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Impact of enantiomer-specific changes in pharmacokinetics between infants and adults on the target concentration of racemic ketorolac: A pooled analysis

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Aims: Ketorolac is a nonsteroidal anti-inflammatory racemic drug with analgesic effects only attributed to its S-enantiomer. The aim of this study is to quantify enantiomer-specific maturational pharmacokinetics (PK) of ketorolac and investigate if the contribution of both enantiomers to the total ketorolac concentration remains equal between infants and adults or if a change in target racemic concentration should be considered when applied to infants.

Methods: Data were pooled from 5 different studies in adults, children and infants, with 1020 plasma concentrations following single intravenous ketorolac administration. An allometry-based enantiomer-specific population PK model was developed with NONMEM 7.3. Simulations were performed in typical adults and infants to investigate differences in S- and R-ketorolac exposure.

Results: S- and R-ketorolac PK were best described with a 3- and a 2-compartment model, respectively. The allometry-based PK parameters accounted for changes between populations. No maturation function of ketorolac clearance could be identified. All model parameters were estimated with adequate precision (relative standard error <50%). Single dose simulations showed that a previously established analgesic concentration at half maximal effect in adults of 0.37 mg/L, had a mean S-ketorolac concentration of 0.057 mg/L, but a mean S-ketorolac concentration of 0.046 mg/L in infants. To match the effective adult S-ketorolac-concentration (0.057 mg/L) in typical infants, the $EC_{50-racemic}$ should be increased to 0.41 mg/L.

Conclusion: Enantiomer-specific changes in ketorolac PK yield different concentrations and S- and R-ketorolac ratios between infants and adults at identical racemic concentrations. These PK findings should be considered when studies on maturational pharmacodynamics are considered.

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1 | INTRODUCTION

Ketorolac tromethamine (ketorolac) is a nonsteroidal anti-inflammatory drug to treat mild to moderate pain.[1–5] The drug consists of an S- and R- enantiomer and is administered as racemic mixture.[6] However, its analgesic effects are only attributed to the S-enantiomer.[7] Ketorolac is primarily metabolised in the liver through oxidation and glucuronidation.[6] Renal excretion is the primary route of elimination for ketorolac and its metabolites.[6] The mechanism of action is not completely understood, but involves the blocking of cyclooxygenases (COX), which are enzymes that convert arachidonic acid into prostaglandins, prostacyclin and thromboxane.[8] By inhibiting both COX-1 and COX-2, pain, fever and inflammation decreases.[8]

In the USA, ketorolac is licensed in children aged >2 years,[9] while in Europe it is licensed in children >16 years.[10] Despite these age restrictions, ketorolac is commonly used from early infancy onwards through paediatric age range. Current intravenous (IV) administration practices are 30 mg of ketorolac tromethamine in adults as a bolus and 0.5–1.5 mg/kg in children and infants as a 10-minute infusion.[9]

The racemic ketorolac concentration (sum of S- and R-enantiomer) providing effective analgesia at 50% of the maximal effect ($EC_{50\text{-racemic}}$) is reported to be 0.37 mg/L after a single dose in adults.[1] No $EC_{50\text{-racemic}}$ has been determined in infants or in children, and simple extrapolation of the adult $EC_{50\text{-racemic}}$ to infants is commonly performed but does not consider the enantiomer-specific changes in the pharmacokinetics (PK) between populations. This is important as previous studies identified changes in the enantiomer-specific ketorolac pharmacokinetics (PK) in various populations separately, such as in infants, toddlers, healthy adults and women at delivery or postpartum.[11–15] These studies showed significant differences in PK parameters between the S- and R-enantiomer, both within and between these populations. To account for population based PK differences, paediatric dosage regimens have been derived that yield the same racemic exposure as in adults.[16] However, due to the effect of maturation and allometry-based changes in the PK for the 2 enantiomers, the same racemic concentration may yield differences in the enantiomer-specific concentrations compared to adults,[11–15] hence a lower/higher S-ketorolac concentration may be obtained with equal racemic concentrations. Since S-ketorolac is solely driving the analgesic effects, more information needs to be obtained on the contribution of S-ketorolac in these populations to assess if population-specific target $EC_{50\text{-racemic}}$ and/or dose adaptions are needed.

To date, no studies have investigated the population PK of ketorolac across a broad range of ages pooled together from different studies. In the present study, data from multiple research groups and studies were pooled in a single population PK modelling analysis approach to quantify the enantiomer-specific PK and study

What is already known about this subject

- The analgesic effects of ketorolac are only attributed to the S-enantiomer.
- Significant differences in pharmacokinetic parameters between the S- and R-ketorolac both within and between various populations have been reported.
- The racemic analgesic concentration reaching 50% of the effect ($EC_{50\text{-racemic}}$) of ketorolac is 0.37 mg/L in adults, and the S-ketorolac contribution, in both adults and infants, to this $EC_{50\text{-racemic}}$ is unknown.

What this study adds

- The $EC_{50\text{-racemic}}$ of 0.37 mg/L contained 0.057 mg/L S-ketorolac in adults and 0.046 mg/L S-ketorolac in infants.
- To reach an S-ketorolac concentration of 0.057 mg/L in typical infants, the target $EC_{50\text{-racemic}}$ in infants should be increased to 0.41 mg/L.
- These pharmacokinetic findings should be considered in studies on maturational pharmacodynamics or optimal dosing regimens.

maturational differences in ketorolac over a range of populations. With the developed population PK model, simulations were performed to investigate the difference in S-ketorolac exposure in infants compared to adults and explore if the contribution of S-ketorolac to the $EC_{50\text{-racemic}}$ is equal between adults and infants or if adjustments to the $EC_{50\text{-racemic}}$ should be made.

