Effect of Concurrent Naproxen Administration on Pharmacokinetics of Isoniazid

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Abstract: Antibacterial drugs, such as isoniazid can interact with other drugs in a wide variety of clinically significant ways. It is frequently administered with other prescription medications. The antibacterial agents may be affected by the action of another co-administered drug. Interactions involving antimicrobials often result from alterations in the hepatic metabolism or renal elimination of the drugs concurrently administered. Nonsteroidal anti-inflammatory drugs (NSAIDS) are the most widely used drugs. Drug interactions with this class of compounds are frequently reported and can be pharmacokinetics and/or pharmacodynamic in nature. Isoniazid and naproxen are co-administered in patients suffering from tuberculosis as well as osteoarthritis (mostly in developing countries). The aim of this investigation was to assess the effect of naproxen (500 mg) on the pharmacokinetics characteristics of isoniazid (300 mg) in ten healthy human volunteers in a complete cross-over design using high performance liquid chromatography (HPLC) method 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. These results signify that naproxen enhances the concentration of isoniazid in serum therefore there is no harm to use them concurrently.

Key words: Naproxen, isoniazid, interaction, pharmacokinetics

INTRODUCTION

Clinically significant interactions occurring during antituberculosis chemotherapy principally involving isoniazid. Such interactions between the antituberculous drugs and co-administered agents are definitely much more important than among antituberculous drugs themselves. These can be associated with consequences even amounting to therapeutic failure or toxicity. Most of the interactions are pharmacokinetics rather than pharmacodynamic in nature (Yew, 2002). Interactions involving antimicrobial often results from alterations in the absorption of the antimicrobial from the gastrointestinal tract or changes in the hepatic metabolism of the drugs concurrently administered. While certain classes of antibacterial drugs are known to interact with many other drugs, the interaction potential of most classes of antimicrobials is not uniform among members of the class. The cytochrome P450 isofrom enzymes are responsible for many interactions (especially those involving isoniazid) during drug biotransformation (metabolism) in the liver and/or intestine (Horn and Hansten, 1995). Generally, isoniazid acts as an inhibitor. Isoniazid interacts principally with paracetamol (acetaminophen) (Murphy et al., 1990); rifampicin (Shishoo et al., 2001) phenytoin (Miller et al., 1979); Theophylline (Torrent et al., 1989) and food (Self et al., 1999).

Naproxen is a stereochemically pure nonsteroidal anti-inflammatory drug of the 2-arylpropionic acid classes like ibuprofen, ketoprofen and fenoprofen. It may offer significant advantages over aspirin, Indomethacin and pyrazol derivatives for many patients, since it is usually better tolerated. Naproxen like most other non-steroidal anti-inflammatory agents inhibits prostaglandin synthesis (Anonymous, 1990). The absorption of naproxen is rapid and complete when given orally. Naproxen binds extensively, in a concentration-dependent manner, to plasma albumin (Davies and Anderson, 1997). Most of drug interactions with this class of compounds are pharmacokinetics in nature e.g. with paracetamol (Seideman, 1993); suglycody (Berte et al., 1988); sucralfate (Caille et al., 1987). We have reported pharmacokinetics interaction of isoniazid with cimetidine (Loothar et al., 1996); ibuprofen (Saleh et al., 1995); ketoconazole (Iqbal et al., 1995); aspirin (Nawaz et al., 1993). To our knowledge there is no data available on pharmacokinetics interaction of naproxen and isoniazid. This study describes the serum concentrations and the pharmacokinetics behavior of isoniazid alone and concurrent combination with naproxen.

MATERIALS AND METHODS

Reagents: Abbott Laboratories donated pure isoniazid powder; Pakistan was used as a standard for HPLC
analysis. Nicotinamide (Fluka) was used as an internal standard for HPLC assay of isoniazid. Isoniazid tablets (Glaxo) and Naproxen tablets (Abbott) were purchased from the market. Methanol (CH₃OH, HPLC grade, BDH), Sodium acetate (CH₃COONa, HPLC grade, Merck), Acetonitrile (CH₃CN, HPLC grade, BDH), Sodium Hydroxide (NaOH, Merck) Glacial Acetic acid (CH₃COOH, Merck), Chloroform (CHCl₃, Merck), Potassium dihydrogen phosphate (KH₂PO₄, Fluka), n-Butanol (C₇H₈O₂, BDH) were used during the studies.

