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Influence of a Low Fat Meal on the Pharmacokinetics and Bioavailability of Nifedipine Tablets

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Abstract: *In vivo* bioavailaibility studies of nifedipine tablets were carried out in six healthy human subjects in fasting state and after a low-fat meal. A simple, reliable and rapid HPLC method of nifedipine estimation preceded by an extraction technique was employed for the determination of plasma and saliva nifedipine levels. Pharmacokinetic parameters were generated by computer application. The low fat meal taken appeared to reduce the absorption rate constant of nifedipine, in plasma and saliva from $0.96h^{-1}\pm0.104$ to $0.57h^{-1}\pm0.168$ and $0.86h^{-1}\pm0.38$ to $0.41h^{-1}\pm0.03$ respectively and increase the lag time in plasma and saliva from 0.13h±0.37 to 0.36h±0.58 and 0.17h±0.08 to 0.34h±0.18, respectively.

Key words: Pharmacokinetics of nifedipine, bioavailability of nifedipine, drug-food interaction

INTRODUCTION

Nifedipine (4,2-Nitrophenyl)-2, 6-dimethyl-3, 5-dimethoxy-1, 4-dihydropyridine) is the active ingredient in Adalat® used in tropical Africa for the treatment of hypertension.

Nifedipine is a dihydropyridine calcium channel blocker, which undergoes extensive first-pass metabolism in man following oral administration[1,2]. Food constituent may interact directly or indirectly with drugs in a number of ways. Results of various studies on the influence of food and diet on the gastrointestinal absorption of a number of drugs have shown that the observed effect is a function of the type and size of meal, the chemical and physical form of the drug, the dosage and the time relationship between eating and drug administration[3-6].

Although, Nigerian foods contain essentially the same major constituents comparable to similar-types of foods in other countries, it is clear that very little work has been reported using Nigerian food and Nigerian subjects specifically. The objective of this study therefore is to assess the influence of low-fat meal which cuts across most breakfast tables in Nigeria, consisting of corn gruel (pap) and fried bean cake (akara, kose) on the pharmacokinetics and bioavailability of nifedipine using healthy subjects.

Experimental: All sample handling and extraction steps were carried out under red-light condition to prevent photo degradation of the nifedipine.

MATERIALS AND METHODS

Adalat® retard tablets containing 20 mg nifedipine (production series number BL 711) was supplied by the manufacturer Bayer, Leverkusen, West Germany, Methanol, Sodium acetate, acetic acid, Dichloromethane and 4-dimethylaminobenzaldehyde were all obtained from BDH chemicals, Poole England. All solvents were glass-distilled. All glassware used during the extraction procedure were cleaned with chromic acid, washed with distilled water and oven dried.

Chromatography: Waters HPLC model 204 was used. The column used for the chromatographic separation was a μ-Bondapak radial pak catridge, 15 cm x 8.0 mm I.D packed with 10μm reversed Phase C_{18} support, Waters part No. 85721 (Waters Associates Inc., Milford, USA). Mobile phase consisting of Methanol-Sodium Acetate (pH 4.0; 0.01M) buffer (55:45, V/V) (pH 5.2) was premixed, filtered under vacuum, ultrasonicated and used at a flow rate of 2.0 mL/min.

In-vivo absorption studies

Fasting state: Six healthy male volunteers aged 21-30 years (mean 24±3 years) and body weight 54-70 kg mean 60±3 kg) took part in the study. Prior to the commencement of the study, the volunteers had to submit a written informed consent.

