

Mechanistic Insights in the Ketamine Pharmacokinetics after Intranasal Administration in the Pediatric Population: Bridging Model Validation to Clinical Application

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Objectives:

- The objective of the present study is to model the pharmacokinetics of intranasal ketamine in pediatric patients using GastroPlus® to aid in the design of a clinical trial.

Background:

- Intravenous ketamine (IVK) is a commonly used emergency pediatric procedural sedative but is resource-consuming and associated with significant child distress.
- Intranasal ketamine (INK) is noninvasive and provides rapid absorption and onset of action, which could improve patient outcomes.

Methodology:

Construction and Optimization of Compartmental and PBPK models for IVK 3 mg/kg using literature data⁽¹⁾



Construction and Optimization of Compartmental and PBPK models for INK 3 mg/kg using literature data⁽¹⁾

- Pulmonary Compartmental Absorption and Transit (PCAT™) module was used to model nasal deposition.
- The model was optimized through optimization of *nasal systemic absorption rate constant* and inclusion of *lysosomal trapping*



Population Simulator for 200 pediatric patients ages 3 months-17 years weighing 10-65 kg at 3 dose levels of INK (4 mg/kg, 6 mg/kg, and 9 mg/kg)

Results:

- Using preexisting *in vivo* data, a compartmental (Figure 1a) and PBPK models (Figure 1b) were built for IVK.
- Prior to optimization of the INK model, the simulation markedly underestimated the exposure to ketamine (Figure 2a).
- Upon optimizing nasal systemic absorption rate constant, the model's prediction of AUC and C_{max} improved but t_{max} was still markedly underestimated (10x difference) (Figure 2b).
- Given its pK_a (6.49) and its Log P (~3), ketamine was suspected to be susceptible to lysosomal trapping.
- Inclusion of Lysosomal K_p in the simulation markedly improved t_{max} prediction and overall PK profile prediction (R² = 0.923) (Figure 2c).
- Optimized parameters were incorporated into the model (Figure 2d).
- Using Population Pharmacokinetics incorporating the demographics of the intended clinical trial population, the PBPK INK model predicted the Cp-time profiles as well as C_{max}, t_{max}, AUC_{0-inf} and AUC_{0-t} over four dose levels of INK (Figures 3-6 & Tables 1-4)

Results Continued:

