F (L) = 1.07	NA	NAT2 genotype polymorphism, age, weight, serum creatinine, sex, HIV infection	NAT2 genotype polymorphism
Rao et al., 2021 [24]	LC-MS/MS	Phoenix NLME/FOCE-extended lease squares	Two-compartment model with a lag time	K_a (h^{-1}) = 0.9 V_1 (L) = 2.9 V_2 (L) = 32.5 CL = (L/ h) = 9.2 CL_2 (L/h) = 9.6 T_{lag} = 0.4	NA	Age, sex, body weight, mid-upper arm circumference (MUAC), TB diagnostic group (confirmed and unconfirmed), NAT2 genotype.	Mid-upper arm circumference (MUAC)

Table II: Model structure, pharmacokinetic parameters, and tested and retained covariates (continued)

Study	Assay	Software/Algorithm	Structure	Final population pharmacokinetic parameters for Isoniazid	Acetylisoniazid	Covariates tested	Retained covariates in the final model
Jing et al., 2020 [25]	LC-MS/MS	NONMEM v7.2/FOCE	A two-compartment model with first-order absorption and elimination	CL/F (L/h) = 31.4 V_1/F (L) = 21.1 V_2/F (L) = 27.7 Q/F (L/h) = 43.7 K_a (h^{-1}) = 1.7 F_{cw} = 0.930 F_{NAT2} Fast = 1.36 Slow = 0.378	NA	NAT2 genotype polymorphism and body weight	NAT2 genotype polymorphism and body weight
Naidoo et al., 2019 [26]	LC-MS/MS	NONMEM v7.3/FOCE-I	Two-compartment disposition with first-order elimination and first-order absorption	CL (L/h) Fast = 40.5 Intermediate = 28.4 Slow = 17.4 $V_{central}$ (L) = 73.4 Intercompartment clearance, Q = 1.1 $V_{peripheral}$ = 19.8 Bioavailability = 1 (Fixed) T_{lag} = 0.13 K_a (h^{-1}) = 3.9 Scaling factor for variability in bioavailability for unobserved doses (-fold) = 3.9	NA	Antiretroviral therapy, treatment phase, NAT2 genotype polymorphism, serum creatinine	NAT2 genotype polymorphism
Zvada et al., 2013 [21]	LC-MS/MS	NONMEM v7/FOCE-INTER	Two-compartment distribution model with absorption transit compartments and first-order elimination	CL (L/h) for Slow = 4.44 Intermediate = 8.49 Fast = 11.3 K_a (h^{-1}) = 2.47 MTT (absorption mean transit time) (h) = 0.179 Number of Transit compartment = 4 (Fixed) $V_{central}$ (L) = 11.0 Q (L/h) = 2.00 $V_{peripheral}$ = 5.03 F = 1 (Fixed)	NA	Sex, NAT2 genotype polymorphism, HIV infection, age, body weight, concurrent meningitis prior TB	NAT2 genotype polymorphism

Table II: Model structure, pharmacokinetic parameters, and tested and retained covariates (continued)

Study	Assay	Software/Algorithm	Structure	Final population pharmacokinetic parameters for Isoniazid	Acetylisoniazid	Covariates tested	Retained covariates in the final model
Panjasatwong et al., 2021 [22]	LC-MS/MS	NONMEM v7.3/FOCE-I	Two-compartment transit model with first-order absorption and linear elimination	F = 1 (Fixed) CL/F (L/h) = 9.43 $V_{central}$ / F (L) = 3.78 MTT (h) = 0.878 MAT_{50} (month) = 12.7 Hill = 4.7 Q/F (L/h) = 28.0 $V_{peripheral}$ = 15.3 Q_{CSF} / (L/h) = 13.7	NA	Body weight, age, sex, disease severity, HIV infection, renal and liver function tests, nutritional status, predicted NAT2 phenotypes, central nervous system (CNS) inflammation markers (CSF protein, CSF lactate, CSF glucose, and CSF/blood glucose ratio)	CSF compartment, body weight, NAT2 genotype polymorphism (Age-based enzyme maturation)
Seng et al., 2015 [19]	LC-MS/MS	NONMEM v7.3/FOCE-INTER	INH: Two-compartment model with first-order absorption AcINH: Two-compartment model with first-order absorption	INH: K_a (h^{-1}) = 0.6 CL/F (L/h) = 65.2 $V_{central}$/F (L) = 18 Q/F (L/h) = 2.8 $V_{Peripheral}$/F (L) = 15.9 F_{INH} = 1 AcINH: F_{AcINH} = 0.973 CL (L/h) = 21.3 $V_{central}$/F (L) = 17 Q (L/h) = 69.2 $V_{Peripheral}$/F (L) = 80.4 K_e (h^{-1}) = 0.48 V (L) = 23.3	F_{AcINH} = 0.965 CL_A (L/h) = 21.3 $V_{central}$/F (L) = 17 Q_A (L/h) = 71.5 $V_{peripheral}$ (L) = 81.2	Age, body weight, height, body surface area (BSA), body mass index (BMI), creatinine clearance, bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gender, race, NAT2 genotype polymorphism	NAT2 genotype polymorphism, creatinine clearance (AcINH)
Fredj et al., 2021 [18]	Spectrocolorimetric	Pmetrics for R/Nonparametric	One-compartment model		NA	Polymorphism in NAT2 genotype polymorphism, age, body weight, gender	NAT2 genotype polymorphism
Van Beek et al., 2021 [27]	UPLC/LC-MS/MS	NONMEM v7.4	INH: Two-compartment disposition model AcINH: Single-compartment first-order elimination	INH: $V_{central}$ (L) = 57.5 K_a (h^{-1}) = 5.42 CL (L/h) Slow = 12.1 Fast = 32.7 $V_{peripheral}$ (L) = 18.7 Q (L/h) = 2.48 AcINH: $V_{central}$ (L) = 39.2 CL (L/h) = 6.65	$V_{central}$ (L) = 39.2 CL (L/h) = 6.65	NA	NAT2 genotype polymorphism

