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CLINICAL TRIAL

# Dose evaluation of intravenous metamizole (dipyrone) in infants and children: a prospective population pharmacokinetic study

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## Abstract

**Purpose** The prodrug metamizole is prescribed intravenously for postoperative pain in children, including off-label use in infants < 1 year. We aimed to assess the pharmacokinetics of the main metabolites of metamizole in children aged 3–72 months.

**Methods** A single dose of 10 mg/kg metamizole was administered intravenously for postoperative analgesia. Pharmacokinetic samples were drawn at predefined time points. Pharmacokinetics of the main active metabolite 4-methylaminoantipyrine and three other metabolites was characterized by both non-compartmental and population pharmacokinetic analysis. $AUC_{0-inf}$ of 4-methylaminoantipyrine was calculated by non-compartmental analysis for two age cohorts (3–23 months, 2–6 years) and compared with the 80–125% range of adult dose–adjusted reference exposure ($AUC_{ref}$). Population pharmacokinetic analysis investigated age and weight dependency of the pharmacokinetics and optimal dosing strategies to achieve equivalent adult exposure.

**Results** A total of 25 children aged 5 months–5.8 years (7.8–24.8 kg) with at least one concentration sample were included; 19 children had ≥ 5 predefined samples up to 10 h after metamizole dose administration. $AUC_{0-inf}$ of 4-methylaminoantipyrine in children 2–6 years was 29.9 mg/L/h (95% CI 23.4–38.2), significantly lower than $AUC_{ref}$ (80–125% range 39.2–61.2 mg/L/h). $AUC_{0-inf}$ of 4-methylaminoantipyrine in infants < 2 years was 43.6 mg/L/h (95% CI 15.8–119.0), comparable with $AUC_{ref}$, while infants < 12 months

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showed increased exposure. Observed variability could be partially explained by covariates weight and age.
**Conclusions** Age-related changes in pharmacokinetics of 4-methylaminoantipyrine requires reduced weight–based IV dosing in infants < 1 year compared with infants and children up to 6 years (5 versus 10–20 mg/kg) to achieve equivalent adult exposure.
**Trial registration** ClinicalTrials.gov identifier: NCT02660177.

**Keywords** Metamizole · Dipyrone · Pharmacokinetics · Children · Infants

**Abbreviations**

| | |
|---|---|
| AA | 4-Aminoantipyrine |
| AAA | 4-Acetyl aminoantipyrine |
| ADR | Adverse drug reaction |
| AEs | Adverse events |
| AIC | Akaike information criterion |
| AUC | Area under the curve |
| BSV | Between-subject variability |
| CL | Clearance |
| $C_{max}$ | Maximal plasma concentration |
| COX | Cyclooxygenase |
| CYP | Cytochrome P450 |
| FAA | 4-Formylaminoantipyrine |
| IV | Intravenously/intravenous |
| $k_h$, | Hydrolysis rate of metamizole, MAA formation rate |
| LLOQ | Lower limit of quantification |
| MAA | 4-Methylaminoantipyrine |
| NAT2 | *N*-Acetyltransferase 2 |
| OFV | Objective function value |
| PACU | Post-anesthesia care unit |
| PK | Pharmacokinetics(s) |
| PPK | Population PK |
| $t_{1/2}$ | Elimination half-life |
| $T_{max}$ | Time of $C_{max}$ |
| TV | Typical value |
| VPC | Visual predictive check |
| WHO | World Health Organization |

## Introduction

Metamizole, or dipyrone, is a pyrazolone derivative used for treatment of severe pain and/or fever [1]. It has spasmolytic properties and a favorable safety profile regarding gastrointestinal, hepatic, and renal adverse effects compared with other non-opioid analgesics [2, 3]. Its use is, however, questioned due to a rare risk of potentially life-threatening agranulocytosis, the reason why it has been banned in multiple countries [4]. The exact mechanism of analgesic action is not fully understood. Inhibition of cyclooxygenase isoforms 1 and 2 and of prostaglandin $E_1$ and $E_2$ synthesis has been demonstrated. Additionally, actions on opioid and cannabinoid systems as well as activation of ATP-sensitive $K^+$ channels are well documented [5–7].

Metamizole is a prodrug that is rapidly non-enzymatically hydrolyzed to an active metabolite, 4-methylaminoantipyrine [8]. 4-Methylaminoantipyrine (MAA) is further metabolized to another active metabolite, 4-aminoantipyrine, and an inactive end-metabolite, 4-formyl-aminoantipyrine (Fig. 1). The influence of cytochrome P450 enzymes on the oxidative biotransformation of MAA to 4-aminoantipyrine (AA) is not yet fully explained [9, 10]. In vitro and in vivo evidence has suggested a role for CYP2C19 and, more recently, also of other cytochrome P450 (CYP) isoforms and human myeloperoxidase in granulocytes [10, 11]. AA is acetylated to inactive 4-acetyl-aminoantipyrine by *N*-acetyltransferase 2 [12]. Also, AA is assumed to be metabolized to the inactive end-metabolite 4-formylaminoantipyrine (FAA). In total, more than 20 metabolites are currently known [8].

The analgesic effect of metamizole seems to correlate mainly with MAA exposure [13]. The drug has been shown to be an effective analgesic in children at doses of 15 mg/kg [14, 15]. Metamizole is one of the few non-opioid analgesics, along with paracetamol and ketorolac, which can be administered intravenously, which is a significant advantage in children postoperatively. But according to the current label, IV use is off-label in infants < 12 months or with a body weight < 9 kg, and intramuscular administration is recommended in these patients [16]. In practice however, IV is favored over IM administration also in infants < 12 months, since IV application allows for complete and rapid absorption, associated with a quick onset of action, whereas IM applications leads to erratic and delayed absorption, pain, and risks of infection/inflammation at the injection site. The licensed parenteral pediatric dosing scheme is summarized in Table 1. However, dosing in mg/kg is more common with inconsistent dosing practices. Among Swiss pediatric hospitals for example, doses ranging from 5 to 20 mg/kg for repetitive dosing, or even up to 40 mg/kg for a single IV dose are used, including off-label IV use in infants of age 3–12 months [16].

Pharmacokinetics of metamizole metabolites is well described in adults (licensed dose 500–1000 mg, max. 4 times daily), while such information is lacking for infants and children, despite its use for almost 100 years. A pharmacokinetic study in children aged 1–11 years reports increased urinary metabolite excretion in younger children compared with adults following a single oral dose of 8 mg/kg suggesting different pharmacokinetic properties [17]. No data in infants < 1 year have been available.

