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Bioavailability of nifedipine suppository in healthy subjects

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Summary

Nifedipine rectal suppositories were prepared with polyethylene glycol as a base as a treatment for hypertensive emergency. The suppository which contained 10 mg of nifedipine had adequate physical characteristics and nifedipine stability for practical use. Bioavailability of the suppository was compared to that of an oral capsule (10 mg of nifedipine content) in healthy subjects. The mean nifedipine plasma concentration curve following rectal administration showed slightly delayed absorption as compared to the oral administration. However, there was no significant difference in the AUC from 0 to 7 h between the suppository and the capsule, which suggested the same extent of bioavailability for both dosage forms. A hypotensive effect of the nifedipine suppository for the subjects was observed 30 min after the administration and the effect was more definite and more prolonged compared to the oral capsule.

Introduction

Nifedipine (NF), 4-(2′-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine is a calcium antagonistic drug which has been widely used in angina

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pectories, and more recently in hypertension because of its strong peripheral vasodilating action (Murakami et al., 1972; Aoki et al., 1982; Banzet et al., 1983). Furthermore, Murakami et al. (1979) have suggested that NF is effective for hypertensive emergencies such as postoperative acute hypertensive crisis. In such cases, however, many patients cannot take the medicine orally. At present, only oral dosage forms are commercially available for NF; therefore, other routes of administration are of interest. A rectal enema of NF has been administered and found to provide a certain hypotensive effect (Tsuda et al., 1981), but the preparation and application of the enema may not be practical for clinical use.

To develop a more useful rectal dosage form for this purpose, we prepared NF suppositories and evaluated their bioavailability in comparison to oral soft gelatin capsules in healthy subjects.

Materials and Methods

Materials

NF soft gelatin capsule (ADALAT, Bayer, F.R.G.) which contains 10 mg of NF in polyethylene glycol (PEG) 400-glycerin (about 16 : 1, w/w), and PEG 400 and 4000 (JP X grade, Maruishi Seiyaku, Japan) were used for preparation of the suppositories.

Preparation of NF suppository

To prepare a NF suppository (NF 10 mg/suppository), 0.39 g of contents of the soft gelatin capsule, 0.25 g of PEG 400 and 1.36 g of PEG 4000 were mixed and melted at 55°C. The melt was poured into a mold (2.2 ml) which had been previously lubricated with liquid paraffin, and congealed into suppositories at 5°C. The formed suppositories were removed from the mold, wrapped with aluminum foil and preserved in tightly-closed light-resistant containers in a refrigerator (5°C). All the procedures were carried out under subdued light conditions to prevent photodegradation of NF.

Physical test of NF suppository

The hardness and melting point were measured by a tablet tester according to the method reported by Iwaoku et al. (1982) and the USP XX procedure for class II, respectively. The NF content in the suppository was measured. Each suppository was dissolved in 100 ml of a mixture of methanol and water (1 : 1, v/v), and an aliquot was assayed for NF.

To evaluate the NF stability in the suppository under the preserved condition as described above, NF content in the suppository was periodically measured over 30 months.

Bioavailability study

Eight healthy male volunteers, aged 23–55 years, participated in the study. All subjects were given routine admission physical examinations and the results of

hematological test and serum chemistries were normal. The study was designed in a randomized crossover fashion with a 14-day interval between doses. Each subject received 10 mg of NF as a rectal suppository or an oral soft gelatin capsule. All experiments started at 09.00 h following an overnight fast, the suppository was inserted after defecation and the capsule was swallowed with 50 ml of water. The subjects were kept at rest after the administration. Measurements of blood pressure and heart rate were made before each blood sampling. About 3 ml of blood were collected for determination of plasma NF at 0, 15, 30 and 45 min and 1, 2, 3, 5 and 7 h following dosage. The plasma samples were then separated and stored frozen at −20°C until assay under light-protected condition.

NF assays

NF in all samples was assayed according to the gas chromatographic method reported by Kurosawa et al. (1984).

Pharmacokinetic analysis and statistics

Each plasma NF concentration versus time curve was fitted to a one- or two-compartment open model with first-order absorption by a non-linear least-squares regression computer program, MULTI (Yamaoka et al., 1981). Choice of the model was made by AIC, an information criterion reported by Akaike (1976). The lag time of absorption (T_{lag}), the absorption rate constant (k_a) and the elimination rate constant (k_{el} or β) were obtained from the best fitted curve. The maximum plasma concentration (C_{max}) and the time to reach the concentration (T_{max}) were determined from the individual curves. The areas under the plasma concentration versus time curve from 0–7 h (AUC_{0-7}) were calculated by the trapezoidal rule. Statistical significance was assessed using the Student's paired *t*-test.