Table II: Model structure, pharmacokinetic parameters, and tested and retained covariates (continued)

Study	Assay	Software/Algorithm	Structure	Final population pharmacokinetic parameters for Isoniazid	Acetylisoniazid	Covariates tested	Retained covariates in the final model
Huerta-García et al., 2020 [28]	HPLC	NONMEM v7.3/FOCE-I	Two-compartment open model with a first-order rate constant of absorption and elimination	CL (L/h) Slow = 11.4 Intermediate = 19.2 Fast = 27.4 $V_{central}$ X BMI (L) = 1.5 $V_{peripheral}$ (L) = 3.8 K_a (h^{-1}) = 2.0	NA	Smoking, alcoholism, concomitant disease, concomitant drugs, NAT2 genotype polymorphism, body mass index (BMI) ($V_{central}$)	NAT2 genotype, body mass index (BMI) ($V_{central}$)
Denti et al., 2015 [29]	LC-MS/MS	NONMEM v7.3/FOCE-I	Two-compartment disposition with transit compartment absorption	CL (L/h) Rapid/Intermediate = 26.1 Slow = 15.5 $V_{central}$ (L) = 48.2 Q (L/h) = 16.1 $V_{peripheral}$ (L) = 16.5 MTT = 0.924 Number of transit compartment = 2.73 F = 1 (Fixed)	NA	HIV co-infection, nutritional status, age, sex, CD4+ lymphocyte count, daily weight-adjusted dose, time on TB treatment, NAT2 genotype	NAT2 genotype
Aruldhas et al., 2019 [23]	LC-MS/MS	NONMEM v7.3/FOCE-I	One-compartment disposition model with a transit absorption model (fixed, n = 5)	CL (L/h) Fast = 2.59 Slow = 7.79 $V_{central}$/F (L) = 29.7 MTT = 0.547 Number of transit compartment = 5 (Fixed) F = 1 (Fixed)	NA	Age, sex, body mass index (BMI), body weight, height and albumin level, NAT2 genotype	NAT2 genotype

CL = Clearance; K_a = Absorption constant; T_{lag} = Lag time V = Volume of distribution; $V_{central}$ = Central volume of distribution; $V_{peripheral}$ = Peripheral volume of distribution; MTT = Mean Transit Time; Q = Intercompartment clearance; F = Bioavailability; NAT2 = N-Acetyltransferase 2; MAT = Maturation of Clearance; BMI = Body Mass Index; CSF = Cerebrospinal fluid

