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The effect of single dose of rifampicin on the pharmacokinetics of oral nifedipine[1]

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Abstract

The pharmacokinetic interaction of oral rifampicin (1200 mg) and oral nifedipine (10 mg capsules), given as single doses, was investigated in six healthy volunteers (mean age 28.5 ± 6.3 years and mean weight 67.0 ± 4/45 kg). The plasma concentrations of nifedipine was monitored using a HPLC technique, 8 h after pre-treatment, with rifampicin. The mean relative bioavailability of nifedipine following pre-treatment with rifampicin 1200 mg was 35.8% ($P < 0.0001$). The mean elimination half life ($t1/2$) of nifedipine decreased from 2.62 to 1.03 h ($P < 0.0001$); and, the total clearance (Cl_T) increased from 17.33 to 50.17 ml min^{-1} kg^{-1} ($P < 0.0001$). There were no significant differences in V_d and T_{max}. The study suggests that the effect of induction by rifampicin decreases the bioavailability of nifedipine by either increasing the first pass effect or decreasing its oral absorption. The induction also increases the clearance of nifedipine. © 1997 Published by Elsevier Science B.V.

Keywords: Nifedipine; Rifampicine drug interaction; Single dose

1. Introduction

Nifedipine, a 1,4-dihydropyridine, is a calcium channel blocker which is now a popular choice drug for the treatment of angina pectoris and hypertension. Studies have shown that following oral administration, nifedipine undergoes extensive first-pass metabolism [3,8]. The cytochrome *P*-450 system has been indicated to be responsible for the metabolism of nifedipine. Due to the intra-and inter subject variability of the system the careful treatment of nifedipine dosage regimens are essential in order to maintain effective plasma concentration level. This becomes especially important when the drug is co-administered with other agents which induce the activity of the oxidative cytochrome *P*-450 system.

Rifampicin, which is prescribed for the treatment of several gram-positive organisms, tuberculosis and leprosy, is a potent inducer of hepatic microsomal enzyme systems [6]. The usual maximum daily dose is 1200 mg. A single dose of 1200 mg is often given for the chemoprophylaxis of

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meningococcal disease and in gonorrhoea. Most study protocols involving rifampicin in drug interaction studies require pre-treatment with rifampicin for a period of 3–14 days. In a similar protocol design, Tada et al. [7] studied the interaction of rifampicin and nifedipine in hypertensive patients. They reported a decrease in the bioavailability and increase in the elimination of nifedipine which were both statistically significant.

The aim of the present work was to study the effect of a single dose of rifampicin 1200 mg in healthy Nigerian subjects rather than the usual 3–14 days pre-treatment protocol design on the disposition of nifedipine.

2. Materials and methods

2.1. Materials

Nifedipine powder (standard) was kindly supplied by Bayer AG Leverkussen, Germany (Pat. No. 198208K). 4-Dimethyl-aminobenzaldehyde (internal standard) and other chemicals used were products of British Drug House, England, and Prolabo Group Rhone-Paulens, Manchester.

The dosage forms administered were conventional 10 mg capsules of nifedipine (Adalat®, A.G. Bayer) and 300 mg rifampicin capsules (Rifampicin, Medicalex, Milan, Italy).

Six healthy male volunteers aged between 22 and 34 years and weighing between 71 and 64 kg participated in the study. None of the volunteers had any history of cardiac, hepatic, renal or gastrointestinal disease. All had normal physical and biochemical/hematological profiles. The volunteers were also non-smokers and did not consume alcohol. They were instructed to abstain from any form of drugs 3 weeks before and during the study. A written consent to participate in the study was obtained from each volunteer.

2.2. Study protocol

The study was conducted in a randomised trial before and after pre-treatment with rifampicin 1200 mg. After each phase, a washout period of 2 weeks was allowed before commencement of the next study.

In the first phase, after an overnight fast, one capsule of 10 mg nifedipine (Adalat®) was administered orally to each volunteer with 200ml of water. Blood samples (5 ml) were taken immediately before and at 0.5, 1, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0 and 12.0 h after the nifedipine administration. The overnight fasting continued 2 h after the administration of nifedipine, after which the volunteers were each given a bottle of soft drink and biscuits.

In the second phase, nifedipine was administered 8 h after pre-treatment of the volunteers with 1200 mg capsules of rifampicin. Blood samples were taken as in phase one. All blood samples were centrifuged at $1000 \times g$ for 20 min, the plasma was collected and stored at $-20°C$ pending analysis. The sample bottles were wrapped with aluminium foil to protect the plasma from light and the analysis was carried out under red light.

