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ARTICLE

Intranasal diamorphine population pharmacokinetics modeling and simulation in pediatric breakthrough pain

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Abstract

Intranasal diamorphine (IND), approved for managing breakthrough pain in the UK, has been identified as an acceptable alternative offering effective, expedient, and less traumatic analgesia for children. However, the current dose regimen in pediatric populations relies on clinical expertise while the pharmacokinetics properties are poorly understood. This study aimed to develop diamorphine population pharmacokinetics (pop-PK) models and simulate the IND dosing in virtual pediatric subjects. An integrated four-compartment pop-PK model with first-order absorption and elimination provided an appropriate fit and characterized publicly available 385 concentration measurements of diamorphine, 6-monoacetylmorphine, and morphine collected from adults. Body weight allometry and renal function maturation (age) were incorporated into the final model, serving as two covariates. The estimated IND relative bioavailability was around 52% compared with intramuscularly injected diamorphine. Using this final model, the morphine plasma concentrations, as the active metabolite for pain relief, were simulated in virtual subjects. The utility of model extrapolation was supported by external verification with acceptable average fold errors of 1.06 ± 0.30 and 0.83 ± 0.07 for morphine maximum concentration and exposures. Meanwhile, the simulated morphine concentration–time profiles could recover the PK profiles observed in children after a single dose of IND. The model-based dosing simulations were therefore assessed in four children age groups to match the therapeutic window of morphine concentrations in steady state (10–20 μg/L). Our study demonstrates that the dose regimen of 0.3 mg/kg loading dose plus 0.1 mg/kg hourly maintenance dose is generally appropriate for multiple pediatric populations with breakthrough pain, in the view of PK.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Diamorphine hydrochloride is primarily used intranasally to manage breakthrough pain in pediatric patients, offering great advantages over injected

administration. However, current dosing practices are largely based on clinical expertise due to limited understanding of its pharmacokinetics in children.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study aimed to develop a population pharmacokinetics (pop-PK) model for diamorphine, 6-monoacetylmorphine, and morphine, using adult data, and extrapolate this model to the pediatric population to assess the feasibility of current intranasal diamorphine dosing regimens.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The study established an integrated four-compartment pop-PK model, standardizing population PK parameters by body weight and incorporating renal function maturation. The model-based simulations demonstrated that the 0.3 mg/kg loading dose followed by the current pediatric dose regimen of 0.1 mg/kg can attain the effective target therapeutic window.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The findings facilitate the "Learn and Confirm" cycle in drug development and provide a scientific foundation for diamorphine optimal dosing in pediatric patients, potentially influencing future therapeutic strategies for managing breakthrough pain in children.

INTRODUCTION

Diamorphine hydrochloride (DIAM, pharmaceutical heroin) has been medically used in many European countries for refractory heroin dependents who have not responded to the standard maintenance treatment.[1] Interestingly, as a strong opioid and the prodrug of morphine, DIAM is also prescribed in the United Kingdom, for breakthrough pain management for patients in palliative care or in the Accident and Emergency (A&E) settings.[2–4] Breakthrough pain is described as severe pain that occurs with episodes of sudden onset despite the regular background opioid treatment given. It raises great challenges because of the few suitable potent, well-tolerated, and fast-acting agents available to manage this pain exacerbation in life-limiting conditions.[2,3] Oral morphine is a usual first-line treatment for children, yet it often takes more than 30 min to achieve the target concentration and to produce analgesic effects.[5] Although injections (intravenous, subcutaneous, and intramuscular) allow faster onset, supervised needle usage inevitably delays pain relief because of the poor acceptability for children and the stress to parents and clinical practitioners. A needle-free, fast-acting pain medicine is needed.

Diamorphine is a semisynthetic diacetylated derivative of morphine, and its many advantageous properties render it a desirable analgesic agent via transmucosal administration (sublingual, intranasal, or buccal). It is considered a morphine prodrug with approximately twice the potency as morphine salt.[6] The parenteral transmucosal delivery results in rapid systemic absorption across richly vascularized mucosa avoiding first-pass metabolism. The lipophilicity of DIAM enables its quick distribution and passage through the blood–brain barrier once it enters systemic circulation. Furthermore, the rapid metabolism of DIAM to the active intermediate metabolite, 6-monoacetylmorphine (MAM) initiates the early analgesia onset (maximum effect within 10 min), and subsequently converts to morphine (MOR), which exerts a potent and lasting pharmacological effect (maximum effect within 1 h).[7,8] The esterase, abundantly distributed in blood and various organs including the brain and liver (Figure 1a), sequentially produces both metabolites, which bind to the opioid μ receptors with different affinity and potency.[9] Morphine is in turn eliminated by phase II metabolism, glucuronidation, and subsequent excretion in the urine in the form of morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).

Specifically, "snorted" intranasal diamorphine (IND) is recognized as an acceptable alternative, offering less traumatic, effective, and expedient analgesia for the pediatric population.[10] Diamorphine hydrochloride nasal spray (Ayendi®) has been licensed for moderate and severe pain in children and adolescents at the age of 2–15 years. Previous research has demonstrated its satisfactory safety profiles, and it is as effective as intramuscular diamorphine (IMD) for acute pain in the A&E department.[11,12] However, there is still a paucity of research evidence and clinical guidelines for IND dosing in children. Conducting pediatric clinical studies present challenges due to ethical and logistical constraints.

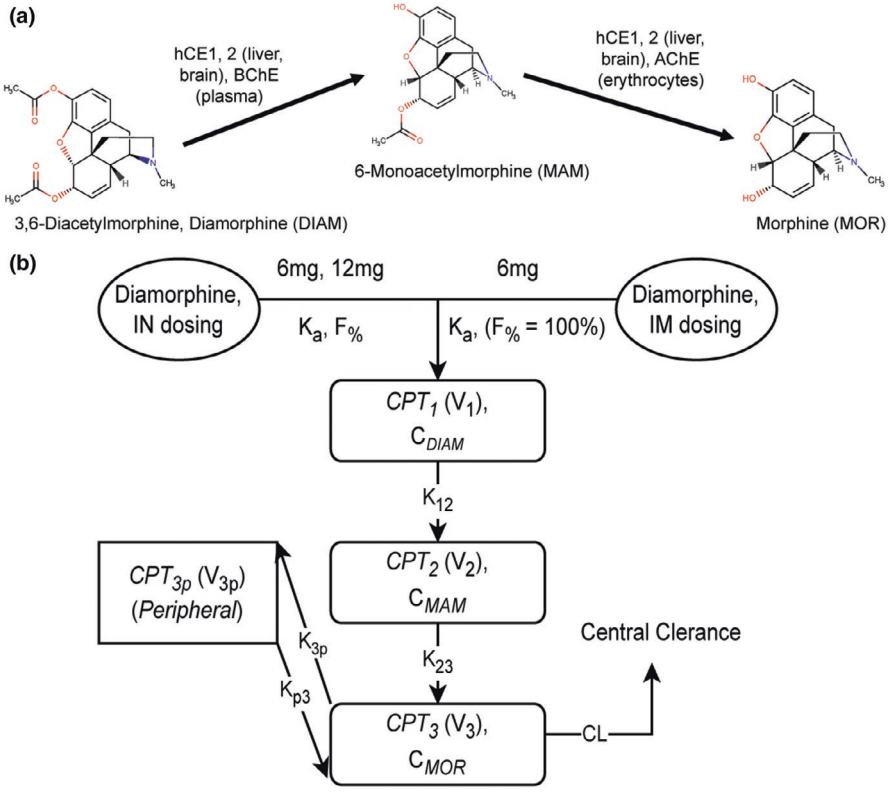

FIGURE 1 Schematic representation of the compartment model. (a) Hydrolytic pathway of heroin in humans executed by various esterases; (b) Schematic representation of the final pharmacokinetic model, an integrated four-compartment model for diamorphine (DIAM), 6-monoacetylmorphine (MAM), and morphine (MOR). AChE, acetylcholinesterase; BChE, butyrylcholinesterase; C, drug concentration; CPT, compartment; hCE, human carboxylesterase; IM, intramuscular route; IN, intranasal route; V_1–V_3, the central volumes; V_{3p}, the peripheral volume for morphine distribution; K, the intercompartmental transfer rate constants.

