A Fit-for-Purpose Physiologically Based Pharmacokinetic Approach for Intranasal Analgesics: Application to Ketamine and Fentanyl Analogs

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Introduction and objectives

Intranasal delivery is widely used for rapidly acting analgesics in emergency and perioperative settings. [1]. However, explicit nasal **physiologically based pharmacokinetic (PBPK) models** typically require detailed information on regional deposition, mucociliary clearance, formulation attributes, and device performance, which is often unavailable in early development.

The objectives of this work were to develop a parsimonious, **fit-for-purpose PBPK** framework to **predict adult systemic exposure following intranasal administration** of ketamine and fentanyl derivatives in data-limited settings and to explore whether such an approach could support **exposure-oriented decision-making** despite limited mechanistic nasal information.

Methods

Systemic pharmacokinetics following intranasal dosing of ketamine and fentanyl derivatives were described using a PBPK framework implemented in Simcyp® V23 R2. The intranasal dose was mechanistically decomposed into **two concurrent systemic inputs (Figure 1) :**

- a rapidly absorbed nasal fraction represented by a short zero-order input,
- a swallowed fraction described using the mechanistic ADAM oral absorption model [4].

To preserve parameter identifiability, the relative nasal and swallowed fractions were fixed a priori using literature absolute intranasal and oral bioavailability values. Tissue distribution was predicted using the Rodgers and Rowland method [5], and systemic elimination was implemented using literature total clearance, assuming linear kinetics.

Model credibility was qualitatively assessed using the **ICH M15 framework**.

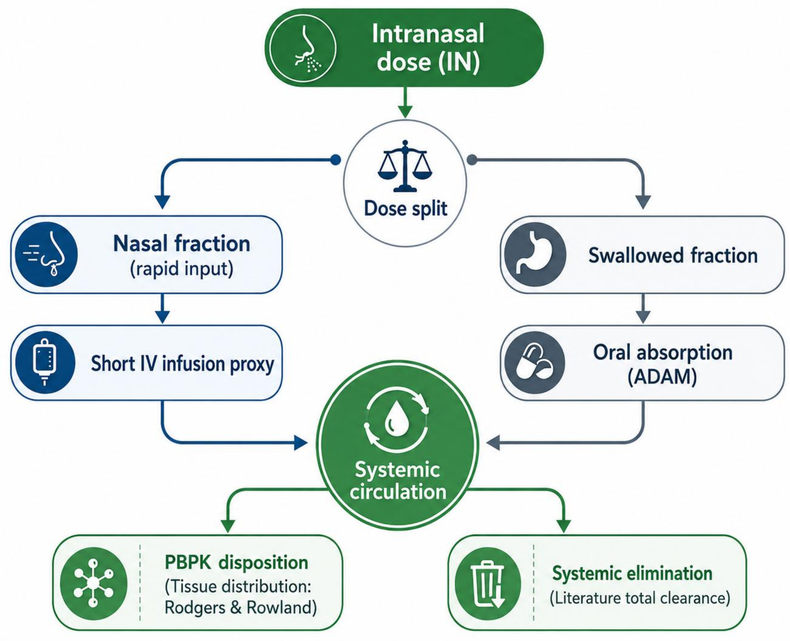

Figure 1. Schematic overview of the modelling strategy used to translate intranasal delivery into systemic exposure predictions.

Results

Systemic exposure after **intranasal administration** was consistently captured by the dual-input PBPK framework (**Figure 3**). Predicted-to-observed **AUC ratios** were **within the predefined 0.5–2.0 acceptance bounds** for **100% (12/12)** of evaluated scenarios (**Figure 2, Table 1**).

Cmax predictions were more variable, with values within the two-fold range for **50% (2/4)** of IV, **75% (3/4)** of oral, and **50% (2/4)** of intranasal datasets. For the intranasal route, **Tmax** was within the two-fold range for **100% (4/4)** of datasets (**Figure 2, Table 1**).

