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# PHARMACOKINETIC STUDY ABOUT INTERACTION OF NAPROXEN AND ISONIAZID

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**ABSTRACT**

Effect of Naproxen (500 mg) was studied on the pharmacokinetic characteristics of Isoniazed (300 mg) in ten healthy human volunteers in a complete cross-over design. A high performance liquid chromatography (HPLC) method was used to analyze serum drug concentrations. Naproxen caused a highly significant ($P<0.001$) increase in AUC, significant ($P<0.05$) increase in elimination half life ($t_{1/2}$) and time for the maximum drug concentration ($t_{max}$) while significant ($P<0.05$) decrease in elimination rate constant ($K_e$). Insignificant decrease and increase was observed in absorption rate constant ($K_a$) and maximum drug concentration ($C_{max}$) respectively.

## INTRODUCTION

Pharmacokinetic drug interaction is the modification of the pharmacokinetic behaviour of one drug by another drug. Therefore, elucidation of pharmacokinetic drug interaction is very useful and important for ensuring the effectiveness and safety of clinical drug therapy (Malik et al, 1995).

Naproxen is a very potent member of propionic acid derivatives like ibuprofen, ketoprofen, and fenoprofen, which represent a group of effective, useful antipyretic, analgesic and non-steroidal anti-inflammatory drugs. It may offer significant advantages over aspirin, indonrethacin, and the pyrazdon derivatives for many patients, since it is usually better tolerated. Naproxen like most other non-steroidal anti-inflammatory agents, inhibits prostaglandin synthesis (Anonymous, 1990). It has 99% tendency to bind with plasma proteins at concentrations within the therapeutic range (Insel, 1991).

Isoniazid (isonicotinyl hydrazide) is widely used as a chemotherapeutic agent for the treatment of tuberculosis. The minimal tuberculostatic concentration of isoniazid is 0.025-0.050 µg/ml in plasma (Fox, 1972; 1975). The drug is remarkably selective for mycobacteria, and concentrations in excess of 500 µg/ml are required to inhibit the growth of other microorganisms. Acetyltransferase is an enzyme responsible for the production of the major metabolic product, acetylisoniazid (Weber and Hein, 1979). It has been reported that isoniazid itself influence the cytochrome P450 oxidative enzyme system (Hoglund, 1987). We have reported pharmacokinetic interaction of isoniazid with cimetidine (Loothar et al, 1996), ibuprofen (Saleh et al, 1995), ketoconazole (Iqbal et al, 1995), aspirin (Nawaz et al, 1993) earlier.

Various interaction studies of Naproxen have been reported in the literature e.g. with antacids (Segre, 1983), chlosetyramine (Calvo, 1984), probencid (Rankel, 1978) and Suglycotide (Berte, 1988) etc but to our knowledge there is no data available on pharmacokinetic interaction of naproxen and isoniazid therefore this study was conducted to investigate the possible effect of naproxen on the isoniazid.

## MATERIAL AND METHODS

### *Drugs and Chemicals*

Pure isoniazed powder (Flub) was used a standard for HPLC analysis Nicotinamide (Flub) was used as an internal standard for HPLC assay of isoniazid. Isoniazid tablets (Glaxo) and Naproxen (Abbott) *were* purchased from the market. Methanol (HPLC grade, BDH), Acetonitrile (HPLC grade, BDH), Chloroform (Merck), Potassium dihydrogen phosphate (Fluka), Sodium acetate (Merck), Sodium hydroxide (Fluka), n-Butanol (BDH) were also used during the studies.

### *Drug Administration and Blood Sampling*

The healthy volunteers were selected with their written informed consent. They *were* instructed to refrain from taking any medicine for a week prior to and during the study period. The drugs were given before the breakfast in the morning. The subjects participated were initially given isoniazid (3*100 mg tablet) alone. After one week of initial dosing, they were concurrently given isoniazid (300 mg) and Naproxen (500 mg). Blood samples were drawn (5 ml) at 0, 1/4, 1/2,1, 2, 4, 6 and 8 hours in both dosing conditions respectively. The samples were then allowed to colt and centrifuged. The serum was separated and stored at -20°C for subsequent analysis within a month.

### *Analytical Method*

Isoniazid concentration in all human serum samples was determined by reversed-phase liquid chromatography using a method (Moulin et al, 1981). This consisted of a Rheodyne model 7161 injector (fitted with 20 vl loop), a Hitachi-4200 variable wavelength monitor, a Hitachi D-2000 chromato-integrator and a stainless column (250 nun * 4 mm I.D.) packed with reverse phase Lichosorb ODS (104, Hiber packed). Methanol (5%) in 0.1M $RHPO_2$ (95%, pH 6.9), after degassing with helium, was used as a mobile phase at a constant flow rate of 1 ml/min.