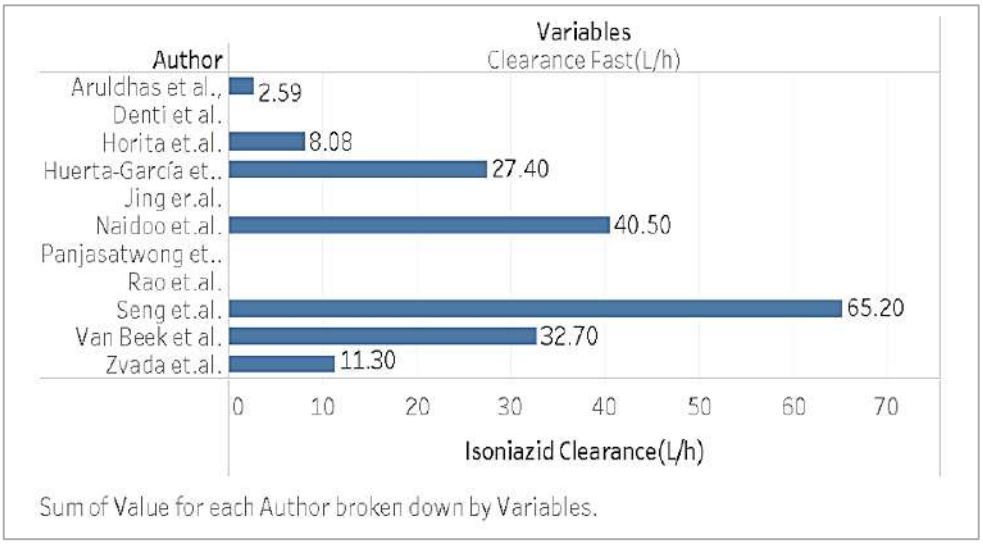

Figure II: Isoniazid (INH) clearance due to NAT2 polymorphism

Model Evaluation

Model evaluation was performed in all twelve studies through basic internal approaches, advanced approaches, and external evaluation. All the studies used basic internal evaluation such as basic goodness-of-fit (GOF) and visual predictive check (VPC) and two [18,28] studies used external validation in model evaluation using an independent dataset, two of which showed acceptable predictability. Five studies have performed advanced basic internal evaluations like normalised prediction distribution error (NPDE) and bootstrap analysis for model evaluation (**Table III**).

DISCUSSION

In this review, the authors focused on the parametric approach to PPK model development. Pharmacokinetics of INH was reported to be described as a two-compartment model in ten studies while a one-compartment model was described in two studies. A single study reported the one-compartment INH model included INH concentration at 3 h after drug intake [18]. This sparse sampling method could be the reason leading to the result obtained being one-compartmental. The sample is only taken at a one-time point and may not have sufficient data to demonstrate a two-compartmental model [18].

There is variability in describing the absorption process of INH in the included studies. Although the majority of studies described the absorption of INH as proportional to the concentration of INH in the gastrointestinal, in certain populations, the absorption of INH was also described to require at least a 1-hour delay to be fully absorbed (MTT was 0.66 h (SD = 0.34) with a range from 0.179 to 0.924 h). This indicates that not only food, but dosage form of INH also determines the absorption of INH. During the DOTs or VOT, patients need to be emphasised on the factor of food so that absorption could be enhanced. Besides the MTT absorption, INH was also described to have at least a 0.13-hour lag time to be absorbed in one study. Nevertheless, the lag time model does not consider the physiological process of absorption, and MTT is reported to be more accurate to describe the absorption phase [22,30].

The NAT2 gene shows large interindividual variability in acetylating activities by genetic polymorphisms in humans. The plasma concentrations of INH are highly variable between subjects, mainly because of the variability in the activities of these enzymes. As shown in **Figure II**, NAT2 genetic polymorphism significantly explains the large intra-and inter-individual variation in CL in most of the studies. The percentage difference of the NAT2 polymorphism effect against mean CL (20.55 L/h) is plotted in **Figure III**. Seng et al. [19] have shown the largest difference from mean CL, which could be explained by the Chinese ethnicity. Most of the studies built a mixture model to describe the clearance profile of INH.

Nevertheless, a study by Rao et al. performed NAT2 genotypic screening in 34 (65.3%) patients, with 29 being of the slow-intermediate type and the remaining rapid metabolisers [24]. There are no significant differences in Cmax or AUC 0-24 values between the slow-intermediate type and the few rapid metabolisers. This indicates that external validation of the developed mixture models is paramount to confirm the effect of NAT2 polymorphism in determining the types of accelerators.

