Nasal Absorption of Nifedipine from Gel Preparations in Rats

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Nasal absorption of nifedipine from polyethylene glycol (PEG) 400, aqueous Carbopol gel and Carbopol–PEG gel was investigated with the aim of obtaining high bioavailability and prolonged action. Nasal administration of nifedipine in PEG resulted in rapid absorption and high maximum concentration ($C_{\text{max}}$). However, the elimination of nifedipine from plasma was very rapid. Nifedipine plasma concentration after nasal administration of nifedipine in aqueous Carbopol gel was very low. On the other hand, Carbopol–PEG gel (containing 50% w/v PEG) showed a relatively high nifedipine concentration and a prolonged action.

Keywords—gel preparation; polyethylene glycol 400; Carbopol 941; nifedipine; nasal administration; nasal absorption

Nifedipine, dimethyl 1,4-dihydro-2,6-dimethyl-4, (nitrophenyl)-3,5-pyridinedicarboxylate, is a highly active Ca$^{2+}$-channel blocker affecting the excitation–concentration coupling in smooth vascular muscle and myocardium, and is used in the treatment of angina pectoris and hypertension. However, nifedipine is a poorly water-soluble drug whose bioavailability is very low when it is administered in crystalline form, and its biological half-life is relatively short. Furthermore, recent studies have indicated that nifedipine shows a first-pass effect following oral administration. Intranasal administration has been employed with drugs which are susceptible to a first-pass effect, such as propranolol and peptides. Recently, new powder dosage forms using water-soluble polymers have been developed for nasal administration.

In the present study, nasal absorption of nifedipine from gel preparations made with polyethylene glycol (PEG) 400, aqueous Carbopol gel and aqueous Carbopol–PEG gel was investigated in order to obtain high bioavailability and prolonged action after intranasal administration.

Materials and Methods

Materials—Nifedipine was obtained from Bayer Yakuhin, Osaka, Japan, Carbopol 941 from B. F. Goodrich Chem. Co., Oh., U.S.A., and PEG 400 from Wako Pure Chem. Ind. Ltd., Osaka, Japan. The other reagents were of the best commercially available grade.

Methods—All experiments were carried out in a dark room in view of the high sensitivity of nifedipine to light.

Preparations—Carbopol gel was prepared with Carbopol 941 presoaked in distilled water at room temperature, and 10% NaOH solution was added to adjust the pH to 6.5 as previously described. The concentrations of Carbopol 941 in the gel were 0.05% (w/v), 0.1% (w/v) and 0.5% (w/v). Carbopol–PEG gel was prepared by dissolution of PEG 400 at the concentration of 35% (w/v), 50% (w/v) or 70% (w/v) in Carbopol gel (0.05% w/v, pH 6.5). Nifedipine (~177 μm particle size) was suspended or dissolved in the vehicles at the concentration of 100 mg/ml. The viscosities of the vehicles were measured with a cone and plate viscometer (Tokyo Keiki Co., Ltd., Tokyo, Japan) at 37°C and at a shear rate of 38.4 s$^{-1}$. The viscosities and pH values are shown in Table I.

Administrations—Wistar-strain male rats, 200—250 g, were fasted for 20 h prior to the experiments but allowed free access to water, and anesthetized with Na-pentobarbital (50 mg/ml body weight) by intraperitoneal...
injection. The surgical operation was carried out as described by Hirai et al.\textsuperscript{10} After an incision had been made in the neck, the trachea was cannulated with polyethylene tubing. Another similar cannula was inserted from the esophagus to the nasal cavity for the administration of nifedipine preparations. The nasopalatine was closed with an adhesive agent to prevent drainage of the drug from the nasal cavity to the mouth. The preparations were administered to the nasal cavity through the tube by means of a syringe at a volume of 1 ml/kg. In a comparative study, nifedipine, dissolved in a mixture of ethanol-PEG 400 (15 : 15 : 17) was intravenously injected and nifedipine powder was administered to the duodenum through a polyethylene catheter to separate groups of rats. Blood samples (0.5 ml) were taken at appropriate times.