The current dosage selection of pediatrics IND is historical and empirical, which is guided by clinical acumen and previous observational studies, rather than the examination of pharmacokinetics (PK). This empirical method is further challenged by the age-related changes in PK seen in children.[13]

The latest British systematic review paper sought, screened, and summarized 19 clinical studies regarding diamorphine PK, of which only one study was conducted in children and two in neonates.[14] It also set the objective to seek diamorphine PK parameters across various age groups, specifically in neonates and children, and emphasized the importance of determining an appropriate IND dosage for managing breakthrough pain in these age groups.[14] The time courses of IND concentration and sequential effects by its active metabolites in children were poorly depicted, despite their extensive applications in acute and palliative care settings. However, pediatric IND dosing remains uncertain because of the different administration routes adopted, the incomplete parameter estimates like the bioavailability ($F_{\%}$) of IND, the lack of age-and-weight standardization, and the reliance of noncompartmental analysis (NCA). The traditional NCA method, originally designed to define individual PK profiles, ignores inter-individual variability and potential covariates influence. Population pharmacokinetics (Pop-PK) modeling and simulation have been applied throughout various stages of drug development.[15] The notable examples of simulation techniques include facilitating dose selection for pediatric patients by leveraging data acquired from adults,[16] guiding the starting dose selection for first-in-human studies based on preclinical and nonclinical data,[17] and serving as a regulatory tool in the drug approval processes.[18] Till now, only one pop-PK model has been reported for diamorphine after intravenous and inhalation administrations in heroin-assisted therapy clinical trials for opioid use disorder.[19] However, the missing step of body weight standardization precluded the potential to perform model simulation using allometric scaling algorithms.

Again, PK properties of IND for breakthrough pain relief need further evaluation, and the dosage for the pediatric population remains disputable due to the limited clinical guidelines. This study aimed to (i) develop a pop-PK model in adults following a single small dose of IND, (ii) extrapolate the model to the pediatric population with allometry (size) and maturation function (age), and (iii) evaluate the appropriateness of commonly used dose regimen (0.1 mg/kg) of IND in children.

METHODS

Dataset preparation

Four published PK datasets were prepared for this pharmacometrics analysis, and the data characteristics and usages are summarized in Table 1. The datasets for the model

TABLE 1 Published clinical PK datasets of diamorphine used in this study.

References	Cone et al.[20]		Skopp et al.[21]		Girardin et al.[22]	Kidd et al.[23]
No. of subjects	6	6	2	4	8	12
Administration	IM	IN	IM	IN	IM	IN
Subject category	I.	I.	I.	I.	II.	III.
Dosage	6 mg	6 & 12 mg	6 mg	6 & 12 mg	<200–250 mg	0.1 mg/kg [1.8–5.8 mg]
Age (years)	28.5 [23–32]		35 [29–41]		32 [24–39]	8.6 [4–13]
Weight (kg)	74.75 [63.6–81.4]		69.4 [60.4–80]		67 [43–85]	30.1 [19–59]
Female %	0		0		37.5%	66.7%
Study medication	Diamorphine hydrochloride					
Dataset format	Numeric individual concentration–time profiles				Graphic mean concentration–time profiles and numeric PK parameters	
Dataset usage	Model development				Model evaluation (adult)	Model evaluation (children)
Bioanalytical method	GC–MS for plasma diamorphine, 6-monoacetylmorphine, and morphine				LC/MS for plasma morphine	RIA for plasma morphine
Research Institute	Addiction Research Center, NIDA/NIH, Baltimore, US				University Hospital, Zürich, Switzerland	University of Edinburgh, Edinburgh, UK

Note: Subject categories include (I) regular heroin users following 3 days of abstinence; (II) opioid-dependents in heroin-assisted treatment; (III) children in acute severe pain treatment. The summary for demographics information was summarized as median [range]. Bioanalytical methods include radioimmunoassay (RIA), gas chromatography/mass spectrometry (GC/MS), and liquid chromatography–mass spectrometry (LC/MS). NIDH/NIH, National Institute on Drug Abuse (NIDA), and National Institutes of Health (NIH).

Abbreviations: IM, intramuscular route group, IN, intranasal route group.

development were collected from two clinical PK studies that were conducted by the National Institute on Drug Abuse (Baltimore).[20,21] Both studies utilized the same dosing regimen, study medication, analytical methods, and blood sampling times. In these two studies, the PK data of diamorphine and its metabolites were analyzed after a single dose of IND (6 and 12 mg) in comparison with IMD (6 mg) in male heroin users, using a double-blind, double-dummy crossover design with a 1-week washout period between three successive administration treatments. In addition, Girardin et al.[22] recruited eight heroin-addict patients to assess IMD with three doses (<200–250 mg), while Kidd et al.[23] enrolled 12 children aged 4 to 13 years to evaluate a single dose of IND (0.1 mg/kg). Both studies fall outside the development dataset scope and thus were used for external verification.

The PK data used in this study include the plasma concentrations for DIAM, 6-MAM, and morphine. During data preparation, the plasma concentration unit was converted from ng/mL to nM (nmol/L) for the parent–metabolite PK model to account for different molecular weights (369.4, 327.4, and 285.34 g/mol, respectively), due to the sequential deacetylation of two ester bonds (molar ratio of 1.29).

Software

We used MonolixSuite™ version 2021R2 (Lixoft, Antony, France) to conduct pharmacometrics analysis, population PK modeling, and simulation. The pop-PK models were developed with Monolix modeling software to describe concentration–time profiles of DIAM, MAM, and MOR. The final pop-PK model was exported to Simulx to simulate clinical trials with two goals: (i) to perform external verifications, (ii) to evaluate current weight-based dosage regimens of IND across various age groups. All virtual subjects were created using the Simcyp™ Simulator version 22 (Certara, Sheffield, UK). Graph plotting was performed using MonolixSutite™ and the R programming language version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Pharmacokinetics analysis

Structural model

Structural models were designed using a user-defined ordinary differential equation (ODE) written in Mlxtran language (codes provided in Supplementary Material S1). Due to the sparse sampling for DIAM and MAM, all PK data of three compounds were pooled together to develop an integrated pop-PK model directly using a simultaneous approach. To manage PK data from different cohorts, we first modeled IMD data as the reference group and thus bioavailability, $F_{\%}$, is regarded as 100%. In this explorative structure modeling process, combined with the first-order absorption model for DIAM, the standard

one- and two-compartment models were tested to determine the best structural model for each compound. Given the unidentifiability of the compartments of metabolites, it is a common practice in previous studies is to equate all central volumes for metabolites with the volume of distribution for parent drugs during simultaneous pop-PK modeling.[24,25] Since morphine is currently available for human use, which is "identifiable", we also tested the model fit when estimating the individual central volumes for MOR.

