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Pharmacokinetics of isoniazid in 30 tuberculosis patients in Abidjan, Côte d'Ivoire

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Isoniazid is a major component in tuberculosis (TB) treatment, which is often used in combination or alone as prophylaxis for its high efficiency on bacilli *of Mycobacterium tuberculosis*. It is responsible for an increased risk of developing serious liver side effects involving the prognosis of the patient. Its coinfection with HIV is currently a real public health problem. The purpose of this study was to establish the pharmacokinetic profile of isoniazid in Ivorian patients infected with TB taking a combination containing isoniazid at Abidjan. A cross-sectional analytical and descriptive study on the pharmacokinetics of isoniazid in 30 adults Ivorian patients on TB treatment was conducted. Blood samples at intervals of time were performed by high performance liquid chromatography-ultra violet (HPLC-UV). 30 adult patients were enrolled, with sex ratio M/F = 2. Mean age was 38.67 (18 to 67 years). 56 (7%) were slow acetylators. 14 (46.7%) were treated for pulmonary TB smear negative and 36.67% had a co-infection TB/HIV. A positive correlation was also observed between body mass index (BMI) and Vd (0.444 and p = 0.14) and a negative correlation between BMI and Tmax (-0.399, P = 0.29). The main biological variable influencing pharmacokinetic parameters according to the analysis is the acetylation profile of the patient.

Key words: Pharmacokinetics, Isoniazid (INH), tuberculosis, Abidjan.

INTRODUCTION

Isoniazid (INH) is the most bactericidal molecule active ingredients commonly used against tuberculosis (TB) (World Health Organization (WHO), 2010). Major TB drugs, INH, is often used in combination with other molecules or alone in prophylaxis for its high efficiency bacilli *Mycobacterium tuberculosis* (WHO, 2010). However, if the effectiveness of this molecule is undeniable, its toxicity is often a ransom for its therapeutic success. Indeed, INH is responsible for the onset of serious liver side effects life-threatening to the patient, which is based on its metabolism and bioactivation made by NAT2 (N- Acetyltransferase 2) and CYP 2E1 (Chamorro et al., 2013).

Dosing of isoniazid is traditionally performed by body

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weight to approximate the WHO recommended dose of 5 mg kg-[1] (WHO, 2009). However, in fixed combinations of antiTB including INH, the doses are not exactly in the normal range and can therefore rise plasma levels concentrations above or below therapeutic. The increase or decrease in plasma concentration cause sides effects or harmful bacterial resistance. Finally, isoniazid is associated with hepatotoxicity and peripheral neuropathy, and slow acetylators may be as a result of increased risk of toxicity (Cho et al., 2007). Also, treatment with isoniazid is further complicated by the expression of the polymorphism in the enzyme system involved in the metabolism, including genetic defect on chromosome involved in the metabolism of INH (acetylators slow and rapid acetylators) (Parkins, 1997).

It is therefore important to ensure an exposure of anti-infective agents or appropriate TB patients in a clinical setting. In addition, HIV and tuberculosis are a lethal combination. Tuberculosis is a major cause of death among HIV-positive. It is responsible for approximately 13% of acquired immuned deficiency syndrome (AIDS) deaths in the world (WHO, 2010). In Africa, HIV is the main determinant of the increase in the incidence of TB in the past decade (WHO, 2010). Co -infection HIV whose estimated prevalence by WHO was 38% in 2009 (WHO, 2009), is reported by the authors as influencing parameters pharmacokinetics of isoniazid and is suspected in the treatment failures and re-emerging disease. TB is also the first opportunistic infection in HIV.

The pharmacokinetics of isoniazid in the Ivorian adult patient has never been done in our context because of the difficulty of implementing a simple and inexpensive analytical method but also because of a limited technical platform. The objective of this study is to perform the pharmacokinetic of isoniazid in the practices of a poor country conditions and provide as an appropriate response to therapeutic optimization, but also to assess the acetylation profile of patients in order to intensify the pharmacological basis and optimize the therapeutic monitoring of patients pharmacology.