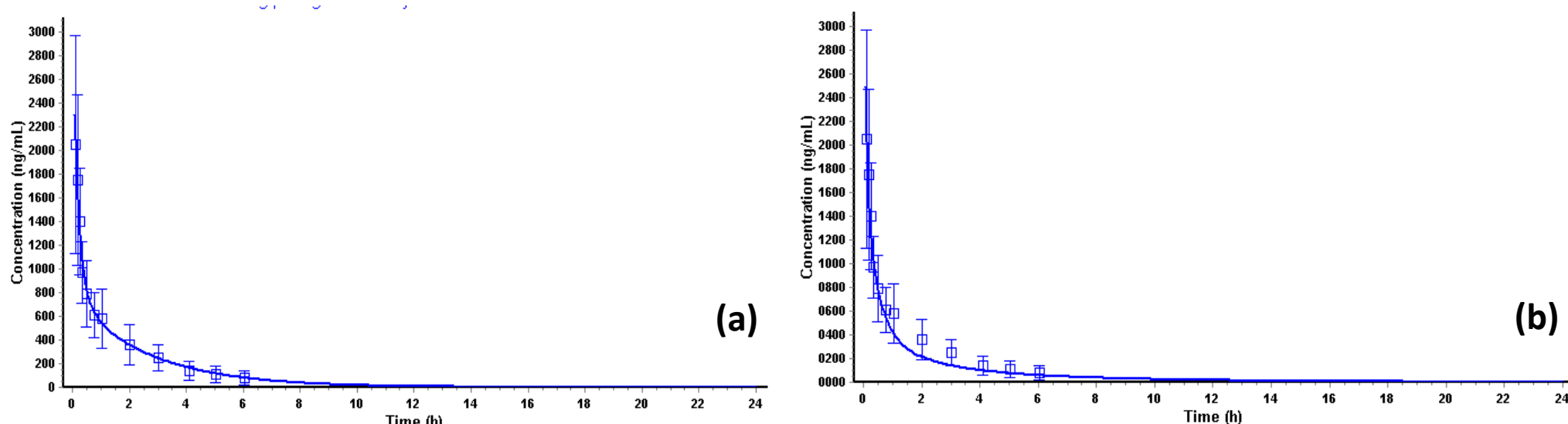


Figure 1: Simulated (lines) and observed (points) Cp-time profiles after IVK 3 mg/kg using (a) compartmental analysis (R²=0.989) and (b) PBPK (R²=0.976)

