INFLUENCE OF RIFAMPICIN PRETREATMENT ON THE PHARMACOKINETICS OF CELECOXIB IN HEALTHY MALE VOLUNTEERS

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SUMMARY

The effect of rifampicin pretreatment on the pharmacokinetics of celecoxib was investigated in 12 healthy male human volunteers. After an overnight fast, celecoxib 200 mg was administered to the volunteers, either alone or after 5 days pretreatment with once daily dose of 600 mg rifampicin. Serum concentrations of celecoxib were estimated by reverse phase HPLC. Pharmacokinetic parameters were determined based on non-compartmental model analysis using the computer program KINETICA. A significant difference was observed in AUC_{0-t} (4531.28 ± 2147 vs 1629.1 ± 1006 $ng.h.ml^{-1}$, $p < 0.0001$), $AUC_{0-\infty}$ (4632.42 ± 2221.75 vs 1629.46 ± 1012.61 $ng.h.ml^{-1}$, $p = 0.0006$), C_{max} (544.89 ± 273.91 vs 238.61 ± 146.34 ng/ml, $p = 0.04$), $t_{½}$ (9.3 ± 3.58 vs 4.0 ± 1.43 h, $p = 0.0317$) and Cl/f (43.14 ± 36.23 vs 122.85 ± 95 $l.h^{-1}$, $p < 0.0001$) of celecoxib administered before and after rifampicin pretreatment. However, time to reach peak concentration, t_{max} (4 ± 0.88 vs 4 ± 0.83 h) and volume of distribution Vd/f (583 ± 251 vs 710 ± 690 l/kg) were not affected significantly. Rifampicin pretreatment reduced the AUC of celecoxib by 64% and increased the clearance by 185%. This may be due to increased

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metabolism of celecoxib due to the induction of cytochrome P4502C9 (CYP2C9) in liver. This interaction has a significant clinical relevance and may warrant dosage adjustment when celecoxib is co-administered with rifampicin in chronic treatment conditions, such as tuberculosis, leprosy and other infections of joints, bones, etc.

KEY WORDS

celecoxib, rifampicin, pharmacokinetics, CYP2C9

INTRODUCTION

Celecoxib is a non-steroidal anti-inflammatory agent indicated for the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis. The mechanism of action is through the inhibition of cyclooxygenase-2 (COX-2) and in turn, inhibition of prostaglandin synthesis /1/. The COX-2 pathway primarily mediates the inflammatory process. In contrast, COX-1 has homeostatic functions, such as effects on the gastrointestinal tract, renal pathway, and platelet function /2/. It is believed that by blocking the COX-2 enzyme preferentially, the adverse effects typically seen with traditional non-steroidal anti-inflammatory medications, which inhibit both COX-1 and COX-2, would be decreased. It is metabolized predominantly through the cytochrome P450 isoenzyme 2C9 (CYP2C9) pathway /3/ and is a weak inhibitor of CYP2D6, resulting in a possibility of *in vivo* drug interaction /4/.

Rifampicin is known as an effective treatment of choice in both mycobacterial (tuberculosis and leprosy) and non-mycobacterial infections (recently reviewed by Vesley and Pien /5/). Rifampicin is a useful drug for several types of bacterial infection because of its broad-spectrum activity and excellent tissue penetration.

Rifampicin is a known inducer of several drug metabolizing enzymes /6-9/ and decreases the plasma concentrations of many drugs, including CYP2C9 probe drugs such as tolbutamide, glyburide, glipizide and tinidazole /10-12/.

Celecoxib is metabolized by CYP2C9. Since rifampicin is a well-known inducer of this isozyme, there is scope for interaction when these two drugs are co-administered. To date, there is no report

available on the effect of rifampicin-mediated enzyme induction on celecoxib. A recent report /13/ in this area indicates the effect of rifampicin on the pharmacokinetics of glyburide and glipizide, both known CYP2C9 substrates. It was found that AUC and elimination $t_{½}$ were moderately decreased, and the authors suggested the mechanism underlying the interaction between rifampicin and glyburide was probably by induction of either CYP2C9 or P-glycoprotein (P-gp), or both.

With this theoretical background, we investigated the effect of rifampicin pretreatment on the pharmacokinetics of celecoxib in healthy human volunteers.

MATERIALS AND METHODS

Chemicals

Celecoxib 200 mg (Revebra 200®, Dr. Reddy's Laboratories Ltd., Hyderabad, India), rifampicin capules 600 mg (R-Cin 600®, Lupin Laboratories Ltd., Aurangabad, India), tolbutamide (gift sample from Cadila Health Care, Ahmedabad, India), acetonitrile (HPLC grade, Qualigens Chemicals, Mumbai, India); all other chemicals used were of AR grade.