Cross-route verification supported extrapolation to the intranasal route without re-estimating systemic parameters. The swallowed fraction was represented using the **ADAM model**.

Model influence, **decision consequence**, **model risk**, and **model impact** were all categorized as **Medium** on the **ICH M15** scale.

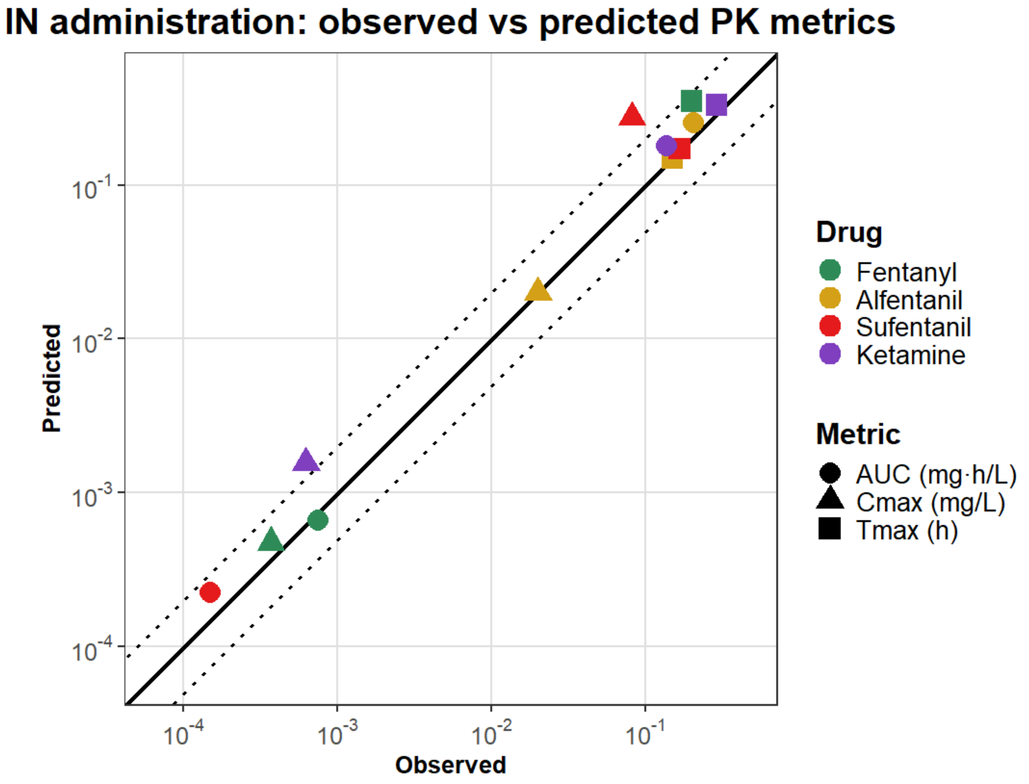

Figure 2. Agreement between observed and predicted intranasal PK metrics across compounds. Solid line represents unity; dotted lines indicate 2-fold deviation boundaries.