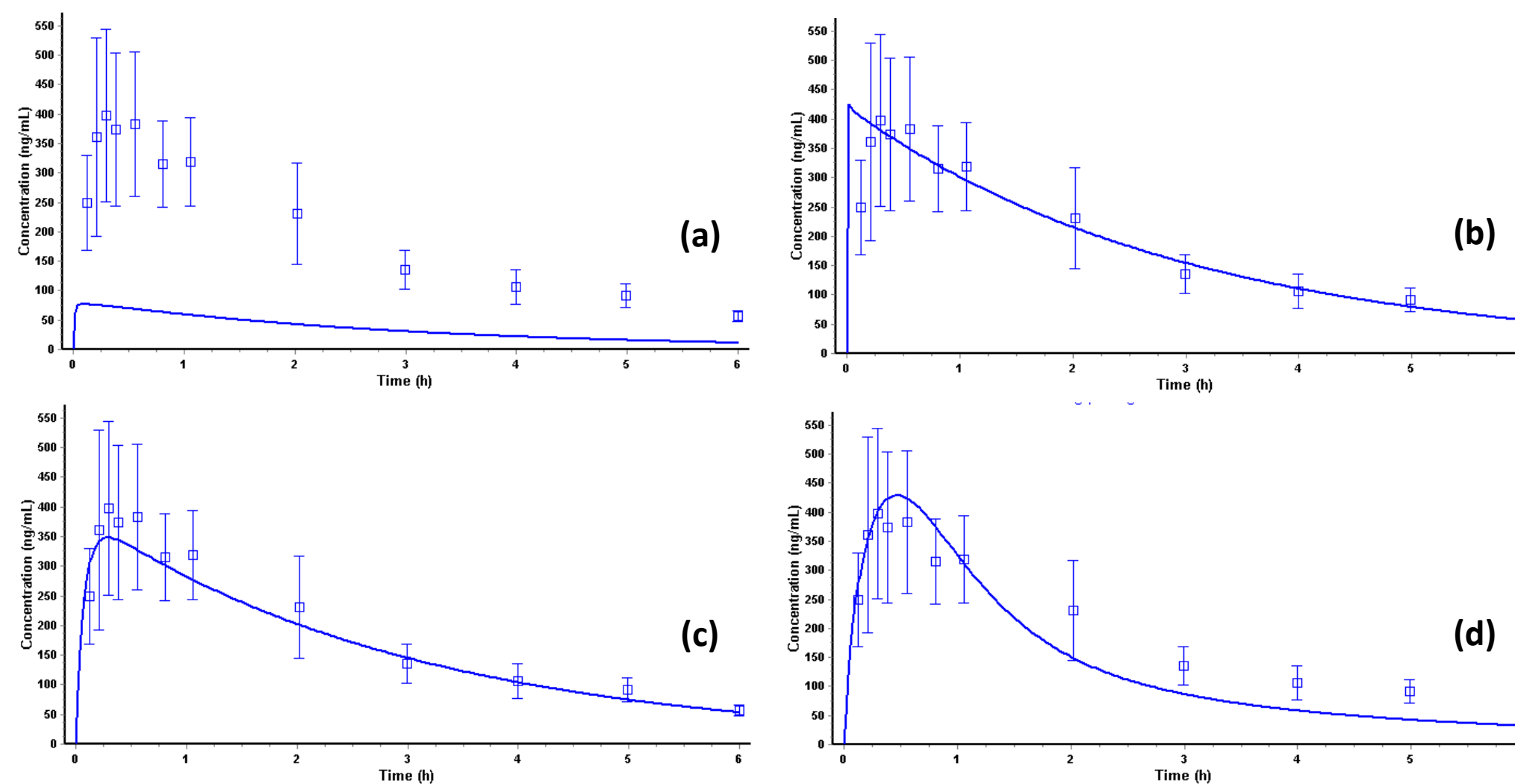


Figure 2: Simulated (lines) and observed (points) Cp-time profiles after INK 3 mg/kg using two-compartment model (a) before optimization of parameters, (b) following optimization of nasal systemic absorption rate constant, (c) following inclusion of lysosomal trapping, and (d) using PBPK model incorporating optimized parameters (R² = 0.923)

