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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 ($t_{½}$) 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 isoform 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 stereo chemically 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 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).. 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); suglycotide (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 (CH_3OH, HPLC grade, BDH), Sodium acetate (CH_3COONa, HPLC grade, Merck), Acetonitrile (CH_3CONO_2, HPLC grade, BDH), Sodium Hydroxide (NaOH, Merck) Glacial Acetic acid (CH_3COOH, Merck), Chloroform ($CHCl_3$, Merck), Potassium dihydrogen phosphate (KH_2PO_4, Fluka), n-Butanol (C_4H_9OH, 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 Lichosorb ODS (104, Hiber packed). CH_3OH (5%) in 0.1M KH_2PO_4 (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 222 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 non-linear interaction (R-STRIP, micro math). The fitted function was used to determine the elimination half life ($t_{½}$). 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±0.046) to (0.675±0.079). Significant increase in elimination half life ($t_{½}$) from (1.750±0.142) to (2.206±0.085), time for the maximum drug concentration (t_{max}) from (1.169±0.041) to (1.441±0.085). Insignificant decrease and increase 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±0.041) to (0.332±0.017) when naproxen was given concomitantly with isoniazid (Table 1). Concentration of isoniazid decreased upto Ist h and increased later when it was co-administered along with naproxen (Fig. 1).

DISCUSSION

Clinically significant interactions occurring during antituberculous chemotherapy principally involve 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. The cytochrome P450 isoform 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 Hansten, 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; Pirzada *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

Parameters	Isoniazid (300 mg) Alone	Isoniazid (300 mg) with Naproxen (500 mg)	t-value
K_a (hr^{-1})	1.569±0.147	1.395±0.101	0.95
K_e (hr^{-1})	0.396±0.041	0.332±0.017	1.81*
AUC (ug.hr ml^{-1})	0.431±0.046	0.675±0.079	6.60**
$T_{1/2}$ (hr^{-1})	1.750±0.142	2.206±0.085	3.49*
T_{max} (hr^{-1})	1.169±0.041	1.441±0.085	2.85*
C_{max} (ug/ml)	0.164±0.041	0.201±0.028	-0.792

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

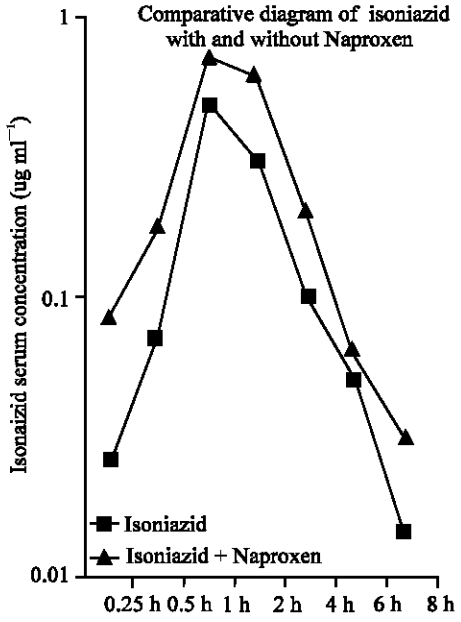

Fig. 1: Comparative means + S.E.M. of isoniazid serum concentration when isoniazid given with Naproxen

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

These results indicate that naproxen interferes with the pharmacokinetics of isoniazid. These findings suggests that naproxen appear to be subjected into enterohepatic circulation and binds with plasma albumin (Davies and Anderson, 1997) more than isoniazid (Sippel *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 (Insel, 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; Santoso, 1985). Antacids did not alter these parameters significantly (C_{max} of 5.62 +/-2.53 microg ml^{-1}) (Peloquin *et al.*, 1999). Increase in absorption rate constant (K_a) was like reported by aspirin (Thomas and Solomonraj, 1977). These results signifies 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

Anonymous, 1990. Microprostol for co-operation with NSAIDS. Drugs and Ther. Bullet., 28: 25-6.

Berte, F., F. Fletti, D. Debarnadi, M. Valserra, M. Nazzari, A. Cenedes and U. Comelli, 1988. Lack of influence of suglycotide on the naproxen bioavailability in healthy Human volunteers. Int. J. Pharmacol. Ther. Tox., 26: 125-30.

Caille, G., P.D. Souich, P. Gervais, J.G. Besner and M. Vezina, 1987. Effects of concurrent sucralfate administration on pharmacokinetics of naproxen. Am. J. Med., 83: 67-73.

Davies, N.M. and K.E. Anderson, 1997. Clinical pharmacokinetics of naproxen. Clin. Pharmacokinet., 32: 268-93.

Hoglund, P., L.G. Nillson and O. Paulson, 1987. Interaction between isoniazid and Theophylline. Europ. J. Resp., 70: 112-18.

