Direct Nose-to-Brain Transport of DB213 via Intranasal Administration Demonstrated by Pharmacokinetics Modeling

Q. Wang, Y. Zhang, S. Peng, Q. Zhang, C-H. Wong, H. E. Chan, Z. Zuo
Chinese University of Hong Kong

**Purpose**

Intranasal administration (IN) has been a popular route for target delivery to the central nervous system (CNS) due to its potential to bypass the blood-brain barrier (BBB). However, there are limited studies and controversial evidence on the direct transport of drug from nasal cavity to the CNS. An HIV-1 replication inhibitor DB213 targeting HIV-associated neurocognitive disorders was chosen as the model drug. The current study aims to 1) investigate the existence of direct nose-to-brain transport and 2) assess the extent of drug transported by this pathway (if it exists) using pharmacokinetics modeling approach.

**Methods**

Sprague-Dawley rats were administered with DB213 water solution via intranasal (IN) route or intravenous (IV) route at a bolus dose of 1 mg/kg (n=6-8 per group). Plasma samples were collected at 0, 5, 10, 15, 20, 30, 45, 60, 90, 120, 240, 360 min post-dosing. Another batch of SD rats obtaining the above treatment was used for the brain uptake kinetics study via sacrificing rats to collect plasma and whole brain at 15, 30, 60, 90 and 120 min post dosing of IN or IV at 1 mg/kg (n=5 per group). All collected plasma and brain samples were analyzed by an established LC/MS/MS method to obtain the relevant plasma and brain concentrations versus time profiles as input for nonlinear mixed-effect modeling (NONMEM).

Structural model building was performed by NONMEM (version VII, level 2.0). The structural models were designed from simple to complicated. In specific, first, a model containing a central compartment and one peripheral compartment were used to analyze IV plasma data. Then a specific brain compartment was added to process plasma and brain data via IV route. For the inclusion of IN data set, two absorption compartments representing nose-to-systemic circulation and nose-to-brain were added. The control stream was written using ADVAN6 TOL=5, and the first-order conditional method with interaction was used for estimation. All models built were evaluated by their reported objective function values (OFV), the coefficient of variation (CV) of pharmacokinetics parameters estimated and the goodness of fit plots generated by Xpose (version 4.5.3).

**Results**

The plasma (or brain) concentration versus time profiles of DB213 via IV and IN were summarized in Figure 1. AUC$_{0\rightarrow360\text{min, plasma}}$ and AUC$_{0\rightarrow120\text{min, brain}}$ were 184422.1 ± 42450.8 ng·min/ml and 857.2 ng·min/g for IV and 15961.6 ± 11062.7 ng·min/ml and 1584.7 ng·min/g for IN, respectively. The AUC$_{\text{brain}}$/AUC$_{\text{plasma}}$ calculated was 0.0073 and 0.14 for IV and IN, respectively.

Among the seven models built, the model with two absorption compartments (nose-systemic circulation compartment and nose-brain compartment), a brain compartment, a central compartment and a peripheral compartment (Figure 2) could best describe the pharmacokinetics data of DB213 obtained with the lowest OFV values (466.110 points) and CV values for all pharmacokinetics parameters estimated less than 25%. It was demonstrated that about 56.73% of the total absorbed DB213 in vivo was contributed by direct nose-to-brain transport. In addition, the absorption of rate of direct nose-to-brain was found to be similar as the rate of nose-to-systemic circulation.

**Conclusion**

The direct-nose-to-brain transport of DB213 via intranasal administration was successfully demonstrated by a multi-compartment pharmacokinetics model with two absorption compartments representing nose-to-systemic circulation and nose-to-brain transport.

This work was generously supported by the Lui Che Woo Institute of Innovative Medicine BRAIN Initiative, Faculty of Medicine, The Chinese University of Hong Kong (Project Number 8303404).