Subjects

Twelve healthy male volunteers, mean age 27.3 ± 4.3 years (range 23-31 years), mean height 164.4 ± 4.0 cm (160-170 cm) and mean weight 61.8 ± 6.6 kg (54-70 kg) participated in the study after undergoing a thorough physical examination. The volunteers were briefed about the study and written informed consent was obtained from all participants. The local ethics committee approved the study protocol.

The volunteers had no history of ill health during the preceding 6 months and none had taken any medication for at least 15 days prior to the study. Volunteers were excluded from the study if they had food allergies or were allergic to celecoxib or rifampicin.

Protocol

After an overnight fast (approximately 12 h), each volunteer received celecoxib 200 mg with 200 ml of water.

Venous blood samples (5 ml) were drawn from the antecubital vein at 0, 0.5, 1, 2, 3, 4, 8, 12, 24, 36 and 48 hours after drug administration. The blood was allowed to clot and centrifuged for 10 minutes at 3,000 rpm (R8C, Remi Instruments, Mumbai, India). Serum was separated into Eppendorf tubes and stored at -20°C until analysis. A once daily dose of rifampicin 600 mg was given for 5 consecutive days (from day 4 to 8) under direct observation. On day 9, celecoxib 200 mg was given again and the sample collection was repeated.

Sample assays

Celecoxib in the serum samples was estimated by a reverse phase high performance liquid chromatography (HPLC) method /14/. The HPLC system (Shimadzu, Japan) consisted of an LC-10AT solvent delivery module and SPD-10A UV-visible spectrophotometric detector. The mobile phase consisted of acetonitrile:0.01 M potassium dihydrogen orthophosphate buffer (50:50, v/v) , pH 3.2, with a flow rate of 1 ml/min. The column used was an SGE C-18 stainless steel column of length 15 cm and internal diameter of 4.6 mm packed with porous silica spheres of 5μ diameter, and the eluent was monitored at 250 nm.

Treatment of bioavailability data

Pharmacokinetic parameters - peak plasma concentration (C_{max}), time to reach peak concentration (t_{max}), area under the curve (AUC), elimination half-life ($t_{½}$), volume of distribution (Vd/f) and total clearance (Cl/f) - for celecoxib were obtained for each subject using the computer program KINETICA (Inna Phase Corporation, 1999) meant for calculation of model independent parameters. In the present study, AUC_{0-t} refers to the AUC from 0 to 48 hours.

Statistical analysis

The resulting means of various pharmacokinetic parameters obtained when celecoxib was given alone and after rifampicin pretreatment were compared in different subjects using Student's t-test for paired data. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

The serum concentrations of celecoxib at different time points before and after rifampicin pretreatment are shown in Figure 1. Pharmacokinetic parameters are presented in Table 1.

There was a statistically significant change in some of the pharmacokinetic parameters of celecoxib after rifampicin pretreatment - C_{max}, AUC, $t_{½}$ and Cl/f. No statistically significant difference was observed in t_{max}; there was a increase in Vd/f of celecoxib after

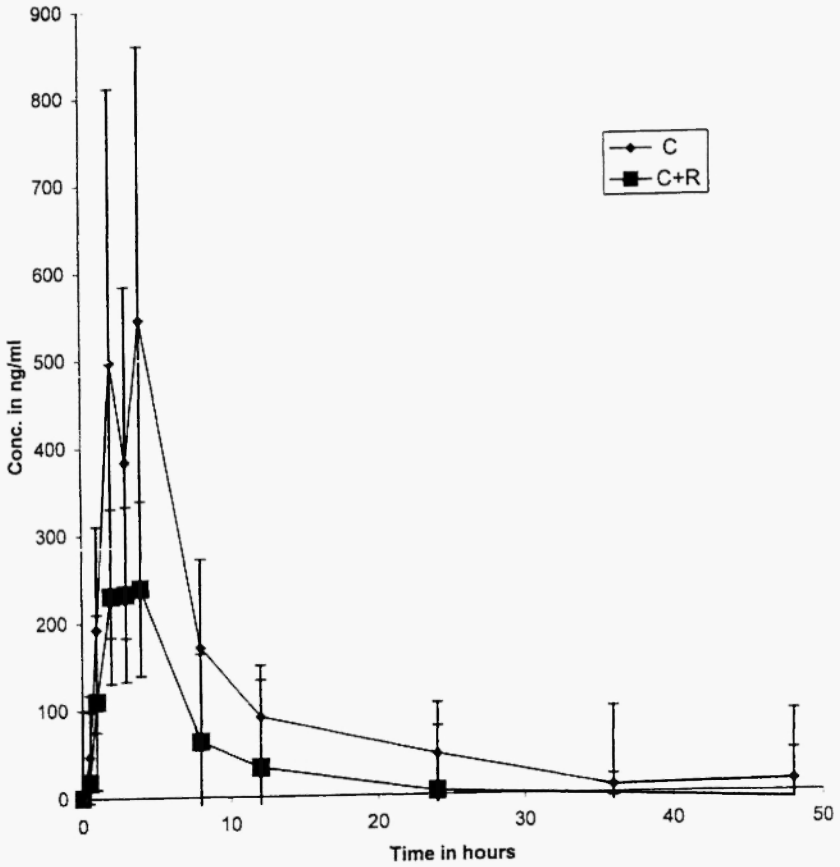

Fig. 1: Serum concentration (mean ± SD) versus time profiles of celecoxib (200 mg) before and after pretreatment with rifampicin (600 mg, once daily for 5 days). C = celecoxib before pretreatment with rifampicin; C + R = celecoxib after pretreatment with rifampicin.