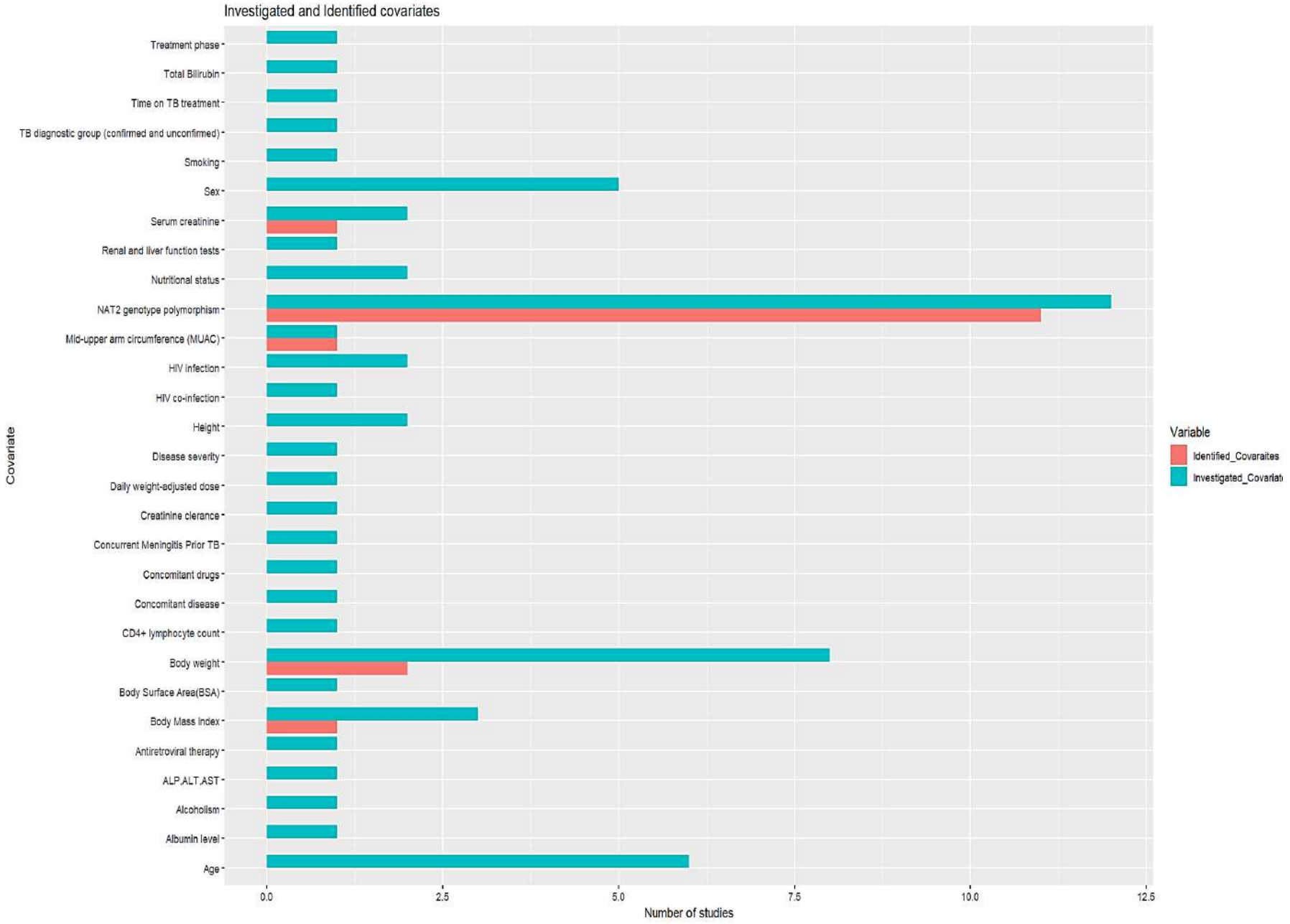

Figure III: Investigated and identified covariates

Table III: Model variability, error and validation

Study	Interindividual variability (IIV)		Residual error model	Residual		Model evaluation
	INH	AcINH		INH (%)	AcINH (%)	
Horita et al., 2018 [20]	K_a (h^{-1}) = 0.567 CL/F_{slow} (L/h) = 0.324 $CL/F_{nonslow}$ (L/h) = 0.48 $V_{central}$ /F (L) = 0.241 Q/F (L/h) = 0.637 $V_{peripheral}$/F (L) = 1.9	NA	Combination	NA	NA	Basic internal (VPC, GOF)
Rao et al., 2021 [24]	K_a(h^{-1}) = 0.9 $V_{central}$ (L) = 0.07 $V_{peripheral}$ (L) = 0.5 CL=(L/h) = 0.8 CL_2(L/h) = 0.0001 T_{lag} = 0.5	NA	Proportional	NA	NA	Basic internal (VPC, GOF)
Jing et al., 2020 [25]	CL/F (L/h) = 25.6 Q/F (L/h) = 63.8 K_a/F (h^{-1}) = 75.8	NA	Exponential	25.1	NA	Basic internal (VPC, GOF, conditional weighted residuals (CWRES) versus time, and CWRES versus PRED), advanced internal (Bootstrap analysis, NPDE)
Naidoo et al., 2019 [26]	CL (L/h) Fast = 26.3	NA	Combination	Proportional:27.8% Additional: 0.004 FIX	NA	Basic internal (VPC), advanced internal (Bootstrap analysis)
Zvada et al., 2013 [21]	CL (L/h) Fast = 25.1 Intermediate = 25.1 Slow = 25.1	NA	Proportional	Cohort 1: 20.6 Cohort 2: 7.00	NA	Basic internal (Conditional weighted residuals versus time, basic GOF, changes in the OFV, VPC)
Panjasatwong et al., 2021 [22]	CL (L/h) = 20.0 $V_{central}$ /F (L) = 18.3 MTT (h) = 64.5	NA	Additive	NA	NA	Basic internal (VPC, GOF plots, change in OFV)
Seng et al., 2015 [19]	K_a (h^{-1}) = 12.6 CL/F (L/h) = 86.1 F_{INH} = 38.1 Cl (L/h) = 15.4	CL(L/h) = 15.4 $V_{peripheral}$/F(L) = 19.4	Additive on log-transformed data	32.6 log(mg/L)	20.7 log(mg/L)	Basic internal (VPC, GOF)

Table III: Model variability, error and validation (continued)