2 | METHODS

2.1 | Study information

Studies including enantiomer-specific ketorolac concentrations were identified in literature with the following search terms: ketorolac, pharmacokinetics, intravenous, enantiomer specific and stereoselective on 28 March 2017, including a citation search (PubMed, Web of Science). Ten relevant studies were identified of which 3 study groups were no longer able to provide their former raw data. We

failed to contact 1 group and another group declined to participate in this pooled analysis. In total, 5 study groups contributed data for this pooled analysis.[11–15] A total of 80 subjects were included: infants (*n* = 33, median age 0.83, interquartile range 0.56–1.03 years), children (*n* = 2, 8 and 14 years), adults (*n* = 45, median age 30, interquartile range 26–36 years). A total of 1020 plasma concentrations for S- and R-ketorolac were available (Figure 1). Concentrations ranged from 0.0050 to 4.9 mg/L and 0.010 to 8.9 mg/L for respectively S- and R-ketorolac. The adult population also included data on women 4–5 months after delivery, as enantiomer specific ketorolac PK in these women was found to be similar compared to nonpregnant women.[15] Detailed information on the individual studies is provided in Table 1.

Ketorolac tromethamine was administered as a racemic mixture in all studies. Ketorolac tromethamine dosages were converted and modelled as ketorolac units, based on their molecular weights (376.409 g/mol ketorolac tromethamine = 255.273 g/mol ketorolac base).[17] In total, 16 (3% of total) of the S-enantiomer concentrations were below the lower limit of quantification, of which 11 were also below the limit of detection. None of the R-enantiomer concentrations were below the lower limit of quantification. All data below limit of detection were removed and all other data were included.[18]

2.2 | Population PK modelling

A population PK model of S- and R- ketorolac was developed using nonlinear mixed effect modelling software NONMEM version 7.3 (ICON Development Solutions, Hanover, MD, USA), using the first-order estimation method with interaction option and subroutine ADVAN13 with TOL4.[19] Pirana (version 2.9.0), R (version 3.3.2)[20] and PsN (version 3.4.2)[21] software were used for data formatting, visualizations and analysis of model outputs.

Model building process was performed as follows: (i) structural- and statistical model; (ii) covariate model; and (iii) internal model validation.[22] Selection between submodels was made by the likelihood ratio test using a difference in objective function value (OFV) of ≥7.88, resulting in statistical significance between nested models with 1 degree of freedom (*P*-value <.005, assuming a χ^2 distribution). Additionally, model selection was based on goodness-of-fit plots, the relative standard errors (RSE) of parameter estimates, normality distribution of the statistical model, and the condition number,[23] which was determined by the ratio of the largest to the smallest value.

Population PK parameters were estimated in separate models for S- and R-ketorolac during structural model building. Allometric scaling
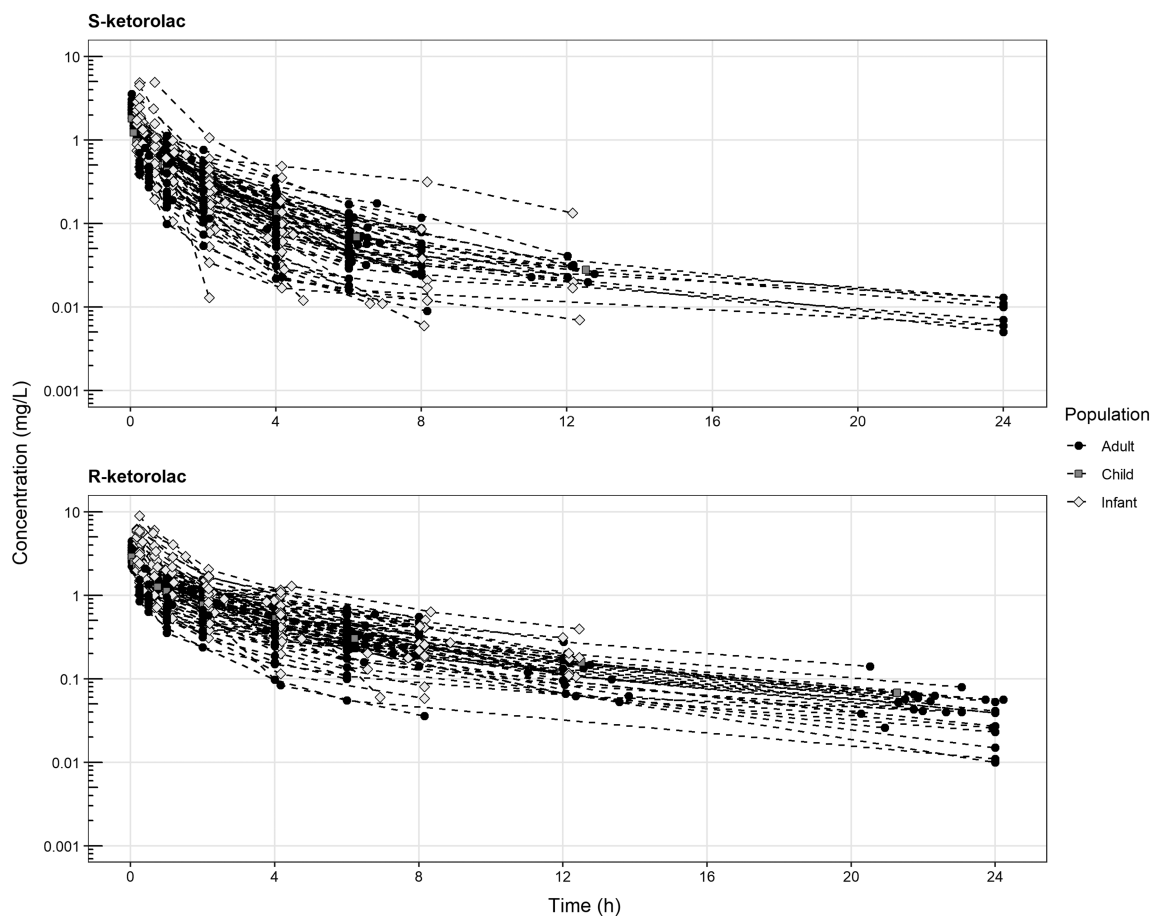