The final structural model explored by the IMD group was then applied to the complete dataset and we utilized the Bayesian approach to set the initial estimates (IEs) of fixed effects. Several models were assessed to describe the intranasal absorption kinetics, such as simple zero- and first-order kinetics, with/without lag time, as well as more complicated transit models. The model-guided bioavailability of IND compared with the reference IMD group was thus obtained (i.e., bioequivalence). The metabolic transfer, distribution, and elimination of DIAM were expected to be similar, once absorbed, regardless of the varying administration routes.

Statistical model

For random effects, all parameters were modeled with log-normal distributions, constraining all individual values to stay positive. As an exception, IND bioavailability ($F_{\%}$) was modeled with a logit-normal distribution to restrict its estimates between 0 and 1. As the population parameters for this pop-PK model were estimated using the adult population, they were scaled to fit the pediatric population using the allometric function (body weight, WT) and maturation function (age).

The inclusion of other covariate effects was judged through the log-likelihood ratio test. Specifically, the stepwise forward addition was carried out with the statistical criteria of log-likelihood $p < 0.05$ followed by a backward elimination process with $p < 0.01$. The details of the model-building process can be found in Supplementary Material S2. Significant correlations between random effects were added to the model according to the Pearson correlation tests. Finally, the error models were optimized to fit residual unexplained variability (RUV) between observations and individual predictions for each drug or drug metabolite. Since the choosing of the IEs is important and can accelerate the estimation convergence process,[26] IEs for our model can be found in Table S1.

Model evaluation

Internal validation

The goodness-of-fit (GOF) for structural modeling was assessed based on the drop in corrected Bayesian information (BIC) criteria, derived from the objective function value (OFV) expressed as − 2log(likelihood). Graphical evaluations include GOF diagnostic plots, such as model-predicted population (PRED) and individual concentration (IPRED) versus observed concentration (OBS), as well as density distribution of the normalized population (NPDE) and individual weighted residuals (IWRES). Estimation precision is determined by relative standard errors (%RSE) calculated via the stochastic approximation using Fisher information matrix. The conditional distribution was employed to obtain random samples for IPRED and IWRES graphical diagnostics, as well as shrinkage computation for individual parameters, to avoid the potential bias in the original data.

During the iterative modeling process, a set of criteria were applied for model selection which include the mechanistic plausibility and utility, the drop in BIC for non-nested models, the minimum OFV determined via importance sampling for nested models, the visual diagnostics plots, and the precision of parameter estimates as judged by %RSE.[27] The predictive performance of the final pop-PK models was further evaluated by visual predictive check (VPC) constructed by 1000 simulations derived from the original index dataset. To reduce the impact of areas with sparse data, the observed and simulated PK data were automatically grouped in multiple bins over successive time intervals based on the optimized least-squares binning criteria.[28,29]

External validation

In Simulx, the diamorphine administration was simulated in 100 virtual subjects with 50 replicates per trial, totally 5000 simulated units. Morphine plasma concentrations were sampled at the same timepoints as those used in corresponding clinical studies. The ages and body weights (covariates) of the virtual adults (24–39 years, 43–85 kg)[22] and virtual children (4–13 years, 19–59 kg)[23] were within the same ranges as those of the study participants. Morphine exposures (AUC) were computed by integrating the concentration profiles from the start to the end of the observation period (Supplementary Material S1).

For PK parameters comparison, the twofold error range, that is, within 0.5–2-fold range, was used to evaluate model predictive performance.[30] The fold error

(predicted/observed ratio, $R_{pred/obs}$) and weighted average fold error (AFE) of morphine C_{max} and AUC_{0-t} were calculated using Equations 1 and 2, where the weight represented the sample size of the corresponding clinical trial. Moreover, for the pediatric simulation, we also assessed the goodness of morphine observed/predicted profiles fitting 1 h after 0.1 mg/kg IND administration.

$$\text{Ratio}_{\left(\frac{\text{pred}}{\text{obs}}\right)} = \frac{\text{Predicted PK parameter (mean value)}}{\text{Observed PK parameter (mean value)}} \quad (1)$$

$$\text{AFE} = \frac{\sum_{i=1}^{N}\left(w_i \times \text{ratio}_i\right)}{\sum_{i=1}^{N} w_i} \quad (2)$$

Dosing regimen simulations

Four representative pediatric populations were created using the Simcyp™ Simulator pediatric module to match the FDA Pediatrics Exclusivity Study Age Groups: neonates (<1 month), infants (1 month–2 years), children (2–12 years), and adolescents (12–16 years).[31] The morphine concentration–time curves over 1 h were simulated at the interval of 0.01 h for 4000 virtual pediatric subjects (1000 subjects per age group). The subjects were generated for the default Caucasian population with the female proportion setting as 0. Two simulated end points were established to assess the percentage of virtual subjects in each age group achieving the reported $AUC_{0\text{-}1h}$ window (*End point 1*, 10.13–58.36 nmol/L) and C_{max} limit (*End point 2*, 13.7–82.7 nmol/L).[23] Furthermore, simulations were used to devise an optimal pediatric intranasal dosing scheme that achieved an effective exposure-matching properties. The reported steady-state target concentration 35–70 nmol/L (10–20 μg/L)[32–35] for morphine was selected, where concentrations above 20 μg/L are associated with respiratory depression.[36,37] Details of the modeling and simulation results of pediatric dosing were provided in Supplementary Material S3.

RESULTS

Study subjects characteristics

For this PK analysis and model development, a total of 385 measured plasma concentrations were applied. The overall demographic information for each treatment group (cohort) is summarized in Table S2. The body weight and age constitute two continuous covariates. The dosage amount and route of administration, as two categorical covariates, were investigated for their potential impacts on diamorphine absorption and disposition. Three cohorts were successively conducted in 10 male volunteers, each having a history of heroin use and undergoing a 1-week washout period. From these cohorts, 28 samples were successfully collected. All 10 volunteers received a single dose of IND treatments twice, accounting for 71.4% of treatment sessions, while only eight out of 10 volunteers received one IMD treatment. The 6 mg dosing of diamorphine, roughly 0.07–0.09 mg/kg, is close to the clinical usage of diamorphine hydrochloride nasal spray in breakthrough pain. Besides, all subjects received a minimum of three consecutive days of negative tests to ensure they are opioid-free.

Pop-PK model development

Structure modeling results

The final pop-PK model, an integrated four-compartment model, consists of a standard one-compartment model for DIAM (CPT_1), a standard one-compartment model for MAM (CPT_2), and a standard two-compartment model for MOR (CPT_3 and CPT_{3p}), as illustrated in Figure 2. The C–T profiles of DIAM and MAM were best described with the one-compartment model (CPT_1 and CPT_2) while the MOR data fitted better with the two-compartment model (CPT_3 and CPT_{3p}). All population estimates of our final model are presented in Table 2. The straightforward first-order absorption model without lag time displayed the best performance for both IND and IMD data. When we separately estimated the absorption rate constant (K_a) for the two administration routes, there were minor differences, and using a common K_a improved the model fit. The model estimated the IND relative bioavailability to be ~52% (IQR: 50%–59.2%) and uncovered a similar first-order absorption behavior for IM injection and IN delivery with an approximate half-life of absorption of 13.6 min.

In our model, all metabolic transformation is unidirectional following the first-order kinetics parameterized with a constant rate (K_{12} or K_{23}). For the parametrization of unidentifiable central volume for metabolites, the inclusion of only morphine central volume (V_3) as an independent parameter achieved the minimum BIC. Thus, this four-compartment sequential PK disposition model assumed the MAM central volume was equal to diamorphine volume ($V_1 = V_2$). Transit models for absorption and metabolite formation were also investigated but it did not improve the model fitting performance and the difference of BIC values is neglectable.