Results and Discussion

Since a rapid hypotensive effect is necessary for treatment of hypertensive emergency, NF should be released promptly from the suppository base. To obtain such a fast release for lipophilic drug, water-soluble bases may be more suitable than fatty ones (Senior, 1974). As NF is highly lipophilic, PEG, a water-soluble base, was chosen for this purpose.

The physical characteristics of our NF suppository are summarized in Table 1. They had enough hardness for insertion and little variation in weight and NF content. The content did not change during the final 6 months under the preserved condition after preparation and decreased slightly to 92.4% at 30 months. Therefore stability of NF in this preparation may be adequate for practical use.

In vivo experiments were designed to compare NF bioavailability of the rectal suppository with that of the oral soft gelatin capsule.

Typical plasma concentration curves of NF are shown in Fig. 1. After oral administration, two distinct types of the plasma concentration curves with fast absorption (T_{max} 30 min) and with slow absorption (T_{max} 2 h) were obtained.

TABLE 1

PHYSICAL CHARACTERISTICS OF NIFEDIPINE SUPPOSITORY

	Mean ± S.D.(n)
Weight (g)	1.99 ± 0.049 (20)
NF content (mg)	10.6 ± 0.468 (10)
Hardness (kg/cm^2)	3.8 ± 0.40 (10)
Melting point (°C)	52.3 ± 0.15 (10)

Jakobsen et al. (1979) also reported this phenomenon, and it might be attributed to individual difference of gastric emptying rate (Foster et al., 1983). In our oral study, six fast and two slow absorption types were observed in eight subjects. While, after the rectal administration the peak concentration occurred at about 2 h for both subjects regardless of their oral absorption patterns, the same patterns were obtained also for the rest. Therefore rectal administration, which avoids the effect of gastric emptying rate, might be better than the oral administration with respect to decreasing the individual differences.

The mean plasma concentration curves and the pharmacokinetic parameters concerned with absorption and elimination for both dosage forms are shown in Fig. 2 and Table 2, respectively. Following oral administration of the soft capsule, NF plasma concentration reached the peak of 110 ng/ml soon after the lag time of 0.245 h and then decreased rapidly. This result was consistent with those of Foster et al. (1983) and Kikuchi et al. (1982). Compared to the plasma concentration for the oral capsule, that for the rectal suppository increased gradually, though the absorption lag time was of the same order. The concentration for the suppository exceeded those for the oral capsule at 1.5 h, reached the peak of 67.8 ng/ml at 1.75 h and maintained higher levels than those for the capsule until 7 h. $AUC_{0\text{-}7}$ for the

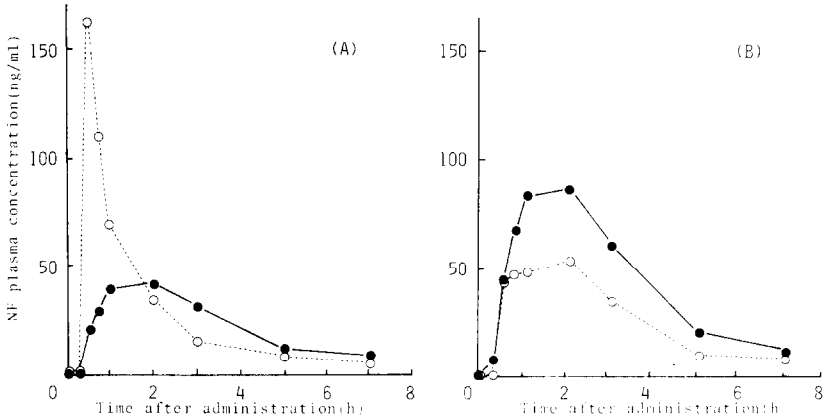

Fig. 1. Two distinct types of NF plasma concentration curves after NF administration of oral capsule (○) and rectal suppository (●): (A: 39 years, 59 kg; B: 31 years, 60 kg).