FIGURE 1 Ketorolac concentrations (mg/L) over time (h) for the S- (top) and R-ketorolac (bottom)

TABLE 1 Characteristics of the subjects included in the pooled pharmacokinetic analysis. Separate columns are shown for the individual studies. Data are reported by absolute number or by median [interquartile range], unless otherwise specified. Abbreviations: IV = intravenous; HPLC-UV = high-performance liquid chromatography–ultraviolet; LC–MS = liquid chromatography–mass spectrometry; LOD = limit of detection; LLOQ = lower limit of quantification

	Lynn et al.[11]	Lynn et al.[12]	Hamunen et al.[13]	Lorenzini et al.[14]	Välitalo et al.[15]	Pooled dataset
Population	Infants	Infants	Adults + children	Adults	Adults	Infants, children and adults
Number of patients	8	25	20	11	16	80
Age (y)	0.37 [0.30–0.41]	0.91 [0.82–1.09]	29 [23.8–38.3]	26 [23.5–33.5]	32 [29.5–34.3]	23 [0.90–31]
Bodyweight (kg)	5.98 [5.58–6.66]	9.4 [8.5–10.6]	70.5 [59.8–76.8]	75 [72–79]	62 [58.6–67.3]	56 [5.36–99]
Ketorolac tromethamine dose	0.5 or 1.0 mg/kg	0.5 or 1.0 mg/kg	0.5 mg/kg	20 mg	30 mg	-
Pure ketorolac dose (mg)	3.865 [3.27–4.36]	5.83 [3.59–6.92]	23.91 [19.41–27.42]	13.56	20.345	6.92 [4.11–20.34]
Number of samples, total	68	243	400	149	160	1,020
Number of samples, per subject	9 [8–9]	10 [10–12]	20 [20–21]	14 [13.5–14]	10	12 [10.0–14.8]
Duration of IV administration	10 min	10 min	30 s	30 s	30 s	-
Blood sample collection at time after administration	0, 5, 30 min or 1,2, 4, 8, 12 h.	0, 5, 30 min, or 1, 2, 4, 8, 12 h.	2, 5, 10, 20, 45 min, 1, 2, 4, 6–8, 12–16 and 24 h.	15, 30 min, 1, 2, 4, 6 and 24 h	1, 2, 4, 6 and 8 h	-
Analytical technique	HPLC-UV	HPLC-UV	HPLC-UV	2-dimensional LC-MS	HPLC-UV	-
LLOQ (µg/mL)	0.01	0.01	0.02	0.005	0.025	-
LOD (µg/mL)	0.001	0.001	0.02	0.005	0.01	-

based on bodyweight (BW) was applied to all PK parameters from the onset of structural model development (equation 1) in which 1, 2 and 3 compartment models were explored.

$$\theta_{TV} = \theta_p \times \left(\frac{Body\ weight}{70}\right)^{exp} \qquad (1)$$

In this equation, θ_{TV} represents the typical parameter estimate, θ_p represent the population parameter estimate for a BW of 70 kg, and *Body weight* represents the BW value for an individual subject. *Exp* is an allometric exponent fixed to 0.75 for clearance (CL) and intercompartmental CL (Q) and fixed to 1 for central and peripheral volumes of distribution. Interindividual variability (IIV) in model parameters was assumed to be log-normal distributed and was tested sequentially on all PK parameters according to equation 2.

$$\theta_i = \theta_{TV} \times \exp(\eta_i) \qquad (2)$$

Where θ_i is the individual parameter value, θ_{TV} is the typical population parameter value and η_i is a random variable from normal distribution with a mean of zero and estimated variance of ω^2. The inclusion of IIV on PK parameters was tested sequentially, with the most significant OFV reduction of ≥7.88 entering the model first. Inclusion of IIV was stopped when a successful completion of the covariance step was not obtained or no further significant reduction in OFV was achieved.

The effect of age as a covariate was explored using a linear and power function based on equation 3.

$$\theta_{TV} = \theta_p \times \left(\frac{Age}{30}\right)^{exp} \qquad (3)$$

In this equation, θ_{TV} represents the typical PK parameter estimate, θ_p represent the population parameter estimate for the covariate relationship, and *age* represents the age value for an individual, which is normalized with the median age value (30 years) representing the median value of the age in the dataset. *Exp* is an exponent fixed to 1 for a linear function or estimated for a power function. Moreover, a sigmoidal maturation model was explored to describe maturation of clearance (equation 4).

$$F_{Age} = \frac{Age^{HillCL}}{Age^{HillCL} + Age50^{HillCL}} \qquad (4)$$

In this equation, F_{Age} is the proportional maturation factor for age on CL, *age* represents the age value for an individual, *Age50* is the age at which CL is 50% that of the mature value and *HillCL* is the Hill coefficient for the maturation function and is estimated or fixed to 1. Covariates were included following a forward inclusion method, in which the most significant covariate was included in the model (OFV reduction of ≥7.88). Subsequently, S- and R-ketorolac models were combined into a single model for the

quantification of covariance between random effects. Covariance between random effects in the combined S- and R-ketorolac model were investigated using full and reduced omega blocks. Additive, proportional and combined residual error models were tested. The residual error was estimated for each enantiomer and for each study separately. Afterwards, similar residual error estimates between studies were combined if required to improve numerical stability.