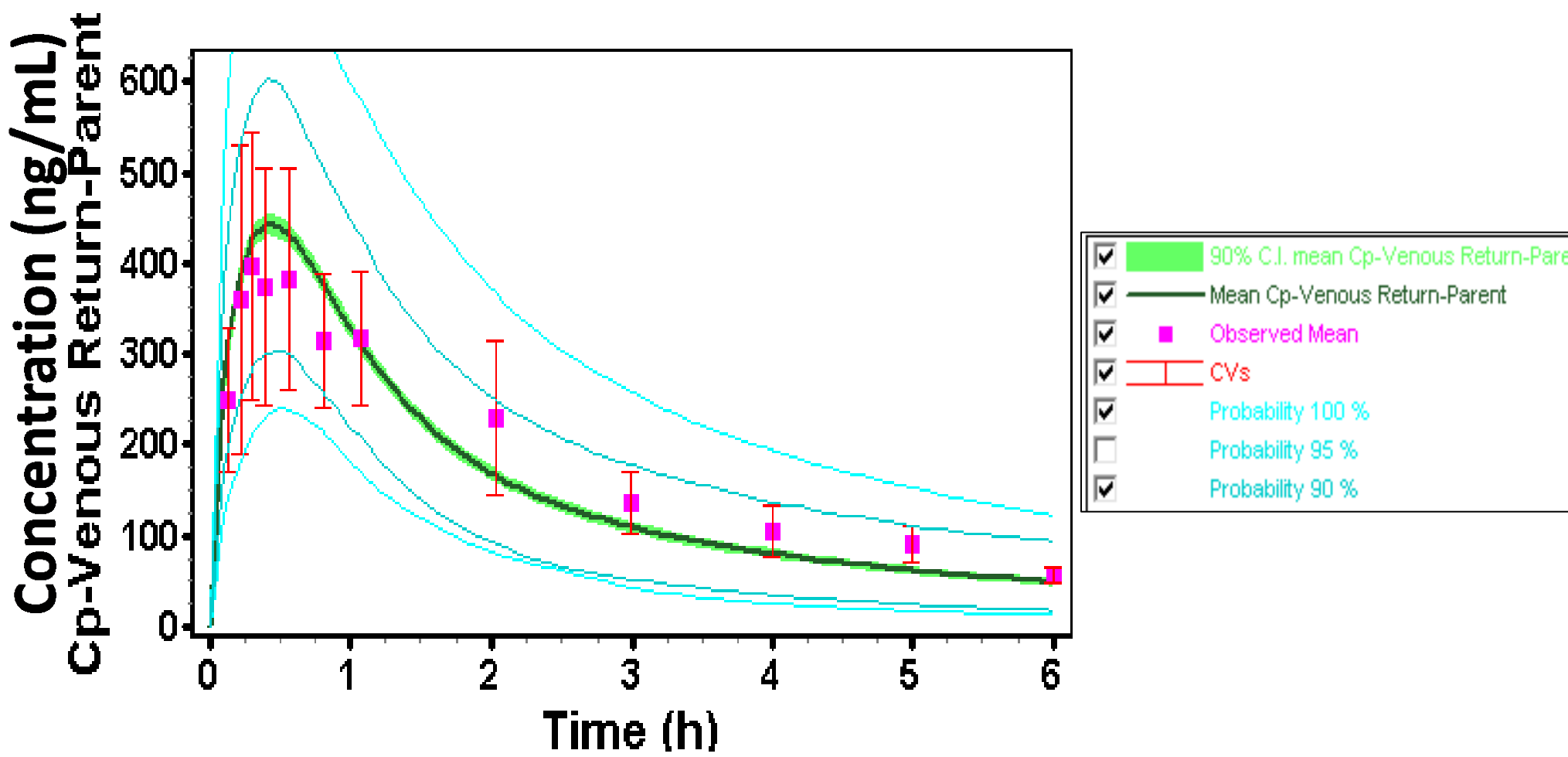


Figure 3: Population Simulator Results of Cp-time profiles of INK 3 mg/kg on 200 pediatric patients

Table 1: PK Parameters Generated by Population Simulator of INK 3 mg/kg on 200 pediatric patients vs Observed Values

Endpoint	Observed Values	Predicted Mean ± SD	CV [%]	Min	Max	Geom. Mean	90% CI
C _{max} [ng/mL]	397	446 ± 130	21	240	817	437	435-457
t _{max} [h]	0.29	0.43 ± 0.1	14	0.3	0.6	0.43	0.42-0.44
AUC _(0-inf) [ng-h/mL]	1197	1186 ± 609	33	562	2496	1125	1140-1232
AUC _(0-t) [ng-h/mL]	1076	961 ± 406	28	503	1902	926	930-992