Horn, J.R. and P.D. Hansten, 1995. Drug interactions with antibacterial agents. J. Fam. Pract., 41: 81-90.

Iqbal, M., B. Ahmed and R. Nawaz, 1995. Study of the interactions between ketoconazole and isoniazid in human volunteers. Pak. J. Pharmacol., 12: 45-50.

Insel, P.A., 1991. The pharmacologic basis of therapeutics. 8th Ed., Gilman, A.G., T.W. Rall, A.S. Nies and P. Taylor. Vol. 1. Chap. 26. PergmanPress, New York.

Loothar, B.A., M. Uzair, M.T. Ansari and M.A. Rana, 1996. Influence of cimetidine on the Pharmacokinetics parameters of isoniazid. J. Res. (Science), 8: 21-23.

Malik, A.W., B. Ahmed, K.H. Janbaz, M.A. Khan, A.S. Ijaz and M.K. Saleh, 1992. Headline determination of ibuprofen in human serum by reverse-phase high performance liquid chromatography. Sci. Int., 4: 63-65.

Miller, R.R., J. Porter and D.J. Greenblatt, 1979. Clinical importance of the interaction Of phenytoin and isoniazid: a report from the Boston collaborative drug Surveillance profram. Chest., 75: 356-8.

Moulin, M.A., F. Albessard, J. Lacotte and R. Camsonne, 1981. Hydrophilic ion impairs. reversed-phase high-performance liquid chromatography for the simultaneous assay. of isoniazid and acetyl isoniazid in serum: a microscale procedure. J. Chromatogr., 226: 250-54.

Murphy, R.S., R. Swartz and P.B. Watkins, 1990. Severe acetaminophen toxicity in a Patient receiving isoniazid. Ann. Intern. Med., 113: 799-800.

Nawaz, R., B. Ahmed, M. Arif, M. Iqbal and H. Pervez, 1993. The influence of aspirin on The Pharmacokinetics parameters of isoniazid. J. Res. (Science), 5: 11-14.

Paulsen, O., P. Hoglund, L.G. Nilsson and H. Gredeby. 1986. No interaction between. H_2 blockers and isoniazid. Eur. J. Respir. Dis., 68: 286-90.

Peloquin, C.A., R. Namdar, A.A. Dodge and D.E. Nix, 1999. Pharmacokinetics of isoniazid under fasting conditions, with food and with antacids. Int. J. Tuberc. Lung Dis., 3: 703-10.

Pirzada, W.M., B. Ahmed, K.H. Janbaz and M. Akram, 1993. The influence of milk and Lassi on the bioavailability of isoniazid. JAPS., 3: 93-96.

Saleh, K.M., B. Ahmed, W.A. Malik, K.H. Janbaz and A.S. Ijaz, 1995. A study to Determine the influence of isoniazid on the pharmacokinetics of ibuprofen in Human volunteers. Sci. Int., 7: 313-16.

Santoso, B., 1985. Impairment of isoniazid clearance by propanolol. Int. J. Clin. Pharmacol. Ther. Toxocol., 232: 134-36.

Seideman, P., 1993. Additive effect of combined naproxen and paracetamol in rheumatoid Arthritis. Br. J. Rheumatol., 32: 1072-82.

Self, T.H., C.R. Chrisman, A.M. Baciewicz and M.S. Bronze, 1999. Isoniazid drug and Food interactions. Am. J. Med. Sci., 317: 304-11.

Shargel, L. and A.B.C. Yu, 1985. Applied Pharmaceutics and Pharmacokinetics. 2nd Ed., Appleton-Century-Crofts, New York.

Shishoo, C.J., S.A. Shah, I.S. Rathod, S.S. Savale and M.J. Vora, 2001. Impaired Bioavailability of rifampicin in presence of isoniazid from fixed dose combination (FDC) formulation. Int. J. Pharm., 228: 53-67.

Sippel, J.E., I.A. Mikhail, N.I. Girgis and H.H. Youssef, 1974. Rifampicin concentration in C.S.F. of patients with tuberculosis-meningitis. Ann. Rev. Respir. Dis., 109: 579-84.

Sprouse, J.S., D.W. Schneck and A.H. Hayes, 1978. The effect of isoniazid and other drugs on the acetylation of procainamide in intact rat. J. Pharmacol. Exp. Ther., 207: 698-704.

Thomas, B.H. and G. Solomonraj, 1977. Drug interactions with isoniazid metabolism in rats. J. Pharm. Sci., 66: 1322-6.

Torrent, J., I. Izquiredo, R. Cabezas and F. Jane, 1989. Theophylline-induced interactions. DICP, 23: 143-5.

Yew, W.W., 2002. Clinically significant interactions with drugs used in the treatment Of tuberculosis. Drug Saf., 25: 111-33.