Study	Interindividual variability (IIV)		Residual error model	Residual		Model evaluation
	INH	AcINH		INH (%)	AcINH (%)	
Fredj et al., 2021 [18]	NA	NA	NA	NA	NA	Basic internal (GOF, NPDE), external (validation group)
Van Beek et al., 2021 [27]	$V_{central}$ (L) = 26.4 K_a (h^{-1}) = 83.2 CL (L/h) Fast/slow = 57.5	$V_{central}$ (L) = 10.3 CL (L/h) =36.7	Proportional	NA	NA	Basic internal (VPC, GOF)
Huerta-García et al., 2020 [28]	CL (L/h) = 47.0 $V_{central}$ = 59.4 $V_{peripheral}$ (L) = 114.0 K_a (h^{-1}) = 113.6	NA	Proportional	42.9	NA	Basic internal (VPC, GOF), advanced internal (Bootstrap analysis, NPDE), external (validation group)
Denti et al., 2015 [29]	CL (L/h) = 30.7 MTT = 37.4 F = 12.8	NA	Combinational	NA	NA	Basic internal (OFV, VPC, GOF), advanced internal (Bootstrap analysis)
Aruldhas et al., 2019 [23]	$V_{central}$/F (L) = 23.4 MTT = 68.2 F = 41.8	NA	Additive	0.0967	NA	Basic internal (OFV, VPC, GOF), advanced internal (Bootstrap analysis)

CL = Clearance; K_a = Absorption constant; V = Volume of distribution; $V_{central}$ = Central volume of distribution; $V_{peripheral}$ = Peripheral volume of distribution; MTT = Mean transit time; Q = Intercompartment clearance; F = Bioavailability.

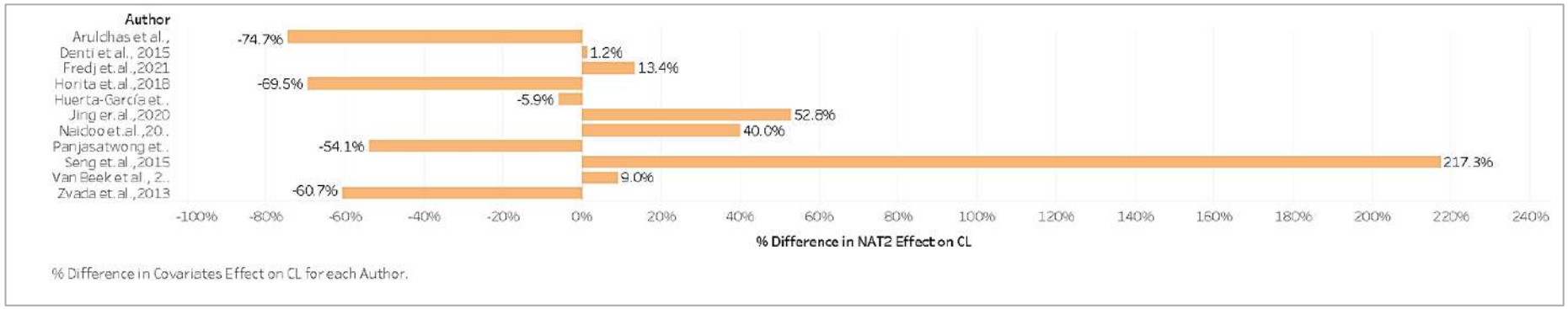

Figure IV: Percentage difference of NAT2 effect on CL compared to mean CL

AcINH is one of the most important urinary metabolites of INH. However, it was not investigated and discussed in most PPK articles (Table II). One study by Seng et al. described the PPK model of AcINH as a two-compartmental model [19]. Metabolite AcINH determines how well a patient metabolises INH [31]. One of the possible reasons for the lack of data in AcINH is the complexity of the assay method used to quantify it. A simple HPLC procedure is plagued by the low selectivity of UV detection, which requires more elaborate sample preparation and chromatographic conditions to achieve complete baseline separation of all peaks and is unsuitable for the rapid detection of these analytes [32]. Thus, patients who are slow acetylators have a higher risk of hepatotoxicity than rapid acetylator [33]. Incorporating the effect of AcINH in optimising the INH dosing is essential, as slow acetylation may lead to isoniazid-induced hepatotoxicity.

The NAT2 polymorphism shows the metabolism difference in ethnicity or race. A study by Naidoo et al. performed on Africans showed that most patients were slow or intermediate acetylators with >80% based on NAT2 genotype polymorphism. In comparison, less than 10-20% of the population tested had a rapid acetylator status [26]. Among the Tanzanian population (East Africa), as many as 48% (n = 48 subjects) were classified as NAT2 slow acetylators, 48% (n = 48 subjects) as intermediate, and 2% (n = 2) as rapid acetylators. In comparison, the acetylation status of 2% (n = 2) subjects could not be determined [29]. In contrast, among the US population, Horita et al. reported mainly slow and intermediate INH acetylator [20]. While in the Asian population, as shown by Seng et al. that the majority of the subjects in his study were classified as fast and intermediate INH acetylators. Similarly, a study from China reported that the majority of the Chinese population in the study were fast and intermediate INH acetylators. This indicates Asian population, especially the Chinese ethnicity are fast INH metabolisers and NAT2 polymorphism was about 20-40% of the population [19,25]. This can be reflected in **Figures II** and **III** where Seng et al. [19] and Jing et al. [25] demonstrate the top and third-highest CL in all studies. Discrepancies within regions and ethnicity highlighted the variable influence of the NAT2 polymorphism on TB patient care, while they also reiterate the need for rapid and slow NAT2 genotype polymorphism identification before INH administration to avoid overdosing or underdosing [19]. Nevertheless, incorporating genetic factors in routine clinical practice may not be feasible in some countries. The application of a mixture model to cater to the unavailability of genetic data could assist in quantifying and specifying different acetylation, which is also applied and described for other drugs [34,35].

