Enteral acetaminophen bioavailability in pediatric intensive care patients determined with an oral microtracer and pharmacokinetic modeling to pptimize dosing

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Enteral Acetaminophen Bioavailability in Pediatric Intensive Care Patients Determined With an Oral Microtracer and Pharmacokinetic Modeling to Optimize Dosing

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Objectives: Decreasing morbidity and mortality by rationalizing drug treatment in the critically ill is of paramount importance but challenging as the underlying clinical condition may lead to large variation in drug disposition and response. New microtracer methodology is now available to gain knowledge on drug disposition in the intensive care. On the basis of studies in healthy adults, physicians tend to assume that oral doses of acetaminophen will be completely absorbed and therefore prescribe the same dose per kilogram for oral and IV administration. As the oral bioavailability of acetaminophen in critically ill children is unknown, we designed a microtracer study to shed a light on this issue.

Design: An innovative microtracer study design with population pharmacokinetics.

Setting: A tertiary referral PICU.

Patients: Stable critically ill children, 0–6 years old, and already receiving IV acetaminophen.

Interventions: Concomitant administration of an oral ^{14}C radiolabeled acetaminophen microtracer (3 ng/kg) with IV acetaminophen treatment (15 mg/kg every 6 hr).

Measurements: Blood was drawn from an indwelling arterial or central venous catheter up to 24 hours after ^{14}C acetaminophen microtracer administration. Acetaminophen concentrations were measured by liquid chromatography-mass spectrometry and ^{14}C concentrations by accelerated mass spectrometry.

Main Results: In 47 patients (median age of 6.1 mo; Q1–Q3, 1.8–20 mo) the mean enteral bioavailability was 72% (range, 11–91%). With a standard dose (15 mg/kg 4 times daily), therapeutic steady-state concentrations were 2.5 times more likely to be reached with IV than with oral administration.

Conclusions: Microtracer studies present a new opportunity to gain knowledge on drug disposition in the intensive care. Using this modality in children in the pediatric intensive care, we showed that enteral administration of acetaminophen results in less predictable exposure and higher likelihood of subtherapeutic blood concentration than does IV administration. IV dosing may be preferable to ensure adequate pain relief. (*Crit Care Med* 2019; 47:e975–e983)

Key Words: acetaminophen; analgesia; children; pain; pediatric intensive care; pharmacokinetics

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To decrease morbidity and mortality, critically ill patients ideally require optimized drug effect with minimized adverse effects. But their underlying condition leads to a large variation in drug disposition and response which

complicates drug choice and dosing (1). As an example, enteral drug dosing in the critically ill is commonly derived from bioavailability studies in healthy volunteers but does not take into account the change in disposition associated with the delayed gastric emptying, hemodynamic instability, and change in gastric pH often found in these patients (2, 3). Dedicated research in the ICU population is therefore of paramount importance to optimize dosing and choice of route of administration. But the extraordinary environment of the ICU raises specific challenges to the design and conduct of research that limit drug research (4). Oral bioavailability is traditionally estimated with crossover studies, by giving a drug dose first via the oral or IV route and then, after washout of the first dose, the same dose in the same patient via the alternate route. After each dose, multiple blood samples are taken to estimate pharmacokinetic variables. The ratio of area under the curves (AUCs) after oral and IV dosing defines the oral bioavailability. Applying this method in the ICU only for research purposes is neither ethically acceptable nor feasible (4). Alternatively, replacing an IV dose by an oral dose during repeated drug dosing is suboptimal, as a patient's clinical situation may change rapidly, resulting in imprecise bioavailability estimations. New techniques allow overcoming these hurdles and offer new opportunities for optimal drug dosing in the ICU. We recently showed the feasibility of a radioactive labeled microtracer study to evaluate pharmacokinetics in children (5, 6). The use of this innovative method is endorsed by the European Medicines Agency and the Food and Drug Administration (7). To study oral bioavailability, a labeled nontherapeutic microtracer (< 1/100 of therapeutic dose) can be given enterally to a patient receiving IV acetaminophen for treatment as per clinical practice, with extremely low radioactive exposure. The oral microtracer is exactly the same molecule, but it contains radioactive carbon isotope (^{14}C) permitting differentiation from the IV treatment dose given at the same time. This microtracer is associated with a very low radiation exposure, that is, 1 microSv for a microdose in a neonate compared with 40 microSv for a single flight from Europe to the United States (8).

