

EFFECT OF PARACETAMOL ON THE RENAL CLEARANCE AND URINARY EXCRETION OF ISONIAZID IN GOATS

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ABSTRACT

Effect of paracetamol on renal clearance and urinary excretion of isoniazid was investigated in eight healthy adult female goats in two phases. In the first phase, each goat was administered isoniazid orally as a single dose at the rate of 10 mg/kg body weight. A washout period of 7 days was given before the second phase in which the same dose of isoniazid was administered along with paracetamol orally at the dose rate of 15 mg /kg. In both phases, blood and urine samples were collected at various time intervals post drug administration and analyzed for isoniazid and creatinine concentrations. The value of diuresis after single administration of isoniazid was 0.084 ± 0.0056 ml/min.kg, while following concurrent administration with paracetamol it decreased to 0.058 ± 0.0067 ml/min.kg ($P > 0.05$). Mean values for renal clearance of creatinine following single and concurrent administration of isoniazid with paracetamol were 2.52 ± 1.151 and 1.82 ± 0.098 ml/min.kg, respectively, while respective values for renal clearance of isoniazid were 1.67 ± 0.116 and 0.80 ± 0.021 ml/min.kg ($P < 0.01$). The ratio between renal clearance of isoniazid and paracetamol remained less than one after the administration of isoniazid alone and concurrently with paracetamol, which was indicative of back diffusion of the drug. Mean values for the cumulative percent of dose of isoniazid excreted at 12 hours following administration of isoniazid alone was 56.51 ± 2.49 versus 27.19 ± 1.96 following its concurrent administration with paracetamol ($P < 0.05$). Thus, it is evident that besides glomerular filtration, renal handling of isoniazid also involved back diffusion and active tubular secretion. It was concluded that isoniazid was reabsorbed at tubular levels following its administration with paracetamol in goats. However, paracetamol reduced GFR inducing less urinary excretion of isoniazid.

Key words: Isoniazid, paracetamol, renal clearance, urinary excretion, goats.

INTRODUCTION

Isoniazid is still considered to be the primary drug for the treatment of tuberculosis (Katzung, 2004). It is readily absorbed when administered either orally or parentally and diffuses rapidly into all body fluids and cells. Isoniazid may also be used as an intermittent therapy for tuberculosis as the patients on rifampin and pyrazinamide may be treated with isoniazid twice weekly. Isoniazid remarkably inhibits the growth of mycobacteria at the concentration of 500 µg/ml (Hardman *et al.*, 2001).

Paracetamol (acetaminophen) is one of the most commonly used analgesic and antipyretic drugs (Katzung, 2004). There is probable potentiation of hepatotoxicity following an overdose from the paracetamol metabolite, N-acetyl-para-benzoquinonimine (NAPQI) by enzyme-inducing drugs (Hardman *et al.*, 2001). Isoniazid is commonly used in combination with paracetamol in patients suffering from tuberculosis (Hardman *et al.*, 2001). Several studies have shown that the pharmacokinetic behavior, optimal dosage, renal clearance and urinary excretion of

various drugs are different under indigenous conditions (Iqbal *et al.*, 2007). Ahmad *et al.* (2008) described pharmacokinetic variations of ofloxacin in normal and febrile rabbits. The present project was planned to study the effect of paracetamol on the renal clearance and urinary excretion of isoniazid in goats, following oral administration under local environmental conditions of Pakistan.

MATERIALS AND METHODS

Experimental animals

In the present study, eight healthy adult female goats with the average body weight of 29 kg were used. All the goats were maintained under similar environmental and managemental conditions at the farm of the Department of Livestock Management, University of Agriculture, Faisalabad, Pakistan. All the animals were fed seasonal green fodder. Fodder was offered to the animals after three hours of drug administration. The study was conducted during the month of March and April, 2006.

For the collection of blood samples, one of the jugular veins of each animal was cannulated with plastic

canula No. 9 (Portex Ltd., England). For the timely collection of the urine samples, a sterilized disposable balloon catheter was lubricated with paraffin jell and inserted into the urinary bladder through urethra of each animal. In all animals, controlled blood and urine samples were collected before the drug administration.

