

Establishment of intranasal administration method to conscious rats



Noriyasu Sano¹, Syunsuke Yamamoto², Yohei Kosugi², Tomoko Igari², Atsutoshi Furuta^{2,3}, Masatoshi Karashima⁴, Kouya Kimoto⁴, Yasushi Fujioka², and Nobuyuki Amano¹

¹ Drug Disposition & Analysis, Axcelead Drug Discovery Partners, Inc.

² Drug Metabolism & Pharmacokinetics Research Laboratories, Research, Takeda Pharmaceutical Company Limited

³ Current address: Biologics and New Modalities Development, Pharmaceutical Sciences, Takeda Pharmaceutical Company Limited,

⁴ Analytical Development, Pharmaceutical Sciences, Takeda Pharmaceutical Company Limited

無断転載禁止

Purpose

Intranasal (i.n.) administration has been considered as an attractive route to deliver drugs to central nervous system as well as to achieve high bioavailability without first-pass effect. Since the methods reported in literatures are performed in rats under anesthesia or surgery, those cannot be applied to some preclinical studies due to their influence on pharmacokinetics, pharmacodynamic markers and efficacy. The i.n. administration to nasal cavity in conscious rats was very difficult because location of nose is hardly fixed and the external nostril is anfractuous and narrow. The aim of this study was to establish i.n. administration method using conscious rats.

Results

A novel method of administration into deep nasal cavity in conscious rats

The original injection device (particular catheter and modified restrainer) for conscious rats was prepared in order to inject dosing solution into the deep nasal cavity and restrain the nose.

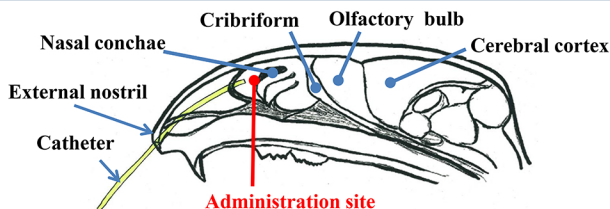


Fig. 1. The administration site in rat nasal cavity by using the original injection device.

The dosing solution was i.n. administered into the nasal cavity of rats by using the original injection device. The i.n. administration to anesthetized rats was achieved by using the catheter into nasal cavity under supine position. The anesthesia and supine position were kept for 5 min. The insertion length of the catheter into rat nasal cavity under both conditions was set 15 mm. In order to evaluate the feasibility of i.n. administration to conscious rats, five compounds (omeprazole, midazolam, paclitaxel, erythromycin and roxithromycin) were selected from the different properties of biopharmaceutics drug disposition classification system (BDDCS).

All animal protocols were approved by the Institutional Animal Care and Use Committee of Shonan Research Center, Takeda Pharmaceutical Company Ltd..

Summary and Discussion

✓ The original device was developed for accurate injection into the nasal cavity of conscious rats (CV values of AUC were from 2.6 to 30%).

✓ AUC comparison

I.N. conscious > Oral

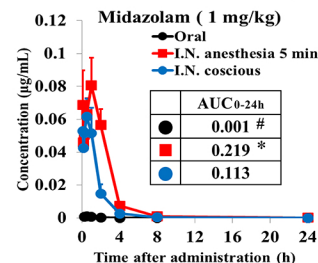
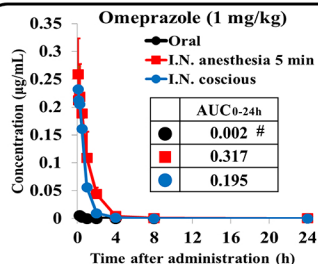
The i.n. administration of dosing solution to conscious rats was achieved since absorption with avoidance of first-pass was confirmed regardless of BDDCS class.

I.N. anesthesia ≥ I.N. conscious

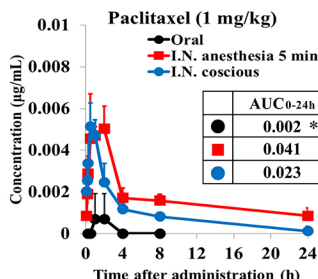
Since supine position were kept for 5 min under the anesthesia condition, the retention time of dosing solution in the nasal cavity under the anesthesia condition could be longer than that under the conscious. Longer retention time could induce overestimate of the nasal absorption.

Conclusion

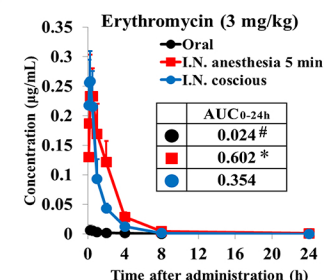
In this study, the novel method of i.n. administration to conscious rats was developed. This established method enables studies on the pharmacokinetics and pharmacology to be performed without anesthesia and surgery.



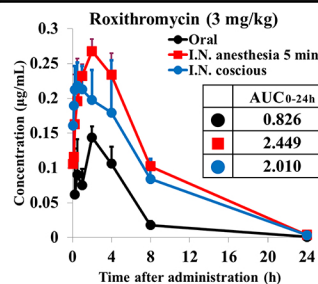
Class 1



Class 2



Class 3



Class 4

Fig. 2. Concentrations of omeprazole, midazolam, paclitaxel, erythromycin and roxithromycin in rat plasma after oral or intranasal administration.

[Mean±S.D. (n=3), *: P<0.05 vs I.N. conscious by student-t test, #: P<0.05 I.N. conscious by Aspin-Welch test]

Class 1: high metabolism/permeability rate and high solubility

Class 2: high metabolism/permeability rate and low solubility

Class 3: low metabolism/permeability rate and high solubility

Class 4: low metabolism/permeability rate and low solubility

COI disclosure information

✓ We have no financial relationship to disclose for our presentation contents.