None of the subjects had received any medication for a period o f 2 weeks prior to the study and none of them

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Table 1: Mean plasma and saliva nifedipine concentration in healthy volunteers following oral administration of 20 mg nifedipine in fasting and non-fasting states

	Concentration (ng mL^{-1})±S.D.			
	Plasma		Saliva	
Time (h)	Fasting state	Non-fasting state	Fasting state	Non-fasting state
0.5	16.54±1.09	6.33±1.08	22.29±1.97	10.20±1.28
1.0	27.73±1.36	14.80±4.64	37.05±6.61	20.34±0.66
2.0	37.28±1.82	27.50±1.57	59.50±2.45	32.63±3.09
3.0	36.53±0.40	34.63±3.16	55.66±10.33	58.08±2.09
4.0	28.50±1.21	31.47±6.22	49.13±7.41	45.94±5.51
6.0	20.04±0.72	20.02±1.80	37.50±4.52	37.12±3.91
8.0	13.18±1.38	13.47±2.45	25.82±1.85	22.07±3.39
12.0	6.34±1.38	8.55±3.30	13.62±2.37	10.25±1.68

Table 2: Pharmacokinetic parameters of nifedipine derived from the mean plasma and saliva concentration data after a single 20 mg oral dose in fasting and non-fasting states

	Concentration (ng mL^{-1})±S.D.			
	Plasma		Saliva	
	Fasting state	Non-fasting state	Fasting state	Non-fasting state
Lag time(h)	0.13±0.37	0.36±0.58	0.17±0.080	0.34±0.180
Absorption half-life ($t_{½}$) ∝(h)	0.71±0.077	1.30±0.34	1.05±0.580	1.72±0.180
Absorption rate constant K_a (h^{-1})	0.96±0.104	0.57±0.168	0.86±0.380	0.41±0.030
Maximum concentration C_{max} (ng/ml)	37.78±1.21	36.90±1.67	61.69±1.34	58.08±2.09
Time to peak t_{max}(h)	2.33±0.47	3.50±0.50	2.33±0.4700	3.50±0.5000
Elimination half-life $t_{½}$ β(h)	3.23±0.33	2.85±0.68	3.44±0.7500	2.47±01.300
Elimination rate constant K_e(h^{-1})	0.22±0.02	0.26±0.07	0.21±0.0450	0.27±0.03600
Area under the curve AUC (0 – 12 h) ng ml/h	235.73±6.65	219.57±29.16	401.29±25.37	338.47±28.87
AUC (0 – ∞ h) ng/ml/h	265.93±13.67	257.44±48.26	469.35±41.98	375.26±35.68
Volume of distribution (L)	349.56±20.64	317.65±46.38	210.64±37.48	190.81±9.9100
Clearance (L/h)	75.40±3.69	80.40±14.60	43.42±3.580	53.79±5.2400

smoked cigarette or used tobacco in any form within the last three years. Beverages containing alcohol and caffeine were not permitted during the study. On the day of each study, an indwelling canula with a heparin lock was inserted into the antecubial vein of the volunteers. Basal measurements were performed in a prone position after a minimal stabilization of 15 min on a couch. Each subject was given Adalat ® retard (20 mg nifedipine) with 100 mL of water after overnight fasting. They remained on the couch and continued to fast for a period of 4 h. Blood samples (5 mL) were withdrawn prior to the dose and at 0.5, 1, 2, 3, 4, 6, 8 and 12 h after the dose. The samples were collected in heparinized tubes, centrifuged for 10 min at 1500 g and plasma was harvested into glass tubes wrapped with aluminium foil and kept at-20°C until analysis. Mixed saliva samples (5 mL) were also collected after stimulation by mastication of a rubber band at the same times as the plasma was collected.

The saliva samples were collected in wrapped plain containers, centrifuged for 10 min and harvested into plastic tubes wrapped with aluminium foil and stored at-20°C until assayed.

Non-fasting state: The above procedure was followed after a 7-day washout period. The same dose (20mg nifedipine tablet) was taken by each of the volunteers after a low fat meal consisting of 300 mL corn gruel (pap) with ten balls of fried bean cake (akara, kose); 0.15 kg for each volunteer. All volunteers received equal and identical meal portions.