Analytical Methods
Plasma was separated by the centrifugation at 3000 rpm/min and nifedipine in plasma was assayed by the high-performance method reported by Pietta et al.\textsuperscript{11}

Results and Discussion

Figure 1 shows the plasma concentration of nifedipine after nasal administration of nifedipine in PEG 400, and after oral and intravenous administration of nifedipine in rats. Nasal administration of nifedipine in PEG 400 caused an early peak in the plasma level and a high maximum concentration compared with oral administration. However, the elimination of nifedipine from plasma was very rapid after the peak.

Figure 2 shows the plasma concentration of nifedipine after nasal administration of nifedipine in aqueous Carbopol gels at various concentrations of Carbopol in rats. Nifedipine plasma concentration profiles and peak plasma concentrations were similar among 0.05\% (w/v), 0.1\% (w/v) and 0.5\% (w/v) Carbopol gels. The nifedipine concentrations in plasma were very low and sustained compared to that in the case of PEG 400.

Figure 3 shows the plasma concentration of nifedipine after nasal administration of nifedipine in Carbopol-PEG gels. Carbopol-PEG gels containing 35\% (w/v) (A), 50\% (w/v) (B) and 70\% (w/v) (C) of PEG 400 in aqueous Carbopol gel (0.05\% w/v, pH 6.5) were administered to rats. The nifedipine plasma profile after administration in Carbopol-PEG gel (C) was similar to that in the case of PEG 400. However, the nifedipine plasma concentration with Carbopol-PEG gel (C) was lower than that with PEG 400. The nifedipine plasma profile after administration of Carbopol-PEG gel (A) was similar to that with Carbopol gel. Carbopol-PEG gel (B) gave lower plasma concentrations as compared with PEG 400 and Carbopol-PEG gel (C) from 30 min to 6 h after administration, but the nifedipine plasma concentration was maintained near the maximum level from 4 to 6 h after administration.

Nasal administration of nifedipine in PEG 400, a water-soluble base resulted in rapid absorption and a high maximum plasma concentration ($C_{\text{max}}$), because the PEG 400 entrapped nifedipine and rapidly dissolved in the mucosal fluid. However, the elimination of nifedipine from plasma was very rapid after the $C_{\text{max}}$. This result was similar to that after rectal administration of nifedipine in a PEG suppository base.\textsuperscript{2} On the other hand, the low

\begin{table}[h]
\centering
\caption{Components and Viscosity of Vehicles}
\begin{tabular}{|c|c|c|c|}
\hline
 & PEG 400 & Carbopol 941 & Viscosity$^a$  \\
 & ($\%$ w/v) & ($\%$ w/v) & cP  \\
\hline
PEG 400 & 100 & — & 51.2  \\
Carbopol gel & — & 0.05 & 256.0  \\
Carbopol gel & — & 0.1 & 366.1  \\
Carbopol gel & — & 0.5 & 1054.7  \\
Carbopol-PEG gel (A) & 35 & 0.05 & 215.0  \\
 & (B) & 50 & 0.05  \\
 & (C) & 70 & 0.05  \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a} The viscosities of vehicles were measured with a cone and plate viscometer at the shear rate of 38.4 s$^{-1}$ at 37 °C.
nifedipine plasma concentration after nasal administration of nifedipine in aqueous Carbopol gel was caused by the poor solubility of nifedipine in aqueous gel. In the case of Carbopol–PEG gel, higher plasma concentrations of nifedipine were obtained with gel preparations containing PEG 400 at higher concentrations. Umeda et al. also reported that in a cellulose acetate phthalate–PEG matrix suppository, PEG enhanced the bioavailability of nifedipine. The reason may be that PEG functions as a cosolvent of nifedipine, a poorly watersoluble drug in the aqueous gel. Carbopol–PEG gel (containing 35% w/v PEG 400) (A); Carbopol–PEG gel (containing 50% w/v PEG 400) (B); Carbopol–PEG gel (containing 70% w/v PEG 400) (C); PEG 400; Carbopol gel (0.1% w/v, pH 6.5). The dose of nifedipine for nasal administration was 20 mg/kg. Each point is the mean ± S.E. of 4 animals.

In conclusion, nasal administration of nifedipine in PEG 400 resulted in rapid absorption and a high Cmax. However, the elimination of nifedipine from plasma was very rapid after the Cmax. Nasal administration of nifedipine in Carbopol–PEG gel (containing 50% w/v PEG) showed a relatively high plasma concentration and a prolonged action.

References