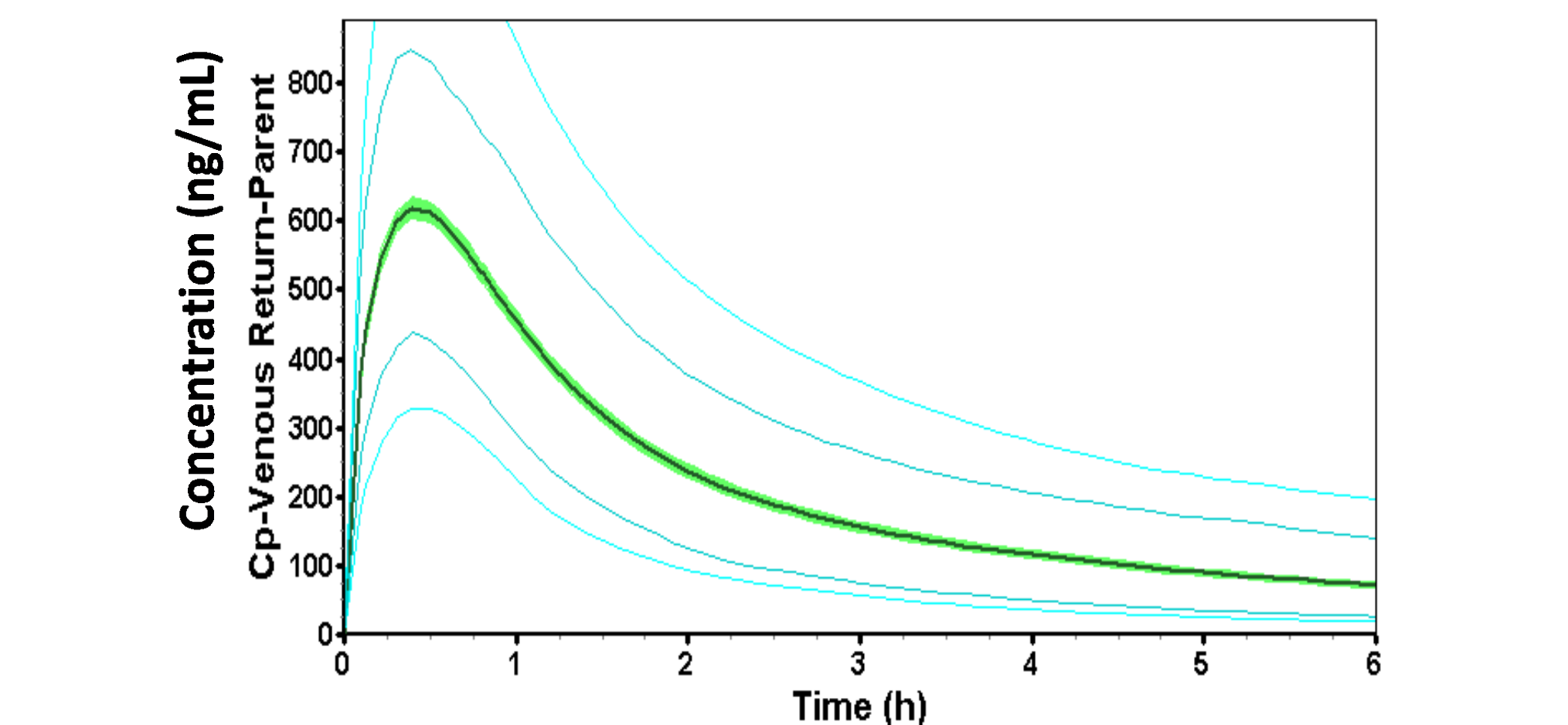


Figure 4: Population Simulator Results of Cp-time profiles of INK 4 mg/kg on 200 pediatric patients

Table 2: PK Parameters Generated by Population Simulator of INK 4 mg/kg on 200 pediatric patients

Endpoint	Mean ± SD	CV [%]	Min	Max	Geom. Mean	90% CI
C _{max} [ng/mL]	623 ± 130	21	329	1121	609	607-638
t _{max} [h]	0.43 ± 0.1	15	0.29	0.6	0.42	0.42-0.43
AUC _(0-inf) [ng-h/mL]	1694 ± 609	36	707	3740	1592	1623-1765
AUC _(0-t) [ng-h/mL]	1354 ± 406	30	616	2794	1296	1306- 1401

Results Continued:

