

SHORT COMMUNICATION

Effect of paracetamol on pharmacokinetics of isoniazid in *Teddy* goats

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Abstract: In this study the effect of paracetamol on pharmacokinetics (PK) of isoniazid (INH) in *Teddy* goats was investigated. INH was administered as a single oral dose at 10 mg/kg body weight to every experimental goat. After a wash out period of 7 days, INH and paracetamol (at the rate of 15 mg/kg body weight) were given simultaneously through oral route for investigation of drug interactions. Both times, following drug administration, blood samples were collected at predetermined time intervals from the jugular vein of each animal and analyzed for INH by spectrophotometric analysis. PK parameters were calculated using two compartment open model. When used with paracetamol, the value of biological half life ($t_{1/2B}$) of INH was significantly decreased ($p < 0.05$) from 2.391 ± 0.216 to 2.17 ± 3.46 hours. The value for apparent volume of distribution (V_d) was also significantly decreased ($p < 0.05$) from 0.905 ± 0.327 to 0.786 ± 0.161 L/kg and total body clearance (CL) was increased insignificantly ($p > 0.05$) from 3.59 ± 2.03 to 4.04 ± 2.61 mL/min/kg. Based on these results, it was concluded that dose of isoniazid should be increased when concomitantly used with paracetamol.

Keywords: Isoniazid, paracetamol, pharmacokinetics, drug interaction, goats.

INTRODUCTION

Drug interactions play pivotal role in multi drug therapy. These interactions affect bioavailability and pharmacokinetic profile of the drugs used in treatment schedule. They may increase the extent of bioactive drug resulting in its toxic effects or decrease it to sub therapeutic levels in the blood that may lead to antimicrobial resistance (Lees and Aliabadi, 2002; Lees *et al.*, 2008). This has become a matter of serious concern in tuberculosis (TB) because *Mycobacterium tuberculosis*, the causative organism of TB, is notorious for getting resistant to antimicrobials very rapidly. Multi-drug resistant TB (MDR-TB) is a rapidly growing challenge for physicians and becoming a major cause of disease recurrence and treatment failure (Zhu *et al.*, 2011). Moreover, treatment of TB is continued for six to nine months and at least four drugs are used in combination for the initial two months of treatment (Chan and Iseman, 2002). Some antipyretic drugs like paracetamol are also added to this combination to control fever during the course of disease. This increase chances of drug-drug interactions, ultimately affecting their pharmacokinetic (PK) behavior. Some studies have explored the impact of combination therapy on PK parameters of anti TB drugs but they are mostly restricted to interactions amongst antimicrobial agents only (Baldan *et al.*, 2007; McIlleron *et al.*, 2007; Nijland *et al.*, 2007).

Isoniazid (INH) is drug of choice in the treatment and prophylaxis of TB (Preziosi, 2007) and is highly effective for the treatment of experimentally induced TB in animals (Hardman *et al.*, 2001). Most often, it is used with paracetamol but their interactions have not been studied in local animals. Keeping in view the frequent concomitant clinical use of INH with paracetamol and little information regarding their drug interactions, the present study was undertaken with the objective to determine the effect of paracetamol on the PK behaviour of INH in *Teddy* goats.

MATERIALS AND METHODS

Experimental animals and drug administration

The study was conducted on eight clinically healthy adult goats, 1-3 years of age and 20-40 kg body weight. The goats were housed in the animal shed in the Department of Clinical Medicine and Surgery, University of Agriculture, Faisalabad, Pakistan. All the animals were provided similar managemental conditions and kept on fresh green fodder and water *ad libitum*. Experiments were performed during the months of April and May, 2006.

After restraining the animals in standing position, INH (as 1% syrup isoniazid) was administered as a single oral dose at the rate of 10 mg/kg body weight to each of the eight goats to study the PK profile of drug. After a wash

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out period of 7 days, INH and paracetamol (as tablet paracetamol, at the rate of 15 mg/kg body weight) were administered simultaneously through oral route to the same group of animals for the investigation of drug interactions.