Preparation of samples for HPLC analysis: Plasma (0.5 mL) was placed in a 15 mL centrifuge tube which 500 ng 4-dimethylaminobenzaldehyde (internal standard) had been added. Sample was deproteinized with acetic acid (0.5 mL) extracted with 5ml dichloromethane, whirl mixed on an auto vortex mixer for 15 sec and centrifuged for 15 min.The aqueous layer was removed using an eppendof pipette; the organic extract was transferred to a clean 15 mL centrifuge tube and evaporated to dryness under a stream of nitrogen at 40°C.The dry residue was dissolved in 100 μL of methanol and 15 μL aliquot was injected into the HPLC.

Saliva (0.5 mL) to which 100 ng 4-dimethylaminobenzaldehyde had been added was also extracted with 5 mL dichloromethane and treated as described above.

Preparation of standard for HPLC: Control plasma samples (0.5 mL) were spiked with 10, 20, 30, 40 and 50 ng nifedipine and with 500 ng 4-dimethylaminobenzaldehyde as internal standard. Control saliva samples (0.5 mL) were spiked with 25, 50, 75, 100, 150 and 200 ng nifedipine and with 1000 ng 4-dimethylaminobenzaldehyde as internal standard. The samples were processed as described above (see c). Standard curve was constructed by plotting the peak height ratio of nifedipine to the internal standard against the drug concentration in each standard. The level of the drug in unknown samples (plasma or saliva) was derived from this curve[7].

RESULTS

The mean nifedipine plasma and saliva concentration levels for the fasting and non-fasting volunteers are shown in Table 1, while Fig. 1 and 2 show the mean plasma and saliva concentration/time curves for the fasting and non-fasting states, respectively.

The pharmacokinetic parameters obtained from the mean concentration data for nifedipine tablets in plasma and saliva of fasting and non-fasting volunteers are shown in Table 2.

DISCUSSION

Differences as well as similarities were observed in the individual calculated pharmacokinetic parameters. For example, the time to reach peak concentration (t_{max}), elimination half-lives and other parameters calculated for each person were slightly different within subjects, in agreement with the Comparing the bioavailability of nifedipine in fasting and non-fasting states, it is obvious that the major cause of differences in rates of nifedipine absorption in the two states is their differing dissolution rates which reflected in the longer lag time and absorption half-life found in the non-fasting state[8]. However, measured area under the plasma concentration curve to 12 h (AUC (0-12 h)) for the fasting and non-fasting volunteers did not differ significantly ($p<0.05$) while the area under the nifedipine saliva concentration curve for fasting volunteers was significantly higher than those of the non-fasting volunteers ($p<0.01$).

The level of significance of AUC (1-12 h) between saliva and plasma for both fasting and non-fasting states were also statistically significant ($p<0.001$).

This increased AUC can be explained by considering the fact that, the time required to reach peak concentration is a representative of the rate of drug absorption while

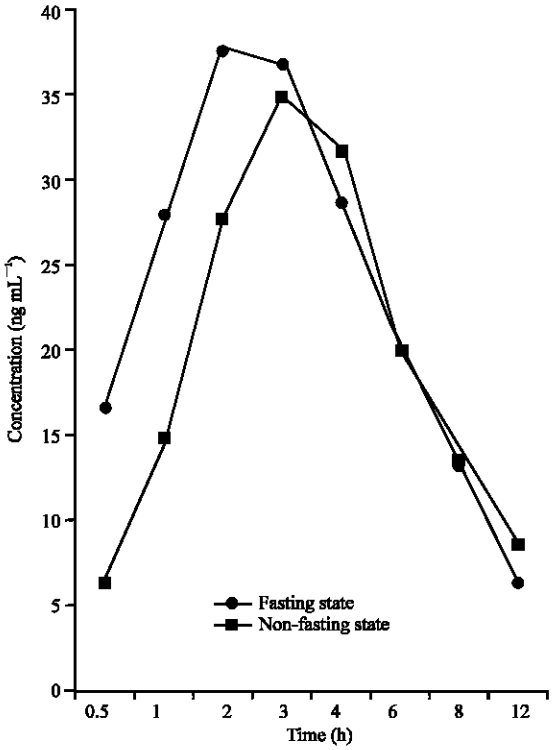

Fig. 1: Mean plasma nifedipine concentration in healthy volunteers following oral administration of 20 mg nifedipine in fasting and non-fasting states