Statistical modeling results

Body weight was incorporated into our base model through the theory-based allometric scaling scheme described in

Supplementary Material S2. Estimation of the allometric exponents as covariates worsened fitting results, as the precision of parameter estimation decreased. Meanwhile, to incorporate developmental changes with age in drug disposition, morphine clearance was described with an empiric sigmoid maturation model.[36] The automatic stepwise covariates modeling did not identify other significant covariates. This indicated that diamorphine absorption and disposition were not dosage-dependent, which corroborated the mechanistic plausibility of our model structure with linear kinetics. It also revealed that the absorption is not influenced by the administration route.

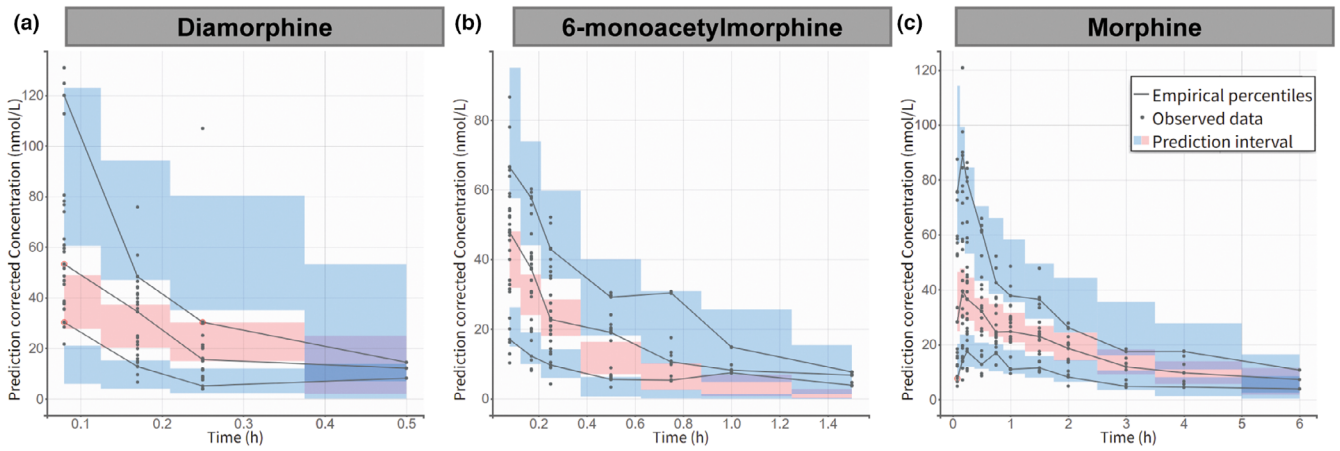

FIGURE 2 Prediction-corrected visual predictive check (pc-VPC) plots for diamorphine (a), 6-monoacetylmorphine (b), and morphine concentration (c) of the final pop-PK models. The gray dots represent the observed data of concentration in nM. The solid gray lines represent the 5th, 50th, and 95th empirical percentiles for the observations. The shaded areas represent the 90% confidence (predictive) interval of the 5th, 50th (reddish color), and 95th percentiles of the simulated data.

TABLE 2 Population pharmacokinetic parameter estimates.

	Fisher information matrix estimates (stochastic approximation)				Bootstrap estimates		
PK parameters [units]	**Estimation (RSE%)**	**BSV (RSE%)**	**Median [IQR]**	**Shrinkage (%)**	**Estimation (RSE%)**	**BSV (RSE%)**	**95% CI**
K_a [h^{-1} per 70 kg]	3.04 (12.9)	0.609 (16.1)	3.70 [1.67–4.63]	−1.85	3.001 (10.2)	0.609 (8.4)	2.44–3.64
$F_{\%}$ [per 70 kg]	0.519 (13.6)	0.568 (27.2)	0.532 [0.504–0.592]	−3.55	0.519 (16.6)	0.568 (40.8)	0.40–0.74
V_1 [L/per 70 kg] (=V_2)	8.21 (28.9)	0.478 (21.8)	9.43 [5.17–12.5]	1.33	8.21 (21.1)	0.478 (12.9)	6.32–13.11
V_3 [L/per 70 kg]	32.5 (13.5)	0.279 (33.5)	34.3 [29.8–38.7]	2.84	32.47 (21.4)	0.279 (26.2)	21.41–48.59
K_{12} [h^{-1}/per 70 kg]	103 (23.5)	0.400 (30.9)	102 [83.6–127]	−7.19	103.31 (16.2)	0.400 (24.1)	70.92–136.37
K_{23} [h^{-1}/per 70 kg]	106 (23.3)	0.295 (30.1)	100 [91.6–115]	−10.6	105.678 (15.6)	0.295 (36.4)	73.81–138.28
K_{3p} [h^{-1}/per 70 kg]	24.2 (14.1)	0.125 (80.0)	23.9 [23.3–24.6]	−0.448	24.16 (28.5)	0.125 (40.2)	16.62–43.57
K_{p3} [h^{-1}/per 70 kg]	2.69 (14.3)	0.385 (29.6)	3.07 [2.14–3.42]	−9.00	2.688 (18.3)	0.385 (42.8)	1.91–3.84
CL [L/h/per 70 kg]	132 (19.0)	0.297 (36.7)	139 [123–164]	−9.98	132.3 (17.7)	0.297 (28.4)	97.05–189.06
corr_V_1_K_a	0.854 (23.7)				0.854 (6.0)		
RUV_1	0.430 (12.0)				0.430 (5.9)		
RUV_2	0.215 (8.34)				0.215 (7.9)		
RUV_3	0.236 (6.74)				0.236 (6.8)		

Note: Median and interquartile range (IQR) and shrinkage values were computed from conditional distribution using Monolix, which was derived from the Fisher information matrix (FIM) via default Markov chain Monte Carlo (MCMC) convergence assessment. The relative standard error (RSE) was calculated using both stochastic approximation for FIM and bootstrap analysis with 1000 resampling times. Fixed effects of parameter estimates and random effects of between-subject variability (BSV) were computed using the Stochastic Approximation Expectation–Maximization (SAEM) algorithm.

Abbreviations: DIAM, diamorphine; $F_{\%}$, bioavailability for intranasal diamorphine; K, intercompartment rate constant; MAM, 6-monoacetylmorphine; MOR, morphine; RUV, residual unexplained variability with proportional error model; V_{1-3}, central compartment volume.

Moreover, the introduction of a correlation coefficient between random effects for K_a and V_1 greatly improved the model performance (ΔBIC = 10.8). Proportional error models were employed to account for RUV in observed plasma concentrations, which effectively captured assay variability and errors in sample timing.

The parameterization of between-occasion variability (BOV) within each volunteer resulted in either unsuccessful minimization or highly imprecise parameter estimates. Therefore, for random effects, each treatment session in Table S2 was assumed to represent one "modeled subject" to only assess between-subject variability (BSV). The population parameter variabilities for K_a (BSV = 0.61) and diamorphine volumes (BSV = 0.48) are still large despite the inclusion of their positive correlation (corr_V_1_K_a) as well as the allometric scaling of WT. The estimated metabolic transfer rate constant (K_{12}) of diamorphine was close to that of 6-monoacetylmorphine (K_{23}), both exceeding 100 h^{-1}.