The PK of INH displayed considerable differences among the different age groups. The estimated CL in paediatrics is also lower than in adults. This can be due to age-based enzyme maturation. At birth time, NAT2 activity is independent of genotype, and the slow-acetylator phenotype predominates. Within the first four years of life, the fast-acetylator phenotype in heterozygous and homozygous wild-type individuals develops [36]. Therefore, the CL of INH in children is lower than in adults because of the Phase II reaction; acetylation in metabolism has not developed completely in children and infants. Children, especially young infants, normally have higher total body water and a lower fat content than adults [36]. Thus, the lipophilicity of INH [37] may explain the lower median V_d of INH in children than that in adults. The higher V_d value in the study by Aruldhas et al. may also attribute to a one-compartmental model built, and the V_d was not distributed to the other compartment [38].

Mid-upper arm circumference (MUAC) was identified as one of the significant covariates affecting the $V_{central}$ in people with HIV and critical illness [24], which could be explained by the hydrophilicity of INH [37]. Compliance assessment has not been carried out in eleven out of the twelve studies to make sure no changes in the INH dosing regimen had occurred before assessing the steady-state PK profile. The only study that carried out compliance assessment was Seng et al. study by pill count and medication diaries [19]. While measuring the plasma level of INH or an anti-TB regimen may provide further insight into the compliance status of patients, the correlation between the serum concentration and compliance towards anti-TB showed conflicting results between adults and children. There was no significant relation between serum concentrations of pyrazinamide and drug compliance in adult patients [39]. However, a significant relationship was reported between INH and RIF in children with TB [40]. Nevertheless, the relationship between INH and serum concentration may require further investigation.

CONCLUSION

In conclusion, the PPK of INH has been extensively reviewed. The clearance of INH has a large difference between people with different NAT2 genotype polymorphism statuses. This review shows that to optimise the dosing regimen of INH, the patient's NAT2 genotype polymorphism status and age should be considered. Considering a larger sample size and a more stringent sampling strategy to be able to assess these factors efficiently as the population data is more likely to follow the law of large numbers and central limit theorem [41]. The application of a mixture model to cater for the unavailability of

genetic data could assist in quantifying and specifying different acetylator status. Besides, previously published models, as well as future models, should be evaluated externally for a more accurate description of models' predictive performance.

ACKNOWLEDGEMENT

All authors meet the criteria of authorship. TWR was responsible for collecting the data. SMSG reviewed and edited the manuscript. IAH reviewed and edited the manuscript. SNH participated in concept development, supported data collection, and reviewed and edited the manuscript. This work was supported by Fundamental Research Grant Scheme (FRGS), Ministry of Higher Education, Malaysia with project code FRGS/1/2019/STG03/USM/02/1.

CONFLICT OF INTEREST

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, patents received or pending, or royalties. There are no conflicts of interest relevant to the content of this review.

REFERENCE

[1] Bardou, F., et al., Mechanism of isoniazid uptake in Mycobacterium tuberculosis. Microbiology 1998 (1350-0872 (Print)). https://doi.org/10.1099/00221287-144-9-2539

[2] Zhang, Y., et al., The catalase-peroxidase gene and isoniazid resistance of Mycobacterium tuberculosis. Nature, 1992. 358. https://doi.org/10.1038/358591a0

[3] Singh, R., et al., Catalase-peroxidases (KatG) Exhibit NADH Oxidase Activity *. Journal of Biological Chemistry, 2004. 279(41): p. 43098-43106. https://doi.org/10.1074/jbc.M406374200

[4] Srivastava, S., et al., Multidrug-resistant tuberculosis not due to noncompliance but to between-patient pharmacokinetic variability. J Infect Dis, 2011. 204(12): p. 1951-9. https://doi.org/10.1093/infdis/jir658

[5] Garner, P. and J. Volmink, Directly observed treatment for tuberculosis. BMJ (Clinical research ed.), 2003. 327(7419): p. 823-824. https://doi.org/10.1136/bmj.327.7419.823

[6] Pasipanodya, J.G., S. Srivastava, and T. Gumbo, Meta-analysis of clinical studies supports the pharmacokinetic variability hypothesis for acquired drug resistance and failure of antituberculosis therapy. Clin Infect Dis, 2012. 55(2): p. 169-77. https://doi.org/10.1093/cid/cis353