2.3. Analysis

The nifedipine concentration in the plasma samples was analysed by High Performance Liquid Chromatography (HPLC) after solvent extraction with dichloromethane as described by Mustapha et al. [5]. The extracted residue was reconstituted with 100 μl methanol and 15 μl aliquots were injected into a Waters model 204 liquid chromatograph fitted with a model U6K universal septumless injector, Waters model 510 pump and U.V. detector model 441 with a 254 nm filter. The stationery phase was a radial-pak reverse phase C_{18} column (1000 × 8 mm I.D., 10 μm particle) obtained from Waters Associate, Sweden. The sensitivity of the detector was kept at 0.005 Aufs, and the flow rate was 2 ml min^{-1} with operating pressure of 2000 psi. The mobile phase consisted of methanol:0.01 M sodium acetate (pH 4.0) 55:45 v/v.

2.4. Data analysis

All the results obtained were further analysed by the use of the computer program GRAPHAD® (1987) and STATIS 3® (1992) to the pharmacokinetics parameters of nifedipine.

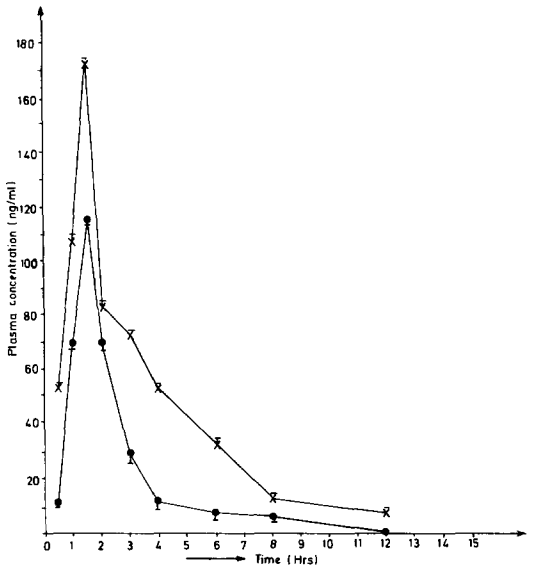

Fig. 1. Mean plasma concentration-time profile of nifedipine capsules 10 mg dose before (x) and after (●) 8 h administration of rifampicin 1200 mg in healthy volunteers.

3. Results

Fig. 1 shows that the plasma nifedipine concentrations were much lower during pre-treatment with rifampicin. The individual pharmacokinetic parameters derived from the plasma concentration profile of nifedinine before and after pre-treatment with rifampicin are shown in Table 1 and Table 2. Some degree of inter-individual variations in the disposition of nifedipine are quite evident. Table 3 shows the mean estimated pharmacokinetic parameters at the two levels of treatment. The total area under the plasma concentration curve ($AUC_{0\text{-}00}$) decreased from 574.4 to 205.25 ng h^{-1} ml^{-1}, a decrease of 64.3% ($P < 0.0001$). The mean (S.D.) relative biovailability of the oral nifedipine capsules following pre-treatment with rifampicin was $35.73 \pm 0.0\%$. Similarly, the peak plasma concentration (C_{max}) and the elimination half-life ($t1/2$) decreased from 173.23 to 116.77 ng ml^{-1} ($P < 0.001$) and from 2.62 to 1.03 h ($P < 0.0001$), respectively. There was an increase in both the total clearance (Cl_T) from 17.33 to 50.17 ml min^{-1} kg^{-1} $P < 0.001$) and the volume of distribution (V_d) from 66.2 to 75.3 ml kg^{-1} ($P < 0.1$). The elimination rate constant also increased from 0.26 to 0.67 h^{-1} ($P < 0.001$). However, there was no change in the time to attain peak plasma concentration.

4. Discussion

The relative decrease in the bioavailability of nifedipine following 8-h pre-treatment with rifampicin as indicated by a 64.2% ($P < 0.001$) reduction in the $AUC_{0\text{-}00}$ and, the decrease of about 67% ($P < 0.001$) in the C_{max} observed in the present study are in agreement with the findings of Toda et al. [7]. The observed effects were said to be the result of increased first-pass metabolism of nifedipine [7,8]. The time to maximum plasma concentration (1.5 h) was however not changed. The decrease (60.7% $P < 0.0001$) in the elimination half-life and the unchanged volume of

Table 1
Plasma pharmacokinetics parameters of nifedipine 10 mg dose in healthy subjects