MATERIALS AND METHODS

Patients

This was a descriptive and analytical prospective study with reference from June, 2012 to April, 2013. People enrolled were adult patients hospitalized in the Department of Pneumology of Cocody Hospital in Abidjan, on TB treatment including INH single dose, taking one tablet in its fixed combination, and having received information and after written informed consent.

Chemicals and reagents

Isoniazid reference substance (European pharmacopoeia ICRS0331) purity 99.8%, Methanol HPLC grade (Chromasolv®), orthophosphoric acid H_3PO_4 (Fluka®), KOH (Sigma Aldrich®), ultra water pure HPLC were kindly provided by the National Laboratory of Public Health (Côte d' Ivoire). White plasma was offered by the National Centre for Blood Transfusion Abidjan.

Sampling

Blood samples were collected on heparin tube after administration of conventional TB treatment according to the weight (4 t 5.45 mg/kg) to fasting. Blood samples were collected, respectively for 30 minutes, 1h, 1h30, 2h, 3h, 4h, 8h and 12 hours after the first oral dosing. The collected blood specimens were centrifuged and plasma was transferred under refrigerated atmosphere at 20°C immediately at the Pasteur Institute in Abidjan Cocody and stored at -80°C for subsequent assay of isoniazid.

Analytical methods

The plasma concentrations of INH were analyzed at the Laboratory of Biochemistry fundamental Pasteur Institute of Côte d' Ivoire by high performance liquid chromatography HPLC–UV (C.E.A.E. Québec, 2009). A technical simple extraction was performed by protein precipitation with 300 µl of methanol in 150 µl plasma (Roht, 2012). The mixture is then homogenized by a vortex and centrifuged at 15,000 rpm/min for 10 min at 4°C. The methanolic supernatant was collected in a test tube with a volume equal to adjust the pH to 5.5 (400 µl), 20 µl was then injected for analysis. HPLC system (Waters®) with detector UV was added to a column infusion (Symmetry®) C18: 3.5 microns, 4.6 × 75 mm. The mobile phase consisting of 1 M phosphate buffer and methanol is diffused by concentration gradient (50/50 v/v for the first minute and 90/10). The phosphate buffer was obtained by dissolving 3.8 g of phosphoric acid in ultra pure water in sufficient quantity. A flow rate of 0.9 ml/min at 254 nm and a retention time of 2 min was applied. The limits of detection (LOD) and quantification (LOQ) were 0.1 and 15 mg/L. The linear correlation coefficient was 0.995.

Pharmacokinetic calculations and statistical analyses

Linear order 1 noncompartmental model based on a mathematical application graphic was used to determine the pharmacokinetic parameters of isoniazid [extraction coefficient (Ke), half - life ($T_{1/2}$), maximum concentration (Cmax) maximal time (Tmax), children on the curve to 12 h and at infinity (AUC_{0-12}), (AUC_{12-00}), clearance (CL), volume of distribution (Vd)]. The determination of the area in the curve (AUC) by the trapezoidal method (Houin, 1990). The course of the semi -log time curve functions plasma concentrations were made with Microsoft Excel 2007 software and allowed to deduce other parameters. Determining the acetylation profile of the patient was made by the Vivien method and Coll inactivation index I_3 according to the formula:

$$I_3 = \frac{(C_3 + 0{,}6)}{D\left(\frac{mg}{kg}\right)}$$

This was after measurement of INH concentration at 3 h (C3 mg/L) after administration of a dose D of medicament. Rapid acetylators are defined as having an index $I_3 < 0.65$. The curve of plasma concentration versus time and statistical package for social sciences (SPSS) version 20 was used for the statistical analysis of our data. The student t-test and Fischer Snedecor F for comparison of means and correlation test Tau B Kendall and Spearman, significance was set at $p < 0.05$. The statistical analyses were performed with statistical package for social sciences (SPSS), version 15.

Ethical considerations

The study protocol was reviewed and approved by and National

Table 1. Clinical and demographic features of patients with tuberculosis.