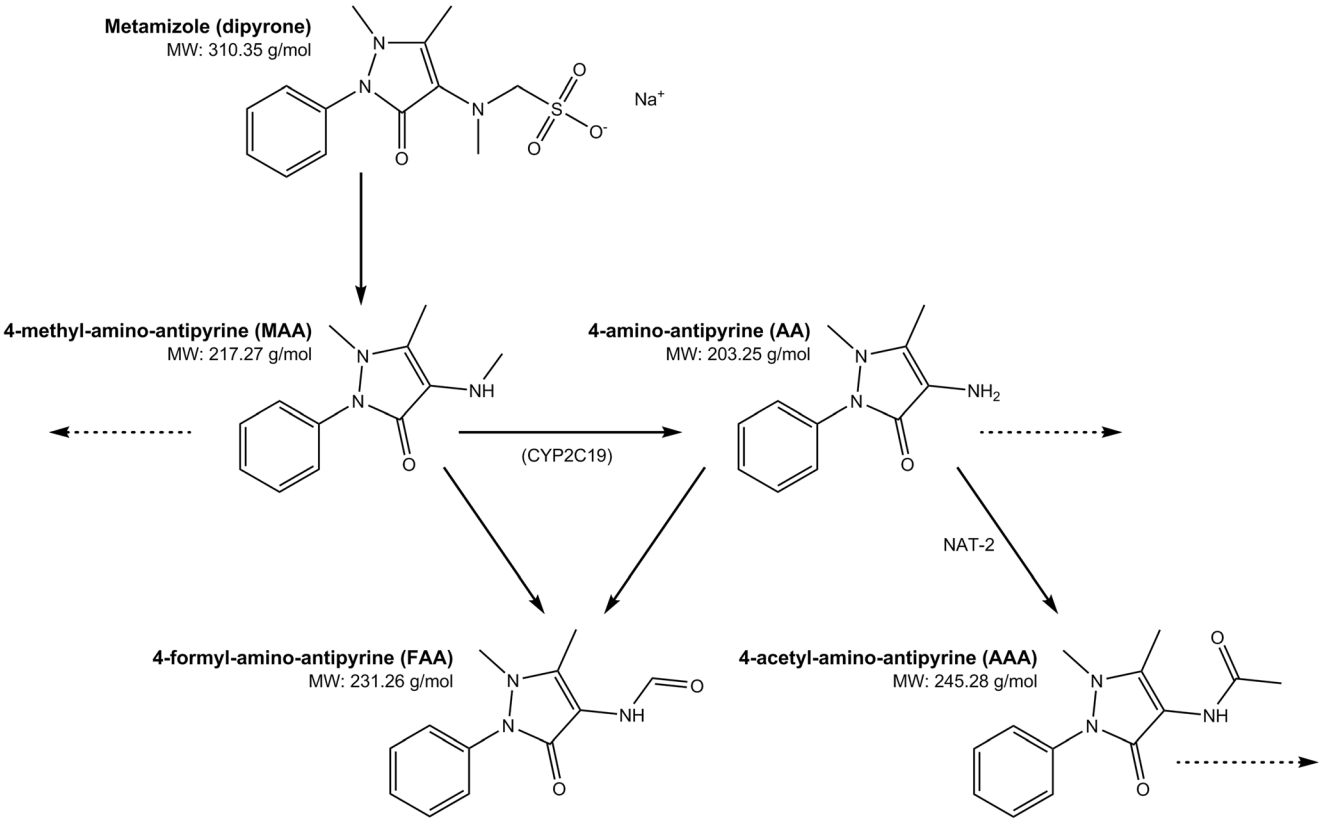


**Fig. 1** The metabolism of metamizole and its major metabolites

The objectives of this study were (i) to characterize the pharmacokinetics of the main metabolites of metamizole following a single IV dose for postoperative analgesia in infants and children 3 to 72 months of age (two age cohorts; infants 3–23 months and children 2–6 years) and (ii) to propose a rationale for an optimal mg/kg-dosing strategy in infants and children.

## Methods

### Trial design

A single-center, open-label, prospective study was conducted at the University of Basel Children's Hospital after approval by the local ethics committee (ClinicalTrials.gov Identifier:

**Table 1** Licensed parenteral dosing of metamizole (Novalgin®, 500 mg/mL, solution for injection) for children < 6 years and adults

| Body weight | Route of administration | Single dose | Corresponding calculated weight-based dose range[a] |
|---|---|---|---|
| 5–8 kg | Only IM | 0.1–0.2 mL = 50–100 mg | 6.2–20.0 mg/kg |
| 9–15 kg | IM or IV | 0.2–0.5 mL = 100–250 mg | 6.7–27.8 mg/kg |
| 16–23 kg | IM or IV | 0.3–0.8 mL = 150–400 mg | 6.5–25.0 mg/kg |
| 24–30 kg | IM or IV | 0.4–1.0 mL = 200–500 mg | 6.7–20.8 mg/kg |
| Adults | | | |
| 50–100 kg | IM or IV | 1–2 mL = 500–1000 mg (max. single dose 5 mL = 2500 mg; max. daily dose 5000 mg) | 5–20 mg/kg (max. single dose 25–50 mg/kg; max. daily dose 50–100 mg/kg) |

*IM* intramuscular, *IV* intravenous

[a] Calculated as follows: minimal recommended single dose / upper limit of body weight range = minimal weight–based dose and maximal recommended single dose / lower limit of body weight range = maximal weight–based dose

In children < 1 year, only IM administration is recommended. Injection may be repeated after 6–8 h

NCT02660177) between January 2016 and December 2017. Infants and children aged between 3 months and 6 years (72 months) of age with a body weight > 5 kg, who were scheduled for elective in- or outpatient surgery with intended administration of IV metamizole as part of the local standard postoperative pain management, were eligible for the study.

The main exclusion criteria were premature birth, kidney or liver disease, hematological abnormalities, asthma, immunosuppression, treatment with strong CYP2C19 inhibitors or inducers or drugs known to induce agranulocytosis within 3 months prior to study, documented previous adverse drug reaction to metamizole, or treatment with metamizole within 30 days prior to study.

## Intervention

After having obtained informed consent from parents of eligible patients, anthropometric parameters and medical history including concomitant treatments were recorded, and a physical examination was performed.

Following inhaled anesthesia, a first peripheral IV line was placed for the purpose of planned surgery and 0.7 mL of blood was drawn for biochemical and hematologic evaluation of exclusion criteria (differential blood count, urea, creatinine, ASAT, ALAT, bilirubin, and albumin). A second peripheral IV line for repeated painless blood sampling was inserted at an extremity on the opposite side.

Before awakening from anesthesia, or immediately after arrival in the post-anesthesia care unit, patients received a single metamizole dose of 10 mg/kg (based on current body weight) through the first peripheral IV line (Novalgin®, metamizole injection, 500 mg/mL, Sanofi-Aventis SA, Vernier, Switzerland) as intravenous injection, followed by a saline flush. Further standard postoperative pain management consisted of regular administration of paracetamol (acetaminophen) and a non-steroidal anti-inflammatory agent (ibuprofen, mefenamic acid, or ketorolac), and opioids (nalbuphine, morphine) when required.

Blood samples, 0.5 mL each, were collected for pharmacokinetic analysis into EDTA tubes (Microvette 500 K3E, Sarstedt, Nümbrecht, Germany) at 5 predefined time points after dosing (1 h, 2 h, 4 h, 6 h, 10 ± 1 h). An additional sample at 24 h was collected from inpatients; patients who underwent day surgery were discharged home after the 10 ± 1 h sample.

At 6 h, i.e., at the end of a regular dosing interval, an additional 0.7 mL blood sample was drawn for biochemical and hematologic safety assessment.

## Pharmacokinetic analyses and dose evaluation

Concentrations of MAA, AA, FAA, and 4-acetyl aminoantipyrine (AAA) were analyzed using an LC-MS/MS method according to Bachmann et al. (for details, see supplement S2) [9]. The calibration range was 0.025–25 mg/L for MAA, AA, and AAA and 0.025–10 mg/L for FAA, i.e., a lower limit of quantification of 0.025 mg/L for all metabolites. Imprecision was max. 12.5% (inaccuracy ± 15% (± 20% at LLOQ)).

Data were analyzed both by non-compartmental analysis and population pharmacokinetic modeling. NCA included all patients having completed at least the predefined 5 blood samples (per protocol analysis), PPK of all patients with at least one concentration sample (intention-to-treat analysis). NCA investigated exposure in two age cohorts: infants 3–23 months and children 2–6 years. Detailed information on performed analyses is provided in the "Non-compartmental analysis" and "Population pharmacokinetic analysis" sections.