Drug administration

Commercial preparations of isoniazid (1% syrup Isozide®, Nabiqasim Pharmaceutical Industries, Karachi, Pakistan) and paracetamol (Tablet paracetamol®, Reckitt Benckiser Ltd., Karachi, Pakistan) were used. Isoniazid was administered orally at the dose rate of 10 mg/kg body weight (Adams, 2001). After a wash out period of seven days, isoniazid at the previous dosage level and paracetamol at the dosage level of 15 mg/kg body weight were administered orally, simultaneously to the same goats (n = 8). Blood samples were collected at 1, 1.5, 2 and 2.5 hours after each medication. After recording pH, blood samples were centrifuged, plasma was separated and stored at -20 °C until analysis.

Renal clearance

For renal clearance studies, the urinary bladder was emptied completely and washed with distilled water through the catheter before the treatment. After washing, four urine samples were collected at equal time intervals (1.25, 1.75, 2.25 and 2.75 hours). The volume and pH of each urine sample was noted. The urine samples collected for renal clearance and afterwards at different time intervals were used for the study of urinary excretion of isoniazid. Isoniazid concentrations in plasma and urine samples were determined by using spectrophotometric method (Amlathe and Gupta, 1988). Creatinine in the blood and urine samples was determined using chemistry analyzer (BTS-330 Biosystem, Spain) with the help of creatinine kit (DDS Diagnostic System, Istanbul, Turkey). Renal clearance of isoniazid and endogenous creatinine was calculated. The renal clearance of endogenous creatinine was used for the estimation of glomerular filtration rate (GFR). The effect of paracetamol on the renal handling of isoniazid following its administration alone and with paracetamol and influence of urine pH, rate of urine flow (diuresis) and the plasma drug concentration on the renal clearance of drug was examined.

Urinary excretion

The urinary excretion of isoniazid was measured in 8 goats used for renal clearance studies following its single and concurrent administration with paracetamol. The urine samples were collected before and at 4, 6, 8 and 12 hours after each treatment. Mean values for the isoniazid in urine samples at different time intervals were calculated. Cumulative percent of dose of isoniazid excreted in the urine until 12 hours following administration alone and with paracetamol was calculated.

Statistical analysis

The mean (\pm SE) values for each concentration in animals given isoniazid alone or with paracetamol were calculated. Student's T-test was used to see the significance of results between isoniazid alone and with concurrent administration of paracetamol. The relationship between the urine flow rate, blood pH and plasma concentrations of the drug was calculated with regression/correlation analysis.

RESULTS AND DISCUSSION

Renal clearance

The results of diuresis, blood pH, urine pH and renal clearance of creatinine and isoniazid following its alone and concurrent administration with paracetamol are presented in Table.1. The mean (\pm SE) value for the renal clearance of creatinine in 8 goats following single administration of isoniazid was 2.52 ± 0.151 ml/min.kg versus 1.82 ± 0.098 ml/min.kg following its concurrent administration with paracetamol ($P < 0.01$) However, the respective values for the renal clearance of isoniazid changed from 1.67 ± 0.116 ml/min.kg to 0.80 ± 0.021 ml/min.kg ($P < 0.01$).

These results show that concurrent administration of isoniazid with paracetamol significantly decreased the renal clearance of isoniazid as well as renal clearance of endogenous creatinine. An earlier study has also shown that concurrent administration of fenbufen reduced the renal clearance of ciprofloxacin by 20% (Naora *et al.*, 1990). Similarly, antacids reduced the clearance of norfloxacin by 15% (Nix *et al.*, 1991). Metamezole significantly reduced the furosemide clearance (Rosenkranz *et al.*, 1992). A decrease in theophylline clearance was observed when given concurrently with ciprofloxacin (Hulsiz and Miller, 1990).