[7] Pasipanodya, J.G., et al., Serum drug concentrations predictive of pulmonary tuberculosis outcomes. The Journal of infectious diseases, 2013. 208(9): p. 1464-1473. https://doi.org/10.1093/infdis/jit352

[8] Peloquin, C.A., Therapeutic drug monitoring in the treatment of tuberculosis. Drugs, 2002. 62(15): p. 2169-83. https://doi.org/10.2165/00003495-200262150-00001

[9] McIlleron, H., et al., Determinants of rifampin, isoniazid, pyrazinamide, and ethambutol pharmacokinetics in a cohort of tuberculosis patients. Antimicrob Agents Chemother, 2006. 50(4): p. 1170-7. https://doi.org/10.1128/AAC.50.4.1170-1177.2006

[10] Dhoro, M., et al., CYP2B6*6, CYP2B6*18, Body weight and sex are predictors of efavirenz pharmacokinetics and treatment response: population pharmacokinetic modeling in an HIV/AIDS and TB cohort in Zimbabwe. BMC pharmacology & toxicology, 2015. 16: p. 4-4. https://doi.org/10.1186/s40360-015-0004-2

[11] Oshikoya, K.A., H.M. Sammons, and I. Choonara, A systematic review of pharmacokinetics studies in children with protein-energy malnutrition. Eur J Clin Pharmacol, 2010. 66(10): p. 1025-35. https://doi.org/10.1007/s00228-010-0851-0

[12] Hall, R.G., 2nd, Evolving Larger: Dosing Anti-Tuberculosis (TB) Drugs in an Obese World. (1873-4286 (Electronic)). https://doi.org/10.2174/1381612821666150625120936

[13] Clinical Practice Guidelines, CPG- Management of Tuberculosis (3rd Edition). 3rd Edition ed. 2012: Malaysia Health Technology Assessment Section (MaHTAS). https://www.moh.gov.my/moh/attachments/8612.pdf

[14] Sherwin, C.M., et al., Fundamentals of population pharmacokinetic modelling: validation methods. 2012(1179-1926 (Electronic)). https://doi.org/10.1007/BF03261932

[15] Joerger, M., Covariate pharmacokinetic model building in oncology and its potential clinical relevance. The AAPS journal, 2012. 14(1): p. 119-132. https://doi.org/10.1208/s12248-012-9320-2

[16] Hong, B.L., et al., A Systematic Review and Meta-analysis of Isoniazid Pharmacokinetics in Healthy Volunteers and Patients with Tuberculosis. Clinical Therapeutics, 2020(1879-114X (Electronic)). https://doi.org/10.1016/j.clinthera.2020.09.009

[17] Stagg, H.R., et al., What are the most efficacious treatment regimens for isoniazid-resistant tuberculosis? A systematic review and network meta-analysis. Thorax, 2016. 71(10): p. 940-9. https://doi.org/10.1136/thoraxjnl-2015-208262

[18] Fredj, N.B., et al., Population pharmacokinetic model of isoniazid in patients with tuberculosis in Tunisia. International Journal of Infectious Disease, 2020(1878-3511 (Electronic)). https://doi.org/10.1016/j.ijid.2021.01.033

[19] Seng, K.-Y., et al., Population pharmacokinetic analysis of isoniazid, acetylisoniazid, and isonicotinic acid in healthy volunteers. Antimicrobial agents and chemotherapy, 2015. 59(11): p. 6791-6799. https://doi.org/10.1128/AAC.01244-15

[20] Horita, Y., et al., Evaluation of the Adequacy of WHO Revised Dosages of the First-Line Antituberculosis Drugs in Children with Tuberculosis Using Population Pharmacokinetic Modeling and Simulations. Antimicrob Agents Chemother, 2018. 62(9). https://doi.org/10.1128/AAC.00008-18

[21] Zvada, S.P., et al., Population pharmacokinetics of rifampicin, pyrazinamide and isoniazid in children with tuberculosis: in silico evaluation of currently recommended doses. Journal of Antimicrob Chemotherapy, 2014(1460-2091 (Electronic)). https://doi.org/10.1093/jac/dkt524

[22] Panjasawatwong, N., et al., Population Pharmacokinetic Properties of Antituberculosis Drugs in Vietnamese Children with Tuberculous Meningitis. LID - 10.1128/AAC.00487-20 [doi] LID - e00487-20. Antimicrob Agents and Chemotherapy, 2021. 65(1098-6596 (Electronic)). https://doi.org/10.1128/AAC.00487-20

[23] Aruldhas, B.W., et al., Optimization of dosing regimens of isoniazid and rifampicin in children with tuberculosis in India. British journal of clinical pharmacology, 2019. 85(3): p. 644-654. https://doi.org/10.1111/bcp.13846