### Reference exposure

Reference area under the plasma concentration-time curve from zero to infinity ($AUC_{0\text{-inf}}$) was derived from 3 healthy volunteer studies in adults after a dose of 1000 mg metamizole IV ($AUC_{1000}$) [8, 18, 19]. The mixed effect estimate of adult MAA $AUC_{1000}$ was re-scaled to a dose of 10 mg/kg, assuming a mean patient weight of 70 kg (reference $AUC_{ref} = AUC_{1000} \times (10\ mg/kg)\ \ (1000\ mg\ \ 70\ kg) = AUC_{1000} \times 0.7$). Median exposure range in adults after an IV dose of 500–1000 mg ($AUC_{500}$–$AUC_{1000}$) was calculated ($AUC_{500} = AUC_{1000} \times 0.5$)

### Sample size

The sample size was determined according to calculations proposed by Wang et al., i.e., the study was prospectively powered to target a 95% confidence interval (95% CI) of $AUC_{0\text{-inf}}$, as derived by NCA, within 80% and 125% of $AUC_{ref}$, with at least 80% power. Accordingly, the choice of study population consisted of 13 patients per age cohort (initially 3 age cohorts were defined: cohort 1: age 3–11 months, cohort 2: age 12–23 months, cohort 3: 24–72 months, but cohorts 1 and 2 needed to be combined as explained below) [20].

### Non-compartmental analysis

NCA was conducted using the *PKNCA* package in R (Version 3.2.4, R Core Team, Vienna, Austria) [21, 22]. MAA $AUC_{0\text{–inf}}$ was calculated as primary outcome according to the linear trapezoidal rule using log-transformed measured concentrations. The 95% confidence interval (95% CI) of the geometric mean $AUC_{0\text{–inf}}$ of MAA was compared with the 80–125% interval of adult $AUC_{ref}$ (see above). Further parameters derived for MAA and the other metabolites were the AUC within a dosing interval of 8 h ($AUC_{0\text{–8h}}$), maximal plasma concentration, time of $C_{max}$, and the elimination half-life. All

parameters were estimated using the PKNCA package in R and then cross-checked visually using the plots. The half-life was estimated from the best-fit line for all available points, again calculated using this package.

### Population pharmacokinetic analysis

Population pharmacokinetic modeling was performed with the software package NONMEM (version 7.4.1, Icon Development Solutions, Ellicott City, MD).

All four metabolites were modeled simultaneously, starting from the structural model illustrated in Fig. 3. MAA formation rate ($k_h$, hydrolysis of metamizole) was modeled as a first-order rate, which was fixed to 20/h (assuming a half-life of 2 min, i.e., complete hydrolysis within 10 min ≈ reported $t_{max}$ after IV administration) [18]. Both one- and two-compartment models were considered to describe the distribution of metabolites. The apparent volume of distribution was set to equal values for all metabolites in the absence of IV metabolite administration data and information on fractions metabolized by different pathways.

Between-subject variability was assigned to all structural model parameters and was assumed to be log-normally distributed. A proportional error model was used for the residual variability.

Covariates considered were weight and age. Standard allometric scaling was used to model the relationship between weight and clearance and volume of distribution (fixed exponents of 0.75 and 1, respectively). The remaining correlation of individual model parameter estimates and patient demographics was attributed to age, considering (piece-wise) linear, power, and sigmoidal ($E_{max}$) functions based on visual inspection. (For sensitivity analyses, see supplement S4.)

Nested models were compared by the likelihood ratio test (alpha = 0.05), based on the NONMEM objective function value (corresponding to − 2 × log-likelihood). Non-nested models were compared by their Akaike information criterion. Further model diagnostics for model development and selection included the decrease in inter-individual and residual variability, correction in bias of individual random effects over covariates (for shrinkage < 20–30%), standard error of parameter estimates (target < 30%), and goodness-of-fit plots (observations versus predictions, residual diagnostics). The final model was internally evaluated using simulation-based diagnostics (visual predictive check): empirical percentiles (median, 2.5th and 97.5th percentiles) of observed concentrations over time were compared with the 95% CI of simulated percentiles.

### Dose evaluation

PPK model simulations were performed to (i) evaluate the studied fixed weight–based dosing strategy of 10 mg/kg IV; (ii) the labeled dose range for 4 weight bands: 50–100 mg for 5–9 kg (only IM administration licensed), 100–250 mg for 9–16 kg, 150–400 mg for 16–24 kg, and 200–500 mg for 24–30 kg (both IM and IV administration licensed); and (iii) a new weight-based dosing strategy accounting for lower MAA clearance in infants compared with children observed.

**Step I** Deterministic model simulations (including parameter uncertainty) were performed to illustrate the model-predicted influence of age and weight on the typical value of MAA total clearance ($TVCL_{MAA,tot}$ = sum of all MAA clearances, Eq. 1) and MAA exposure (area under the curve, $TVAUC_{0\text{-}inf}$, Eq. 2) after a dose of 10 mg/kg. 95% confidence intervals were calculated as 2.5th and 97.5th percentiles from 1000 multivariate simulations of the covariance matrix.

$$TVCL_{MAA,tot} = TVCL_{MAAtoAA} + TVCL_{MAAtoFAA} + TVCL_{rest} \quad (1)$$

$$TVAUC_{0-inf} = \frac{D_{metamizole}}{TVCL_{MAA,tot}} \cdot \frac{MW_{MAA}}{MW_{metamizole}} \quad (2)$$

where $D_{metamizole}$ is the dose of metamizole in mg (10 mg/kg × weight in kg) and $MW_{MAA}$ and $MW_{metamizole}$ are the molecular weights of MAA (217.27 g/mol) and metamizole (333.34 g/mol), respectively.

$TVAUC_{0-inf}$ was illustrated over weight, considering the age-specific weight distribution (3rd to 97th percentiles) according to the World Health Organization (WHO) percentile curves for children aged 3, 6, 12, 18, 24, 48, and 72 months, and was compared with the median exposure in healthy adults reported after a 500–1000 mg IV dose ($AUC_{500}$–$AUC_{1000}$).

**Steps II and III** Stochastic model simulations (including inter-patient variability) of individual MAA total clearance ($CL_{MAA,tot,i}$) and corresponding individual $AUC_{0\text{-}inf,i}$ were performed to illustrate the expected exposure distribution (95% prediction intervals) following administration of the labeled dose range (II) or a weight-based dosing that accounts for age-dependent MAA clearance observed (III). A dataset of 140,000 children aged 3 to 72 months old (1000 patients for each month and gender) was created according to the WHO Box-Cox distribution parameters provided for weight for age. $CL_{MAA,tot,i}$ was then simulated and corresponding $AUC_{0\text{-}inf,i}$ was derived as described in step I. Pediatric exposures were compared with the median exposure in adults with a 500–1000-mg IV dose.

## Assessment of adverse events

Incidence, nature, and severity of clinical adverse events and laboratory parameter changes between time of drug administration and 6 h post-dose were recorded systematically.

## Results

### Demographics

Due to the lower than expected number of eligible patients for the two younger cohorts 1 and 2, the study was amended and these two cohorts were combined according to ICH-E11 age groups, with the aim of including 13 patients in the combined cohort [23]. At the end of the 2-year study period, 25 patients with at least 1 concentration sample were included, and 19 patients completed the predefined sampling for NCA analysis (6 infants < 24 months) (demographics: Table 2, flowchart: Supplemental Fig. S1).

### Pharmacokinetics

Plasma concentration-time profiles of all metabolites are shown in Fig. 2.