As the renal clearance of endogenous creatinine is an index of GFR, an obvious decrease in the renal clearance of endogenous creatinine may be indicative of lower GFR for isoniazid following its concurrent administration with paracetamol. Following the administration of isoniazid alone and with paracetamol, regression/correlation analysis showed non significant ($P > 0.05$) correlation among urine pH, diuresis and endogenous creatinine concentrations both in blood and urine.

However, a significant ($P < 0.05$) positive correlation was observed between plasma concentration of isoniazid after administration of isoniazid alone and with paracetamol. A highly significant ($P < 0.01$) negative correlation was observed between urine concentration of isoniazid and ratio of renal clearance (ratio between renal clearance of isoniazid and renal clearance of endogenous creatinine) which is indicative of reabsorption of isoniazid at tubular level (Figs. 1 and 2).

Table 1: Comparison of renal clearance of isoniazid in goats following its single and concurrent oral administration with paracetamol

Parameters		Isoniazid alone	Isoniazid with Paracetamol
Diuresis (ml /min.kg.)		0.084 ± 0.0056	0.058 ± 0.0067 ^{NS}
pH	Blood	7.51 ± 0.018	7.38 ± 0.018 ^{NS}
	Urine	8.46 ± 0.019	8.31 ± 0.011 ^{NS}
Creatinine conc. (µg/ml)	Blood	6.66 ± 0.181	6.69 ± 0.211 ^{NS}
	Urine	200 ± 8.55	221.5 ± 8.27 ^{NS}
Isoniazid conc. (µg/ml)	Blood	5.31 ± 0.128	5.89 ± 0.158*
	Urine	120.61 ± 7.27	78.24 ± 2.85**
Renal cl. (ml/min.kg.)	Creatinine	2.52 ± 0.151	1.82 ± 0.098**
	Isoniazid	1.67 ± 0.116	0.80 ± 0.021**
Clearance ratio		0.67 ± 0.046	0.46 ± 0.019**

NS = Non significant (P>0.05), * = significant (P<0.05), ** = highly significance difference (P<0.01) from the respective values.

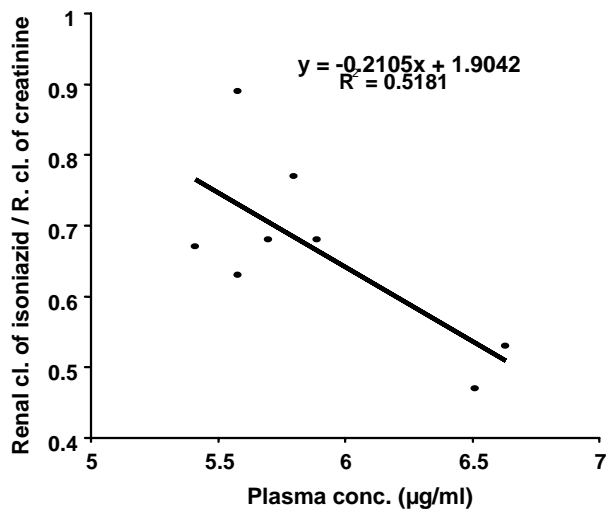


Fig. 1: Effect of plasma concentrations of isoniazid on its renal clearance following single administration.

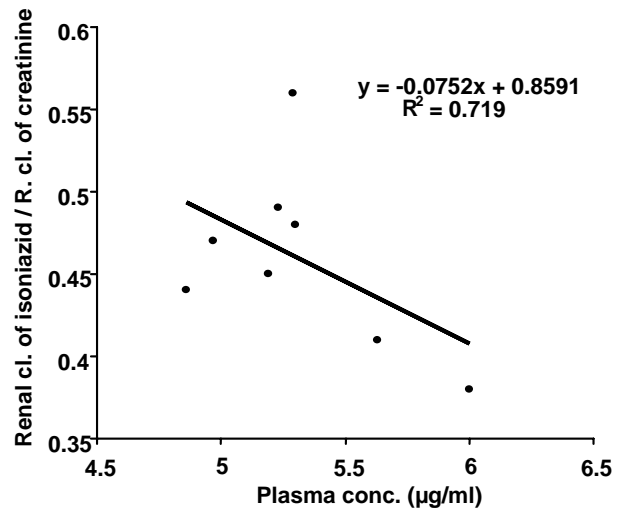


Fig. 2: Effect of plasma concentrations of isoniazid on its renal clearance following its concurrent oral administration with paracetamol.