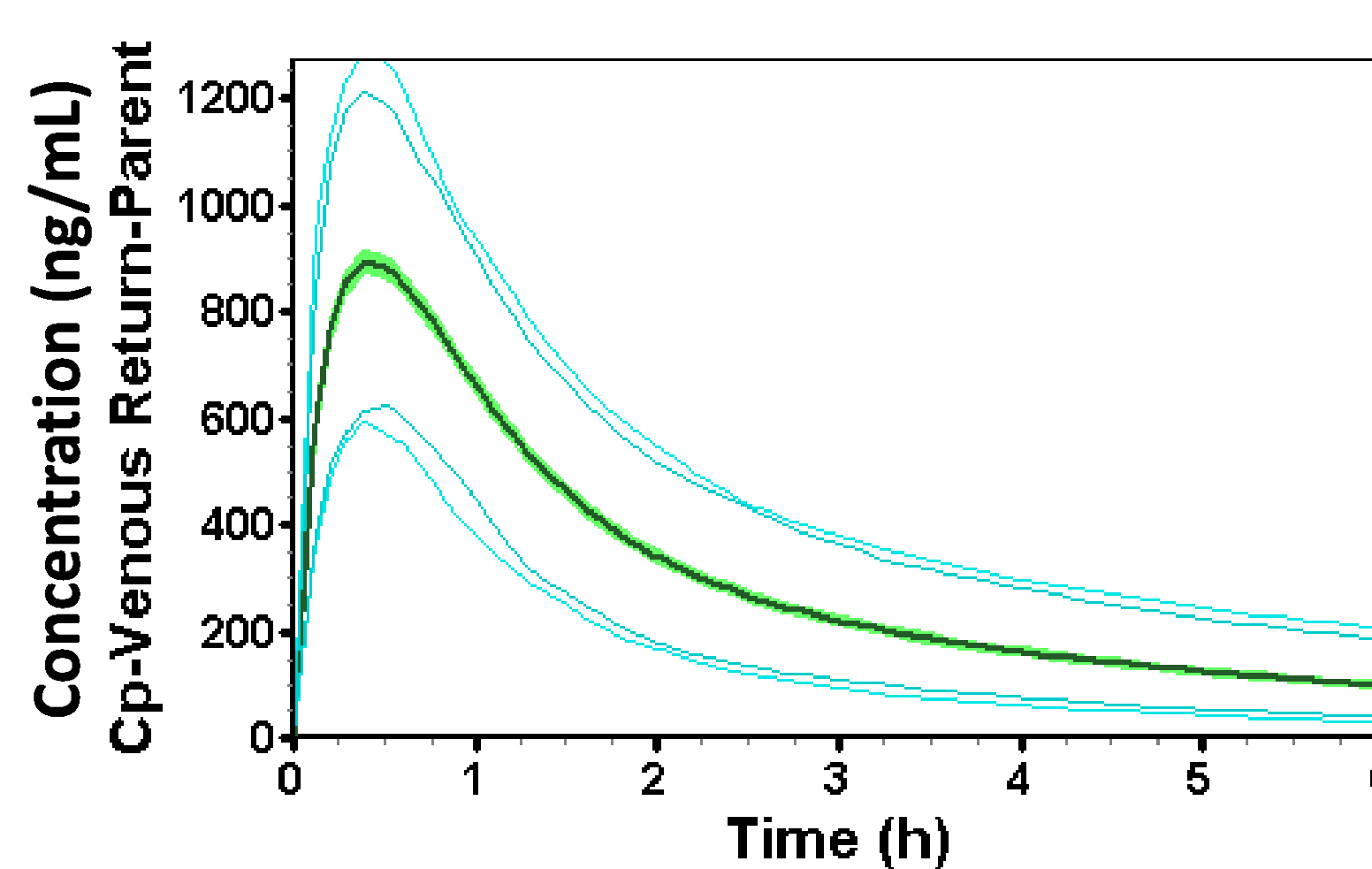


Figure 5: Population Simulator Results of Cp-time profiles of INK 6 mg/kg on 200 pediatric patients

Table 3: PK Parameters Generated by Population Simulator of INK 6 mg/kg on 200 pediatric patients

Endpoint	Mean ± SD	CV [%]	Min	Max	Geom. Mean	90% CI
C _{max} [ng/mL]	899 ± 180	20	540	1471	881	878- 921
t _{max} [h]	0.43 ± 0.1	15	0.3	0.6	0.4	0.42- 0.44
AUC _(0-inf) [ng-h/mL]	2395 ± 783	33	1013	4717	2269	2304- 2487
AUC _(0-t) [ng-h/mL]	1937 ± 529	27	880	3213	1864	1875- 1999