2.3 | Internal model validation

A nonparametric bootstrap analysis was performed (*n* = 1000) to evaluatev the stability and robustness of the final model. Median values and the 95% confidence interval of parameter estimates obtained from the bootstrap were compared with parameter estimates obtained from the final model.

A prediction-corrected visual predictive check was conducted by simulating the original dataset 500 times, using the final PK model in NONMEM. The prediction-corrected median and 5th and 95th percentiles of the simulated data were calculated and compared with the distributions of the observations to evaluate the predictive performance of the median trend and variability of the final PK model. Additionally, a normalized prediction distribution error (NPDE) analysis was performed to evaluate the performance of the final model. For this, the original dataset was simulated 1000 times. Thereafter, each observed concentration was compared to the simulated concentrations using the NPDE package in R.[24]

2.4 | Model simulation

Using the PK parameter estimates from the final model, simulations were performed to investigate the difference in the S-ketorolac exposure over time. Due to minimal data availability in the children population (*n* = 2), simulations were performed for the infant and adult populations only. Simulations were performed for typical adults over a BW range of 48.6–99.6 kg receiving a fixed IV bolus dose of 30 mg ketorolac tromethamine (racemic ketorolac) over 30 seconds. Simulations were performed for typical infants over a BW range of 5.3–10.6 kg. Since recommended doses for infants were not available, doses as reported in the clinical studies (0.5 mg/kg IV ketorolac tromethamine over 10 minutes) were used.[11,12]

From these simulations, the time point at which the racemic ketorolac concentration reached the $EC_{50-racemic}$ of 0.37 mg/L was determined as a measure for the time above EC_{50}, and stratified at this time point into the S- and R-enantiomer specific contribution per BW. Thereafter, the contribution of S-ketorolac at the racemic ketorolac concentration of 0.37 mg/L in typical infants was compared with the adult derived S-ketorolac concentrations and changes to the $EC_{50-racemic}$ parameter resulting in similar S-enantiomer values were proposed for the different populations.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

3.1 | Population PK modelling

For S-ketorolac, a 3-compartment model best described the data in infants, children and adults. IIV was identified on CL, and on both intercompartmental clearances (Q2 and Q3). R-ketorolac concentrations were best described with a 2-compartment model for all populations. IIV was identified on CL, central volume of distribution (V1) and peripheral volume of distribution (V2) for R-ketorolac. A schematic model structure of the combined models is provided in Figure S1.

Age as a covariate with a linear or power relationship did not give a significant reduction in the OFV. Furthermore, the addition of a sigmoidal maturation function of CL gave a nonsignificant drop in OFV (ΔOFV = −10.8) after the addition of 4 parameters and resulted in high RSEs for the *Age50* parameters (RSE > 500%). Fixing the *HillCL* to 1 also did not improve the model fit. Therefore, no maturation of ketorolac CL could be identified on top of the allometry-based changes in this population.

Residual variability was best described using a proportional error model for both enantiomers. Both studies of Lynn *et al.*[11,12] had a proportional residual error (σ^2) of approximately 0.05 for both enantiomers and the remaining studies had a residual error of approximately 0.02 for both enantiomers. Therefore, the residual variability for both studies of Lynn were combined into 1 residual parameter for both enantiomers while the residual variability of the remaining studies were combined into a different residual parameter for both enantiomers, which increased numerical stability of the model. The condition number was high but acceptable with a value of 882. An omega block matrix, with covariance between all random effects was implemented. Overall, there was good agreement between estimated parameters and bootstrap derived estimates and their confidence intervals (Table 2, Table S1), suggesting that the model is robust and supported by the data.

Figures 2 and S2–S4 show the individual empirical Bayes estimates and η distributions of S- and R-ketorolac PK parameters *vs* BW. No bias over BW was identified, indicating that the allometry-based scaling was able to account for the BW changes in the PK parameters. Figure S5 displays the goodness-of-fit plots of the final model. The individual predicted concentration was normally distributed around the line of unity and the conditional weighted residuals with interaction were mostly symmetrically distributed around zero and therefore showed the model accurately described the data. Most conditional weighted residuals with interaction were heterogeneously scattered around zero. However, a small bias for points at $t = 4$ h and $t = 6$ for S-ketorolac could be observed.

The prediction-corrected visual predictive check for the final model is presented in Figure 3. The 5th, 50th and 95th percentiles of observed concentrations were mostly within the predicted 95% confidence interval of these percentiles, demonstrating good predictability of the model in the median trend and the variability of the data. For both enantiomers, the NPDEs follow a normal distribution (Figures S6 and S7). No trends were observed in NPDE *vs* time and NPDE *vs* predicted concentrations, confirming that the model adequately quantified both the typical trend and variability in observed concentrations across all studies.

3.2 | Simulations to investigate the contribution of S-ketorolac at the EC$_{50\text{-racemic}}$ between infants and adults

Figure 4 shows the predicted racemic ketorolac concentrations over time in typical infants (Figure 4A) and typical adults (Figure 4B). Less variability was observed in the typical profiles of infants compared to adults, due to the flat dosing schedule of ketorolac in adults compared to weight-based dosing in infants. In adults, the concentration may decrease to the EC$_{50\text{-racemic}}$ of 0.37 mg/L in a range of 4.5–6 h after dosing, dependent on an individual's BW (Figure 4B), whereas the racemic concentrations remained above 0.37 mg/L until only 4 h with current dose recommendations in infants (Figure 4A).