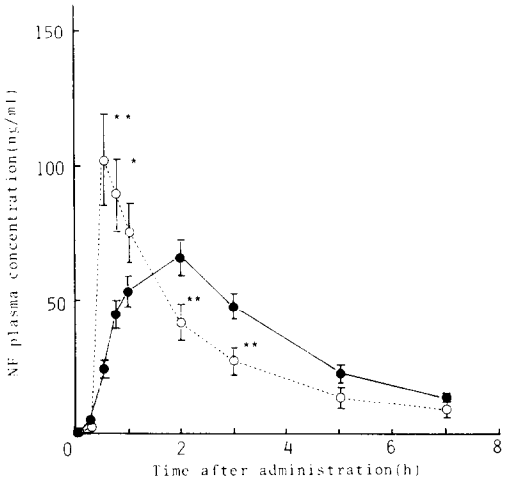

Fig. 2. Mean NF plasma concentration after NF administration of oral capsule (○) and rectal suppository (●) (mean ± S.E., n = 8): p.o. vs rectal; * $P < 0.05$, ** $P < 0.01$.

suppository was slightly higher than for the oral capsule, which might be due to a decrease in the first-pass effect possibly due to the metabolism in the gastrointestinal tract (Waller et al., 1984). However, the differences in $AUC_{0\text{-}7}$ were not significant; therefore the extent of bioavailability of both formulations were practically the same.

According to the pharmacokinetic analysis (Table 2), the plasma concentration curves after the oral administration fitted to 1-compartment model for 3 subjects and 2-compartment model for 5 subjects, while all of those after the rectal administration fitted to 1-compartment model. The mean elimination half-life ($t_{1/2}$) calculated from k_{el} or β was 1.6 h for the oral administration which was similar to that reported by Kleinbloesem et al. (1984). This $t_{1/2}$ was almost the same as that for

TABLE 2

PHARMACOKINETIC PARAMETERS AFTER RECTAL AND ORAL ADMINISTRATION OF NIFEDIPINE

Parameters	Mean ± S.E. (n = 8)	
	p.o.	Rectal
T_{lag} (h)	0.245 ± 0.0023	0.207 ± 0.0030
K_a (h^{-1})	15.3 ± 5.92	1.06 ± 0.157 *
K_{el} or β (h^{-1})	0.426 ± 0.0874	0.468 ± 0.0441
T_{max} (h)	0.78 ± 0.186	1.75 ± 0.164 **
C_{max} (ng/ml)	110 ± 16.0	67.8 ± 6.26
$AUC_{0\text{-}7}$ (ng·h/ml)	216 ± 39.2	251 ± 22.8

* p.o. vs rectal $P < 0.05$.
** p.o. vs rectal $P < 0.01$.

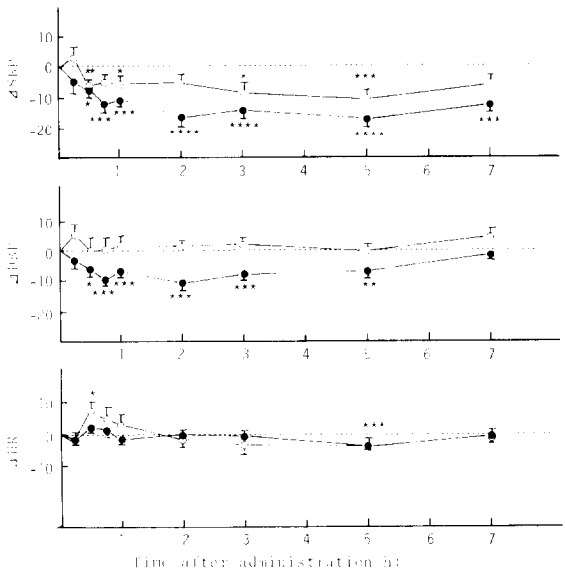

Fig. 3. Changes in SBP, DBP and HR after NF administration of oral capsule (○) and rectal suppository (●) (mean ± S.E., n = 8): compared to the value of before administration; * $P < 0.05$, ** $P < 0.02$, *** $P < 0.01$, **** $P < 0.001$.

rectal administration. On the other hand, k_a for rectal administration was significantly smaller than that for oral administration. Therefore the differences in the plasma concentration curves between these administrations were brought about exclusively by the absorption process including release from the vehicles.

The hypotensive effect of NF in hypertensive patients was related to the plasma concentration (Aoki et al., 1982; Banzet et al., 1983) and the minimum NF concentration for the effect was about 12 ng/ml (Kikuchi et al., 1982). Applying this data to our results (Fig. 2), we may expect that the effect begins about 15–30 min after both administrations and continues for 5 h after oral and 7 h after rectal administration.

With respect to the cardio-vascular effect of NF in our healthy subjects, the rectal suppository was compared with the oral capsule (Fig. 3). The diastolic blood pressures (DBP) were not changed but the systolic blood pressures (SBP) were lowered significantly at 0.5, 1, 3 and 5 h after the oral administration. Corresponding to the lowering of SBP, heart rates (HR) increased significantly at 0.5 h. Similar results were reported in healthy subjects (Kleinbloesem et al., 1984) and hypertensive patients (Aoki et al., 1982). After rectal administration, reductions in both of SDP and DBP were observed from 30 min and lasted for more than 5 h, but a significant rise in HR was not observed. The hypotensive effect after rectal administration was more potent than that after oral administration: significantly different in SDP at 2 h ($P < 0.02$); significantly different in DBP at 45 min ($P < 0.05$), 2 h ($P < 0.01$) and 3 h ($P < 0.05$). These differences might be associated with baroreflex and sympathetic stimulation, as suggested by Kleinbloesem et al. (1984). The relationship between the

pharmacological effect and the plasma concentration curves for both administrations seem to fairly well support our prediction about the duration of action based on the minimum effective concentration.