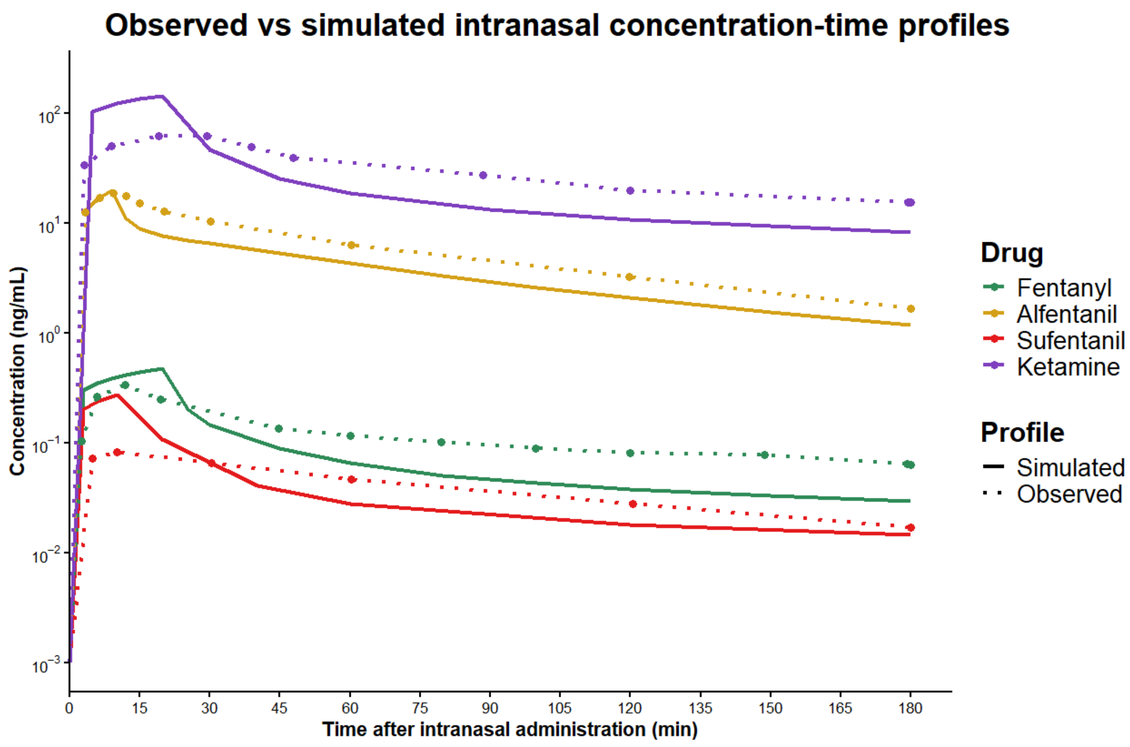

Figure 3. Observed and simulated intranasal concentration–time profiles across compounds. Solid lines represent simulated pharmacokinetic profiles, and dotted lines represent observed data.

Table 1. Prediction accuracy summary across metrics

Parameter	Fentanyl	Alfentanil	Sufentanil	Ketamine	Median ratio	Within 2-fold
AUC ratio	0.89	1.23	1.51	1.31	**1.27**	**100%**
Cmax ratio	1.29	1.00	3.38	2.49	**1.89**	**50%**
Tmax ratio	1.75	1.00	1.03	1.13	**1.08**	**100%**

Conclusion

The dual-input **PBPK approach** enabled transparent characterization of systemic exposure following **intranasal administration** of ketamine and fentanyl derivatives in data-limited settings. Accurate prediction of intranasal AUC and Tmax supported contextualization of systemic exposure expectations for **exposure-oriented regulatory assessment**, while systematic Cmax overprediction highlighted the sensitivity of peak concentrations to formulation properties, sampling design, and characterization of early absorption processes **for peak-related decisions**.

References: [1] Erdő F, Bors LA, Farkas D, Bajza Á, Gizurarson S. Evaluation of intranasal delivery route of drug administration for brain targeting. *Brain Res Bull.* 2018;143:155–170. doi:10.1016/j.brainresbull.2018.10.009. [2] International Council for Harmonisation. *ICH M15 guideline: General principles for model-informed drug development.* 2024. [3] EMA. *Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation.* EMA/CHMP/458101/2016; 2018. [4] Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A. The Simcyp population-based ADME simulator. *Expert Opin Drug Metab Toxicol.* 2009;5(2):211–223. doi:10.1517/17425250802691074. [5] Rodgers T, Rowland M. Mechanistic approaches to volume of distribution predictions: Understanding the processes. *Pharm Res.* 2007;24(5):918–933. doi:10.1007/s11095-007-9258-3.

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