[24] Rao, P.S., et al., Population Pharmacokinetics and Significant Under-Dosing of Anti-Tuberculosis Medications in People with HIV and Critical Illness. LID - https://doi.org/10.3390/antibiotics10060739

[doi] LID - 739. Antibiotics, 2021. 10(2079-6382 (Print)). https://doi.org/10.3390/antibiotics10060739

[25] Jing, W., et al., Population Pharmacokinetic Analysis of Isoniazid among Pulmonary Tuberculosis Patients from China. LID - 10.1128/AAC.01736-19 [doi] LID - e01736-19. Antimicrobial Agents and Chemotherapy, 2020. 64(1098-6596 (Electronic)). https://doi.org/10.1128/AAC.01736-19

[26] Naidoo, A., et al., Effects of genetic variability on rifampicin and isoniazid pharmacokinetics in South African patients with recurrent tuberculosis. Pharmacogenomics, 2019(1744-8042 (Electronic)). https://doi.org/10.2217/pgs-2018-0166

[27] Van Beek, S.W., et al., A Model-Informed Method for the Purpose of Precision Dosing of Isoniazid in Pulmonary Tuberculosis. Clinical Pharmacokinetics, 2021. 60(7): p. 943-953. https://doi.org/10.1007/s40262-020-00971-2

[28] Huerta-García, A.P., et al., Population pharmacokinetics of isoniazid and dose recommendations in Mexican patients with tuberculosis. 2020(2210-7711 (Electronic)). https://doi.org/10.1007/s11096-020-01086-1

[29] Denti, P. et al., Pharmacokinetics of Isoniazid, Pyrazinamide, and Ethambutol in Newly Diagnosed Pulmonary TB Patients in Tanzania. PLOS ONE, 2015. 10(10): p. e0141002. https://doi.org/10.1371/journal.pone.0141002

[30] Savic, R.M., et al., Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. J Pharmacokinet Pharmacodyn, 2007. 34(5): p. 711-26. https://doi.org/10.1007/s10928-007-9066-0

[31] Flockhart, D.A. and Z. Desta, Chapter 21 - Pharmacogenetics of Drug Metabolism, in Clinical and Translational Science, D. Robertson and G.H. Williams, Editors. 2009, Academic Press: San Diego. p. 301-317. https://doi.org/10.1016/B978-0-12-802101-9.00018-1

[32] Cao, X., et al., Simultaneous Determination of Isoniazid and Acetylisoniazid in Human Plasma by Hydrophilic Interaction Liquid Chromatography Tandem Mass Spectrometry and Its Application to a Pharmacokinetics Related to N-Acetyltransferase2 Genetic Polymorphism. Analytical Letters, 2012. 45(15): p. 2125-2135. https://doi.org/10.1080/00032719.2012.682236

[33] Wang, P., et al., Isoniazid metabolism, and hepatotoxicity. Acta pharmaceutica Sinica. B, 2016. 6(5): p. 384-392. https://doi.org/10.1016/j.apsb.2016.07.014

[34] Chow, N.K., et al., The association between cigarette smoking and efavirenz plasma concentration using the population pharmacokinetic approach. Br J Clin Pharmacol, 2021. 87(10): p. 3756-3765. https://doi.org/10.1111/bcp.14783

[35] Hussein, R., et al., Population pharmacokinetics of perhexiline from very sparse, routine monitoring data. Ther Drug Monit, 2001. 23(6): p. 636-43. https://doi.org/10.1097/00007691-200112000-00007

[36] Fernandez, E., et al., Factors and Mechanisms for Pharmacokinetic Differences between Pediatric Population and Adults. Pharmaceutics, 2011. 3(1): p. 53-72. https://doi.org/10.3390/pharmaceutics3010053

[37] Information, N.C.f.B. PubChem Compound Summary for CID 3767, Isoniazid. 2021; Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Isoniazid

[38] Antwi, S., et al., Pharmacokinetics of the First-Line Antituberculosis Drugs in Ghanaian Children with Tuberculosis with or without HIV Coinfection. Antimicrobial agents and chemotherapy, 2017. 61(2): p. e01701-16. https://doi.org/10.1128/AAC.01701-16

[39] Chaikoolvatana, A et al. The Application of the Therapeutic Drug Monitoring (TDM) of First and Second-Line Drugs for Multidrug-Resistant Tuberculosis Patients (MDRTB). Siriraj Medical Journal, 69(2), (2017). 85–93. https://he02.tci-thaijo.org/index.php/sirirajmedj/article/view/80897

[40] Tersigni, C., et al., Real-life isoniazid, and rifampicin plasma concentrations in children: a tool for therapeutic drug monitoring of tuberculosis. BMC Infectious Diseases, 2021. 21(1): p. 1087. https://doi.org/10.1186/s12879-021-06764-7

[41] Kwak, S.G. and J.H. Kim, Central limit theorem: the cornerstone of modern statistics. Korean Journal of anesthesiology, 2017. 70(2): p. 144-156 https://doi.org/10.4097/kjae.2017.70.2.144