Pop-PK model evaluation

Internal validation results

As shown in Table 2, bootstrap estimates showed that precisions were generally acceptable with %RSE < 30% for fixed effects and %RSE < 50% for random effects, and the low shrinkage values suggested that the individual parameters (EBEs) were precisely estimated. Diagnostic GOF plots (Figure S1) for the PRED versus OBS indicated that there was no major bias in the population component. Likewise, IPRED versus OBS demonstrated that the final structural model should be useful to most individuals with <10% outliers. Figure 3 shows the result of prediction-corrected visual predictive checks (pc-VPC), while Figure S2 compares the empirical residual distribution and the theoretical Gaussian distribution. Despite its overall reasonable predictive performance, the final model tended to underpredict observed DIAM concentrations in the early sampling time bins (0–0.12 h) and MAM concentrations in late time bins (0.6–1.5 h), as illustrated in Figure 3a,b, respectively. Correspondingly, a mild misspecification was found for predicted DIAM concentrations in PRED versus OBS (Figure S1a) and predicted MAM concentrations in the NPDE residual distribution (Figure S2b).

These issues are likely attributed to the challenge of simultaneously fitting three compounds and the limited availability of measured data to explain the high BSV of PKs in the two precursor drugs (K_a, $F_{\%}$, V_1). Additionally, the early phase of sampling in PK studies, essential for gathering comprehensive data, poses a significant challenge. This results in a problematic estimation of absorption parameters due to the insufficiency of available data.

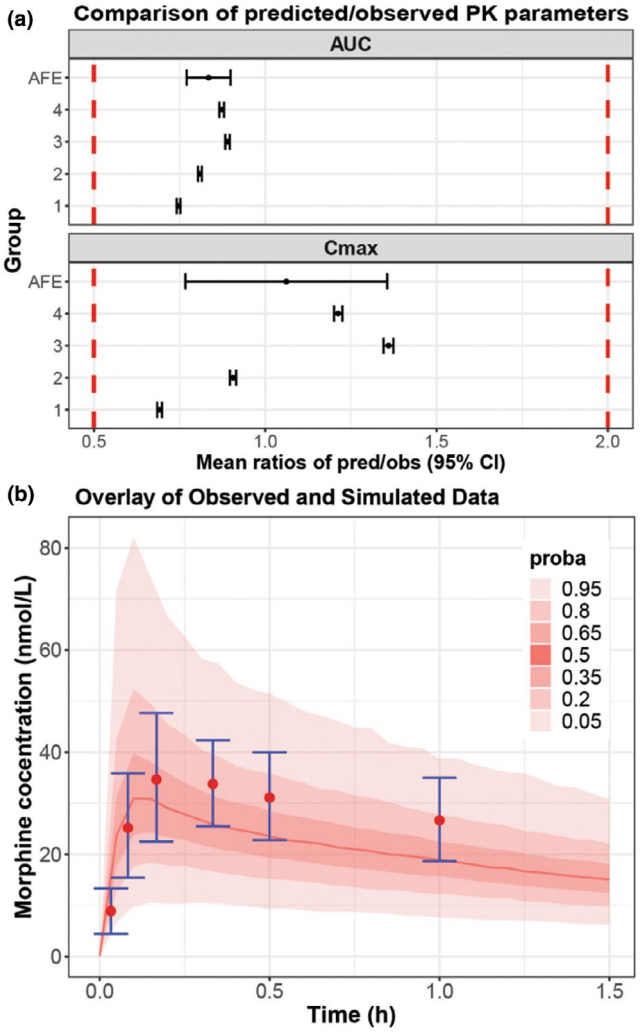

FIGURE 3 External verification of morphine PK data after diamorphine dosing. (a) Comparison of predicted/observed C_{max} (μmol/L) and $AUC_{0\text{-}t}$ (μmol.min/L). CI, confidence interval. AFE, average fold errors. (b) Overlay of observed and simulated morphine plasma concentration–time data. The solid red line represents the simulated median concentration. The red dots represent the mean observations from children of Group 4 treated with intranasal diamorphine, and blue error bars represent 95% CI.

Nonetheless, the model was found to accurately predict the time course of morphine concentrations, reproducing both the central trend and variability observed in the original dataset (Figure 2c). Consequently, in the next stage, we only evaluated morphine PKs, as they also exhibit a stronger correlation with analgesic efficacy.

External validation results

The robustness of model extrapolation was assessed by external verification of observed and predicted morphine PK parameters in adults after IMD dosing[22] and children after IND dosing.[23] Table 3 compared the observed and

TABLE 3 Summary of results of the clinical studies (observed and simulated) used to verify the final model extrapolation.

		Observed PK parameters (mean ± SD)		Predicted PK parameters (mean [trial range])		Predicted/observed (mean ± SD)	
Groups	Study design	C_{max} (μmol/L)	AUC_{0-t} (ng·min/mL)	C_{max} (ng/mL)	AUC_{0-t} (ng·min/mL)	C_{max}	AUC
1	181 μmol, IMD	1.1 ± 1.1	120 ± 64	0.76 [0.47–1.25]	89.64 [61.94–125.13]	0.69 ± 0.11	0.75 ± 0.09
2	366 μmol, IMD	1.7 ± 1.6	224 ± 154	1.54 [0.95–2.40]	181.26 [125.23–252.96]	0.91 ± 0.15	0.81 ± 0.09
3	548 μmol, IMD	1.7 ± 0.8	305 ± 153	2.31 [1.38–3.92]	271.39 [187.45–378.96]	1.36 ± 0.23	0.89 ± 0.10
4	0.1 mg/kg, IND	0.0361 [0.014–0.083]	1.794 [0.608–0.350]	0.04 [0.02–0.07]	1.57 [1.06–2.48]	1.21 ± 0.19	0.87 ± 0.11
Weighted average fold errors						1.06 ± 0.30	0.83 ± 0.07

Note: The observed PK parameters include the mean values previously reported from six adult subjects injected with intramuscular diamorphine (IMD), and the median value reported from 12 pediatric subjects (aged 4–13 years) treated with intranasal diamorphine (IND). The predicted values were obtained from corresponding PK simulations in virtual adults or children, both having matched weight and age to those subjects in clinical trials.[22,23] The fold errors (predicted/observed ratio, $R_{pred/obs}$) of PK parameters in each scenario were calculated accordingly.

predicted PK parameters of external test datasets, which consisted of four study designs, after exporting the final model to trial simulations using virtual patients with matched information. The external validation results can be seen in forest plots in Figure 3a, where all error bars fell within the range of twofold difference (red dashed lines). The weighted AFEs of 1.06 (95% CI: 0.77–1.36) for C_{max} and 0.83 (95% CI: 0.76–0.90) for AUC_{0-t} are adequately acceptable. In addition, the validity of the model extrapolation was further supported by the VPC results shown in Figure 3b. It demonstrated that the clinical pediatric morphine plasma level observed in children following IND fell within the 60% prediction interval of the simulated morphine C–T profile.

PK-guided dosing simulations

To better understand the model generalizability performance across age and weight changes in children, the model was simulated in four representative pediatric populations, as shown in Figure S3. Table S3 demonstrates that a single dose of 0.1 mg/kg of IND resulted in 88.8% of all virtual subjects having plasma morphine levels within the previously reported C_{max} limit. Additionally, 82.6% reached levels within the reported $AUC_{0\text{-}1h}$ window observed from 12 children following the IND dosing in acute clinical setting. Overall, the simulated end points were attained in around 80% of subjects of every age group.

To target an effective plasma concentration of morphine, we optimized the IND dosage regimen for each pediatric population to ensure exposure-matching properties. Figure 4 illustrates that the median C–T profiles for each age group at steady state fell within the reported steady-state target morphine concentration (35–70 nmol/L), when administered a 0.3 mg/kg loading dose followed by 0.1 mg/kg maintenance dose IND hourly.

