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Rapid Communication

Correlation between Nasal Membrane Permeability and Nasal Absorption Rate

Hefei Zhang,[1] Chih-Wei Lin,[2] and Maureen D. Donovan[3,4]

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Abstract. The objective of this study was to investigate the relationship between *in vitro* permeability (P_{app}) values obtained from isolated nasal tissues and the absorption rates (k_a) of the same compounds following nasal administration in animals and humans. The P_{app} of a set of 11 drug compounds was measured using animal nasal explants and plasma time–concentration profiles for each of the same compounds following intravenous (IV) and intranasal (IN) administration were experimentally determined or obtained from literature reports. The plasma clearance was estimated from the IV plasma time–concentration profiles, and k_a was determined from the IN plasma time–concentration profiles using a deconvolution approach. The level of correlation between P_{app} and k_a was established using Pearson correlation analysis. A good correlation (r=0.77) representing a point-to-point relationship for each of the compounds was observed. This result indicates that the nasal absorption for many drug candidates can be estimated from a readily measured *in vitro* P_{app} value.

KEY WORDS: bioavailability; drug transport; nasal administration; nasal mucosa; permeability.

INTRODUCTION

Nasal drug delivery has received considerable attention over the past two decades. More than 20 nasal products intended for systemic absorption have been brought to market and more compounds are under development using this route (1). Both *in vitro* permeability studies using cell culture or tissue explants and *in vivo* bioavailability studies using animal models are commonly employed to evaluate drug compounds for their potential for nasal absorption. *In vitro* experiments have also been used to investigate transport pathway-, metabolism-, and formulation-related issues (2).

Permeability is a primary determinant of the extent of absorption for compounds without solubility limitations (3). The systemic concentration of a drug is determined by its absorption and clearance rates, but typically the absorption rate is best related to the permeability value because they both represent the successful passage of the drug across the epithelial membrane. Due to the combined effect of absorption and clearance on the resulting systemic concentration, an accurate estimation of the absorption rate can be made from the pharmacokinetic profile when the clearance rate of the drug has previously been determined. Convolution and deconvolution, classical *in vitro–in vivo* correlation methods, are used in this study to describe the relationship among input rate, unit impulse response (UIR), and system response (plasma concentration profile) (4). When applied to nasal absorption, the input rate (absorption rate) can be calculated by deconvolution of the system response by the UIR.

Several investigations of the correlation between *in vitro* permeability and *in vivo* absorption at various administration sites have been reported (5–7). Other investigators have attempted to correlate the permeability across nasal tissue explants and nasal bioavailability or fraction absorbed (5,8), yet a quantitative relationship between nasal absorption rate and nasal permeability has not been developed.

To examine whether the permeability values obtained from *in vitro* methods can be used to predict *in vivo* absorption rates, the permeability and the systemic plasma concentration profiles of 11 compounds including baclofen, chlorcyclizine, cocaine, diazepam, dopamine, hydroxyzine, lidocaine, nicotine, propranolol, sumatriptan, and triprolidine were investigated. The compounds were selected because information was available from the literature describing: (1) permeability values across explanted nasal tissue and (2) plasma time–concentration profiles following intranasal and intravenous administration in humans or rats. While there could also be local, mucosal metabolism of these compounds, which would result in a lower measured *in vitro* permeability (P_{app}), little information is known regarding the metabolism of these compounds in the nasal mucosa. Therefore, metabolism was assumed to have a minimal role when developing this correlation.

MATERIALS AND METHODS

In Vitro and *In Vivo* Data from Literature

Permeability values were collected using explant tissues obtained from two animal species, bovine and porcine, and

[1] Oncology Clinical Pharmacology, Novartis Pharmaceuticals Corporation, 180 Park Avenue, Florham Park, New Jersey 07932, USA.
[2] Clinical Pharmacology and Pharmacometrics, 100 Abbott Park Road, R4PK AP13A, Abbott Park, Illinois 60064, USA.
[3] Division of Pharmaceutics and Translational Therapeutics, College of Pharmacy, University of Iowa, 115 South Grand Avenue, Iowa City, Iowa 52242, USA.
[4] To whom correspondence should be addressed. (e-mail: maureen-donovan@uiowa.edu)

were reported by two different research groups (5,8–12). Plasma concentration–time profiles following intravenous and intranasal administration in rats and humans were also obtained from separate literature reports (13–18).

Estimation of UIR (Clearance Rate)

The plasma concentration–time profiles following intravenous administration were fit using GastroPlus™ with a multiple exponential decay equation (Simulations Plus Inc, Lancaster, CA, USA; Eq. 1).

$$C_t = \sum_{j=1}^{n} A_j e^{-a_j t} \quad (1)$$

Where C_t is the blood concentration at time t, j is the number of decay phases, A_j is the jth constant before the decay exponential, and α_j is the jth clearance rate constant. The clearance rates for the 11 compounds were estimated using a nonlinear least-squares regression analysis.