#### Reference exposure

MAA $AUC_{ref}$ in adults was 48.9 mg/L/h (95% CI 44.3, 53.4), resulting in a 80–125% $AUC_{ref}$ range of 39.2–61.2 mg/L/h [8, 12, 18, 19]. $AUC_{1000}$ and $AUC_{500}$ were 69.9 and 34.9 mg/L/h.

#### Non-compartmental analysis

$AUC_{0-inf}$ and other estimates from NCA are summarized for each cohort in Table 3. $AUC_{0-inf}$ of MAA in the cohort of children aged 2–6 years was with 29.9 mg/L/h (95% CI 23.4, 38.2) significantly lower than the 80% limit of $AUC_{ref}$. $AUC_{0-inf}$ of MAA in infants 3–23 months was with 43.6 (95% CI 15.8, 119.0) mg/L/h comparable with $AUC_{Ref}$, but the latter showed considerable variability.

#### Population pharmacokinetic analysis

Two samples with an MAA concentration increase > 50% were observed, resulting in the exclusion of one patient (> 24 months) for the primary PPK analysis. A one-compartment model was chosen to describe the distribution of all metabolites. All metabolic rates were described by first-order constants (CL/V); there was no evidence of saturable processes. The final structural model is illustrated in Fig. 3.

More than half of inter-individual variability in MAA clearance could be explained by the covariates weight and age ($CL_{MAAtoAA}$ decreased from 86 to 52% and 31%; $CL_{MAAtoFAA}$ from 112 to 73% and 40%; $CL_{MAArest}$ from 184 to 151% and 54%, Supplemental Fig. S4.1). Both a piece-wise linear and power model with age could describe the observed lower weight-corrected clearance in patients < 24 months (corresponding to the time when most enzyme maturation processes are considered complete, and time where no age dependency could be observed in the present dataset) [24]. As final model, a "piece-wise" power relationship with age was chosen (lowest OFV, exclusion of negative values in simulations):

$$CLTV = \theta_1 \cdot \left(\frac{weight}{15}\right)^{0.75} \cdot \left(\frac{age}{24}\right)^{\theta_{age}} \text{ for age} < 24 \text{ months, and}$$

$$CLTV = \theta_1 \cdot \left(\frac{weight}{15}\right)^{0.75} \text{ for age} \geq 24 \text{ months}$$

where CLTV is the typical clearance parameter for the given covariates weight and age and $\theta_1$ is the typical clearance for a patient with weight = 15 kg (median in the analyzed dataset) and age ≥ 24 months; weight is given in kg, and age in months.

A similar age relationship was also observed with $CL_{FAAother}$ (exponent 0.84, RSE 26%; BSV → 0) and $V$ (exponent 0.51, RSE 21%; BSV decrease by 35%) in infants < 24 months (Supplemental Fig. S4.2), but was not

**Table 2** Patient demographics. Continuous variables are given as median and interquartile range (IQR) for all patients with at least 1 concentration sample

| | Infants 3–11 months (cohort 1) | Infants 12–23 months (cohort 2) | Children 2–6 years (cohort 3) |
|---|---|---|---|
| Number of individuals (*n*) | | | |
| - With at least 1 concentration sample[a] | 4 | 4 | 17 |
| - With at least 5 predefined samples[b] | 3 | 3 | 13 |
| Gender | 3 m, 1 f | 4 m | 11 m, 6 f |
| Age (months) | 8 (6.5; 9.3) | 20.5 (17.8; 22.0) | 56 (43; 64) |
| Weight (kg) | 8.9 (8.5; 9.7) | 11.5 (10.8; 12.0) | 17 (15; 19) |
| *z*-Score weight (for age) | 0.58 (0.41;1.10) | 0.14 (− 0.08; 0.31) | − 0.09 (− 0.83; 0.45) |
| Type of surgery (*n*) | Urologic (3), other (1) | ENT (2), urologic (2) | ENT (12), urologic (3), other (2) |

[a] All individuals included in population pharmacokinetic analysis

[b] Included in non-compartmental analysis

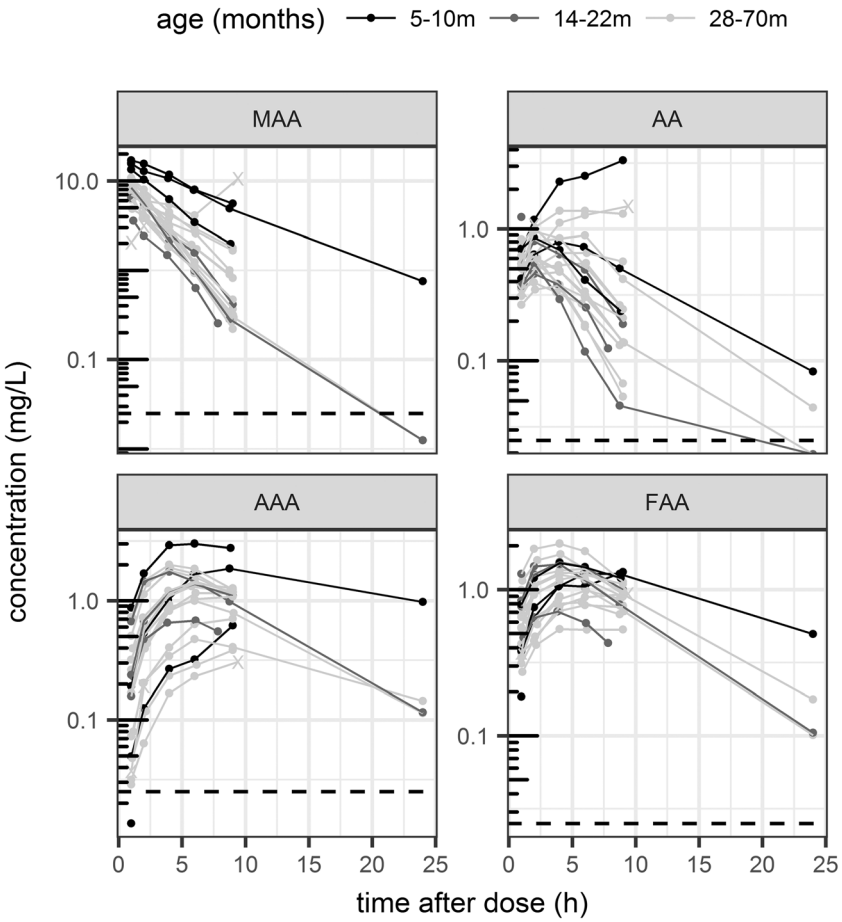


**Fig. 2** Measured individual concentration-time profiles of all metamizole metabolites. Three age groups are differentiated by grey shades: < 1 year (4 patients aged 5–10 months, among 3 with ≥ 5 samples), 1 year old (4 patients aged 14–22 months, among 3 with ≥ 5 samples), and 2–6 years (17 patients aged 28–70 months, among 13 with ≥ 5 samples). X means MAA concentrations increasing > 50% from its previous value (physiologically not plausible and excluded in PPK analysis, but included in NCA). Dashed horizontal lines represent lower limit of quantification (LLOQ). Concentrations measured below LLOQ are plotted at LLOQ/2

included in the final model (no influence on MAA total clearance estimate; unclear physiologic meaning of lower weight–adjusted volume in younger children—rather, the opposite would be expected from a hydrophilic drug). Large inter-patient variability in metabolic clearance of AA to AAA (mediated by polymorphic *NAT2*) could be explained by a latent variable, corresponding to a slow or fast metabolizer phenotype (≈ 7 times faster clearance estimated in patients assigned to the rapid metabolizer, frequency of slow metabolizers estimated to 26%), which was not measured in the present study [12].