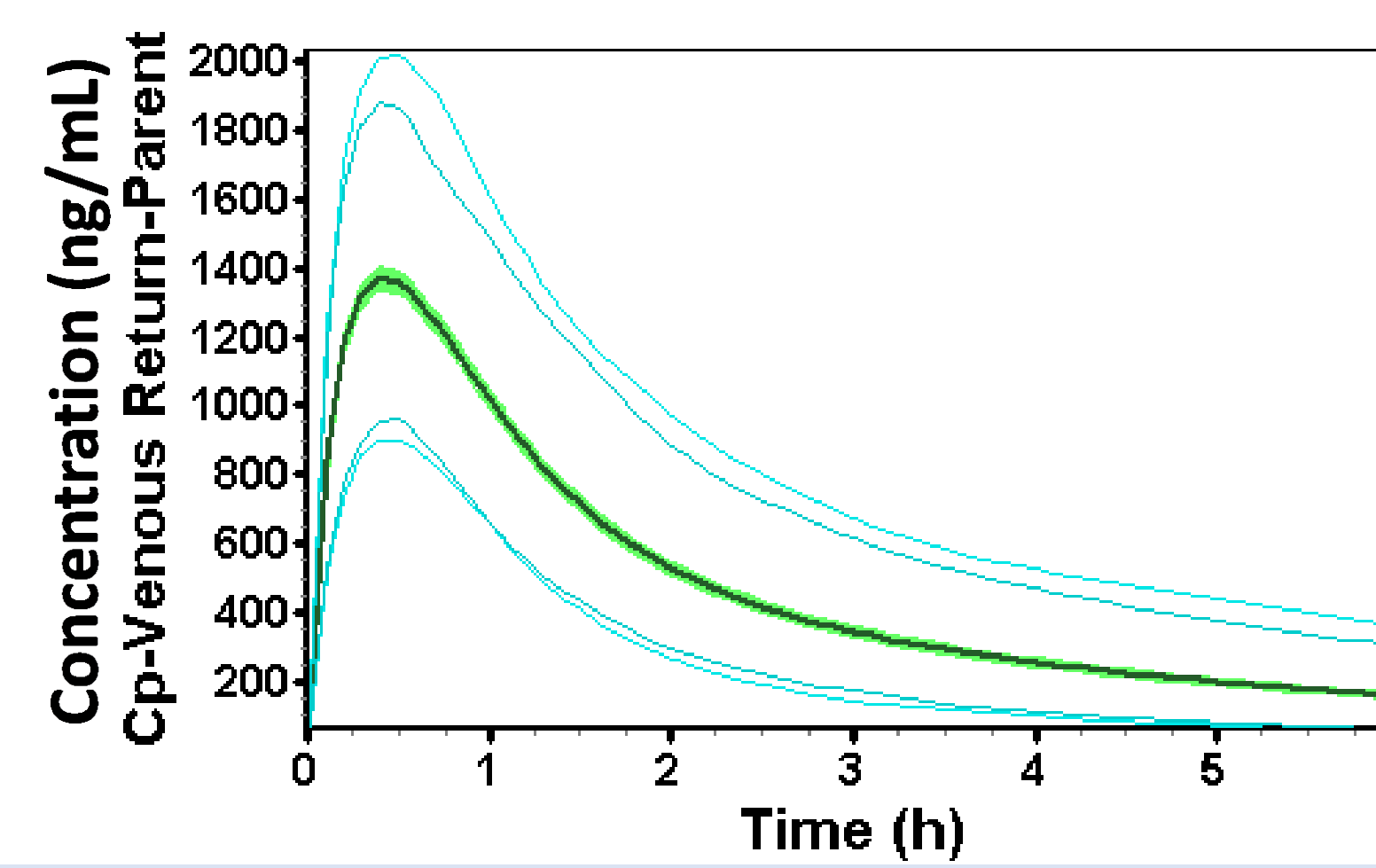


Figure 6: Population Simulator Results of Cp-time profiles of INK 9 mg/kg on 200 pediatric patients

Table 4: PK Parameters Generated by Population Simulator of INK 9 mg/kg on 200 pediatric patients

Endpoint	Mean ± SD	CV [%]	Min	Max	Geom. Mean	90% CI
C _{max} [ng/mL]	1378 ± 290	21	790	2219	1348	1344- 1411
t _{max} [h]	0.43 ± 0.1	14	0.3	0.6	0.43	0.43- 0.44
AUC _(0-inf) [ng-h/mL]	3723 ± 1309	35	1553	7843	3507	3570- 3876
AUC _(0-t) [ng-h/mL]	2994 ± 883	29	1428	5878	2870	2891- 3097

Conclusion & Recommendations:

- A PBPK model was successfully developed and used to predict the PK of INK in the pediatric population at three different doses. This data represents a valuable strategic tool to aid in the careful planning of pediatric clinical trials.

Reference:

(1) Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. Br J Anaesth. 1996 Aug;77(2):203-7. doi: 10.1093/bja/77.2.203. PMID: 8881626