TABLE 1

Pharmacokinetic parameters (mean ± SD) of celecoxib (200 mg) in human volunteers (n = 12) before and after pretreatment with rifampicin (600 mg, DX5)

	Before rifampicin	**After rifampicin**	**p**
C_{max} (ng/ml)	544.89 ± 273.91	238.61 ± 146.34	<0.05*
t_{max} (h)	4 ± 0.88	4 ± 0.83	>0.05
AUC_{0-t} (ng.h/ml)	4531.28 ± 2147	1629.1 ± 1006	<0.001*
$AUC_{0-\infty}$ (ng.h/ml)	4632.42 ± 2221.75	1629.46 ± 1012	<0.001*
$t_{½}$ (h)	9.30 ± 3.58	4 ± 1.43	<0.05*
Cl/f (l/h)	43.14 ± 36.23	122.85 ± 95	<0.05*
Vd/f (l/kg)	583 ± 251	710 ± 690	>0.05

* Statistically significant, paired t-test.
DX5 = once daily for 5 days.
C_{max} = peak serum concentration; t_{max} = time to reach C_{max};
AUC = area under the concentration-time curve; $t_{½}$ = elimination half-life;
Cl/f = total body clearance; Vd/f = volume of distribution.

rifampicin pretreatment, but this did not reach significance. The serum concentrations of celecoxib were significantly lowered in volunteers after rifampicin pretreatment. Rifampicin decreased the mean $AUC_{0-\infty}$ of celecoxib by 64% ($p < 0.001$) and C_{max} by 56% ($p < 0.05$); the $t_{½}$ of celecoxib was shortened from 9.3 to 4 h by rifampicin, and Cl/f was increased by 185%.

DISCUSSION

This study describes the effects of rifampicin pretreatment on the pharmacokinetics of celecoxib in healthy male human volunteers. The AUC, C_{max} and $t_{½}$ were reduced significantly and there was also a significant increase in clearance. t_{max} was not affected by rifampicin pretreatment.

The effect of rifampicin on celecoxib could be due to the increased expression of cytochrome P450 enzyme systems and P-gp in liver

and/or intestine. It is known that rifampicin is a potent inducer of cytochrome P450 enzyme systems (including CYP2C9) and P-gp /15/, and celecoxib is a known substrate for CYP2C9.

The increased metabolism and/or excretion of celecoxib after pretreatment with rifampicin may be due to increased expression of CYP2C9 in liver and/or P-gp mediated exsorption into the intestines. There have been some reports supporting this hypothesis, one of which states that rifampicin pretreatment significantly reduced the AUC of tinidazole, a CYP2C9 substrate, by 23% and increased its Cl/f by 29% in healthy male volunteers. This may be due to increased metabolism of tinidazole as a result of the induction of CYP2C9 and/or P-gp in liver and/or intestine /10/. Similarly, Niemi *et al.* /11/ studied the effect of rifampicin on the pharmacokinetics and pharmacodynamics of glyburide, which is metabolized by CYP2C9. Rifampicin decreased the AUC of glyburide by 39% and peak plasma concentrations by 22%. The mechanism involved in the interaction between rifampicin and glyburide is probably induction of either CYP2C9 or P-gp, or both.

Based on these reports, we also expect a possible role of increased expression of cytochrome P450 enzymes and P-gp in liver/intestine by rifampicin pretreatment, resulting in the increased metabolism and exsorption of celecoxib. However, further studies are needed to confirm the role of P-gp regarding increased exsorption of celecoxib into the intestines.

CONCLUSIONS

Based on the results of the present study, we suggest that pretreatment with rifampicin increased the metabolism of celecoxib in liver and/or intestine because of induction of CYP2C9 and/or increased expression of P-gp which might have resulted in decreased bioavailability of celecoxib. The AUC of celecoxib was decreased by 64% after rifampicin pretreatment, which has great clinical significance because the metabolic pathway of celecoxib is exclusively through CYP2C9 /15/. Finally, we feel that the co-administration of celecoxib during chronic treatment with rifampicin may result in reduced bioavailability of celecoxib. This, in turn, may lead to decreased pharmacological actions of celecoxib in patients with osteoarthritis, rheumatoid arthritis, etc. Hence, an increased dosage of

celecoxib could be recommended in patients who are under chronic rifampicin treatment.

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