Estimation of In Vivo Nasal Drug Absorption from In Vitro Parameters Based on New Pharmacokinetic Model Incorporating Nasal Physiologic Function

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Purpose
Advantages of nasal drug delivery include rapid absorption and avoidance of presystemic metabolism. In addition, nasal drug delivery is non-invasive which improve the patient compliance. Although the nasal route has attracted much attention as a systemic delivery route, only a few nasal formulations are on the market now. To promote the development of nasal preparations, we aimed to develop an evaluation system for precise prediction of drug absorption after intranasal application based on a pharmacokinetic (PK) model incorporating nasal physiologic function. Previously, we have developed a new PK model including a factor of nasal mucociliary function as a physiologic parameter. Using this model, the possibility of accurate estimation on the rate of drug absorption after nasal administration was suggested. In the present study, in order to enable more precise prediction of nasal drug absorption, we attempted to reveal a relationship between in vivo nasal drug absorption and in vitro permeability of drugs across nasal epithelium.

Methods
In vitro permeability of drugs across Calu-3 monolayers: Calu-3 cell line, derived from human lung carcinoma, was used as a nasal epithelium model and was cultured under air-interfaced condition. Model drugs, of which physicochemical properties are different each other, were selected based on the results from the preliminary experiment on membrane permeability. The permeability of various model drugs from the apical to the basal compartment was tested, and the apparent permeability coefficient was calculated as an index of the membrane permeability. In situ rat nasal perfusion study: In situ perfusion of drug solution through the rat nasal cavity was performed for the estimation of drug permeability through the nasal mucosa. The same model drugs as used in in vitro study mentioned above were utilized. The drug concentration in the perfusate was determined every 15 min, and the profile of the concentration vs. time was obtained for the calculation of the absorption rate constant of drugs through the nasal mucosa. In vivo study on the nasal drug absorption: The drug concentration in the rat plasma after intranasal administration was determined by HPLC or LC/MS. The bioavailability of drugs after nasal application was calculated from the area under the plasma concentration -time profiles after intravenous and intranasal administration, and was used for the analysis on the correlation between in vitro / in situ parameters.

Results
According to results from in situ nasal perfusion, the decrease in the drug concentration in the perfusate follows the first order kinetic for all the model drugs. Consequently, the absorption rate constant can be calculated from the elimination profiles, assuming no degradation and negligible amount of the drug in the nasal tissue. The permeability through the nasal epithelium derived from in situ nasal perfusion study was significantly correlated with in vitro permeability across Calu-3 monolayers (r²=0.895, p<0.001), indicating that in vivo drug absorption through the rat nasal epithelium can be estimated from the in vitro permeability data. In addition, the comparison of in vitro membrane permeability and in vivo absorption after nasal application revealed that the in vivo bioavailability was increased with the increase in the Calu-3 permeability of drugs (r²=0.9971, p<0.001). These results suggest that in vivo drug absorption after intranasal administration to rats can be predicted precisely from the data on in vitro permeability. Therefore, the analysis in this study on the relationship between in vivo data and in situ in vitro data, the permeation through the nasal mucosa is an important factor determining the bioavailability after intranasal administration.

Conclusion
The results indicated that in vivo nasal drug absorption or nasal drug permeation through the nasal mucosa can be estimated through the assessment of in vitro membrane permeability across Calu-3 monolayers. Based on the data derived from the in vitro study, easy and precise prediction on the nasal drug absorption is possible. The relationship between nasal drug absorption and in vitro membrane permeability clarify that our pharmacokinetic model incorporating nasal physiologic function should be advanced for more precise prediction from in vitro data that is available easily. At present, we are trying to separate transmucosal absorption through nasal epithelium from total drug absorption. These researches will lead us to more accurate prediction of the drug absorption after nasal application. The highly accurate prediction system of nasal drug absorption can be an efficient tool for the development of nasal preparations.