DISCUSSION

In this study, we collected and analyzed the publicly available PK data from subjects given low-dosage diamorphine via two administration routes (IM and IN) across a twofold dose range. An integrated four-compartment pop-PK model was developed to describe the concentration–time profiles of diamorphine, 6-monoacetylmorphine, and morphine. The external verification by the AFEs of PK parameters as well as C–T profiles supported the predictive utility of model extrapolation. Optimal pediatric IND dosing was derived using model-based simulation for four broadly representative pediatric populations across different age groups.

All typical values of PK parameters of the final model are standardized by WT 70 kg while a model capturing the maturation of renal function was used to characterize the total clearance of the morphine. Our estimated morphine central volumes (32.5 L, 95% CI: 21.4–48.6 L) are consistent with reported population estimates (47.1 L, 95% CI: 42–55 L) for morphine PK.[35,38] The high estimated values of CL and its large variability (132 L/h, 95% CI: 97–189 L/h) agreed with the observed clearances (range: 0.066–203.6 L/h) from 257 subjects spanning different age groups.[36,38] The model estimated the IND relative bioavailability to be around 52% and uncovered a similar first-order absorption behavior for IM injection and IN delivery with the same absorption half-life of ~13.6 min. This agreed with the reported 50% bioavailability derived from NCA results.[20,21,23] A relatively high variability was associated with bioavailability for IND absorption (BSV = 0.57) but no covariates available were found to lower the BSV value.

Previous research has suggested that (acetyl)-metabolites are barely recovered in the urine, and that morphine along with its glucuronide metabolites M3G and M6G, are the major detectable forms.[39–41] This is the

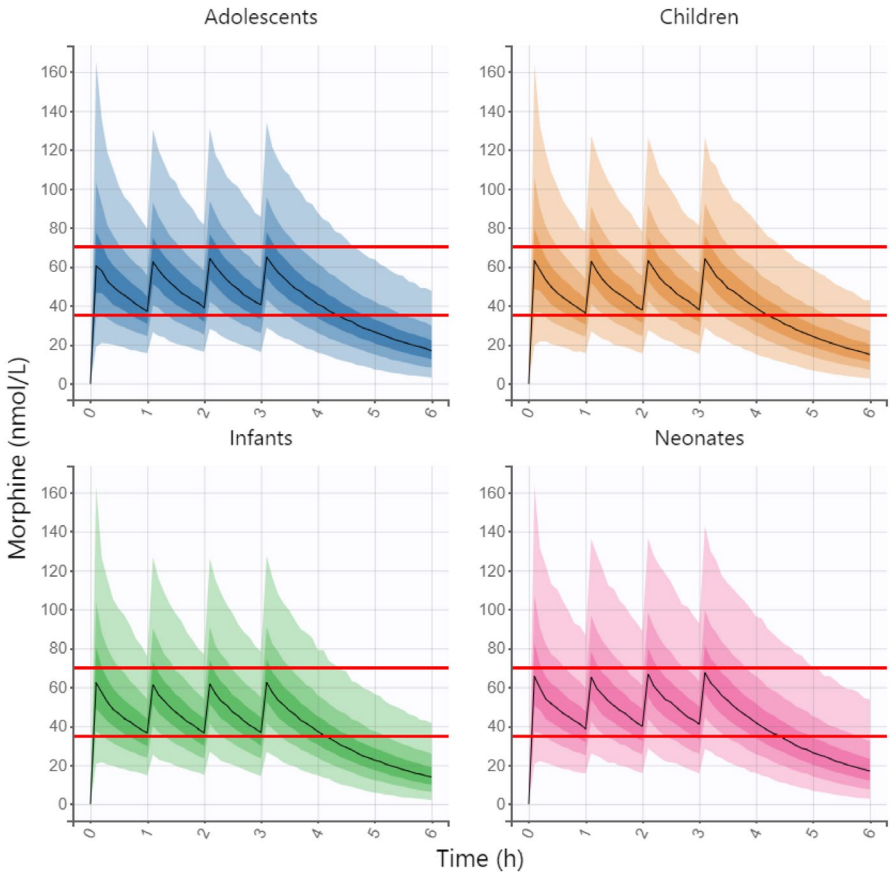

FIGURE 4 Simulated pediatric morphine concentration–time profiles for four different age groups after administering intranasal diamorphine with a loading dose of 0.3 mg/kg followed by a 0.1 mg/kg maintenance dose every hour. The red lines indicate the target steady-state morphine concentration range of 35–70 nmol/L.

reason why we discarded the renal elimination of DIAM and MAM, believing that both compounds are fully converted into morphine. Morphine is clinically available for human use and its central volume has been reported, serving as the prior information of Bayesian estimation. Conversely, the intermediate metabolite, MAM, is not directly administered and thus any combination of biotransformation rate (K_{12} and K_{23}) in the model structure is sufficient to fit PK data. Thus, the estimation of unidentifiable MAM volumes (V_2) would pose a challenge to model fitting as any change in superfluous V_2 can be offset by adjusting other parameters. Moreover, no significant associations between dosage amount and the PK parameters were found, indicating that the structure design of linear kinetics should be statistically and mechanically reasonable. Notably, the current "dosage-independent" finding is only feasible for the diamorphine usages of low dosage.

The saturation metabolism assumption was not considered due to the widespread distribution of various esterases that are abundant in the human body. Besides, the administration of a small dose of diamorphine is less likely to result in saturation metabolism. Therefore, our model described a mono-exponential decline of rapidly metabolized precursors (DIAM and MAM) observed in concentration–time curves. The estimated metabolic conversion half-life for deacetylation was 0.4 min. It refers to the biotransformation rate by hydrolysis that occurs in the circulatory system and is carried out by the butyrylcholinesterase (BChE) in erythrocytes and human carboxylesterase (hCES) in hepatocytes (Figure 1).[42,43] Rook et al.[19] employed a two-compartment model to estimate a system biotransformation half-life (~2–4 min) in both central and peripheral tissues. The gaps in estimated biotransformation rates implied that peripheral esterase might represent a slow-metabolizing enzyme for diamorphine. Intriguingly, this is consistent with the findings of Salmon et al.[43] and Kim et al.[44] that BChE and hCES are the primary contributors to diamorphine deacetylation. Also, these enzymes are fully functional at birth, and thus no maturation function is required.[45]

Although we incorporated reported population PK parameters of diamorphine and morphine as prior information using the Bayesian approach, the final model showed some differences in estimated values compared with the sole published pop-PK analysis of diamorphine.[19] Attempts to fix some parameters resulted in marginal improvements in model fitting and generated less reliable estimates. It is possible that the discrepancies stem from differences in model structure, quantification limits based on varying bioanalysis methods (GC/MS vs. LC–MS/MS given in Table 1), and vastly different dosage

amounts of the study medication used (with a dosage ratio of 10–50 times). It is still worthwhile to note that our model is tailored to the indication of pain management, rather than the heroin-assisted treatment prescribed for opioid addicts. Furthermore, the state-of-the-art SAEM (Stochastic Approximation Expectation–Maximization) algorithm applied in Monolix is superior to the traditional first-order approaches. For example, FOCE-I (first-order conditional estimation with interaction) that Rook et al. adopted,[19] is of concern to generate biased estimates of random effects.[27]