### Model evaluation

Residual diagnostics and VPCs are illustrated in the Supplement (Figs. S4.3–S4.4). VPC suggests good agreement between observed and simulated percentiles. Residual diagnostics indicate unbiased predictions of MAA, while some bias for other metabolites remained, which was considered acceptable, given the main purpose of the study, and satisfying VPC diagnostics. Parameter estimates of the final selected model are summarized in Table 4.

## Dose evaluation

Figure 4 illustrates model-predicted $TVAUC_{0-inf}$ with 95% CI over weight for different ages; corresponding $TVCL_{MAA,tot}$ and individual NCA and PPK $AUC_{0-inf}$ estimates are shown in the Supplement (Figs. S5.1–S5.2). Figure 5 and Supplemental Fig. S5.2 illustrate the expected exposure distribution for the labeled dose range (while for < 1 year only IM administration is licensed) and for a weight-based dosing scheme accounting for lower clearance in infants.

## Safety

AEs were fever ($n = 4$), nausea ($n = 1$), vomiting ($n = 1$), abdominal pain ($n = 1$), and pain at the surgical site ($n = 1$), all of which were classified mild to moderate and unlikely related to the study drug. There were no clinically significant changes in hematology and biochemistry parameters before, and 6 h after, the administration of metamizole (see Supplement S3). No clinically significant drop in blood pressure requiring treatment was recorded. No serious adverse event occurred during the study. No patient developed agranulocytosis within the study period.

**Table 3** Non-compartmental analysis. Pharmacokinetic parameters of the metamizole metabolites after a single intravenous dose of 10 mg/kg metamizole

| | Infants 3–23 months ($n = 6$) | Children 2–6 years ($n = 13$) |
|---|---|---|
| MAA (main active metabolite) | | |
| $AUC_{0-inf}$ (mg/L/h) [a] | 43.6 (15.8, 119.0) | 29.9 (23.4, 38.2) |
| $AUC_{0-\lambda}$ (mg/L/h) [a] | 31.7 (14.8, 67.9) | 22.7 (19.5, 26.5) |
| $C_{1h}$ (mg/L) [b] | 10.6 [8.3, 15.0] | 7.8 [6.5, 9.4] |
| $t_{max}$ (h) | 1 | 1 |
| $t½$ (h) [b] | 2.4 [1.7, 3.9 | 2.0 [1.9, 3.1] |
| $\lambda z$ ($h^{-1}$) [b] | 0.3 [0.2, 0.4] | 0.3 [0.2, 0.4] |
| Metabolite AA | | |
| $AUC_{0-\lambda}$ (mg/L/h) [a] | 3.6 (2.0, 6.4) | 3.1 (2.5, 3.9) |
| $C_{max}$ (mg/L) [b] | 0.8 [0.6, 0.9] | 0.6 [0.6, 1.0] |
| $t_{max}$ (h) [b] | 2.0 [2.0, 3.3] | 2.0 [2.0, 4.0] |
| Metabolite AAA | | |
| $AUC_{0-\lambda}$ (mg/L/h) [a] | 4.6 (2.0, 10.9) | 3.3 (2.0, 5.4) |
| $C_{max}$ (mg/L) [b] | 1.6 [0.8, 1.8] | 1.2 [0.7, 1.5] |
| $t_{max}$ (h) [b] | 6.0 [5.9, 6.0] | 6.0 [5.8, 6.0] |
| Metabolite FAA | | |
| $AUC_{0-\lambda}$ (mg/L/h) [a] | 5.7 (4.4, 7.4) | 5.1 [4.0, 6.6] |
| $C_{max}$ (mg/L) [b] | 1.4 [1.3, 1.5] | 1.3 [0.9, 1.4] |
| $t_{max}$ (h) [b] | 4.0 [4.0, 4.0] | 5.8 [4.0, 6.0] |

$AUC_{0-inf}$ area under the plasma concentration-time curve from 0 to infinity, $C_{1h}$ plasma concentration 1 h after dosing, $C_{max}$ maximal plasma concentration, $T_{max}$ time of $C_{max}$, $t½$ elimination half-life, $\lambda z$ terminal elimination rate constant

[a] Presented as geometric mean (95% confidence interval)

[b] Presented as median [interquartile range]

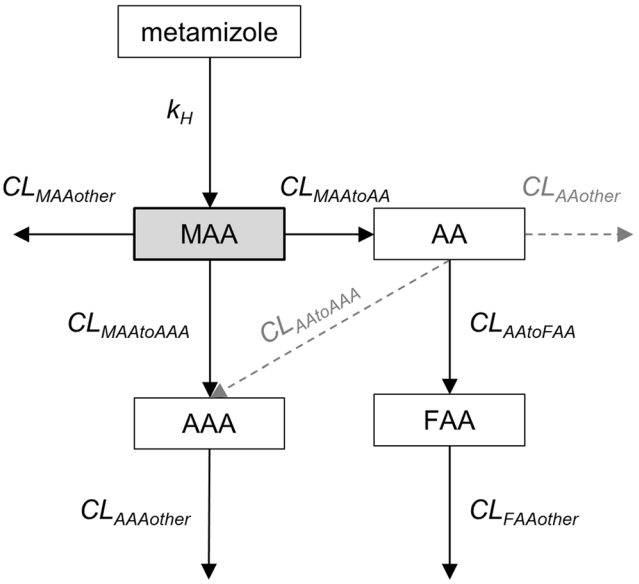


**Fig. 3** Illustration of structural model of metamizole and its metabolites considered. Initially, all metabolic pathways (arrows) reported by Levy et al. [8] were considered. Gray dashed arrows indicate pathways that were not identifiable in this modeling work. $k_H$ first-order hydrolysis rate. $CL_{MAAtoAA}$, $CL_{MAAtoAAA}$, $CL_{AAtoFAA}$, and $CL_{AAtoAAA}$ metabolic clearances. $CL_{MAAother}$, $CL_{AAother}$, $CL_{AAAother}$, and $CL_{FAAother}$ sum of other clearance routes. Modeling work focused on unbiased description of MAA, the main active metabolite of the prodrug metamizole. Volumes of distribution for all metabolites were assumed to be equal in the absence of data on single IV metabolite administration

## Discussion

This is the first study that describes the pharmacokinetics of the main metabolites of metamizole after IV administration in infants and children younger than 6 years of age. After a single IV dose of 10 mg/kg, children aged 2–6 years had a significantly (39%) lower exposure ($AUC_{0-inf}$) than the 80% limit of adult $AUC_{Ref}$ for the active metamizole metabolite MAA, suggesting that children receiving the recommended 10 mg/kg dose may be slightly under-dosed compared with a 70-kg adult receiving the same weight-based dose (700 mg for a 70 kg adult). On the other hand, infants < 2 years had comparable average exposure to adults, with a large (~ 10-fold) variability in MAA $AUC_{0-inf}$. Increased MAA concentrations were measured in infants < 1 year, suggesting that they may be overdosed when receiving same weight-based IV doses. PPK modeling and simulation demonstrated that a dose of 5 mg/kg in infants < 1 year and 10–20 mg/kg in children 1–6 years would achieve a more consistent exposure in infants and young children compared with that observed in adults at the approved dose of 500–1000 mg (corresponding to 7–14 mg/kg for a 70 kg adult). Considering a weight range of 50–100 kg in adults, such dose recommendations would lie within the corresponding adult weight–adjusted dose range of 5–20 mg/kg (Fig. 5 and Table 1).