**Drug administration and blood sampling:** Ten healthy subjects (male) between 21 to 27 years of age participated. All were healthy, ambulatory adults with no evidence of medical diseases and no one was taking any medicine. Subjects participated in a two way crossover trial, the two ways of dosing were as follows:

- The control subjects were orally given 300 mg of isoniazid alone.
- In the next round the same subjects received 300 mg of isoniazid in combination with 500 mg of naproxen.

All drugs were given in fasting state (after an overnight fast, with an unlimited take of water). After the drug administration, the subjects remained fasting for 2.5 h. Venous blood samples (5 ml) were drawn in a vacutainer serum tubes at 0, 0.25, 0.5, 1, 2, 4, 6 and 8 h interval. Serum was separated within 30 min. and stored at-20°C till analysis. At least two weeks interval between each trial was given to every volunteer as a wash out period (Moulin et al., 1981)

**High performance liquid chromatography (HPLC), assay of isoniazid:** Isoniazid concentration in all human serum samples was determined by employing reversed phase HPLC using a method (Malik et al., 1992). The method consisted of a Rheodyne model 7161 injector (fitted with 20 ul loop), a Hitachi-4200 variable wavelength monitor, a Hitachi D-2000 chromato-integrator and a stainless steel column (250 mm * 4 mm I.D.) packed with reverse phase Lichrosorb ODS (104, Hiber packed). CH₃OH (5%) in 0.1 M KH₂PO₄ (95%, pH 6.9), after degassing with helium, was used as a mobile phase at a constant flow rate of 1 ml min⁻¹ at 220 nm wavelength. This enabled, a good separation and efficient resolution of the required analyte.

**Pharmacokinetics analysis:** Serum concentration-time curves after oral administration of isoniazid alone and in combination with naproxen was analyzed using the nonlinear interaction (R-STRIP, micro math). The fitted function was used to determine the elimination half life \( t_{1/2} \). The total area under the serum concentration-time curve (AUC) was calculated by the trapezoidal rule and extrapolated to infinity (Paulsen et al., 1986). The value of absorption rate constant \( K_{a} \) was determined from the slope of the upper linear portion of semilog plot of the serum drug concentration-time profile by applying the method of residuals (Shargel and Yu, 1985).

**RESULTS**

Isoniazid showed highly significant increase in Area under the concentration time curve (AUC) from \( (0.431 \pm 0.046) \) to \( (0.675 \pm 0.079) \). Significant increase in elimination half life (\( t_{1/2} \)) from \( (1.750 \pm 0.142) \) to \( (2.206 \pm 0.085) \), time for the maximum drug concentration \( (t_{max}) \) from \( (1.169 \pm 0.041) \) to \( (1.441 \pm 0.085) \). Insignificant decrease in absorption rate constant \( (K_{a}) \) and maximum drug concentration \( (C_{max}) \), respectively was observed when naproxen was co-administered with isoniazid. On the other hand isoniazid exhibited significant decrease in elimination rate constant \( (K_{e}) \) from \( (0.396 \pm 0.041) \) to \( (0.332 \pm 0.017) \) when naproxen was given concomitantly with isoniazid (Table 1). Concentration of isoniazid decreased up to 1st h and increased later when it was co-administered along with naproxen (Fig. 1).