Parameter	N=30 (%)
Sex	
Female	10 (33.3)
Male	20 (66.7)
Age (years)	
-40	18 (60.0)
+40	12 (40.0)
Income	
with IGA*	18 (60.0)
Without IGA	12 (40.0)
Weight (Kg)	
+60	16 (53.33)
-60	14 (46.66)
Body mass index (BMI)	19.39 (12.48-24.80)
Dose/kg	4.75 (4.05-5.45)
HIV	
Negative	19 (63.3)
Positive	11 (36.7)
Acetylators	
Slow	17 (56.7)
Rapid	13 (43.3)
Type of TB	
Extra pulmonary	6 (20.0)
Disseminated	14 (46.7)
Pumlonary	10 (33.3)

IGA * income generating activity

Research Ethics Review Committees. All the patients have given their consent.

RESULTS

Patient characteristics

A total of 30 newly diagnosed inpatient adults TB patients with a mean age of 38.67 years (18 to 67 years) were enrolled in the study. Table 1 summarizes details of demographic and clinical features of the participants.

Pharmacokinetics

Well resolved peak of HPLC chromatograms were obtained for all samples. INH concentration after dosing, which is frequently quoted in the literature as a convenient reference point, varied from as low as 1.76 µg/ml to as high as 7.67 µg/ml. At 2 and 3 h post-dose INH plasma concentration of 3 to 5 µg/ml (Peloquin et al., 1996) and 1.5 µg/ml (Schaaf et al., 2005), respectively have been suggested as a required range for optimal bactericidal effects. Univariate regression analyses showed that there was no association ($P > 0.2$) between INH pharmacokinetic parameters and the covariates: weight, sex, type of TB and concomitant drug use.

There was no significant linear correlation between the biological parameters and pharmacokinetic variables with the exception of blood glucose and the Tmax. In effect, the linear correlation coefficient is positive ($p = 0.377$; 0.044) between blood glucose and Tmax. However on the other hand there is also a positive correlation between body mass index (BMI) and Vd (0.444 with $p = 0.14$) and a negative correlation between BMI and Tmax (-0.399 with $P = 0$ is observed, 29). Patients with a high BMI have a high Vd and relatively low Tmax. The main biological variable influencing pharmacokinetic parameters according to the analysis is the acetylation profile of the patient. In fact, this variable is significantly correlated to all pharmacokinetic parameters (except Vd), acetylation is negatively correlated with Tmax - Cmax - $T_{1/2}$ and AUC_{00}. The slow acetylators have Tmax, Cmax, $T_{1/2}$, and AUC_{00} higher than the rapid acetylators patients, while slow acetylators have Ke lower clearance than rapid acetylators. Finally, HIV status did not influence the pharmacokinetic parameters.

DISCUSION

The study on the pharmacokinetics of isoniazid is the first of its kind in Cote d'Ivoire. The main aim of this work was to assess pharmacokinetic data of Ivorian patients with TB. Our work has not used pharmacokinetics software for the analysis and interpretation of biological information on the future of INH in the blood but rather it has used graphic mathematical method to determine the graphics settings pharmacokinetic (Hoin, 1999). Many inherent difficulties were encountered. Apart from the weakness of our sample, we had to cope with the prohibitive cost of reagents and inputs but also to our lack of experience in plasma assay for pharmacokinetics because Côte d'Ivoire is still in its infancy. However, this study has the advantage to show the pharmacokinetic profile of isoniazid for the analytical and methodological feasibility of clinical pharmacokinetic data for patients in an African context to optimize the care of patients for therapeutic monitoring pharmacologique (Peloquin et al., 2002).

The study involved 30 patients, including 20 men (66.66%) and 10 women (33.33%), with a sex ratio = 2. Some authors have reported the same results in male-dominated work in Africa. This predominance of male

subjects could be explained by the fact that TB primarily affects males in accordance with national and international trends (WHO, 2012). The average age of patients was 38 years, with a range of 18 to 67 years. Young adults (18 to 40 years) were the most represented with 73.33%. TB affects young patients still in have a lower average weight (Table 1).