Collection of blood samples

Blood samples were collected from the jugular vein of each animal under strict aseptic conditions using disposable syringes and carefully transferred to heparinized plastic centrifuge tubes. The blood samples were collected at 0 (before drug administration), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours after the drug administration. Plasma was isolated after centrifuging at 4000 rpm for 15 minutes and stored in capped plastic bottles at -20°C until analysis.

Analytical procedure

INH concentrations in plasma samples were determined by spectrophotometric method as described by Amlathe and Gupta (1988) using Spectronic 21 (Bausch and Lomb, Germany).

The plasma concentration versus time data was used to calculate different PK parameters using software, MW/PHARM version 3.02, a MEDIWARE product, Holland. This software calculates area under curve (AUC) using trapezoidal method. Least square regression analysis was applied to discriminate the best model and correlation coefficient was taken as measure of goodness-of-fit.

STATISTICAL ANALYSIS

PK parameters for INH alone and when given with paracetamol were calculated in individual animals and their mean (\pm SD) values were also calculated using Microsoft Office Excel version 2003. Two values (INH alone and with paracetamol) for each parameter were compared with each other using student t-test and value of $P < 0.05$ was considered as significant.

RESULTS

The mean plasma concentrations of INH in *Teddy* goats after its oral administration alone and with paracetamol are shown in fig. 1. Following an oral administration of INH, the peak plasma concentration (C_{max}) of $3.79 \pm 0.335 \mu\text{g/mL}$ was achieved at 2.5 hour (T_{max} , time to reach maximum concentration). After concurrent administration of INH with paracetamol, the C_{max} was $5.66 \pm 1.04 \mu\text{g/mL}$ at T_{max} , 2.5 hours and this was a significant increase ($p < 0.05$) and this difference remained significant until 12 hours.

The plasma concentration versus time data plotted on graph revealed a biexponential fall and it was best

described by two compartment open model. Mean \pm SD values of PK parameters for INH alone and when given with paracetamol are shown in table 1.

DISCUSSION

In present study following an oral dose of 10 mg of INH, the plasma concentration at 1 hour was $2.43 \pm 0.398 \mu\text{g/mL}$. This value is higher ($p < 0.05$) than $1.85 \pm 1.6 \mu\text{g/mL}$ at 1 hours following an oral administration of 10 mg/kg body weight INH in human subjects (Conte *et al.*, 2002). The difference in these values may be due to species as well as environmental differences (Javed *et al.*, 2006; Iqbal *et al.*, 2011). During present investigations, C_{max} of INH in goats was achieved at T_{max} of 2.5 hours. This value of T_{max} was greater than 1.5 hours as investigated in human beings by Notterman *et al.* (1986). Following a dose of 200 mg in healthy subjects the T_{max} ranged from 1-2 hours and C_{max} from 8.5 to 15 mg/L (Gurumurthy *et al.*, 1992). However, Jayaram *et al.* (2004) found that after 120 mg dose, T_{max} was 0.16 to 0.5 hours.

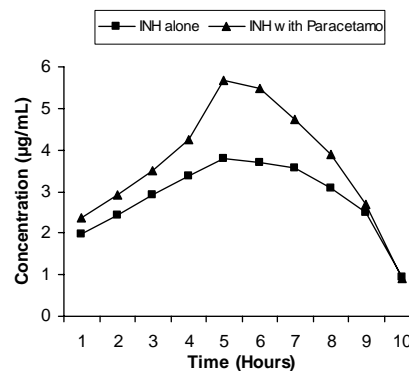


Fig. 1: Mean plasma concentrations ($\mu\text{g/mL}$) of isoniazid administered alone and with paracetamol in goats.

In our study, apparent volume of distribution (V_d) of INH alone, $0.905 \pm 0.327 \text{ L/kg}$, was more than $0.786 \pm 0.161 \text{ L/kg}$ when INH was given with paracetamol. However, these values are statistically non-significant ($p > 0.05$). Higher values of V_d $4.29 \pm 1.25 \text{ L/kg}$ and $3.02 \pm 0.55 \text{ L/kg}$ were observed in rabbits after oral and intravenous administration of INH, respectively (Walubo *et al.*, 1991). This reflects more tissue penetration of the drug in these studies. However, lower value of V_d 0.6 L/kg has been reported in human subjects after a single oral administration of INH (Boxenbaum and Riegelman, 1974). The difference in V_d of present study to other studies may be due to age, body weight and species difference.

