Application of Nifedipine Sustained-Release Suppositories to Healthy Volunteers

NORIAKI OHNISHI, TERUYOSHI YOKOYAMA, TSUNEKO Umeda, YOSHIKUMI KIYOHARA, TSUTOMU KURODA, YOSHIKI KITA, and KOJI KURODA

Hospital Pharmacy, Kobe University School of Medicine, Kusunoki-cho, Chuo-ku, Kobe 650, Japan

(Received June 25, 1986)

Double layer suppositories (D-15) of nifedipine (NF), prepared by using a solid dispersion system of polyethylene glycol 4000 as a water-soluble carrier and cellulose acetate phthalate as a poorly water-soluble carrier, were administered to healthy volunteers, and their sustained-release characteristics, bioavailability and clinical utility were investigated. It was found that D-15 was able to maintain a therapeutically effective level of NF from 30 min to 10 h without causing an excessively high peak level and offered good bioavailability. From the results of pharmacokinetic analysis by using the compartment model method, it appeared that the plasma concentration-time course after rectal administration of D-15 is satisfactorily accounted for by a one-compartment model with first-order release and absorption steps. The value of release rate constant of D-15 obtained was smaller than that of absorption rate constant, and the sustained-release effect was apparently attributed to the slow release of NF from the suppository.

The plasma level of NF rapidly decreased as removing D-15, and the plasma level showed hardly any irregularities arising from the removal and the renewal of suppositories.

Accordingly, it was concluded that D-15 is an effective sustained-release dosage form and represents a convenient mode of therapy with reduced frequency of drug administration and reduced risk of side-effects.

Keywords—nifedipine; sustained-release suppository; cellulose acetate phthalate-polyethylene glycol matrix; solid dispersion; rectal administration; pharmacokinetic analysis

Nifedipine (NF), a calcium channel blocker, is increasingly used in the treatment of hypertension and angina pectoris. However, NF is inactivated rapidly through oxidative biotransformation, resulting in a short duration of action. Therefore, several sustained-release dosage forms of NF have recently been developed in an attempt to reduce the frequency of drug administration and the incidence and intensity of side-effects. A few studies on rectal sustained-release dosage forms of NF have been carried out. Kleinbloesem et al. reported that NF could be given rectally through an osmotic pump system at zero-order rate for 24 h.

In the previous paper, we reported that double layer suppositories of NF prepared by using a solid dispersion system of polyethylene glycol 4000 (PEG) as a water-soluble carrier and cellulose acetate phthalate (CAP) as a poorly water-soluble carrier show a sustained-release effect and good bioavailability in rabbits.

In this paper, the double layer suppositories of NF reported previously were administered to healthy volunteers, and their bioavailability and clinical utility were investigated.

**Experimental**

Materials—NF (Lot No. 2044100) was a gift from Sawai Pharmaceutical Co., Ltd. PEG and CAP were
purchased from Wako Pure Chemical Ind., Ltd. All other chemicals were reagent-grade commercial products.

**Preparation of Suppositories**—(1) Conventional Suppositories (C-0): C-0 was prepared by the fusion method using PEG alone as a base according to the previous paper.7)

(2) Double Layer Suppositories (D-15): D-15 was prepared by the use of 15% (w/w) CAP-PEG matrix as a base according to the previous paper.7) D-15 included NF only in the outside layer of the suppositories.

The content of NF in all suppositories was 10 mg.

**Administration Experiment**—Our volunteers were five healthy men aged 25 to 43 years (mean age: 32 years) and weighing 52 to 65 kg (mean body weight: 57 kg). All volunteers gave their consent after receiving full verbal and written information about purpose and risks of the study.

Each administration experiment was performed for a group comprising three volunteers, who were randomly selected from all volunteers. The interval between the various parts of the experiment was at least 2 weeks in all volunteers. None was on any medication during the course of the experiment, and all volunteers could move around freely during the experiments.

Blood samples (3–4 ml) were drawn from a forearm vein before and at 0.5, 1, 2, 3, 4, 6, 8, and 10 h after rectal administration. The plasma was immediately separated after centrifugation and frozen at −4 °C until assay.

**Data Analysis**—The computer simulations of plasma concentration–time courses were carried out using the MULTI program9) with a personal computer (NEC, PC-9801VM). The nonlinear least-squares algorithm used was the Simplex method at the preliminary fitting, and the converged values were further analyzed by the modified Marquardt method.

---

**Results and Discussion**

**Plasma Levels of NF after Rectal Administration**

Figure 1 shows the plasma concentration–time curves of NF after rectal administration of C-0 and D-15. The absorption of NF after administration of C-0 was very fast, and the mean maximum plasma concentration was 80.1 ng/ml at 1 h. Subsequently, the plasma level declined rapidly to a value below 10 ng/ml at 8 h after administration (Fig. 1). On the other hand, the administration of D-15 resulted in a plateau plasma level in the range of 20–35 ng/ml from 30 min to 10 h (Fig. 1).

Aoki et al.10) reported that the lowest therapeutically effective level of NF may be in the range from 20 to 30 ng/ml, and Stern et al.11) reported that the minimum toxic concentration of NF is not necessarily constant, but adverse effects such as headache and flushing may be

---

Fig. 1. Plasma Concentrations of NF after Rectal Administration of C-0 and D-15 to Healthy Volunteers

○, C-0; ●, D-15.