In conclusion, our NF suppository prepared with PEG has enough absorption characteristics for the treatment of hypertensive emergency. Furthermore this suppository may be useful as a sustained released formulation for the long-term treatment of essential hypertension.

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References

Akaike, H., An information criterion (AIC). Math. Sci., 14 (1976) 5–9.

Aoki, K., Sato, K., Kawaguchi, Y. and Yamamoto, M., Acute and long-term hypotensive effects and plasma concentrations of nifedipine in patients with essential hypertension. Eur. J. Clin. Pharmacol., 23 (1982) 197–201.

Banzet, O., Colin, J.N., Thibonnier, M., Singlas, E., Alexandre, J.M. and Corvol, P., Acute antihypertensive effect and pharmacokinetics of a tablet preparation of nifedipine. Eur. J. Clin. Pharmacol., 24 (1983) 145–150.

Foster, T.S., Hamann, S.R., Richards, V.R., Bryant, P.J., Graves, D.A. and McAllister, R.G., Jr, Nifedipine kinetics and bioavailability after single intravenous and oral doses in normal subjects. J. Clin. Pharmacol., 23 (1983) 161–170.

Iwaoku, R., Arimori, K., Nakano, M. and Uekama, K., Enhanced absorption of phenobarbital from suppositories containing phenobarbital-β-cyclodextrin inclusion complex. Chem. Pharm. Bull., 30 (1982) 1416–1421.

Jakobsen, P., Lederballe Pedersen, O. and Mikkelsen, E., Gas chromatographic determination of nifedipine and one of its metabolites using electron capture detection. J. Chromatogr., 162 (1979) 81–87.

Kikuchi, K., Kobayashi, H., Nakao, T., Kondo, A., Mito, T., Tsuzuki, M., Iimura, O., Fujise, Y. and Hanawa, K., Interrelationships between hemodynamic changes and pharmacokinetics following oral administration of nifedipine in healthy subjects and patients with essential hypertension. Jpn. J. Clin. Pharmacol. Ther., 13 (1982) 623–637.

Kleinbloesem, C.H., van Brummelen, P., van de Linde, J.A., Voogd, P.J. and Breimer, D.D., Nifedipine: kinetics and dynamics in healthy subjects. Clin. Pharmacol. Ther., 35 (1984) 742–749.

Kurosawa, N., Morishima, S., Owada, E., Ito, K., Ueda, K., Takahashi, A. and Kikuiri, T., Determination of nifedipine in human plasma by gas chromatograph equipped with flame thermionic detector (FTD). Yakugaku Zasshi, 104 (1984) 775–779.

Murakami, H., Murakami, E. and Takekoshi, N., Effectiveness of dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridine decarboxylate (nifedipine, Adalat) on treatment of severe hypertension and hypertensive emergency. Rinsho to Kenkyu, 56 (1979) 603–608.

Murakami, M., Murakami, E., Takekoshi, N., Tsuchiya, M., Kin, T., Onoe, T., Takeuchi, N., Funatsu, T., Hara, S., Ishise, S., Mifune, J. and Maeda, M., Antihypertensive effect of 4(-2′-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonic acid dimethylester (nifedipine, Bay-a 1040), a new coronary dilator. Jap. Heart J., 13 (1972) 128–135.

Senior, N., Advances in Pharmaceutical Sciences, Vol. 4, Rectal Administration of Drugs, Academic Press, London, 1974, pp. 363–435.

Tsuda, T., Komatsu, T., Yoshida, R. and Ishii, T., Rapid hypotensive effect of nifedipine: effectiveness of rectal administration of nifedipine enema. Rinsho Masui, 5 (1981) 785–790.

Waller, D.G., Renwick, A.G., Gruchy, B.S. and George, C.F., The first pass metabolism of nifedipine in man. Br. J. Clin. Pharmacol., 18 (1984) 951–954.

Yamaoka, K., Tanigawara, Y., Nakagawa, T. and Uno, T., A pharmacokinetic analysis program (MULTI) for microcomputer. J. Pharmacobio-Dyn., 4 (1981) 879–885.