In Figure 4C and D, the contribution of S- and R-ketorolac concentrations to the total racemic concentration is presented when a racemic concentration of 0.37 mg/L is reached. The S-ketorolac concentrations in infants remained constant with increasing BW due to weight based dosage regimens, while in Figure 4D, the S-ketorolac concentrations in adults increased with increasing BW. Based on the simulations in adults, the EC$_{50\text{-racemic}}$ of 0.37 mg/L correlated with a mean of 0.057 mg/L S-ketorolac in typical adults over the BW range of 48.6–99.6 kg (Figure 4D). While in typical infants over the BW range of 5.3–10.6 kg, a racemic concentration of 0.37 mg/L only had a mean of 0.046 mg/L S-ketorolac (Figure 4C). These results indicate that at identical racemic concentrations, active S-ketorolac concentrations were on average 19.3% lower in infants. Furthermore, this racemic concentration was reached at shorter times after dosing, reducing the duration of efficacy even further.

Subsequently, we investigated at what racemic ketorolac concentration the S-ketorolac concentration of 0.057 mg/L was reached (Figure 4E,F). This was reached at a racemic ketorolac concentration of 0.41 mg/L in infants and remained constant over different weights. These results also show that even if there is only a small change in EC$_{50\text{-racemic}}$ from 0.37 to 0.41 mg/L, an almost 20% increase in S-ketorolac concentrations is achieved and racemic concentrations should therefore be interpreted with caution.

TABLE 2 Population pharmacokinetic parameters of the final model for both S- and R-ketorolac, and the results of the bootstrap analysis

Parameter	Final S-parameter value (relative standard error %) [shrinkage %]	S-bootstrap median [95% confidence interval]	Final R-parameter value (relative standard error %) [shrinkage %]	R-bootstrap median [95% confidence interval]
CL (L/h/70 kg)$^{0.75}$	3.97 (6)	3.89 [3.41-4.53]	1.45 (6)	1.43 [1.33-1.55]
V1 (L/70 kg)	4.03 (11)	4.08 [3.51-4.72]	4.43 (11)	4.31 [3.92-4.79]
Q2 (L/h/70 kg)$^{0.75}$	1.86 (7)	1.81 [1.36-2.15]	1.90 (7)	1.92 [1.50-2.26]
V2 (L/70 kg)	43.3 (12)	43.8 [22.4-58.7]	5.18 (12)	4.95 [4.27-5.50]
Q3 (L/h/70 kg)$^{0.75}$	19.7 (11)	19.1 [15.1-24.1]	-	-
V3 (L/70 kg)	5.90 (13)	5.49 [4.89-6.11]	-	-
Interindividual variability [ω²]				
ω² CL	0.221 (22) [3]	0.210 [0.134-0.304]	0.112 (25) [4]	0.108 [0.0728-0.168]
ω² V1	-	-	0.158 (43) [6]	0.147 [0.0719-0.252]
ω² Q2	0.178 (41) [15]	0.191 [0.0947-0.440]	-	-
ω² V2	-	-	0.158 (52) [10]	0.148 [0.0702-0.247]
ω² V3	0.195 (30) [9]	0.204 [0.113-0.350]	-	-
Residual variability [σ²]				
σ² proportional error[11,12]	0.075 (16) [16]	0.0663 [0.0403-0.110]	0.0585 (16) [13]	0.0559 [0.0365-0.0868]
σ² proportional error[13-15]	0.0169 (11) [15]	0.0159 [0.0122-0.0202]	0.0176 (14) [14]	0.0169 [0.0130-0.0213]

