Effects of hydroxypropyl-cellulose (HPC) on the nasal drug absorption from powder formulations

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ABSTRACT SUMMARY

Hydroxypropyl-cellulose (HPC) is generally used as a binder for the manufacture of tablets and granules. Since HPC in the formulation likely increase the viscosity of dosage forms in the nasal cavity, it may improve the nasal absorption through the increase in the nasal residence of the formulation. The aim of this study is to examine the effect of HPC on the drug absorption after nasal application of its powder formulation. Three types of HPC were used. The absorption lag was observed in the profile of the plasma concentration of piroxicam (PXC) following nasal application of the powder formulation containing HPC(H) and HPC(M) to rats in vivo. Concentrations of PXC in the plasma following application with HPC(M) were much higher. In comparison with control (PXC bulk powder without HPCs), the fractional absorption of PXC was increased by 42% by HPC(M), while HPC(H) and HPC(SL) decreased it. These results indicated that HPC(M) is the most suitable for the enhancement of drug absorption. The absorption of sumatriptan were evaluated after nasal application of IMIGRAN® (solution) and the powder formulation containing HPC(M). The plasma concentration after application of powder sumatriptan was higher than those of IMIGRAN®. In addition, HPC(M) showed neither histologic damages nor physiologic toxicity on the nasal epithelium. These findings indicate that the powder dosage form containing HPC is a valuable and promising approach to increase the nasal drug absorption.

INTRODUCTION

In recent years, the nasal delivery has received a great deal of attention as a convenient method for systemic administration of drugs. This is due to the rapid and better drug absorption, the high drug permeability to the highly vascularized nasal epithelium¹, and passing directly into the systemic circulation, thereby avoiding hepatogastrointestinal first-pass metabolism².

The mucociliary clearance (MC) is known to be one of the important factors limiting the nasal drug delivery, which removes applied dosage forms rapidly from the absorption site. Conventional nasal formulations such as liquid drops or sprays are rapidly cleared from the nasal cavity within 12-15 min after administration³. Solution, powder and gel formulations are widely used for nasal drug administration. The advantages of powder formulations are the stability of drugs, the higher dose and the increase in the nasal residence time⁴. However, little information is available on the nasal absorption of drugs, including macromolecules, after nasal application of their powder formulations. Therefore, detail information on the drug absorption from the powder is highly desirable. Among the various strategies available, addition of polymers to the powder to increase the viscosity appears suitable to improve the nasal drug absorption. Hydroxypropyl-cellulose (HPC) is generally used as a binder to increase the viscosity of formulation in the manufacturing process of tablets and granules. Additionally, since various types of HPC with different degrees of polymerization are commercially available, the relation between the characteristics of HPC and their effect on the drug absorption can be evaluated quantitatively.

The aim of this study is to evaluate the effect of HPCs on the nasal drug absorption and the toxicity using powder formulations. The effect of HPC on the absorption of sumatriptan, which has been clinically applied in Japan as a nasal spray formulation for a migraine, was also examined. In vivo absorptions of sumatriptan after application of IMIGRAN® and a powder containing sumatriptan and HPC were compared. The damage and toxicity on the nasal mucosal membrane by nasally-applied HPC powder was also evaluated.

EXPERIMENTAL METHODS

Three types of HPC with different degrees of polymerization were used. The average molecular weight of HPC(SL), HPC(M) and HPC(H) are 100 kDa, 620 kDa and 910 kDa, respectively. Piroxicam (PXC) was selected as a model drug.

In vitro study: MDCK cells were used. In the transepithelial transport study, no medium was added to the apical side of MDCK monolayers (Air-interface condition, AIC) for the similarity of the in vivo situation of the nasal epithelium. PXC powder or 50% PXC powder containing HPC were sprayed on the apical side of the cell monolayer. Thereafter, an aliquot of the sample was taken from the basal chamber over 360 min. The temperature and relative
humidity around monolayers were maintained at 25-37°C and 35-80%\(^\circ\) throughout the experiments. Drug concentrations were determined with HPLC.

**Animal study:** All the animal studies were previously approved by the Ethics Committee at Kyoto Pharmaceutical University and conducted in accordance with the Guidelines. For powder formulations, 1 mg of the nasal formulation was administered into the rat nasal cavity with the special device. The rat was kept conscious in a cage throughout the experiment. Blood samples were collected for 360 min after drug administration. Drug concentrations were determined with HPLC.

To evaluate the damage and toxicity on the nasal membrane by HPC, 1 mg of HPCs was given into nostrils of rats. The nasal cavity was perfused with 8 mL of PBS 6 hr after HPC application. The activity of lactate dehydrogenase (LDH) in the perfused solution was determined as an index of membrane damage. The mucociliary function of the nasal epithium was determined in **vivo**, according to the methods by Inoue et al.\(^5\). Nasal septum was excised surgically from rats pretreated with HPC. The suspension of fluorescent microspheres (FMS) was applied on the surface of the excised nasal septum and the movement of FMS was recorded with a fluorescent microscope. The movement velocity of FMS was calculated as an index of mucociliary function.

**RESULTS AND DISCUSSION**

Plasma concentration-time profiles and the change of the fractional absorption of PXC following nasal application of powder formulations to rats are shown in Fig.1(A) and Fig.1(B). The absorption lag was observed in the profiles of powders containing HPC(H) and HPC(M). In the nasal cavity after application, HPC(H) and HPC(M) likely dissolve in a small volume of the surface fluid to give the higher viscosity, resulting in the delay of drug absorption. The plasma concentration of PXC after application with HPC (M) was much higher than others. Fractional absorption of PXC at the end of the study after administration of powder containing HPC (M) was 42% greater, while those after administration of powder containing HPC(H) and HPC(SL) were 18% smaller as compared to PXC powder. These results suggested that the higher viscosity of the formulation in the nasal cavity does not always result in the increase in the drug absorption. Absorptions of sumatriptan from solution (IMIGRAN\(^®\)) and a powder formulation were evaluated in **vivo**. Concentrations of sumatriptan in the plasma were higher after application of the powder with HPC(M) than those after application of IMIGRAN\(^®\). The membrane damage to the nasal tissue and the toxicity to the nasal function by HPC were examined. Neither significant increases of LDH activity in the nasal lavage fluid after nasal administration of HPC nor significant change of the transport velocity of FMS on the excised nasal septum were observed, suggesting the safety of HPC.

**CONCLUSION**

Results obtained in this study clearly indicated additional advantages of the powder formulation containing HPC on the drug absorption. The nasal absorption of some other model drugs from HPC powder formulation is now under investigation and the data may be presented at the meeting.

**REFERENCES**