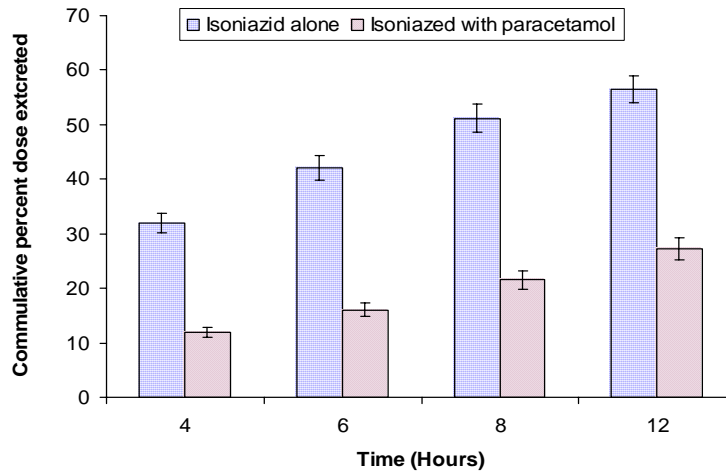


Fig. 3: Mean (± SE) values for cumulative percentage of dose of isoniazid extracted in urine of goats following its alone and concurrent administration with paracetamol.

The clearance ratio of less than one (ratio between the renal clearance of isoniazid and the renal clearance of endogenous creatinine) was observed which indicated back diffusion. Thus, it appears that besides GFR, renal handling of isoniazid alone and following its concurrent administration with paracetamol involved active tubular secretion and back diffusion.

Based on these results, it is evident that in goats the renal clearance of isoniazid was significantly decreased following its concurrent administration with paracetamol as the clearance ratio was significantly reduced which indicated back diffusion (reabsorption) of isoniazid at kidney level. However, paracetamol reduced the GFR of isoniazid, inducing less renal clearance.

Urinary excretion

Mean (\pm SE) value for the cumulative percent of dose of isoniazid excreted at 12 hours following administration of isoniazid alone was 56.51 ± 2.49 which decreased to 27.19 ± 1.96 following its concurrent administration with paracetamol (Fig. 3). Both the values were significantly ($P < 0.05$) different from each other and about 45% reduction was noticed. In earlier studies, drug interaction was also found to reduce the urinary output of the drug in human beings. Antacids reduced the urine output of norfloxacin (Nix *et al.*, 1991). Metamezole reduced the urinary excretion of furosemide (Rosenkranz *et al.*, 1992). The mean percentage of ciprofloxacin dose recovered in urine was significantly lower following its administration in combination with sucralfate (Marika *et al.*, 1999). Fenbufen significantly reduced the cumulative urinary excretion of quinolones (Naora *et al.*, 1990).

Under current investigations, lower urinary excretion of isoniazid in goats following its concurrent administration with paracetamol may be evidenced by the results regarding its renal handling. These results show that regardless the involvement of active tubular secretion, the administered dose has also been absorbed at kidney tubular level through back diffusion.

Moreover, paracetamol following its concurrent administration with isoniazid, reduced GFR. Lower the GFR, less will be the urinary excretion of the drug (Hasan, 1998). Further, isoniazid is a weakly acidic drug. When the pH of urine in goats increases, the ionized moiety of drug will also increase. The result of renal clearance also indicated that following concurrent administration of isoniazid with paracetamol, urine pH was not changed. At lower urine pH the ionized moiety of the weakly acidic drug will reduce, giving way to unionized moiety for reabsorption at kidney level.

Conclusion

In isoniazid and paracetamol administered goats, GFR was lower than that with isoniazid alone. Renal

handling of isoniazid, besides glomerular filtration, involved back diffusion and active tubular secretion. However, the renal clearance and urinary excretion of isoniazid was significantly reduced after its concurrent administration with paracetamol.

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