### *Pharmacokinetic and Statistical Analysis*

Serum drug concentration-time data were analyzed using a non-linear interaction (R-STRIP, Micromath). The derived parameters were subjected to statistical analysis using SAS system .The pharmacokinetic parameters were calculated as follows:

$$\text{Distribution half life } (t_{1/2}) = 0.693/\alpha$$
$$\text{Elimination half life } (t_{1/2}) = 0.693/\beta$$
$$\text{Area under curve (AUC)} = A/e\ \alpha\ B/\ \beta^2$$
$$\text{Area under moment curve (AUMC)} = Al\ \alpha^2 + B/\ \beta^2$$
$$\text{Mean residence time (MRT)} = AUMC/AUC$$

## RESULTS AND DISCUSSION

The potential pharmacokinetic interaction of the non-steroidal anti-inflammatory drug, Naproxen, and the anti-tuberculosis agent, isoniazid, with other drugs is of considerable importance, since these two drugs are among the most widely prescribed in the world and are very likely to be frequently co-administered. The present investigation was, therefore, designed with the aim of assessing the pharmacokinetic interaction of naproxen with isoniazid.

In order to obtain preliminary information on the presence or absence of such an interaction, variation in the area under serum concentration-time curve (AUC), elimination half life ($t_{1/2}$) elimination rate constant ($K_e$), absorption rate constant ($K_a$), MRT, $C_{max}$, $t_{max}$, of isoniazid caused by co-administration with naproxen was examined. Figure indicates the comparative serum concentrations (μg/ml) of isoniazid alone and in combination with naproxen, while table shows the comparative pharmaokinetic parameters of isoniazid when administered alone and concomitantly with naproxen.

Isonaiazid is widely prescribed in the treatment of tuberculosis. Its main metabolic pathway is N-acetylation in man (Barclay, 1953; Ellard, 1972; Weber, 1979). Our results indicate that naproxen interferes with the pharmacokinetics of isoniazod. A significant ($P<0.05$) reduction in the value of elimination rate constant ($K_e$), time for maximum drug concentration ($T_{max}$) was observed because the major metabolic pathway of naproxen in man involves the O-demthylation and conjugation mainly with glucuronic acid (Inset, 1991) and in some animals isoniazid itself has been demonstrated to influence oxidative enzyme system (Hoglund, 1987), these metabolic oxidative reactions were used for the metabolism of naproxen which affected the N-acetylation pathway of isoniazid, as in the case of p-aminosalicylic acid (Bell, 1957). In addition naproxen binds with protein more than isoniazid (Sippel et al, 1974). Similarly, the value(s) of area under the serum concentration/time curve (AUC) increased significantly ($P<0.001$), while absorption rate constant ($K_a$) and elimination half life (qrz) increased significantly. Bioavailability of isoniazid after dosing concurrently with naproxen was 40% more than, when it was given alone. This highly significant increase seems to be due to the metabolic inhibition of the enzyme acetyltransferase, present in the liver, which converts isoniazid into more hydrophilic acetylisoniazid. Similarly, a significant increase ($P<0.05$) was observed in the value of ($T_{max}$). These results of isoniazid interaction are in agreement with our previously reported results with aspirin (Nawaz et al, 1993), and ibuprofen (Saleh et al, 1993). While in the cases of Ka and $C_{max}$, the relative differences were found to be insignificant (Table).

Table
Pharmacokinetic parameters of isoniazid when given alone and with naproxen

| Parameters | Isoniazid (300mg) alone | Isoniazid (300 mg) with naproxen (500mg) | t-value |
|---|---|---|---|
| Ka ($hr^{-1}$) | 1.569 ± 0.147 | 1.395 ± 0.101 | 0.95 |
| Ke ($hr^{-1}$) | 0.396 ± 0.041 | 0.332 ± 0.017 | 1.810* |
| AUC (μg.hr/ml) | 0.431 ± .046 | 0.675 ± 0.079 | 6.60** |
| t ½ (hr) | 1.750 ± 0.142 | 2.206 ± 0.085 | 3.49* |
| $t_{max}$(hr) | 1.169 ± 0.041 | 1.441 ± 0.085 | 2.85* |
| $C_{max}$ (μg/ml) | 0.164 ± 0.041 | 0.201 ± 0.028 | -0.792 |

*Significant (P<0.05)
**Highly significant (P<0.001)

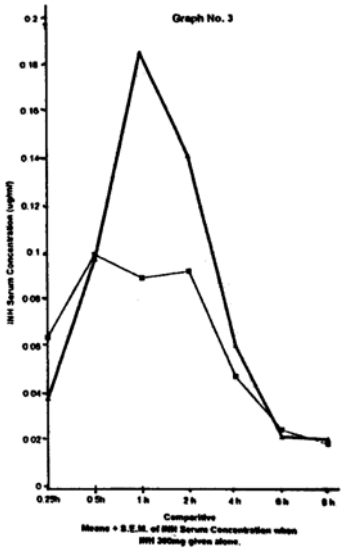


Fig. 1: Comparative Means ± S.E.M. of INA Serum Concentration when MH 300 mg given alone.

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