Each point represents the mean ± S.D. (n = 3).
observed at plasma concentrations exceeding 50—70 ng/ml. In our experiments, all volunteers experienced side-effects such as headache, flushing or dizziness after administration of C-0, in particular at the time of peak plasma level. However, no marked side-effects were observed during administration of D-15.

From these results, it was concluded that D-15 is a suitable dosage form for obtaining a desirable level of NF for a long time.

Pharmacokinetic Analysis

The plasma concentration–time course of NF after intravenous administration to rabbits or man follows a two-compartment model. On the other hand, it is known that the plasma concentration–time course after oral administration is consistent with a one-compartment model with a first-order absorption step because of the fusion of compartments, even though the plasma concentration–time course after intravenous administration is explained by a two-compartment model.

Therefore, the pharmacokinetic analysis of the plasma concentration–time course of NF after rectal administration of C-0 was performed according to a one-compartment model with a first-order absorption step, as shown in Fig. 2 (model A). The calculated plasma concentration–time curve fitted well with the observed plasma data, as can be seen in Fig. 1. These results suggest that the plasma concentration–time course after rectal administration of C-0 follows a one-compartment model with a first-order absorption step.

Furthermore, the curve fitting of the plasma concentration–time course data after rectal administration of D-15 was carried out by using a one-compartment model with two consecutive first-order steps in order to clarify the release rate of NF from a suppository, as shown in Fig. 2 (model B). The computer analysis was done by simultaneous fitting of the equation for both C-0 and D-15. The calculated plasma concentration–time curve was successfully fitted to the observed plasma data (Fig. 1). From these results, it appears that the plasma concentration–time course after rectal administration of D-15 is satisfactorily accounted for by a one-compartment model with first-order release and absorption steps. The pharmacokinetic parameters obtained are listed in Table I.

The value of absorption rate constant ($k_a$) or elimination rate constant ($K$) was not significantly different between C-0 and D-15, and the value of release rate constant ($k_r$) was smaller than that of $k_a$. From these results, it was concluded that the sustained-release effect achieved by D-15 is apparently attributable to the slow release of NF from a suppository.

---

**model A** one-compartment model with first-order absorption

$$C_p = H \cdot [e^{-K(t-t_0)} - e^{-k_a(t-t_0)}] \quad (k_a > K)$$

![Fig. 2. Pharmacokinetic Compartment Models Used for NF](image)

**model B** one-compartment model with two consecutive first-order input steps

$$C_p = P \cdot e^{-k_a(t-t_0)} + Q \cdot e^{-K(t-t_0)} + R \cdot e^{-k_a(t-t_0)}$$

($P + Q + R = 0$, $k_a > K > k_r$)

$D$, dose administered; $F$, fraction of drug absorbed; $X_i$, amount of drug in release site; $X_a$, amount of drug in absorption site; $V$, apparent volume of distribution; $k_r$, release rate constant; $k_a$, absorption rate constant; $K$, elimination rate constant; $t_{0a}$, lag time.
On the other hand, the areas under the plasma concentration–time curves (AUC) of C-0 and D-15 were almost the same.

**Removal and Renewal of D-15**

One serious disadvantage of oral sustained-release preparations is the lack of flexibility on administration.\(^{15}\) In the case of an oral sustained-release dosage form, it is difficult to respond to changes in the condition of a patient, because its action is maintained for 8—12 h once it is administered.

Figure 3 shows the effect of removal of D-15 at 2 h after administration on the plasma concentration–time course. When the suppository was removed, the plasma level of NF rapidly decreased. These results suggest that D-15 is much safer than oral sustained-release preparations.

The effect of renewal of D-15 on the plasma concentration–time course is shown in Fig. 4; i.e., D-15 was removed at 2 h after administration and then a new D-15 was inserted after
30 min. The plasma level curve showed hardly any irregularity in spite of the removal and renewal of suppositories. These results indicate that, even when the suppository is eliminated due to defecation and so on, readministration of a new D-15 provides a therapeutically effective level of NF for a long time without causing an excessively high peak level. However, this dosage form might be unsuitable for patients with serious diarrhea.

In this administration experiment, no pain or discomfort in the rectal loop was encountered.

**Conclusion**

The rectal administration of D-15 to healthy volunteers resulted in a therapeutically effective level of NF from 30 min to 10 h without causing an excessively high peak level, and bioavailability was good. Therefore, it appears that the administration of D-15 containing 10 mg of NF will be sufficiently effective in the treatment of hypertension if D-15 is taken twice daily. In addition, this dosage form may be useful to prevent the frequent crises of angina pectoris early in the morning if D-15 is given before bedtime.

Accordingly, it was concluded that D-15 should represent a convenient mode of therapy with reduced frequency of administration and reduced risk of side-effects.

**References and Notes**


6) N. Hamakawa, T. Koga, K. Ushimaru, M. Gogo, and S. Sugiyma, Abstracts of Papers, the 35th Meeting of the Kinki Branch, Pharmaceutical Society of Japan, Kyoto, November 1985, p. 56.


