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EFFECT OF NAPROXEN ON THE PHARMACOKINETIC PARAMETERS OF RIFAMPICIN

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ABSTRACT

The effect of naproxen (500 mg) on the pharmacokinetics of rifampicin (450 mg) was evaluated in healthy human subjects (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). Insignificant 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.

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 basis (Clark *et al.*, 1992). Pharmacokinetic interactions are those which can affect the processes by which drugs are absorbed, distributed, metabolized and excreted (the so-called ADME interactions). Therefore, determination of pharmacokinetic drug interactions is very important for ensuring the efficacy and safety margin of clinical drug therapy (Kristensen, 1983).

Rifampicin is a first choice antituberculosis drug. It is a powerful inducing agent of hepatic drug-metabolising enzymes and this may account for a variety of drug interactions noted with rifampicin (Ohnhaus *et al.*, 1979; Breimer *et al,* 1977; Kenny and Strates 1981; Remmer *et al.*, 1973). It has been reported that on repeated oral administration, most likely as a consequence of self-induced (autoinduction) metabolism, there is a reduction in half-life as well as in blood levels (Acocella 1978; Kohno *et al.*, 1984; Loose *et al.*, 1985) of rifampicin.

Naproxen is a nonsteroidal anti-inflammatory, analgesic antipyretic drug, used for the relief of signs and symptoms of rheumatoid arthritis. It is also effective in clinical treatment of osteoarthritis, ankylosing spondylitis and acute gout (Segre *et al.*, 1974). Patients suffering from tuberculosis and arthritis at a time, could receive rifampicin and naproxen for a long time. The possibility of pharmacokinetic drug interaction involving both the drugs is therefore, of considerable importance.

Some clinically important interactions of rifampicin with ketoconazle, ibuprofen, cimetidine and phenytoin have been reported in the literature (Brass *et al.*, 1982; Doble *et al*., 1985; Doble *et al*., 1988; Abadi *et al*., 1988; Ochs *et al*., 1985; Bachman *et al*., 1986). Previously we have

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reported our results about the possible influence of aspirin, chlorpropamide, cimetidine, ketoconazole, diclofenac on the pharmacokinetics of rifampicin (Arif *et al*., 1993; Bashir *et al*., 1996; Iqbal *et al*., 1994; Nawaz *et al*., 1993; Loothar *et al*., 1998). Our present study evaluated the influence of concurrent dosing of naproxen and rifampicin on the pharmacokinetics of a single dose of rifampicin in healthy subjects.

EXPERIMENTAL

Reagents:

Pure rifampicin powder was donated by Abbott Laboratories, Pakistan. Methanol (HPLC grade, BDH), Sodium acetate (Merck), acetonitrile (HPLC grade, BDH), glacial acetic acid (Merck), Chloroform (Merck), Potassium dihydrogen phosphate (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 of age participated in this study. 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:

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 an overnight fast, with an unlimited take of water). After the drug administration, the subjects remained fasting for 2.5 hours. Venous blood samples (5ml) were drawn in a vacutainer serum tubes at 0, 0.25, 0.5, 1, 2, 4, 6 and 8 hours interval. Serum was separated within 30 minutes and stored at $-20^{o}C$ till analysis. At least two weeks interval between each trial was given to every volunteer as a wash out period.

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 column (250 mm * 4 mm I.D.) packed with reverse phase Lichosorb ODS (104, Hiber packed). Methanol (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 at 222 nm wavelength. This enabled, a good separation and efficient resolution of the required analyte.

Pharmacokinetic Analysis

Serum concentration-time curves after oral administration of rifampicin alone and in combination with naproxen were analysed using the non-linear iteration (R-STRIP, micromath). The fitted function was used to determined 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. 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

As shown in the Table 1, rifampicin showed significant increase in elimination rate constant (K_e) from (0.194 + 0.0098) to (0.358 + 0.020), clearance (Cl) from (99.996 + 11.137) to (224.11 + 13.552), volume of distribution (V_d) from (321.621 + 56.343) to (482.31 + 37.108). Insignificant increase in absorption rate constant (K_a) from (0.681 + 0.131) to (0.705 + 0.186) were observed when naproxen was co-administered with rifampicin.