Pharmacokinetic parameters	Subjects						
	I	II	III	IV	V	VI	Mean ± S.E.M.
C_{max} (ng ml^{-1})	182.7	142.7	166.0	184.8	186.8	176.4	173.2 ± 6.2
T_{max} (h)	1.5	1.5	1.5	1.5	1.5	1.5	1.5 ± 0.0
$t1/2$ (h)	2.76	2.35	2.70	2.81	2.62	2.48	2.62 ± 0.07
Kel (h^{-1})	0.25	0.30	0.28	0.25	0.26	0.28	0.26 ± 0.01
Cl_T (ml min^{-1} kg^{-1})	17.0	19.0	17.0	16.0	17.0	18.0	17.33 ± 0.37
Vol. (ml kg^{-1})	67.0	66.0	67.0	66.0	65.0	66.0	66.20 ± 2.5
$AUC_{0\text{-}00}$ ng/ng h^{-1} ml^{-1}	596.09	513.90	581.36	609.45	587.11	546.51	572.40 ± 14.0.17

Table 2
Plasma pharmacokinetics parameters of nifedipine 10 mg dose following 8 h pre-treatment with rifampicin 1200 mg dose in healthy subjects

Pharmacokinetics parameters	Subjects						
	I	II	III	IV	V	VI	Mean ± S.E.M.
C_{max} (ng ml^{-1})	140	86.3	110.0	120.0	124.8	116.5	115.77 ± 7.69
T_{max} (h)	1.5	1.5	1.5	1.5	1.5	1.5	1.5 ± 0.0
$t1/2$ (h)	1.07	1.07	1.07	0.94	0.97	0.07	1.03 ± 0.02
Kel (h^{-1})	0.65	0.65	0.65	0.74	0.71	0.65	0.67 ± 3.88
Cl_T(ml min^{-1} kg^{-1})	57.00	55.00	55.00	37.0	39.0	58.0	50.17 ± 3.88
Vol. (ml kg^{-1})	87.0	84.0	84.0	50.0	54.0	89.0	75.3 ± 2.5
AUC_{0-00} (ng/ng h^{-1} ml^{-1})	177.9	184.1	184.2	247.1	262.5	173.7	204.92 ± 0.0

distribution together with the increase (194%, $P < 0.0001$) in the total body clearance are suggestive of the direct inducing effect of rifampicin on the cytochrome P-450 systems. It was observed that in a similar study carried out by Ohnhaus and Park (1979) to investigate the inductive effect of rifampicin on the hepatic microsomal system, pre-treatment with rifampicin for 7 days, significantly increased the total body clearance of antipyrine by about 122.7%. Thus, taking increase in the metabolic clearance as index of enzyme induction in vivo, the workers inferred that the study demonstrated inductive effect of rifampicin on the hepatic microsomal system. By similar inference, and despite the short interval of pre-treatment period (8 h), our study has demonstrated that, rifampicin significantly induced the hepatic metabolism of nifedipine.

Guengerich et al. [4]; Bork et al. [1] and Combalbert et al. [2] in their studies have identified some liver cytochrome-P450 which belonged to the gene super family of cytochrome P-450 III (P-$450_{NF-25)}$ P-450_{NF-10} and P-450_{PCN1}) as the main microsomal enzymes responsible for the oxidation of nifedipine to its nitropyridine analogue and referred to as nifedipine oxidase. Combalbert et al. [2] showed that these enzyme systems are inducible by rifampicin.

In conclusion, the study has shown that an 8-h pre-treatment with rifampicin is a sufficient period to bring about statistically significant increase in the metabolism of nifedipine probably by inducing nifedipine cytochrome-P450 oxidase. This is important in therapy where high doses of rifampicin are indicated for example, in the chemoprophylaxis of meningococcal and gonorrhoeal

Table 3
Mean Pharmacokinetics Parameters of Nifepidine (10 mg) before and 8 h after rifampicin administration in healthy subjects

Pharmacokinetics parameters	Mean ± S.E.M.[a]		P-value (t-test)
	Before	After	
C_{max} (ng ml^{-1})	173.23 ± 6.23	115.77 ± 17.69	$P<0.0001$
T_{mx} (h)	1.50 ± 0.00	1.50 ± 0.00	$P>0.5000$
$t1/2$ (h)	2.62 ± 0.07	1.03 ± 0.02	$P>0.5001$
Kel (h^{-1})	0.26 ± 0.00	0.26 ± 0.16	$P<0.0001$
Cl_T(ml min^{-1} Kg^{-1})	17.33 ± 0.04	50.17 ± 3.88	$P<0.0001$
V_d (ml kg^{-1})	66.20 ± 0.00	75.30 ± 2.50	$P>0.0100$
$AUC_{(0-00)}$ (ng h^{-1} ml^{-1})	573.40 ± 14.29	205.25 ± 16.20	$P<0.0001$

[a] S.E.M.: Standard error of the mean, 6.

infections in conjunction with other drugs whose metabolism is induced by rifampicin. However, this effect will only be temporary because only single doses of rifampicin rather than chromotherapy are given. The clinical effect of this temporary decrease in nifedipine concentration is unknown.

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