The total body clearance (CL) of INH in our study ranged from 0.304 to 5.195 with mean \pm SD value of $3.59 \pm 2.03 \text{ mL/min/kg}$. When INH was given simultaneously with

paracetamol, CL increased to 4.04 ± 2.61 mL/min/kg. But this increase was statistically insignificant ($p > 0.05$). Higher value of CL (5.68 ± 1.9 mL/min/kg) has been observed in rabbits after oral administration of 50 mg/kg INH (Thomas et al., 1981).

Table 1: Mean \pm SD values of two compartment open model kinetic parameters after oral administration of isoniazid alone and with paracetamol in goats.

Parameters	Isoniazid alone	Isoniazid with paracetamol
C_{max} ($\mu\text{g/mL}$)	3.705 ± 0.403	$4.99 \pm 0.546^*$
T_{max} (hr)	3.144 ± 0.193	2.955 ± 0.156
K_{ab} (hr^{-1})	0.356 ± 0.163	0.3514 ± 0.055
$t_{1/2 \text{ abs}}$ (hr)	2.047 ± 0.720	2.010 ± 0.256
A ($\mu\text{g/mL}$)	65.80 ± 42.70	$18.70 \pm 20.30^*$
α (mL)	18.20 ± 12.40	$11.90 \pm 12.50^*$
$t_{1/2 \alpha}$ (hr)	0.58 ± 1.01	$1.02 \pm 1.05^*$
B ($\mu\text{g/mL}$)	7.41 ± 2.76	$10.13 \pm 2.17^*$
β ($\mu\text{g/mL}$)	0.291 ± 0.024	$0.319 \pm 0.042^*$
$t_{1/2 \beta}$ (hr)	2.391 ± 0.216	$2.17 \pm 0.346^*$
K_{12} (hr)	16.80 ± 10.20	$8.04 \pm 8.77^*$
K_{21} (hr)	1.97 ± 1.08	$4.37 \pm 5.04^*$
K_{el} (hr^{-1})	2.17 ± 1.35	$1.10 \pm 1.05^*$
Vc (L/kg)	0.305 ± 0.373	$0.506 \pm 0.261^*$
Vd (L/kg)	0.905 ± 0.327	$0.786 \pm 0.161^*$
CL (mL/min/kg)	3.59 ± 2.03	4.04 ± 2.61
Lag Time (hr)	1.73 ± 2.81	$0.241 \pm 0.644^*$

*= Significant difference at $P < 0.05$

Elimination half-life ($t_{1/2\beta}$) represents the elimination rate of drug from the body. Shorter half-life shows rapid elimination of drug from the body while longer half-life indicates delayed elimination. The mean \pm SD value of half-life of INH recorded in goats of our study was 2.39 ± 0.216 hours. However, when the same was administered concurrently with paracetamol, the $t_{1/2\beta}$ was 3.46 ± 0.216 hours which was shorter than the value obtained when INH was given alone. However, this difference was statistically insignificant ($p > 0.05$). Almost similar value of elimination half life (2.67 ± 0.36 hours) was seen in rabbits after oral administration of 50 mg/kg INH (Thomas et al., 1981). This variation from the foreign counterparts may be due to differences in species and environmental conditions. The scarcity of literature on the drug interactions of INH in food animals was the main reason to compare the results of present study with those of human beings because it is mostly prescribed for human use. Another possible explanation of this comparison may be that it was merely an interaction study to see effect of paracetamol on the PK of INH and the findings of our study may be referred to for dose adjustment of INH when both drugs are used concomitantly in human beings.

CONCLUSIONS

Based on the results of present study, it was concluded that paracetamol has a significant effect on the pharmacokinetics of isoniazid in goats and the dose of isoniazid should be increased when concomitantly used with paracetamol.

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