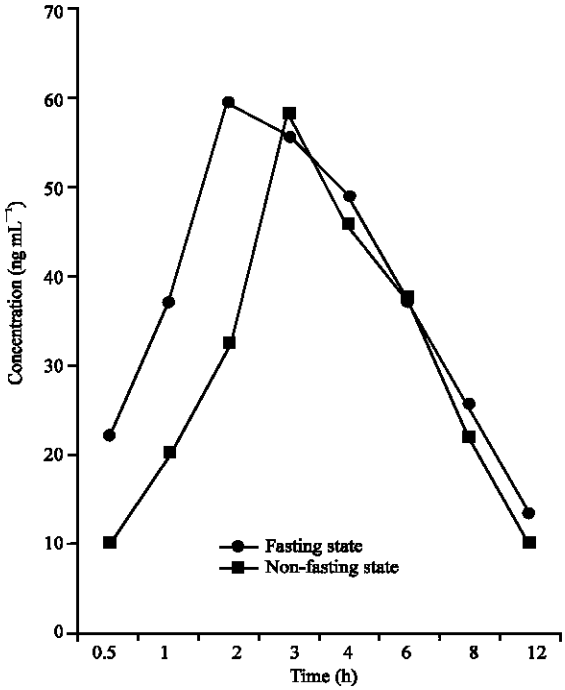

Fig. 2: Mean saliva nifedipine concentration in healthy volunteers following oral administration of 20 mg nifedipine in fasting and non-fasting states

AUC is proportional to the amount or extent of drug absorption. The greater the total amount of drug absorbed the greater the AUC and the greater will be the bioavailability[9].

CONCLUSION

The low fat meal employed in this study appeared to reduce the rate of nifedipine absorption as indicated from the delayed time to peak in both plasma and saliva. Conclusively, the result of this study had shown that total bioavailability of nifedipine is unaffected on ingestion of low fat meal, but the rate of absorption is reduced while t_{lag}, which is a measure of the appearance of drug in the plasma, is increased.

REFERENCES

1. Foster, T.S., S.R. Hamman, V.R. Richard, P.J. Bryant, D.A. Graves and R.G. McAllister Jr., 1983. Nifedipine kinetics and bioavailability after single intravenous and oral doses in normal subjects J. Clinical Pharmacol., 23: 161-170.
2. Waller D.G., A.G. Renwick B.S. Gruchy and C.F. George, 1984. The first pass metabolism of nifedipine in man British J. Clinical Pharmacology, 18: 951-954.
3. Welling, P.G., 1977. Influence of food and diets on absorption of drugs. pharmacokinetics and Bio. Pharmacy, pp: 5-291.
4. Owoyale J.A., J.I. Ayodele and Y.O. Aliu, 1981. Effect of bitterleaf on chloroquine blood level in rats. The Nigerian J. Pharmacy, 12: 13-15.
5. Ogunbona, F.A. and O.O. Oluwatodimu, 1986. Effects of a non-European (Nigerian) meal on the bioavailability of nitrofurantoin in man. International J. Pharmaceutics, 29: 191-193.
6. Ayodele, J.I., J.A. Owoyale and Y.O. Aliu, 1995. Influence of dietary spinach (Amaranthus hybridus LINN on chloroquine blood level in rabbit. J. Chemical Society of Nigeria, 20: 1-4.
7. Anhoff, M. and B.A. Person, 1990. Chromatography of calcium channel blockers: Review. J. Chromatography, 531: 181-213.
8. Challenor, V.F., D.G. Waller, B.S. Gruchy, A.G. Renwick and C.F. George, 1986. The effect of food and posture on the pharmacokinetics of a biphasic release preparation of nifedipine. British J. Clinical Pharmacol., 22: 565-570.
9. Abdel-Monem, M.M. and J.G. Henkel, 1978. Drug product selection based on bioequivalence. Essentials of drug product quality. The C.V. Mosby Company, pp: 23-32.