Most clinical and biological data are within normal values (Table 2). However, 56.7% of subjects were slow acetylators, the predominance of slow acetylators in our study is slightly inconsistent with the work of Marquet and others (Marquet, 2004) with estimated 40% proportion of slow acetylators in the black population against 60% of rapid acetylators. The patients studied were mostly treated for pulmonary TB smears as negative 14 (46.67%) (Table 2). The anti-Tb treatment was therefore administered as presumptive without the presence of diagnostic elements because of diagnostic difficulties related to the lack of resources for patients and the equipment facilities in public health system in Côte d'Ivoire. Although some authors required the demonstration of tubercle bacilli in sputum microscopy by culture or histological examination in TB patients before treatment, medical decision becomes complex in this context. 36.67% had a co-infection with TB-HIV. Some authors have reported different proportions in a similar work. Indeed, Wilkins et al. (2011) reported in South Africa a proportion of 15.2% of HIV positive subjects detected in a study of the pharmacokinetic variability of Isoniazid. The proportion of co-infection HIV reported in our study is close to the estimated prevalence by WHO (38%) (WHO, 2004).

The pharmacokinetic parameters (Table 2) are similar to those in the literature. Authors have reported similar results in work targeting the pharmacokinetics of isoniazid. Indeed, Mclleron et al. (2006) reported the following medium: maximal concentration Cmax 3.07 mg/L vs 3.33 mg/L, with a range of 1.82 and 5.66 mg/L; $T_{1/2}$ 1.59 h against 2.39 h, with a range of 1.21 and 2.17 h. Peloquin et al. (2002) obtained the following average, for a population of 24 subjects: 3.14 ± 0.92 C_{max} mg/L, 1.06 ± 0.58 Tmax h and 13.82 ± 6.87 AUC mgl/h for patients receiving 250 mg Isoniazid and Cmax of 3.77 ± 1.11 mg /L, 1.06 ± 0.58 Tmax h and 16.59 ± 8.24 AUC mg.l/h. The volume of distribution (Vd) 0.9 ± 0.27 showed that INH distribution in plasma was correlated with the data found in most publications (Elmendorf et al., 1952). This study has showed that despite the high interindividual variability and intra-individual pharmacokinetic data, plasma concentrations of Ivorian adults subjects are superimposed values of plasma concentrations of other subjects.

Most of our patients have a relatively rapid absorption of isoniazid (0 to 1 h), according to some published earlier in which isoniazid was shown to be rapidly and completely absorbed (Elmendorf, 1952; Des Prez, 1961). Multivariate analysis of pharmacokinetic parameters and linear correlation (Kendall tau b and Spearman's rho) (Table 3) showed no significant differences between age and $T_{1/2}$, AUC and Cmax (P, respectively 0.27, 0.74 and 0.81). The difference between age is significant for Tmax (P = 0.03). In our study, the $T_{1/2}$, AUC and Cmax did not affect age. The Tmax ranged against one age to another. These results suggest that only the time to reach maximum concentration Isoniazid is influenced by age, and is particularly high in the extreme age brackets. Authors have obtained different results by exploring the influence of age on the pharmacokinetics of isoniazid. Indeed, Kergueris (1986) rather highlighted the influence of age on the half-life of elimination. Rey et al. (1998, 2001) has observed the decrease in the half-life when age increased. McIlleron (2006) observed in their work a growth of 6% of the maximum concentration for each additional year. Age can be considered as a prime factor variation in pharmacokinetic parameters of isoniazid.

Our work shows no significant difference between sex and pharmacokinetic factors (Table 3). Indeed, some authors have noted this lack of influence of gender on the pharmacokinetics. McIlleron (2006) reported to this effect no significant difference between the maximum concentrations observed in both sexes (P = 0.104). Thee (2011) had found no significant difference between the famous genres for the following parameters: Cmax, Tmax, AUC (P = 0.742, respectively, 0.083 and 0.476). However, McIlleron et al. (2006) led to the conclusion of its work on the pharmacokinetics of Isoniazid young TB that gender was a factor in convincing risk of failure of TB treatment by interference on Cmax. Substantial variability in absorption kinetics means that the use of a single consistent time point for Therapeutic Drugs Monitoring (TDM) is unlikely to provide a reliable estimate of true isoniazid exposure. In any event, TDM is of limited practical use in resource-poor high-burden countries, where it is currently unavailable and unlikely to become available in the foreseeable future.