Calculation of Absorption Rate Constants Using Deconvolution

After deconvolution of the curve describing the plasma concentration–time profile following nasal administration by the values for the clearance obtained from Eq. 1 (WinNonlin™ Version 5.0.1, Pharsight Co., Mountain View, CA, USA), cumulative absorption data sets were obtained. A first-order absorption equation was fit to each of the datasets (Eq. 2) using GraphPad Prism 5.0 (GraphPad Software Inc., San Diego, CA, USA), and k_a values were obtained:

$$y = A\left(1 - \exp^{-k_a t}\right) \quad (2)$$

Where y is the cumulative amount absorbed, A is the fraction of the dose absorbed and k_a is the absorption rate constant.

Correlation Analysis

The level of correlation between the experimentally measured P_{app} and the calculated k_a values was evaluated by plotting values of log k_a *versus* log P_{app} for each compound to check for a point-to-point relationship. Pearson correlation analysis was carried out using GraphPad Prism 5.0 and the correlation coefficient, mean square error (MSE), and residual error were calculated to quantitatively describe the relationship.

RESULTS

The permeability coefficients of the 11 drug compounds are tabulated in Table I. All of the compounds are water soluble with molecular weights ranging between 150 and 300 Da.

Plasma concentration–time profiles following intravenous administration for all 11 compounds could be well-described using either one- or two-phase decay equations, and absorption rates for these compounds were successfully estimated using Eq. 2. The estimated clearance and absorption rates of the 11 compounds are summarized in Table II.

A good linear correlation ($y = 0.92x + 4.86; r = 0.77$) was observed between the *in vitro* permeability and the *in vivo* systemic absorption rate for the 11 drug compounds (Fig. 1). The residual error and MSE were calculated to be 0.39 and 0.16, respectively. A good correlation was observed for baclofen, cocaine, dopamine, chlorcyclizine, hydroxyzine, lidocaine, and nicotine which were contained within a 95% confidence interval of the regression line. Sumatriptan, propranolol, diazepam, and triprolidine showed somewhat greater deviations from the P_{app}/k_a correlation.

DISCUSSION

The development of computational approaches to predict human systemic distribution and bioavailability is gaining

Table I. Experimental Conditions for *In Vitro* and *In Vivo* Studies, and Reported Permeability Coefficient Values for 11 Drug Compounds

Reagent	Species used for *in vivo* pharmacokinetic evaluation	Dose administered *in vivo*	Species used for *in vitro* permeability	Donor chamber concentration used *in vitro*	P_{app} ($\times 10^{-6}$cm/s) (mean or mean±SD)
Baclofen	Rat	1 mg	Bovine	0.2 mM	5.11±1.17[a]
Chlorcyclizine	Rat	15.4 μmol/kg	Bovine	0.09 mM	4.3[b]
Cocaine	Rat	5 mg/kg	Bovine	2 mM	25±4.9[a]
Diazepam	Rat	1 mg/kg	Bovine	1 mg/ml	6.55±0.62[c]
Dopamine	Rat	50 μCi	Porcine	1 mM	2.6±0.95[d]
Hydroxyzine	Rat	8.7 μmol/kg	Porcine	1 mM	13.36±3.75[b]
Lidocaine	Rat	600 mg/ml for 10 μl	Bovine	1 mM	52±8.3[e]
Nicotine	Human	2 mg	Porcine	0.025 mM	128±42[e]
Propranolol	Rat	20 mg	Porcine	0.1 mM	20±8[e]
Sumatriptan	Human	20 mg	Bovine	12 mM	14±3.3[e]
Triprolidine	Rat	16.5 μmol/kg	Bovine	1 mg/ml	16.80±4.98[b]

[a] Zhang [12]
[b] Kandimalla and Donovan [10]
[c] Maitani *et al.* [11]
[d] Jansson [9]
[e] Wadell *et al.* [5]

Table II. Estimated Clearance Profiles and Calculated Absorption Rate Constants of 11 Investigated Drug Compounds

Reagent	Fitted exponential expression for clearance (goodness of fit)	Estimated absorption rate (h^{-1})
Baclofen	$y = 2.58e^{-1.75t} + 0.34e^{-0.03t} (r^2 = 0.95)$	0.47
Chlorcyclizine	$y = 17.19e^{-4.34t} + 0.75e^{-0.06t} (r^2 = 0.93)$	0.91
Cocaine	$y = 8.88e^{-32.04t} + 1.63e^{-1.52t} (r^2 = 0.99)$	2.46
Diazepam	$y = 0.25e^{-5.09t} + 0.16e^{-0.46t} (r^2 = 0.99)$	10.53
Dopamine	$y = e^{-0.55t} (r^2 = 0.98)$	0.46
Hydroxyzine	$y = 49.73e^{-24.66t} + 0.34e^{-0.26t} (r^2 = 0.99)$	1.85
Lidocaine	$y = e^{-0.82t} (r^2 = 0.99)$	8.4
Nicotine	$y = 0.0074e^{-7.98t} + 0.0057e^{-0.33t} (r^2 = 0.99)$	19.47
Propranolol	$y = 2.39e^{-10.93t} + 0.39e^{-0.53t} (r^2 = 0.99)$	1.15
Sumatriptan	$y = 0.06e^{-1.69t} + 0.01e^{-0.35t} (r^2 = 0.98)$	0.96
Triprolidine	$y = 1.63e^{-2.36t} + 0.29e^{-0.02t} (r^2 = 0.97)$	10.36