Several factors contributed to the uniform underprediction of AUC observed in external validation. Firstly, the full extrapolation in PK modeling can lead to discrepancies between observed profiles and predicted outcomes, a common issue in PK modeling of special patient populations where data are scarce. This is further complicated by the fact that there was only one clinically observed concentration–time dataset for children post-IND in the A&E department, as reflected in the external validation shown in Figure 3b. Additionally, differences in bioanalytical methods (GC–MS vs. LC–MS vs. RIA) used by three different research institutes have introduced inherent biases in the fitting. Finally, the model, originally developed with data from male adults, did not account for gender differences in the pediatric dataset, potentially affecting the accuracy of the predictions. Despite these challenges, our model demonstrated its ability to accurately predict C_{max}, which is more critical for managing breakthrough pain effectively, given the rapid onset and duration of maximum pain intensity typical in such cases.[5,46]

The utilization of model-based simulation to investigate the dose-exposure relationship is favored by drug regulatory bodies. This approach has been applied to guide pediatric dosing for various drugs,[16] including vancomycin,[47] olanzapine[48] and metoclopramide,[49] etc. In the case of diamorphine, Morse et al.[45] proposed an age-related dosage strategy for children derived from simulation results of the "patchwork" models, which lacked a comprehensive modeling step. We constructed a new pop-PK model using the adult IND data, which allowed us to estimate the previously unknown intranasal absorption parameter (K_a, $F_{\%}$). Our modeling work also introduced reasonable individual parameter distributions with small shrinkage values to yield predictive intervals of the morphine concentration–time curves seen in the population. Furthermore, the virtual pediatric populations we created have a range of weights and ages, instead of the representative with standard covariates, to better reproduce real-world scenarios. Our simulation results indicated that a single dose of 0.1 mg/kg IND, as recommended for pediatric patients, typically leads to exposure levels that align with the morphine ranges observed in children.[23] Furthermore, to correlate drug exposure with analgesic efficacy, we optimize the IND dosing regimen to target an effective morphine steady-state concentrations of 10–20 μg/L. This effective morphine concentration range obtained from empiric studies[36] has effective postoperative analgesia[32,34,35] while minimizing the risk of respiratory depression associated with higher concentrations.[37] However, caution is still advised when considering neonates and infants due to the potential variability in nasal anatomical development and the absence of model verification for these two age groups. Hence, the intranasal dosage prediction for neonates and infants remains speculative, and further research is warranted. Moreover, given that the optimal morphine steady-state concentration might vary with age or the intensity of the pain, it is imperative to tailor dosing regimens dynamically, adjusting according to the evolving pain experience of the pediatric patient.

This study still has some limitations. First, the exclusion of females from the pharmacometrics analysis may limit the generalizability of our findings. Besides, the limited number of subjects and samples, along with missing clinically relevant covariates, for example, kidney function, genotype information of esterase, and concomitant drug usage, may have reduced the power and ability to detect covariate relationships. This could have contributed to the high BSV estimates of population parameters (K_a, K_{12}, and V_1) involved in diamorphine absorption and the anticipated errors shown in VPC results. Lastly, the pediatric simulation results of IND dosing are only compared with the morphine level. The role of the active intermediate metabolite, 6-mono-acetylmorphine, could not be assessed due to the lack of measurements in the external dataset. Albeit these limitations, the previously reported pop-PK model demonstrated that there was no significant impacts of covariates, including sex and cocaine or alcohol abuse on diamorphine PK.[19] Moreover, the external verification confirmed the usefulness to predict morphine PK parameters when extrapolating our model to a population outside the study group (from adults to children)[23] and to treatment outside the study dosing (from low to high dosage).[22] Particularly, the simulated morphine concentration–time profile can recover the clinically observed data in children given a single dose of 0.1 mg/kg.[23] This provides additional evidence of the utility of our model in PK prediction for pediatric breakthrough pain management.

In conclusion, we developed an integrated pop-PK model to describe the pharmacokinetics of diamorphine, 6-monoacetylmorphine, and morphine in adults following a single dose of diamorphine. Specifically, the relative bioavailability of IND was estimated to be ~52% compared with intramuscular delivery following a similar absorption kinetics. Moreover, model external evaluation suggested

that the model can be extrapolated to children based on body weight allometry and renal function maturation. The final model was thus applied to simulate morphine plasma concentrations in various pediatric age groups. For ~80%, virtual subjects across four pediatric populations, a single intranasal dose of 0.1 mg/kg produced the C_{max} and $AUC_{0\text{-}1h}$ levels are within the previously reported ranges. The model-derived IND dosing strategy of a 0.3 mg/kg loading dose followed by a 0.1 mg/kg maintenance dose hourly can attain effective steady-state morphine concentrations for multiple pediatric populations. We must emphasize that no clinical data are available to validate our model for neonates and infants. However, we believe that the proper extrapolation of a pop-PK model can guide initial clinical assessment and therapeutic strategy, while the model-based dosage recommendation should be taken with great caution. Future PK studies on diamorphine could be strategically conducted with a smaller cohort of children and infants, utilizing an opportunistic sampling design. This will enhance both the robustness and the applicability of our findings, contributing significantly to pediatric pharmacotherapy.

AUTHOR CONTRIBUTIONS

L.C., J.W., F.H., T.N., and L.W. wrote the manuscript. L.C., J.W., and B.J. designed the research. L.C., and J.Z. performed the research. L.C., J.Z., B.J., and J.W. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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REFERENCES

1. Strang J, Groshkova T, Uchtenhagen A, et al. Heroin on trial: systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction. *Br J Psychiatry*. 2015;207:5-14.
2. Jamieson L, Harrop E, Johnson M, et al. Healthcare professionals' views of the use of oral morphine and transmucosal diamorphine in the management of paediatric breakthrough pain and the feasibility of a randomised controlled trial: a focus group study (DIPPER). *Palliat Med*. 2021;35:1118-1125.
3. Harrop E, Liossi C, Jamieson L, et al. Oral morphine versus transmucosal diamorphine for breakthrough pain in children: methods and outcomes: UK (DIPPER study) consensus. *BMJ Support Palliat Care*. 2021;13:e1019-e1028.
4. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain*. 1999;81:129-134.
5. Friedrichsdorf S, Postier A. Management of breakthrough pain in children with cancer. *J Pain Res*. 2014;7:117-123.
6. Robinson SL, Rowbotham DJ, Smith G. Morphine compared with diamorphine. *Anaesthesia*. 1991;46:538-540.
7. Bourquin D, Lehmann T, Hammig R, Buhrer M, Brenneisen R. High-performance liquid chromatographic monitoring of intravenously administered diacetylmorphine and morphine and their metabolites in human plasma. *J Chromatogr B Biomed Sci Appl*. 1997;694:233-238.
8. Rook EJ, Huitema AD, van den Brink W, van Ree JM, Beijnen JH. Pharmacokinetics and pharmacokinetic variability of heroin and its metabolites: review of the literature. *Curr Clin Pharmacol*. 2006;1:109-118.
9. Dinis-Oliveira RJ. Metabolism and metabolomics of opiates: a long way of forensic implications to unravel. *J Forensic Leg Med*. 2019;61:128-140.
10. Kendall JM, Latter VS. Intranasal Diamorphine as an alternative to intramuscular morphine. *Clin Pharmacokinet*. 2003;42:501-513.
11. Kendall J, Maconochie I, Wong ICK, Howard R. A novel multipatient intranasal diamorphine spray for use in acute pain in children: pharmacovigilance data from an observational study. *Emerg Med J*. 2015;32:269-273.
12. Kendall JM, Reeves BC, Latter VS, Nasal Diamorphine Trial Group. Multicentre randomised controlled trial of nasal diamorphine for analgesia in children and teenagers with clinical fractures. *BMJ*. 2001;322:261-265.
13. Van Den Anker J, Reed MD, Allegaert K, Kearns GL. Developmental changes in pharmacokinetics and pharmacodynamics. *J Clin Pharmacol*. 2018;58:S10-S25.
14. Gastine S et al. Diamorphine pharmacokinetics and conversion factor estimates for intranasal diamorphine in paediatric breakthrough pain: systematic review. *BMJ Support Palliat Care*. 2022;13:e485-e493.
15. Chien JY, Friedrich S, Heathman MA, de Alwis DP, Sinha V. Pharmacokinetics/pharmacodynamics and the stages of drug development: role of modeling and simulation. *AAPS J*. 2005;7:E544-E559.
16. Laer S, Barrett JS, Meibohm B. The in silico child: using simulation to guide pediatric drug development and manage pediatric pharmacotherapy. *J Clin Pharmacol*. 2009;49:889-904.
17. Agoram BM. Use of pharmacokinetic/pharmacodynamic modelling for starting dose selection in first-in-human trials of high-risk biologics. *Br J Clin Pharmacol*. 2009;67:153-160.