Our results also show no significant difference between the patients and biological parameters of the pharmacokinetic variables with the exception of blood glucose and the Tmax (Table 4). In effect, the linear correlation coefficient is positive (p = 0.377 and 0.044). Thus, the plasma concentrations of INH are higher in patients with high blood glucose levels. High blood sugar increases the risk of exposure to INH and increase the frequency of occurrence of side effects. However on the other hand there is also a positive correlation between BMI and Vd (0.444 with p = 0.14) and a negative correlation between BMI and Tmax (-0.399 with P = 0.29). Patients with a high BMI have a significant Vd and relatively low Tmax. The main biological variable that influences the pharmacokinetic parameters analysis by acetylation is the profile of the patient (Table 4). In fact, this variable is significantly correlated to all pharmacokinetic parameters except Vd. The acetylation is negatively correlated with Tmax - Cmax - $T_{1/2}$ and

Table 2. Pharamcokinetics characteristic (Kendall and spermann tests).

Parameter	Tmax (h)	Cmax (µg/ml)	$T_{1/2}$ (h)	Ke (h-1)	AUC_{00}	Clearance ($l.h^{-1}.kg^{-1}$)	Vd (l/kg)
Sex							
----	-0.044	-0.15	0.093	-0.093	-0.048	0.067	0.233
P-value	0.796	0.33	0.548	0.548	0.756	0.663	0.13
Age (Years)							
---	0.072	0.044	-0.109	0.109	-0.095	0.146	-0.026
P-value	0.615	0.734	0.401	0.401	0.464	026	0.844
Type tuberculosis							
---	-0.02	0.188	0.023	- 0.023	0.142	-0.176	-0.08
P-value	0.904	0.200	0.877	0.877	0.332	0.229	0.587
Acetylators							
---	-0.477**	-0.332*	-0.364*	0.364*	-0.545**	0.571**	0.197
P-value	0.005	0.031	0.018	0.018	0	0	0.202
BMI (kg/m^2)							
----	-0.235	-0.099	0.223	-0.23	-0.103	0.094	0.393**
P-value	0.098	0.443	0.084	0.084	0.422	0.464	0.002
Urea (g/L)							
-----	-0.037	0.186	-0.084	0.084	0.159	-0.175	-0.138
P-value	0.804	0.171	0.539	0.539	0.242	0.197	0.312
Créatinine (g/L)							
-----	0.025	0.038	-0.043	0.043	0.124	-0.108	0.016
P-value	0.868	0.781	0.751	0.751	0.361	0.427	0.905
ALT (IU)							
-----	-0.094	0.137	0.142	-0.142	0.087	-0.087	-0.022
P-value	0.519	0.301	0.284	0.284	0.511	0.511	0.866
AST(IU)							
----	-0.119	-0.057	0.017	-0.017	0.022	-0.002	0.042
P-value	0.412	0.666	0.895	0.895	0.866	0.985	0.75
Hb (g/dl)							
-----	-0.243	0.014	-0.042	0.042	-0.158	0.172	0.13
P-value	0.09	0.915	0.748	0.748	0.224	0.186	0.317
Glucose (g/L)							
----	0.357*	0.107	0.057	-0.057	0.087	-0.102	-0.296*
P-value	0.014	0.419	0.666	0.666	0.511	0.441	0.025
Status HIV							
----	0.150	0.136	0.068	-0.001	0.244	-0.008	-0.182
P-value	0.428	0.472	0.722	0.998	0.193	0.968	0.336

**The correlation is significant at the 0.01 level (bilateral). *The correlation is significant at the 0.05 level (bilateral). b. Calculation impossible because at least one variable is a constant.

Table 3. Pharmacokinetics parameters and HIV.