It has been suggested before that MAA metabolism occurs faster in children > 1 year than in adults by Balogh et al., who studied 38 children aged 1–11 years after a single oral dose of metamizole (8 mg/kg) compared with healthy adults. Urinary excretion of the metabolites AA, FAA, and AAA within 6 h was significantly higher in younger children than in adults, but plasma concentrations were unfortunately not measured in their study [17]. In line with those findings, plasma $C_{max}$ of those metabolites tended to be lower and $t_{max}$ tended to be earlier in our study (Table 3), compared with mean values reported in adults after an IV dose of 1 g (AA 1.5–1.6 mg/L and 3.1–4.8 h; AAA 1.4–1.6 mg/L and 13–17.3 h; FAA 1.4 mg/L and 7.2–8.2 h) [8]. No pharmacokinetic data in infants < 1 year is available to compare our findings of slower metabolism in this age group. However, our results are in line with lower CYP activity seen in young children during the first 1–2 years of life. CYP-specific isoforms,

**Table 4** Estimates of population pharmacokinetic model

| Parameter | Estimate (RSE) | Inter-individual variability (RSE) |
|---|---|---|
| Structural kinetic model | | |
| $k_h$ (1/h) | 20 (fixed) | – |
| $V$ (L) for 15 kg[a] | 9.98 (5%) | 21.6% (18%) |
| $CL_{MAAtoAA}$ (L/h) for 15 kg[b,c] | 1.07 (11%) | 38%* (18%) |
| $CL_{MAAtoFAA}$ (L/h) for 15 kg[b,c] | 0.844 (13%) | 51%* (17%) |
| $CL_{MAAother}$ (L/h) for 15 kg[b,c] | 1.26 (14%) | 45% (21%) |
| $CL_{AAtoAAA}$ *fast* (L/h) for 15 kg[b] | 7.46 (14%) | 51% (18%) |
| $CL_{AAtoAAA}$ *slow* (L/h) for 15 kg[b] | 0.972 (27%) | (Same) |
| Proportion of slow metabolizers | 0.259 (39%) | – |
| $CL_{AAA}$ (L/h) for 15 kg[b] | 2.72 (11%) | 39% (23%) |
| $CL_{FAA}$ (L/h) for 15 kg[b] | 1.83 (8%) | 25% (24%) |
| Covariate model for age < 24 months | | |
| $\theta_{age,MAAtoAA}$ [−] | 0.663 (29%) | |
| $\theta_{age,MAAtoFAA}$ [−] | 0.969 (25%) | |
| $\theta_{age,MAAother}$ [−] | 2.39 (24%) | |
| Error model | | |
| $\varepsilon_{MAA}$ proportional (%) | 23 (10) | |
| $\varepsilon_{AA}$ proportional (%) | 13 (9) | |
| $\varepsilon_{AAA}$ proportional (%) | 19 (11) | |
| $\varepsilon_{FAA}$ proportional (%) | 10 (9) | |

*RSE* relative standard error

*Estimated correlation 96% (RSE 36%)

[a] Allometrically scaled and centered to 15 kg: $V_{TV} = V \times (\text{weight}/15)^{1}$

[b] Allometrically scaled and centered to 15 kg: $CL_{TV} = CL \times (\text{weight}/15)^{0.75}$

[c] Age as covariate included as follows for age < 24 months: $CL_{TV} = CL \times (\text{weight}/15)^{0.75} \times (\text{age}/24)^{\theta age}$

*CV* coefficient of variation calculated as $\sqrt{(\omega^2 - 1)}$, where $\omega^2$ is the variance of log-normally distributed inter-individual variability

including CYP2C19, show developmental expression patterns that can affect drug metabolism [24–27].

Model-predicted MAA clearance for a 70-kg adult (167 mL/min) is in excellent agreement with reported values, suggesting usefulness of the model for extrapolation to older children [8]. Model-derived average half-lives for a 70-kg adult are as follows: MAA 3.2 h, AA 10.5 h (slow metabolizers) and 1.4 h (fast metabolizers), AAA 3.7 h, and FAA 5.6 h. Those extrapolated half-lives of active metabolites MAA and AA are in line with data reported in adults [12]. Predicted AAA and FAA (non-active metabolites) half-lives are shorter than reported from NCA, likely because of limited data available for the elimination phase of those metabolites [8]. The discrepancy may potentially also indicate age-dependent elimination in children that the model did not account for, and limited usefulness of the model for extrapolation of the pharmacokinetics of inactive metabolites. Data suggest potential for considerable accumulation of MAA in infants < 1 year and of other metabolites (AA in slow metabolizers, AAA and FAA; exposure ≈ 10% of MAA, Fig. 2) after multiple dosing. The relevance of AA, AAA, and FAA for drug safety and efficacy is not well described. Additional clinical studies are needed to characterize multiple-dose pharmacokinetics and safety of metamizole in infants. Because of these uncertainties, use of metamizole should be limited to short-term use, or may be completely avoided in infants < 1 year.

*NAT2* genotypes were not determined in this study, but the presence of two phenotypes (26% slow and 74% fast metabolizers) was suggested. Since age appeared unrelated to the metabolic activity, we may assume that maturation of this enzyme already is high in infants > 3 months (no age relationship shown in this study). Literature suggests that *NAT2* genotypes may even be grouped into three phenotypes, but many pharmacokinetic studies have reported two phenotypes only (e.g., for sulfamethoxazole, isoniazid, or caffeine) [28].

Therapeutic efficacy and concentration dependency could not be evaluated in our study due to concomitant use of standard analgesic combination therapy. Effectiveness of our recommended dose of 10–20 mg/kg for children > 1 year is however supported by studies having demonstrated effective pain relief in children after a dose of 15 mg/kg [14, 15]. Our single-

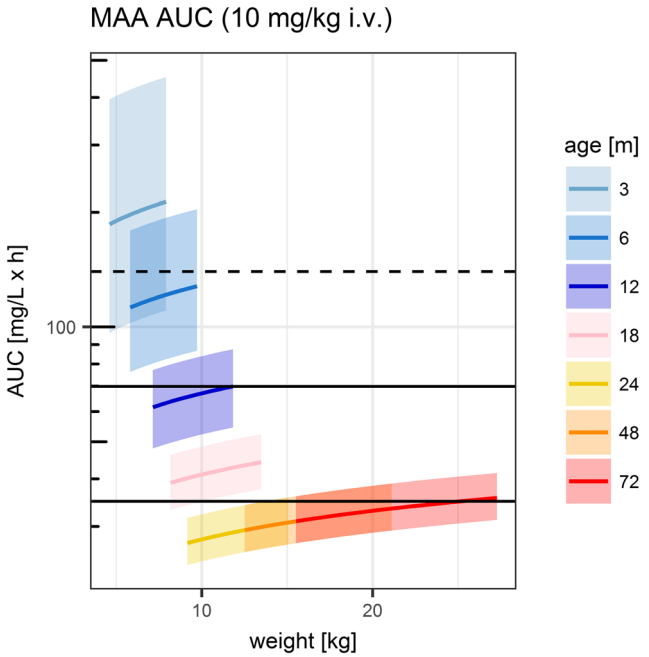


**Fig. 4** Illustration of model-predicted typical AUC for patients of different age and weight values with 95% confidence intervals (shaded areas), receiving an intravenous (IV) dose of metamizole of 10 mg/kg. Weight for age bands were simulated according to WHO percentiles curves (extending from 3rd to 97th percentiles). Black horizontal lines represent reference AUC in healthy volunteers receiving a dose of 500 mg or 1000 mg metamizole ($AUC_{500}$, $AUC_{1000}$). Dashed horizontal line represents a 2-fold increase in $AUC_{1000}$

dose study in a small number of children does also not allow characterization of the safety profile of metamizole or evaluation of dose dependency of AE in infants and children. Recorded AEs were deemed not related to the study drug, due to the latency time between drug administration and AE occurrence, and alternative explanations for the AEs by the surgical procedures or administered co-medications. The use of metamizole is controversial due to its risk of agranulocytosis [29–31]. With an incidence rate of 0.46–1.63 cases per million person-days, and approximately 4% of reported cases in patients < 19 years, the probability for observing such a severe AE in our study was very low [32–34]. Also, the probability to observe serious hemodynamic, anaphylactic, or respiratory AEs was low (estimated incidence < 0.3% after a single IV dose of metamizole) [35]. A recent adult study further reported a dose-dependent risk of acute kidney injury in an intensive care unit, which has not yet been studied in children [36]. As aforementioned, there are uncertainties regarding accumulation and pharmacological safety properties, especially in infants < 1 year. For these reasons, we recommend to limit administration to 1 or 2 days. If administered over several days, regular monitoring for clinical and laboratory abnormalities is warranted [37].