18. Wang Y, Sung C, Dartois C, et al. Elucidation of relationship between tumor size and survival in non-small-cell lung cancer patients can aid early decision making in clinical drug development. *Clin Pharmacol Ther*. 2009;86:167-174.
19. Rook EJ, Huitema ADR, Van Den Brink W, Van Ree JM, Beijnen JH. Population pharmacokinetics of heroin and its major metabolites. *Clin Pharmacokinet*. 2006;45:401-417.
20. Cone EJ, Holicky BA, Grant TM, Darwin WD, Goldberger BA. Pharmacokinetics and pharmacodynamics of intranasal "snorted" heroin. *J Anal Toxicol*. 1993;17:327-337.
21. Skopp G, Ganssmann B, Cone EJ, Aderjan R. Plasma concentrations of heroin and morphine-related metabolites after intranasal and intramuscular administration. *J Anal Toxicol*. 1997;21:105-111.
22. Girardin F. Pharmacokinetics of high doses of intramuscular and oral heroin in narcotic addicts. *Clin Pharmacol Ther*. 2003;74:341-352.
23. Kidd S, Brennan S, Stephen R, Minns R, Beattie T. Comparison of morphine concentration-time profiles following intravenous and intranasal diamorphine in children. *Arch Dis Child*. 2009;94:974-978.
24. Kamp J, Jonkman K, van Velzen M, et al. Pharmacokinetics of ketamine and its major metabolites norketamine, hydroxynorketamine, and dehydronorketamine: a model-based analysis. *Br J Anaesth*. 2020;125:750-761.
25. Zhao X, Venkata SLV, Moaddel R, et al. Simultaneous population pharmacokinetic modelling of ketamine and three major metabolites in patients with treatment-resistant bipolar depression. *Br J Clin Pharmacol*. 2012;74:304-314.
26. Han S, Jeon S, Yim D-S. Tips for the choice of initial estimates in NONMEM. *Transl Clin Pharmacol*. 2016;24:119-123.
27. Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. *CPT Pharmacometrics Syst Pharmacol*. 2013;2:e38.
28. Traynard P, Ayral G, Twarogowska M, Chauvin J. Efficient pharmacokinetic modeling workflow with the MonolixSuite: a case study of remifentanil. *CPT Pharmacometrics Syst Pharmacol*. 2020;9:198-210.
29. Lavielle M, Bleakley K. Automatic data binning for improved visual diagnosis of pharmacometric models. *J Pharmacokinet Pharmacodyn*. 2011;38:861-871.
30. Rasool MF, Ali S, Khalid S, et al. Development and evaluation of physiologically based pharmacokinetic drug-disease models for predicting captopril pharmacokinetics in chronic diseases. *Sci Rep*. 2021;11:8589.
31. US Food and Drug Administration (FDA). Pediatric Exclusivity Study Age Group 2014. 2014 [cited 2023 March 4]. https://www.fda.gov/drugs/data-standards-manual-monographs/pediatric-exclusivity-study-age-group
32. Lynn AM, Opheim KE, Tyler DC. Morphine infusion after pediatric cardiac surgery. *Crit Care Med*. 1984;12:863-866.
33. Nahata MC, Powell DA, Durrell DE, Miller MA. Acetaminophen accumulation in pediatric patients after repeated therapeutic doses. *Eur J Clin Pharmacol*. 1984;27:57-59.
34. Bray RJ, Beeton C, Hinton W, Seviour JA. Plasma morphine levels produced by continuous infusion in children. *Anaesthesia*. 1986;41:753-755.
35. Bouwmeester NJ, van den Anker JN, Hop WC, Anand KJ, Tibboel D. Age- and therapy-related effects on morphine requirements and plasma concentrations of morphine and its metabolites in postoperative infants. *Br J Anaesth*. 2003;90:642-652.
36. Holford NHG, Ma SC, Anderson BJ. Prediction of morphine dose in humans. *Pediatr Anesth*. 2012;22:209-222.
37. Lynn AM, Nespeca MK, Opheim KE, Slattery JT. Respiratory effects of intravenous morphine infusions in neonates, infants, and children after cardiac surgery. *Anesth Analg*. 1993;77:695-701.
38. Holford N. Dosing in children. *Clin Pharmacol Ther*. 2010;87:367-370.
39. Cone EJ, Jufer R, Darwin WD, Needleman SB. Forensic drug testing for opiates. VII. Urinary excretion profile of intranasal (snorted) heroin. *J Anal Toxicol*. 1996;20:379-392.
40. Yeh SY, Gorodetzky CW, Mcquinn RL. Urinary-excretion of heroin and its metabolites in man. *J Pharmacol Exp Ther*. 1976;196:249-256.
41. Gyr E, Brenneisen R, Bourquin D, Lehmann T, Vonlanthen D, Hug I. Pharmacodynamics and pharmacokinetics of intravenously, orally and rectally administered diacetylmorphine in opioid dependents, a two-patient pilot study within a heroin-assisted treatment program. *Int J Clin Pharmacol Ther*. 2000;38:486-491.
42. Meyer MR, Schutz A, Maurer HH. Contribution of human esterases to the metabolism of selected drugs of abuse. *Toxicol Lett*. 2015;232:159-166.
43. Salmon AY, Goren Z, Avissar Y, Soreq H. Human erythrocyte but not brain acetylcholinesterase hydrolyses heroin to morphine. *Clin Exp Pharmacol Physiol*. 1999;26:596-600.
44. Kim K, Yao J, Jin Z, Zheng F, Zhan CG. Kinetic characterization of cholinesterases and a therapeutically valuable cocaine hydrolase for their catalytic activities against heroin and its metabolite 6-monoacetylmorphine. *Chem Biol Interact*. 2018;293:107-114.
45. Morse JD, Anderson BJ, Gastine S, Wong ICK, Standing JF. Pharmacokinetic modeling and simulation to understand diamorphine dose–response in neonates, children, and adolescents. *Pediatr Anesth*. 2022;32:716-726.
46. Davis MP. Recent development in therapeutics for breakthrough pain. *Expert Rev Neurother*. 2010;10:757-773.
47. Mulubwa M, Griesel HA, Mugabo P, Dippenaar R, van Wyk L. Assessment of vancomycin pharmacokinetics and dose regimen optimisation in preterm neonates. *Drugs R D*. 2020;20:105-113.
48. Maharaj AR, Wu H, Zimmerman KO, et al. Population pharmacokinetics of olanzapine in children. *Br J Clin Pharmacol*. 2021;87:542-554.
49. Ge S, Mendley SR, Gerhart JG, et al. Population pharmacokinetics of metoclopramide in infants, children, and adolescents. *Clin Transl Sci*. 2020;13:189-1198.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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