Parameter	HIV negative	HIV positive	P
	19	11	
$T_{1/2}$ (h)	2.35 ± 0.75	2.47 ± 0.95	0.72
AUC ($mg.l^{-1}.h^{-1}$)	17.90 ± 4.90	21.32 ± 9.23	0.19
Tmax (h)	1.95 ± 0.81	2.18 ± 0.68	0.43
Cmax (mg/l)	3.25 ± 0.75	3.47 ± 0.89	0.48
Clearance ($l.h^{-1}.kg^{-1}$)	0.28 ± 0.08	0.28 ± 0.18	0.96
Vd (l/kg)	0.93 ± 0.31	0.83 ± 0.20	0.33

The differences were not significatives bethween patient's HIV status and pharmacokinetics parameters.

Table 4. Pharmacokinetic parameters and type of acetylators.

Parameter	Genotype slow	Genotype Rapid	P
	17	13	
$T_{1/2}$ (h)	2.66 ± 0,67	2.05 ± 0.88	0.037
AUC (mg.h/L)	22.70 ± 6.28	14.52 ± 4.50	0.0001
Tmax (h)	2.38 ± 0.70	1.58 ± 0.61	0.003
Cmax (mg/l)	3.64 ± 0.63	2.93 ± 0.83	0.012
Clairance ($l.h^{-1}.kg^{-1}$)	0.22 ± 0.05	0.98 ± 0.34	0.001
Vd (l/kg)	0.83 ± 0.20	0.36 ± 0.15	0.135

The differences were not significant between acetylation phenotypes and following pharmacokinetic parameters: $T_{1/2}$, AUC, Tmax, Cmax, and Cl (P 0.037, 0.0001, 0.003, 0.012 and 0.001, respectively), but not significant on Vd.

AUC_{00}, and the slow acetylators are more likely to have a higher INH concentration thus making more side effects exposure (Cho H. et al 2007; Possuelo LG. et al, 2008).

The differences are not significant between the weight and the following pharmacokinetic parameters: $T_{1/2}$, AUC. Our study has highlighted a lack of influence of the weight on the pharmacokinetic parameters. Helen McIlleron et al. (2006) put out the positive impact of weight on increasing the level of exposure (AUC). High weight increases the risk of toxic events appearances. Comparison of pharmacokinetic parameters based on HIV status (Table 5) did not show any significant difference. HIV infection does not change so significantly elements pharmacokinetic analysis contrary to the results of Gurumurthy et al. (2004) who observed a significant decrease in half- life, Tmax, AUC and clearance. The comparison of the two arms (slow acetylators and fast acetylators) office pharmacokinetic characteristics by testing Tau -B and Kendahl shows that there are significant differences between subjects with phenotypes of acetylation on the following pharmacokinetic parameters: $T_{1/2}$, AUC, Tmax, Cmax and Cl (P = 0.037, 0.0001 , 0.003 , 0.012 and 0.001, respectively) but not significant for the Vd. In our study, $T_{1/2}$, AUC, Tmax, Cmax and Cl varied phenotype acetylation, by Vd does not vary against a different phenotype. The slow acetylators subjects tend to metabolize more slowly INH than rapid acetylators. (Cho H. et al 2007), (Possuelo LG. et al, 2008). Their studies showed that NAT -2 acetylator, status of a patient, gender and ethnicity can be considered as significant risk factors for the development of hepatotoxicity.

In summary, the results of the feasibility analysis of plasma drug dosage in Côte d'Ivoire are encouraging, though much remains to be done.

Conclusion

This study provides the originator of data that clinical feasibility of determination of INH is very relevant. The pharmacokinetic parameters were determined by simple mathematical calculations. It shows that patients have rapid acetylators plasma exposure levels INH, and is therefore more likely to make students have serious liver side effects. Given the increase in tuberculosis cases and incidence rate of liver secondary effects and costs associated with hospitalization, it may also be useful to know the state of acetylation of patients before or at the beginning of the initiation treatment against tuberculosis.

Conflict of Interest

The authors have not declared any conflict of interest.

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