CL = clearance; V1 = central volume of distribution; V2 = peripheral volume of distribution; V3 = peripheral volume of distribution; Q2 = intercompartmental clearance between V1 and V2; V3 = peripheral volume of distribution; Q3 = inter-compartmental clearance between V1 and V3.
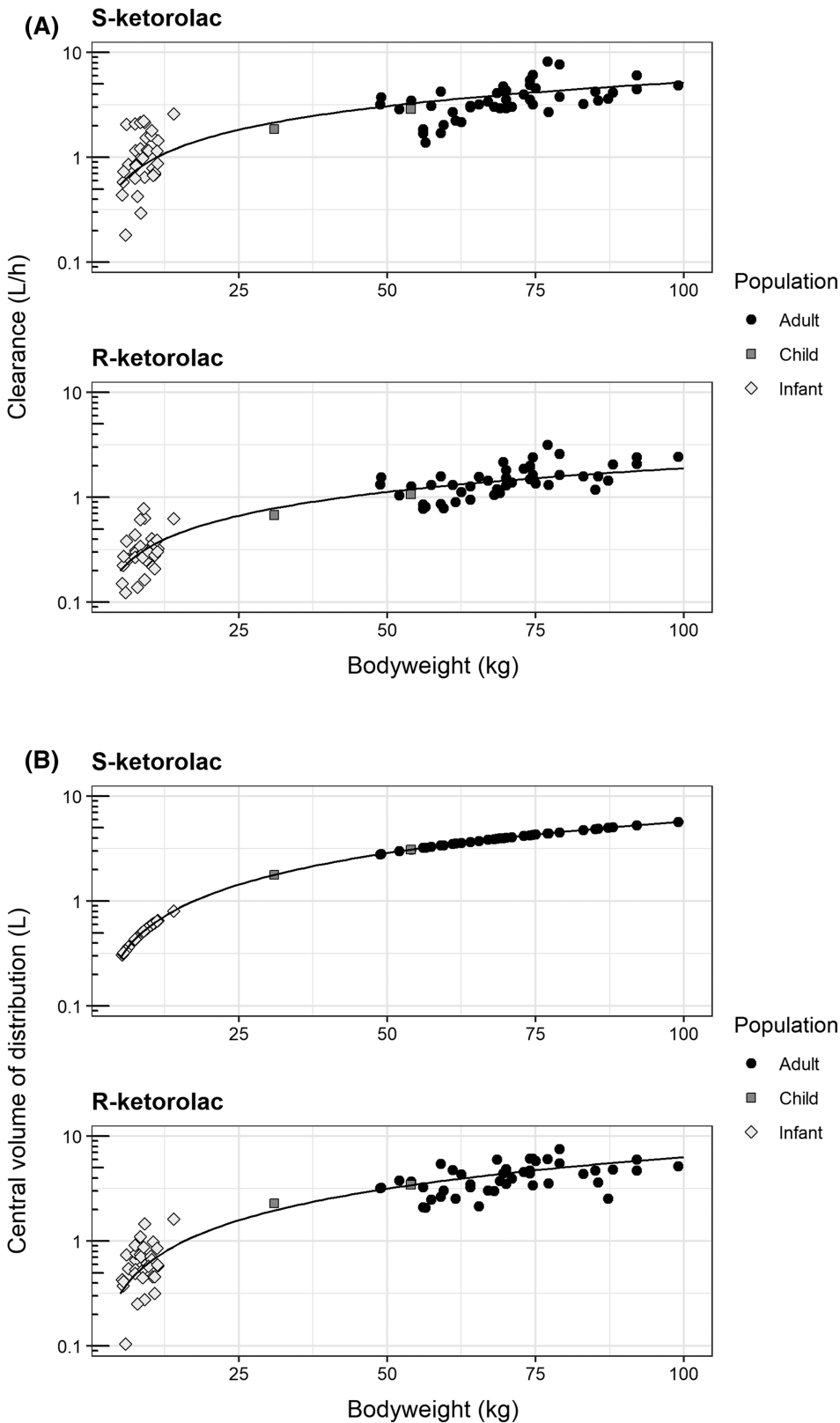
FIGURE 2 (A) Semilogarithmic plots of ketorolac clearance (L/h) *vs* bodyweight (kg) for S- and R-ketorolac. The black line denotes the typical relationship between ketorolac clearance *vs* bodyweight using an allometric function with an exponent of 0.75. (B) Semilogarithmic plots of ketorolac central volume of distribution (V1, L) *vs* bodyweight (kg) in S- and R-ketorolac. The black line denotes the typical relationship between ketorolac clearance *vs* bodyweight using an exponential function with an exponent of 1

Moreover, based on Figure 4C and E, the contribution of S- and R-ketorolac concentrations in typical infants remained the same across all BW, while a lower contribution of R-ketorolac can be observed at the higher BW in adults. Therefore, to reach the same ketorolac concentrations across all BW, dose adjustment in adults based on BW may be required, which would reduce the variability in this population.
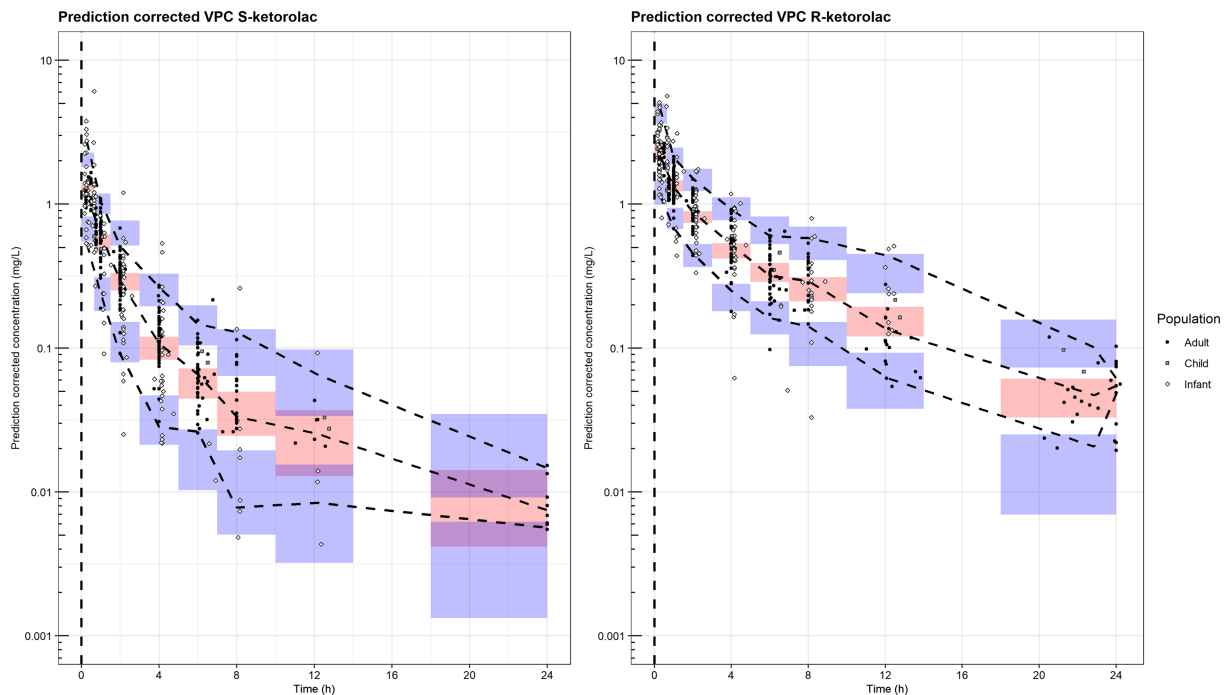
FIGURE 3 Prediction-corrected visual predictive check (VPC) of the final pharmacokinetic model for S-ketorolac (left) and R-ketorolac (right). Dots represent observed data points; the dashed black lines represent the 5th, 50th and 95th percentile of observed data. Shaded blue areas depict the model predicted 95% confidence intervals of the simulated percentiles. Vertical dashed line indicates time of start infusion

4 | DISCUSSION

This study had 2 objectives. Firstly, to perform a pooled analysis to quantify the enantiomer-specific ketorolac PK across multiple populations, ranging from infants to adults. Secondly, to investigate the differences in S-ketorolac exposure in infants compared to adults to better understand the analgesic properties.

