Journal of Medical Sciences

ISSN 1682-4474

science alert

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Research Paper

J. Med. Sci., 3 (1): 24-29
January-February, 2003

Pharmiacockinetic Interaction Between Naproxen and Rifampicin

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Rifampicin and Naproxen are commonly co-administered to patients suffering from tuberculosis as well as osteoarthritis, so the effect of naproxen (500 mg) on the pharmacokinetics of rifampicin (450 mg) was evaluated in healthy human subject (n=10). Subjects participated in a two way crossover trial, the first dosing condition was rifampicin alone (control) and the second dosing condition was naproxen with rifampicin. The concentrations of rifampicin from the serum samples were determined by HPLC. The pharmacokinetic parameters indicated a significant ($P<0.05$) increase in elimination rate constant (K_e), clearance (Cl), volume of distribution (V_d), while significant decrease in the mean residence time (MRT) and area under the concentration-time curve (AUC) when rifampicin given with naproxen. Non-significant increase and decrease in absorption rate constant (K_a) and elimination half life ($t_{1/2}$), time for maximum concentration (T_{max}), maximum drug concentration (C_{max}), respectively was observed. It may be concluded that these drugs may not be administered concomitantly due to their kinetic interactions.

Key words: Naproxen, rifampicin, interaction

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JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publish original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued six times per year on paper and in electronic format.

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Introduction

A drug interaction is said to occur when the effects of one drug are changed by the presence of another drug. The drug-drug interactions have pharmacokinetic rather than pharmacologic basic (Verbeeck, 1990). Pharmacokinetic interactions are those, which can effect the processes by which drugs are absorbed, distributed, metabolized and excreted (Loothar ***et al.***, 1998). Therefore determination of pharmacokinetic drug interaction is very important for ensuring the efficacy and safety margin of clinical drug therapy (Kristensen, 1983).

Rifampicin is a first choice anti-tuberculosis drug. It is a powerful inducing agent of hepatic drug-metabolizing enzymes and this may account for a variety of drug interactions (Ohnhaus ***et al.***, 1979; Breimer ***et al.***, 1977; Kenny and Strates, 1981). Repeated oral administration, most likely as a consequence of self-induced (auto-induction) metabolism, there in a reduction in half life as well as in blood levels (Kohno ***et al.***, 1984; Loos ***et al.***, 1985) of rifampicin.

Naproxen is a non-steroidal anti-inflammatory, analgesic, antipyretic drug, used for the relief of signs and symptoms of rheumatoid arthritis (RA). It is also effective in clinical treatment of osteoarthritis, ankylosing spondylitis and acute gout (Skeith ***et al.***, 1994; Segre ***et al.***, 1974). Patients suffering from tuberculosis and arthritis at a time, could receive rifampicin and naproxen for a long time (Nichols, 1995).

Some clinically important interactions of rifampicin with ketoconazole, ibuprofen, cimetidine and phenytoin have been reported in the literature (Doble ***et al.***, 1988; Abadi ***et al.***, 1988; Ochs ***et al.***, 1985). Previously we have reported our results about the possible influence of aspirin, chlorpropamide, cimetidine, ketoconazole, diclofenac on the pharmacokinetics of rifampicin (Arif ***et al.***, 1993; Loothar ***et al.***, 1999; Iqbal ***et al.***, 1994; Nawaz ***et al.***, 1993; Loothar ***et al.***, 1998). But the present study was conducted to evaluate the influence of concurrent dosing of naproxen and rifampicin on the pharmacokinetics of a single dose of rifampicin in healthy subjects.

Materials and Methods

Reagents

Pure rifampicin powder was donated by Abbott Laboratories, Pakistan. Methanol (CH_3OH, HPLC grade, BDH), Sodium acetate (CH_3COONa, HPLC grade, Merck), Acetonitrile (CH_3CONO_2, HPLC grade, BDH), Glacial Acetic acid (CH_3COOH, Merck), Chloroform ($CHCl_3$, Merck), Potassium dihydrogen phosphate (KH_2PO_4, Fluka) were used during the course of work. Rifampicin tablets (Ciba) and Naproxen (Abbott) were purchased from the local market.

Drug administration and blood sampling

Ten healthy subjects (male) between 21 to 27 years old was participated in this study. Subjects participated in a two way crossover trial, the two ways of dosing were as follows:

1. The control subjects were orally given 450 mg of rifampicin alone
2. In the next round the same subjects received 450 mg of rifampicin in combination with 500 mg of naproxen

All drugs were given in fasting state. 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 Rifampicin

Rifampicin 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 µl 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 O.1 M 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 analyze.

Pharmacokinetic Analysis

Serum concentration-time curves after oral administration of rifampicin alone and in combination with naproxen were analyzed using the non-linear 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 semilong plot of the serum drug concentration-time profile by applying the method of residuals (Shargel and Yu, 1985).