**DISCUSSION**

Clinically significant interactions occurring during antitubercular chemotherapy principally involve isoniazid. Such interactions between the antitubercular drugs and co-administered agents are definitely much important than among antitubercular drugs themselves. These can be associated with consequences even amounting to therapeutic failure or toxicity. Most of the interactions are pharmacokinetics rather than pharmacodynamic in nature. The cytochrome P450 isorom enzymes are responsible for many interactions especially those involving isoniazid during drug biotransformation (metabolism) in the liver and/or intestine (Yew, 2002). Interactions involving antimicrobials often result from alterations in the absorption of the antimicrobial from the gastrointestinal tract or changes in the hepatic metabolism or renal elimination of the drugs concurrently administered. While certain classes of antibacterial drugs are known to interact with many other drugs, the interaction potential of most classes of antimicrobials is not uniform among members of the class. (Horn and Hansen, 1995).

Some published results reveal that absorption and elimination of isoniazid decreased (Sprouse et al., 1978; Thomas and Solomonraj, 1977). Similar type of results have been reported in the literature by other scientists (Iqbal et al., 1995, Pizzada et al., 1993).

Generally, isoniazid acts as an inhibitor. Isoniazid interacts principally with anticonvulsants, theophylline,
Table 1: Pharmacokinetics parameters of isoniazid when given alone and with naproxen

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Isoniazid (300 mg)</th>
<th>Isoniazid (300 mg) with Naproxen (500 mg)</th>
<th>t-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alone</td>
<td>with Naproxen</td>
<td></td>
</tr>
<tr>
<td>K_{e} (hr^{-1})</td>
<td>1.56±0.147</td>
<td>1.39±0.101</td>
<td>0.95</td>
</tr>
<tr>
<td>K_{e} (hr^{-1})</td>
<td>0.39±0.041</td>
<td>0.33±0.017</td>
<td>1.81</td>
</tr>
<tr>
<td>AUC (µg·hr·ml^{-1})</td>
<td>0.43±0.046</td>
<td>0.67±0.079</td>
<td>6.60*</td>
</tr>
<tr>
<td>T_{1/2} (hr)</td>
<td>1.75±0.142</td>
<td>2.20±0.085</td>
<td>3.49*</td>
</tr>
<tr>
<td>T_{max} (hr)</td>
<td>1.16±0.041</td>
<td>1.44±0.085</td>
<td>2.85*</td>
</tr>
<tr>
<td>C_{max} (µg/ml)</td>
<td>0.16±0.041</td>
<td>0.20±0.028</td>
<td>-0.792</td>
</tr>
</tbody>
</table>

* Significant (p < 0.05)
** Highly Significant (p < 0.001)

Fig. 1: Comparative means ± S.E.M. of isoniazid serum concentration when isoniazid given with Naproxen

benzodiazepines, paracetamol (acetaminophen) and some food (Yew, 2002).

These results indicate that naproxen interferes with the pharmacokinetics of isoniazid. These findings suggest that naproxen appears to be subjected into enterohepatic circulation and binds with plasma albumin (Davies and Anderson, 1997) more than isoniazid (Sipple et al., 1974), as a result absorption of isoniazid is reduced. 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-demethylation and conjugation mainly with glucuronic acid (Inselt, 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. Bioavailability of isoniazid after dosing concurrently with naproxen was 40% more than when it was given alone. This increase seems to be due to the metabolic inhibition of the enzyme acetyl transferase, present in the liver, which converts isoniazid into more hydrophilic acetyl isoniazid. Highly significant increase in area under the serum concentration/time curve (Pirzada et al., 1993) while significant increase in elimination half life (t_{1/2}) was noted of isoniazid (Iqbal et al., 1995; Santos, 1985). Antacids did not alter these parameters significantly (C_{max} of 5.62-2.53 microg ml^{-1}) (Pelchquin et al., 1999). Increase in absorption rate constant (K_{e}) was like reported by aspirin (Thomas and Solomonraj, 1977).

The results signify plausible mechanism of these interactions could be associated with protein-binding of naproxen which displaces isoniazid due to which time for maximum concentration was decreased and area under concentration/time curve was increased. Elimination half life was increased due to inhibitory nature of isoniazid which suggests that these two drugs may be administered with interval instead concomitantly yet further studies are needed to fully establish these findings.

REFERENCES