Focusing on the first objective, a single model was developed that was able to describe the PK over all populations. Furthermore, the PK parameters obtained from the final PK model of both S- and R-ketorolac confirm that significant differences exist between populations and between enantiomers, driven by allometry-based changes in the parameters.[11–15]

By use of a simulation-based modelling approach, the contribution of S-ketorolac to the racemic concentration was investigated, which showed clear differences in the reached S-ketorolac concentrations and the time above the EC_{50} in both populations. This study further illustrates that a $EC_{50-racemic}$ of 0.37 mg/L should be used with caution for the optimization of dosage regimens in infants and targeting a higher $EC_{50-racemic}$ or using a target S-ketorolac concentration should be performed.[1]

Since BW with allometric scaling was included a priori in the structural model on all PK parameters of both S- and R-ketorolac, the racemic ketorolac concentrations would change with increasing BW, also when a fixed dose was administrated in adults. This resulted in variability in the S- and R-ketorolac concentrations in typical adults in various BW in our simulations. However, current guidelines recommend a fixed racemic ketorolac IV single dose of 30 mg or 30 mg

every 6 h in all patients aged <65 years and >50 kg. These results show that from a PK perspective, the effect of BW on S-ketorolac exposure might be crucial to adjust dosing. This might suggest using BW-dependent dosing in adults to attain similar S-ketorolac concentrations over the BW range.

Assuming that a S-ketorolac concentration of 0.057 mg/L is targeted, the $EC_{50-racemic}$ in infants should be increased to 0.41 mg/L. This corresponds with an 11% increase in $EC_{50-racemic}$ in typical infants to attain the same S-ketorolac concentration as in typical adults. Remarkably, an 11% increase in $EC_{50-racemic}$ would result in 20% higher S-ketorolac concentrations in typical infants. This could be explained by the differences in PK parameter estimates between S- and R-ketorolac and allometric scaling based on BW to all PK parameters, giving rise to a change of the contribution of each enantiomer to the racemic concentration over time.