Since only 4 infants below the age of 1 year could be included in this study, there remains uncertainty about the exact optimal dose for this age group (as illustrated by 95% CI in Fig. 4). The requirement for dose reduction was still perceived highly appropriate for this age group, due to highest MAA exposure (≈ 2-fold higher than $AUC_{1000}$) observed in these patients and plausible maturation of metabolic enzymes. For older children aged 2–6 years, there is some uncertainty concerning the appropriate reference weight for scaling of $AUC_{ref}$ (weight of healthy volunteers not reported in all studies). For a lower adult reference weight (reported range 54–68 kg), the relative difference to adults exposure would be slightly lower than the calculated 39% [8, 12, 18, 19]. It also has to be noted that $AUC_{0-inf}$ estimates from NCA tended to be lower than from PPK, which is to be expected, since higher peak concentrations are assumed to occur within 10 min after IV administration in PPK analysis compared with those measured with the first sample at 1 h post-dose (with the sampling

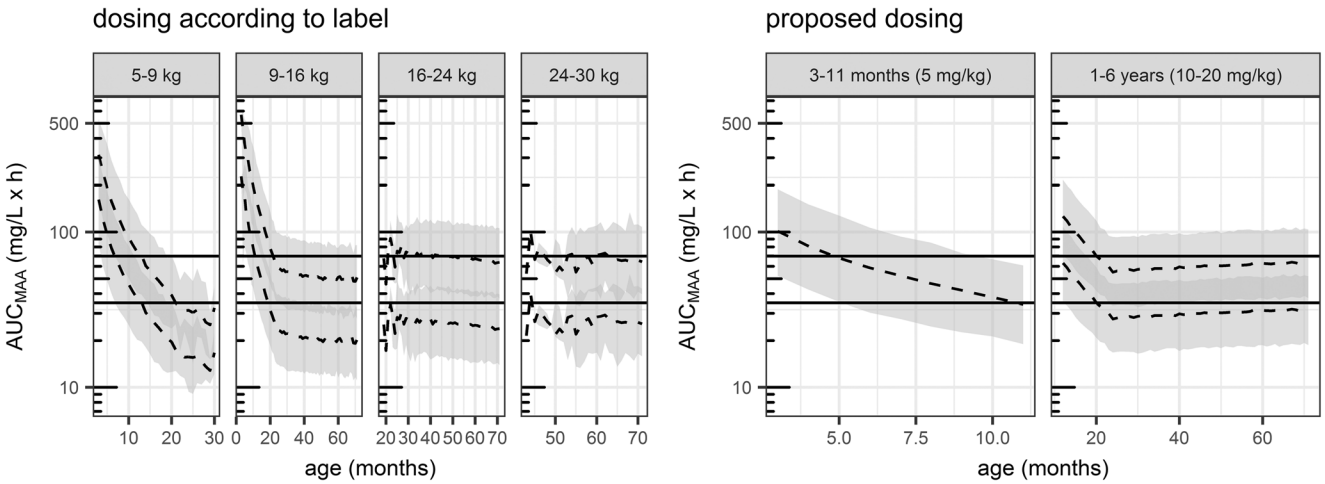


**Fig. 5** Illustration of model-predicted distribution of individual $AUC_{0-inf}$ for patients of different age values (1000 individuals per month of age and gender simulated). Left represents an exposure following labeled dosing (Table 1, for 5–9 kg, only IM administration is licensed). Right represents an exposure following a new proposed weight-based IV dosing strategy for children 3–11 months and 1–6 years. Dashed lines represent the median. Shaded area represents the 90% prediction interval

scheme being designed to describe the elimination phase). The proposed doses for both age groups are hence also based on practical considerations, targeting a simple dosing scheme, which may reduce dosing errors.

We consider that polymorphisms of genes encoding for the enzymes involved in drug metabolism might have contributed to the above-mentioned variability. Genotyping of these enzymes, however, was not a goal of this study, and sample size of this pharmacokinetic study would be too small to draw valid conclusions.

In conclusion, this prospective single-dose study reports for the first time plasma pharmacokinetics data of IV metamizole in infants and children up to 6 years old. Body weight–adjusted dosing in children, assuming a linear relationship between weight and dose, is arbitrary and does not account for any specific differences in drug pharmacokinetics between children of different ages and adults. Significant age dependency of the elimination kinetics of the main active metabolite MAA was found, resulting in higher exposure in infants <1 year compared with older children and adults. This suggests the need for a reduced weight–based (off-label) IV dose in infants < 1 year compared with older children up to 6 years (5 mg/kg versus 10–20 mg/kg) to achieve equivalent adult exposure and mitigate the risk for overdosing in young infants. Additional clinical studies are warranted to further evaluate efficacy and safety of proposed dosing in infants.

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**Author contributions** F.R., M.P., A.A., T.O.E., M.H., N.G., and J.N.v.d.A. designed the research; V.C.Z., F.R., and J.A.B. performed the research; A.A., V.G., C.B., U.D., F.B., and V.C.Z. analyzed the data; M.H., U.D., and F.B. performed the bioanalysis; V.C.Z., F.R., V.G., and M.P. wrote the manuscript, J.N.v.d.A, T.O.E., M.H., N.G., and S.H.-C. critically revised the manuscript. All authors reviewed and approved the final version of the manuscript before submission.

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## Compliance with ethical standards

**Conflict of interest** V.C.Z.: none
F.R.: none
A.A.: none
V.G.: none
C.B.: none
J.A.B.: Her husband is a senior corporate counsel at Novartis International AG, Basel, Switzerland, and holds Novartis stock and stock options.
M.H.: none
T.O.E.: none
U.D.: none
F.B.: none
N.G.: none
S.H.-C.: none
J.N.v.d.A.: none
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**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