increasing interest. These techniques are useful to predict *in vivo* drug performance from *in vitro* data or, even more simply, from molecular structure (19). Due to the complexity of the absorption and distribution processes, together with concurrent metabolism and carrier-mediated transport mechanisms involved in disposition, these models currently provide predictions of limited accuracy.

A popular alternative approach is to develop permeability-based models where the effects of active uptake, efflux, and local metabolism are included in both the permeability dataset and the absorption process, thus the deviation caused by these effects can be limited. Chemuturi *et al.* studied the correlation between nasal bioavailability and permeability using human tracheal/bronchial epithelial cell culture and bovine nasal respiratory explants for nine compounds (8), and a predictive relationship was observed between the *in vitro* permeability and reported bioavailability for five compounds whose logarithmic distribution coefficient (log D) values were greater than 1 and whose permeabilities were greater than 1×10^{-6}cm/s. In another study, Wadell *et al.* correlated human nasal absorption with permeability values of seven agents across porcine nasal mucosa (5). A weak correlation (r=0.42) was observed between the permeability values and the corresponding reported fraction absorbed after nasal administration in humans and a closer correlation was found for passively transported drugs than for substances where other mechanisms, such as carrier-mediated transport or possible efflux, may have been involved.

Permeability is broadly used to estimate the absorption potential of drug candidates, and the value is commonly calculated from diffusion measurements resembling permeation processes. The bioavailability of drugs following nasal administration is dependent on absorption (*in vivo* time course input) and clearance processes. However, only the absorption process is directly related to the permeation process. Compared to Chemuturi's and Wadell's studies, which attempted to develop a relationship between fractional nasal absorption and permeability, the estimation of absorption rate using a deconvolution method can minimize the variation due to differences in clearance among various compounds. A significant difference in clearance was observed among the 11 drugs selected for this investigation and an improved correlation between the calculated absorption rate constant after deconvolution and the *in vitro* permeability across bovine or porcine nasal tissues was obtained for all of the compounds.

It should be recognized that different animal species were used to obtain the *in vitro* and the *in vivo* data utilized to derive the correlation developed in this study. In addition, the nasal cavity was not isolated from the downstream gastrointestinal tract in the absorption studies involving diazepam, lidocaine, nicotine, and sumatriptan, leading to subsequent oral absorption and, potentially, an inaccurate determination of the nasal absorption rate. These factors contributed to the less-than-optimal correlation observed between permeability and absorption rate. A more predictive correlation would likely be obtained by using a single type of tissue and a well-controlled pharmacokinetic testing protocol to estimate absorption.

CONCLUSIONS

Permeation across the nasal mucosa represents one of the key determinants of intranasal bioavailability. Permeability can be readily measured *in vitro*, but the ability to use these values in a predictive manner is limited without an established *in vitro–in vivo* correlation to the *in vivo* situation. The correlation developed in this study using numerical deconvolution provides a useful method for the approximation of nasal absorption from measured permeability values. The results of this research provide evidence that *in vitro* permeability measurements across nasal explants can be used to approximate the *in vivo* nasal absorption in a rodent model, and results from the rodent model can be extrapolated to humans in many situations.

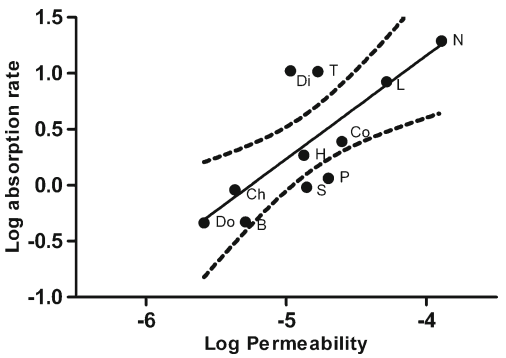

Fig. 1. Correlation between *in vitro* permeability and *in vivo* absorption rate constant. *Dotted curves* represent 95% confidence interval of the regression line. Equation of regression line: $y = 0.92x + 4.86$; $r = 0.77$. *B* baclofen, *Ch* chlorcyclizine, *Co* cocaine, *Di* diazepam, *Do* dopamine, *H* hydroxyzine, *L* lidocaine, *N* nicotine, *P* propranolol, *S* sumatriptan, *T* triprolidine

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