Results

As shown in the Table 1 rifampicin showed significant increase in elimination rate constant (K_e) from 0.194±0.098 to 0.358±0.020, clearance (C1) from 99.996±11.137 to 224.110±13.552, volume of distribution (V_d) from 321.621±56.343 to 482.310±37.108. Non-significant increase in absorption rate constant (K_a) from 0.681±0.131 to 0.705±0.087 were observed when naproxen was co-administered with rifampicin. On the other hand rifampicin showed significant decrease in area under the concentration time curve (AUC) from 3.441±0.090 to 2.005±0.134, mean residence time (MRT) from 4.374±0.411 to 3.904±0.177. Non-significant decrease in elimination half life ($t_{1/2}$) from 2.759±0.159 to 1.562±0.178, time for maximum serum concentration (T_{max}) from 1.855±0.101 to 0.404±0.098 when naproxin was given concomitantly with rifampicin. Fig. 1 shows that concentration of rifampicin lowed at all times when it was co-administered along with naproxen.

Table 1: Pharmacokinetic parameter values of rifampicin (450 mg) given with naproxen (500 mg)

Parameters	Rifampicin	Rifampicin+Naproxen	t-value
K_a (h^{-1})	0.681±0.131	0.705±0.087	0.180
K_c (h^{-1})	0.194±0.098	0.358±0.020	7.454*
AUC (ug hr/ml)	3.441±0.090	2.005±0.134	9.088*
Cl (h^{-1})	99.996±11.137	224.110±13.552	7.082*
V_d (Lit)	321.62±56.343	482.310±37.108	2.383*
$T_{1/2}$ (h)	2.759±0.159	1.562±0.178	2.046
MRT (h)	4.374±0.411	3.904±0.177	1.053*
T_{max} (h)	1.885±0.101	1.835±0.062	0.168
C_{max} (ug ml^{-1})	0.692±0.023	0.404±0.098	0.025

* Significant (P> 0.05)

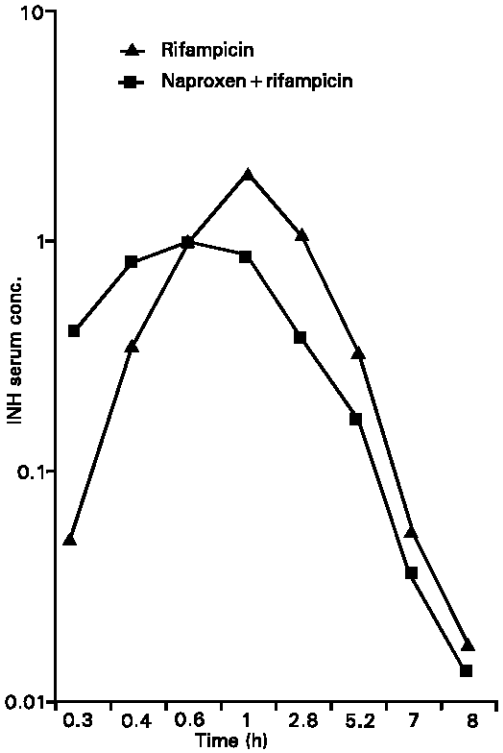

Fig. 1: Comparative Mean±S.E. of rifampicin serum conc.

Discussion

As rifampicin is a potent inducers of hepatic cytochrome P-450 with auto-induction of its metabolizing hepatic enzymes leading to reduced $t_{1/2}$ and plasma levels of rifampicin after repeated doses (Acocella, 1978) it has been suggested that a "first-pass" hepatic effect might occur and as a consequence, a reduction in bio-availability for rifampicin might follow during continued rifampicin therapy (Kenny and Strates, 1981). Some published results reveal that due

to auto-induction systemic clearance of rifampicin increased to 60% and AUC decreased 32% (Loos ***et al.***, 1985). Similar type of results have also been reported in the literature by other workers (Doble ***et al.***, 1985, 1988 and Mehta ***et al.***, 1986).

Our results indicate that naproxen interferes with the pharmacokinetics of rifampicin. Our findings suggested that naproxen appear to be subjected into enterohepatic circulation (Segre ***et al.***, 1974) which disturbs the hepatic metabolizing enzymes, as a result metabolism of rifampicin is enhances. Aspirin reduced the AUC and C_{max} and increased C1 of rifampicin (Nawaz ***et al.***, 1993); rifampicin reduced the AUC significantly of chlorpropamide (Arif ***et al.***, 1993); cimetidine decreased the AUC, AUMC and C_{max} while increased t_{max} of rifampicin (Loothar ***et al.***, 1998) and ketoconazole reduced AUC and C_{max} highly significant while $t_{1/2}$ and K_e increased significantly of rifampicin (Iqbal ***et al.***, 1994); these results signifies plausible mechanism of these pharmacokinetic interaction could be associated with high protein-binding of naperoxen which displaces rifampicin and free rifampicin seems available for the rapid metabolic conversion, which is caused by induction of cytochrome P-451 and P-452 enzymes without elevating total cytochrome P-450 contents (Loos ***et al.***, 1985) which suggests that these two drugs may be administered with interval instead concomitantly yet further studies are needed to fully establish these findings.

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