## References

1. Brogden RN (1986) Pyrazolone derivatives. Drugs 32(Suppl 4): 60–70
2. Laporte JR, Ibanez L, Vidal X, Vendrell L, Leone R (2004) Upper gastrointestinal bleeding associated with the use of NSAIDs: newer versus older agents. Drug Saf Int J Med Toxicol Drug Exp 27(6): 411–420
3. Zapater P, Llanos L, Barquero C, Bellot P, Pascual S, Carnicer F, Palazon JM, Gimenez P, Esteban A, Llorca L, Frances R, Horga JF, Such J (2015) Acute effects of dipyrone on renal function in patients with cirrhosis: a randomized controlled trial. Basic Clin Pharmacol Toxicol 116(3):257–263
4. Andrade S, Bartels DB, Lange R, Sandford L, Gurwitz J (2016) Safety of metamizole: a systematic review of the literature. J Clin Pharm Ther 41(5):459–477
5. Vazquez E, Hernandez N, Escobar W, Vanegas H (2005) Antinociception induced by intravenous dipyrone (metamizol) upon dorsal horn neurons: involvement of endogenous opioids at the periaqueductal gray matter, the nucleus raphe magnus, and the spinal cord in rats. Brain Res 1048(1–2):211–217
6. Rogosch T, Sinning C, Podlewski A, Watzer B, Schlosburg J, Lichtman AH, Cascio MG, Bisogno T, Di Marzo V, Nusing R, Imming P (2012) Novel bioactive metabolites of dipyrone (metamizol). Bioorg Med Chem 20(1):101–107
7. Alves D, Duarte I (2002) Involvement of ATP-sensitive K(+) channels in the peripheral antinociceptive effect induced by dipyrone. Eur J Pharmacol 444(1–2):47–52
8. Levy M, Zylber-Katz E, Rosenkranz B (1995) Clinical pharmacokinetics of dipyrone and its metabolites. Clin Pharmacokinet 28(3):216–234
9. Bachmann F, Duthaler U, Rudin D, Krahenbuhl S, Haschke M (2018) N-demethylation of N-methyl-4-aminoantipyrine, the main metabolite of metamizole. Eur J Pharm Sci 120:172–180
10. Martinez C, Andreu I, Amo G, Miranda MA, Esguevillas G, Torres MJ, Blanca-Lopez N, Blanca M, Garcia-Martin E, Agundez JA (2014) Gender and functional CYP2C and NAT2 polymorphisms

determine the metabolic profile of metamizole. Biochem Pharmacol 92(3):457–466
11. Abdalla SO, Elouzi AA, Saad SE, Alem MD, Nagaah TA (2014) Study on the relationship between genetic polymorphisms of cytochrome CYP2C19 and metabolic bioactivation of dipyrone. J Chem Pharm Res (6)
12. Levy M, Flusser D, Zylber-Katz E, Granit L (1984) Plasma kinetics of dipyrone metabolites in rapid and slow acetylators. Eur J Clin Pharmacol 27(4):453–458
13. Rohdewald P, Drehsen G, Milsmann E, Derendorf H (1983) Relationship between saliva levels of metamizol metabolites, bioavailability and analgesic efficacy. Arzneimittel-Forschung 33(7): 985–988
14. Caliskan E, Sener M, Kocum A, Ozyilkan NB, Ezer SS, Aribogan A (2013) The efficacy of intravenous paracetamol versus dipyrone for postoperative analgesia after day-case lower abdominal surgery in children with spinal anesthesia: a prospective randomized double-blind placebo-controlled study. BMC Anesthesiol 13(1):34
15. Kocum AI, Sener M, Caliskan E, Bozdogan N, Micozkadioglu D, Yilmaz I, Aribogan A (2013) Intravenous paracetamol and dipyrone for postoperative analgesia after day-case tonsillectomy in children: a prospective, randomized, double blind, placebo controlled study. Braz J Otorhinolaryngol 79(1):89–94
16. Sanofi Aventis (Suisse) SA (2017) Novalgin® - Summary of Product Characteristics (SPC). Last updated: November 2017. Accessible via URL http://www.swissmedicinfo.ch/. Accessed 28 May 2019
17. Balogh A, Melzer K, Ziehl U, Finke G, Voigt L, Hoffmann A (1989) Elimination von Metamizol (Analgin®)-Metaboliten im Kindesalter. Z Klin Med 44(3):213–215
18. Asmardi G, Jamali F (1985) Pharmacokinetics of dipyrone in man; role of the administration route. Eur J Drug Metab Pharmacokinet 10(2):121–125
19. Luus HG, Meyer BH, Müller FO, Swart KJ, Badian M (1989) Absolute bioavailability of dipyrone film tablets [abstract]. In: Eur J Clin Pharmacoled, ppA240:209.237
20. Wang Y, Jadhav PR, Lala M, Gobburu JV (2012) Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. J Clin Pharmacol 52(10):1601–1606
21. Denney W, Duvvuri S, Buckeridge C (2015) Simple, automatic noncompartmental analysis: the PKNCA R package [abstract]. J Pharmacokinet Pharmacodyn 42(S1):11–107 S165
22. R Core Team (2014) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/. Accessed 28 May 2019
23. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - ICH (2001) ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf. Accessed 18 Aug 2016
24. Johnson TN, Rostami-Hodjegan A, Tucker GT (2006) Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. Clin Pharmacokinet 45(9):931–956
25. Stevens JC, Marsh SA, Zaya MJ, Regina KJ, Divakaran K, Le M, Hines RN (2008) Developmental changes in human liver CYP2D6 expression. Drug Metabol Dispos Biol Fate Chem 36(8):1587–1593
26. Hines RN (2007) Ontogeny of human hepatic cytochromes P450. J Biochem Mol Toxicol 21(4):169–175
27. Duan P, Wu F, Moore JN, Fisher J, Crentsil V, Gonzalez D, Zhang L, Burckart GJ, Wang J (2019) Assessing CYP2C19 ontogeny in neonates and infants using physiologically based pharmacokinetic models: impact of enzyme maturation versus inhibition. CPT Pharmacometrics Syst Pharmacol 8(3):158–166
28. McDonagh EM, Boukouvala S, Aklillu E, Hein DW, Altman RB, Klein TE (2014) PharmGKB summary: very important pharmacogene information for N-acetyltransferase 2. Pharmacogenet Genomics 24(8):409–425
29. The International Agranulocytosis and Aplastic Anemia Study (1986) Risks of agranulocytosis and aplastic anemia. A first report of their relation to drug use with special reference to analgesics. JAMA 256(13):1749–1757
30. Hedenmalm K, Spigset O (2002) Agranulocytosis and other blood dyscrasias associated with dipyrone (metamizole). Eur J Clin Pharmacol 58(4):265–274
31. Ibanez L, Vidal X, Ballarin E, Laporte JR (2005) Agranulocytosis associated with dipyrone (metamizol). Eur J Clin Pharmacol 60(11):821–829
32. Blaser LS, Tramonti A, Egger P, Haschke M, Krahenbuhl S, Ratz Bravo AE (2015) Hematological safety of metamizole: retrospective analysis of WHO and Swiss spontaneous safety reports. Eur J Clin Pharmacol 71(2):209–217
33. Stammschulte T, Ludwig WD, Muhlbauer B, Bronder E, Gundert-Remy U (2015) Metamizole (dipyrone)-associated agranulocytosis. An analysis of German spontaneous reports 1990-2012. Eur J Clin Pharmacol 71(9):1129–1138
34. Ziesenitz VC, Erb TO, Trachsel D, van den Anker JN (2018) Safety of dipyrone (metamizole) in children-what's the risk of agranulocytosis? Paediatr Anaesth 28(2):186–187
35. Fieler M, Eich C, Becke K, Badelt G, Leimkuhler K, Messroghli L, Boethig D, Sumpelmann R (2015) Metamizole for postoperative pain therapy in 1177 children: a prospective, multicentre, observational, postauthorisation safety study. Eur J Anaesthesiol 32(12): 839–843
36. Stueber T, Buessecker L, Leffler A, Gillmann HJ (2017) The use of dipyrone in the ICU is associated with acute kidney injury: a retrospective cohort analysis. Eur J Anaesthesiol 34(10):673–680
37. Stamer UM, Gundert-Remy U, Biermann E, Erlenwein J, Meibetaner W, Wirz S, Stammschulte T (2017) Dipyrone (metamizole) : considerations on monitoring for early detection of agranulocytosis. Schmerz 31(1):5–13