However, it is important to note that the simulated S-ketorolac concentrations in infants and adults and the racemic ketorolac concentrations are obtained after simulation of a single dose of 30 mg in adults and 0.5 mg/kg in infants, typically used in clinical practice. The S-ketorolac exposure will be different after multiple dosing due to different CL rates for S- and R-ketorolac; therefore the contribution of S- and R-ketorolac to the racemic concentration changes constantly over time in both infants and adults. However, as the $EC_{50-racemic}$ of 0.37 mg/L in adults was established upon a single dose, the established contribution of the active S-ketorolac concentration to this value is reliable. Overall, this pooled analysis revealed that the racemic ketorolac $EC_{50-racemic}$ cannot simply be extrapolated between different populations when the pharmacological effect is
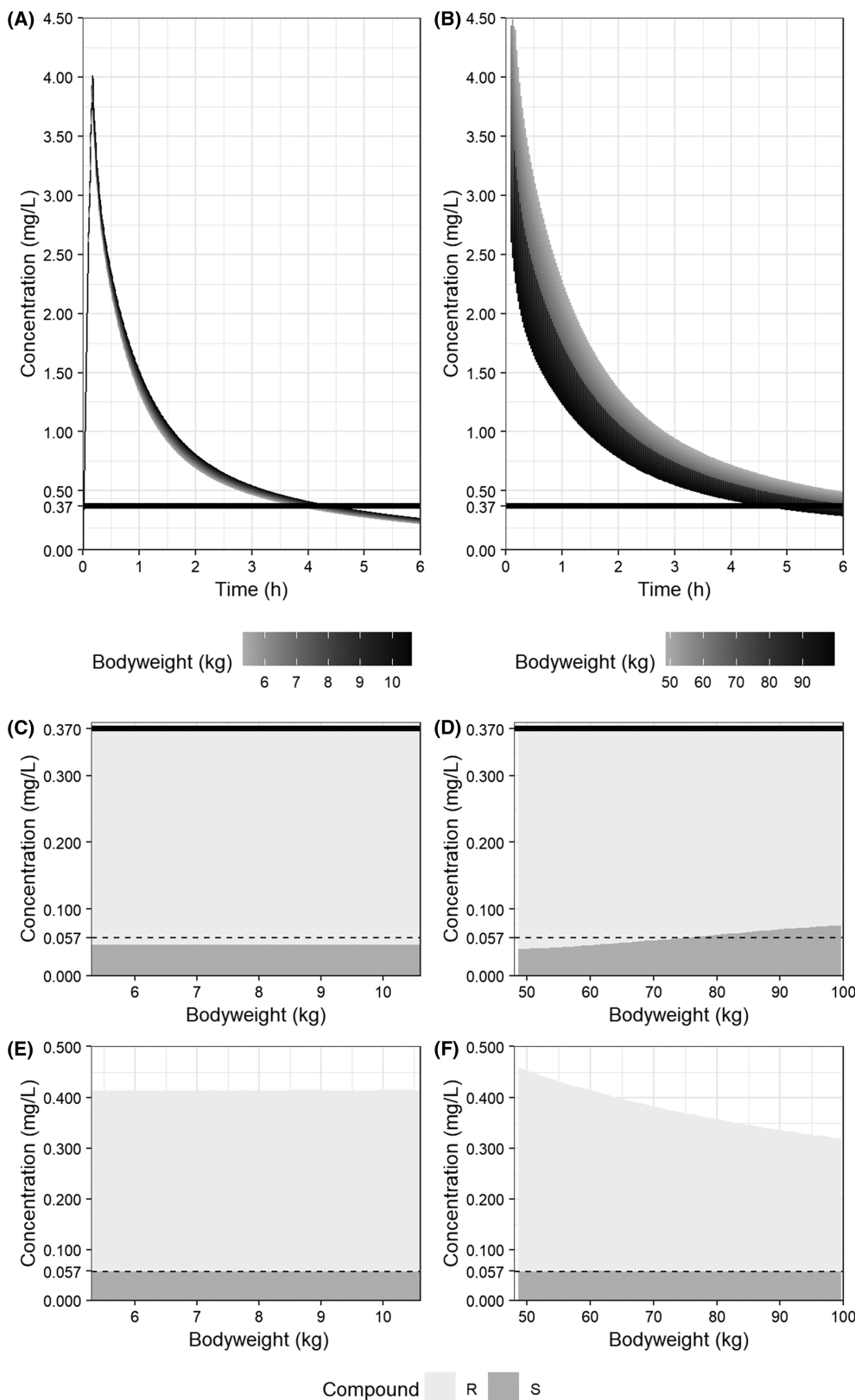
FIGURE 4 Simulated concentrations of ketorolac in typical infants (bodyweight range of 5.3–10.6 kg; left column) and adults (bodyweight range of 48.6–99.6 kg; right column), respectively. The grey–black colour trend reflects the bodyweight range in infants (A) and adults (B), respectively; dark grey reflects the S-enantiomer ketorolac concentration (C–F), light grey the racemic (S + R) ketorolac concentration (C–F). The black line indicates the analgesic $EC_{50-racemic}$ of 0.37 mg/L (A–D). The black dashed line indicates the mean adult S-ketorolac concentration at the $EC_{50-racemic}$ (0.057 mg/L, C–F). (A) Ketorolac concentrations over time after a single intravenous dose of 0.5 mg/kg over 10 minutes in typical infants. (B) Ketorolac concentrations over time after a single intravenous dose of 30 mg over 30 seconds in typical adults. (C) Enantiomer-specific composition of ketorolac in typical infants, when using the $EC_{50-racemic}$ of 0.37 mg/L in adults. (D) Enantiomer-specific composition of ketorolac in typical adults, when using the $EC_{50-racemic}$ of 0.37 mg/L in adults. (E) Composition of racemic ketorolac in typical infants when the adult S-ketorolac concentration (0.057 mg/L) is applied. (F) Composition of racemic ketorolac in typical adults, when the adult S-ketorolac concentration (0.057 mg/L) is applied. The EC_{50} ketorolac concentration of 0.37 mg/L yields adequate analgesia in 50% of the adults. Simulations of single doses revealed that this concentration had a mean of 0.057 mg/L S-ketorolac in typical adults, but a mean of only 0.046 mg/L S-ketorolac in typical infants

only due to 1 specific enantiomer. Consequently, this analysis also serves as an example to not only focus on the changes in racemic ketorolac concentrations between populations, but also to reflect on the enantiomer-specific contributions if relevant for a given compound.[25]

A limitation of this study is solely the focus on PK based differences between the studied populations. This study does not take potential maturational differences in pharmacodynamics of the S-enantiomer into account. Unfortunately, no data are currently available on these maturational differences which should be a priority

for future research to further improve dose optimization and combine the current findings with the pharmacodynamic response in each population. Secondly, not all available PK data from literature were included in this study and there was a limited number of children (n = 2) included. The reason is our inability to include all published datasets in children.[13,26,27] Based on a systematic search, we identified and contacted all relevant research groups with data in children, and provided them with access to the study protocol. Based on this study protocol, some groups could not retrieve their historical datasets, while others decided not to share data. As highlighted by Anderson and Merry, data sharing—also within an academic setting—remains an issue.[28] The inclusion of additional studies would also enable the identification of other covariates besides BW that may explain the remaining variability between patients, specifically in infants (Figures 2, S2, S3). Additional data in patients younger than 2 years may assist in the quantification of maturational changes in CL with improved parameter certainty. Lastly, IIV between patients was not included in the simulations, therefore variability in ketorolac concentrations per BW was not determined. Consequently, a larger variability in ketorolac concentrations across various BW could be expected, since only typical individuals were simulated in this study.

In conclusion, the present study is the first to quantify enantiomer-specific changes in ketorolac PK between multiple populations in a pooled analysis. This analysis revealed differences in concentrations and the ratios of both enantiomers over time between infants and adults. Simulations showed the difference in S-ketorolac exposure between infants and adults, in which a deviation between S-ketorolac concentrations between infants and adults is present at equal racemic concentrations. These differences in S-ketorolac concentrations may influence the analgesic efficacy of ketorolac dosing in all populations and should be investigated further.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

Wrote, provided critical revisions and approved manuscript: M.E.C., M.J.E., A.M.L., A.S., D.T., Y.D., K.T.O., K.A., P.M. Designed research: M.E.C., M.J.E., K.A., P.M. Collected data: A.M.L., A.S., Y.D., K.T.O., K.A. Analysed data: M.E.C., M.J.E., K.A., P.M.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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