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

Parameters	Rifampicin	Rifamicin + Naproxen	t-value
K^a (hr)	0.681 + 0.131	0.705 + 0.087	0.180
K^e (hr)	0.194 + 0.098	0.358 + 0.020	7.454*
AUC (ug hr/ml)	3.441 + 0.091	2.005 + 0.134	9.088*
Cl (hr)	99.996 + 11.137	224.110 + 13.55	7.082*
V^d (Lit)	321.62 + 56.343	482.31 + 37.108	2.383*
$t^{1/2}$ (hr)	2.759 + 0.559	1.562 + 0.178	2.046
MRT (hr)	4.374 + 0.411	3.904 + 0.177	1.053*
T^{max} (hr)	1.885 + 0.101	1.835 + 0.062	0.168
C^{max} (ug/ml)	0.692 + 0.023	0.404 + 0.098	0.025

*Significant (p > 0.05)

Comparative Rifampicin with and without Naproxen

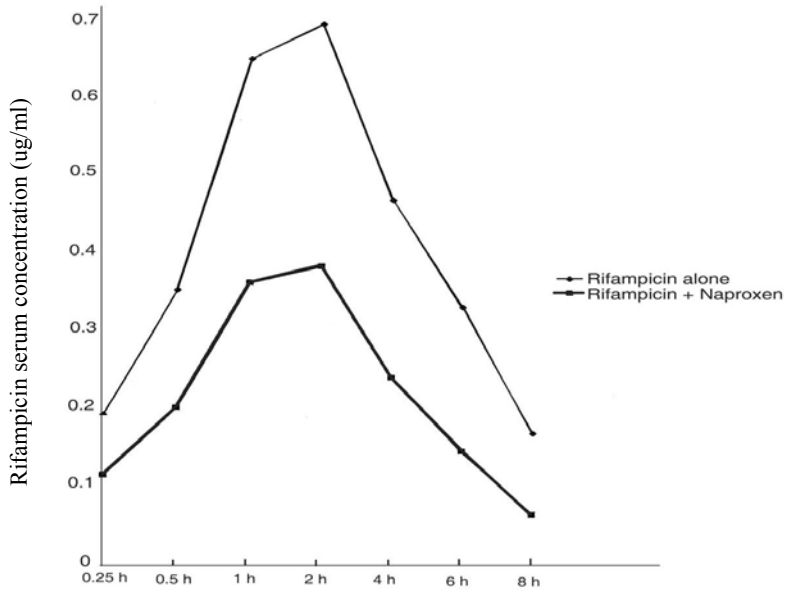

Fig. 1: Comparative means + S.E.M. of Rifampicin serum concentration when Rifampicin (450mg) given with Naproxen (500 mg)

On the other hand rifampicin showed significant decrease in area under the concentration/ time curve (AUC) from (3.441 + 0.090) to (2.005 + 0.137), mean residence time (MRT) from (4.374 + 0.411) to (3.904 + 0.177). Insignificant 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 (1.885 + 0.101) to (1.835 + 0.062), maximum serum concentration (C^{max}) from (0.692 + 0.023) to (0.404 + 0.098) when naproxen was given concomitantly with rifampicin.

Fig. 1 signifies that concentration of rifampicin lowered at all times when it was co-administered alongwith naproxen.

DISCUSSION AND CONCLUSIONS

As rifampicin is a potent inducer of hepatic cytochrome P-450, with autoinduction 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 bioavailability for rifampicin might follow during continued rifampicin therapy (Kenny and Strates, 1981). Some published results reveal that due to autoinduction 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; Doble *et al*., 1988, Mehta *et al.*, 1986).

Our results indicates that naproxen interferes with the pharmacokinetics of rifampicin. Our findings suggest 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 enhanced. Our results are in accordance with the reported results of aspirin, chlorpropamide, cimetidine and ketoconazole (Nawaz *et al.*, 1993; Arif *et al.*, 1993; Loothar 1998; Iqbal *et al.*, 1994), yet further studies are needed to fully established these findings.

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