Sick children receive 15% of the drugs orally despite absent bioavailability data (9) including acetaminophen, an effective analgesic (10), and antipyretic (11). When available, IV acetaminophen is increasingly prescribed by pediatric intensivists. It offers an advantage when the enteral route may not be tolerated. It is unclear whether it should be preferred over the oral route (12) in children tolerating enteral drug administration as acetaminophen oral bioavailability data in children are lacking. Most physicians prescribe the same oral and IV doses as recommended in labeled dosing guidelines (60 mg/kg/d; maximum dose: 1 g). Achieving similar drug exposure with oral and IV routes would only be possible, if absorption is nearly complete in all patients (complete bioavailability with small interpatient variability). Yet, bioavailability estimations in studies in healthy volunteers range from 60% to 97% (13–15). Critically ill children will likely show a higher variability (16).

We therefore aimed to estimate the oral bioavailability of acetaminophen in the pediatric intensive care using the innovative ^{14}C microtracer approach.

METHODS

Setting

This prospective study was embedded in a larger ^{14}C microtracer study (5, 6, 8) carried out in tertiary care PICU of the Erasmus MC-Sophia Children's Hospital. The Dutch Central Committee on Research Involving Human Subjects approved the study. Parental written informed consent was obtained.

Population

All patients up to 6 years old admitted to the PICU who received IV acetaminophen and had an arterial or central venous catheter in place were eligible (5, 6). To minimize interindividual variability due to critical illness, the exclusion criteria were defined to obtain a subpopulation with low disease severity. These criteria were renal disorder (according to pediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease [pRIFLE] criteria, an estimated creatinine clearance decrease by 25% or more compared with a baseline prior to study inclusion or urine output of less than 0.5 mL/kg per hour for 8 hr [17]) and liver failure (> 2 SD in age-appropriate liver enzyme measurement [aspartate aminotransferase and alanine aminotransferase]), gastrointestinal disorder (ileus, diarrhea, any underlying bowel disease, pancreatic insufficiency), coadministration of drugs known to interact with acetaminophen pharmacokinetics, the use of more than one vasopressor drug and extracorporeal membrane oxygenation. Introduction and progression of feeds were left at the discretion of the treating physician.

Study Design

A single dose of enteral acetaminophen-containing radioactive carbon isotope (radiolabeled microtracer dose: [^{14}C] acetaminophen at 3.3 ng/kg, 60 Bq/kg, 0.25 mL/kg) oral acetaminophen was administered by the researcher simultaneously with the IV acetaminophen treatment given by the bedside nurse IV (Fresenius Kabi, Schelle, Belgium; 10 mg/mL) (5). The oral microdose was derived from a previous healthy adult [^{14}C] acetaminophen microdose study (18). The [^{14}C] acetaminophen formulation for oral administration was prepared by adding [^{14}C] acetaminophen to an acetaminophen formulation for IV use (VU University Medical Center, Amsterdam; good manufacturing practice license number NL/H 11/0005). The final concentrations were 13 ng/mL for [^{14}C] acetaminophen and 6.7 μg/mL for nonlabeled acetaminophen both being negligible in relation to the IV treatment dose and thus considered irrelevant for the pharmacokinetic estimation of the IV acetaminophen pharmacokinetics. To ensure proper delivery to patients fed by a nasogastric tube, 1 mL of saline was used to flush the gastric tube. In vitro adhesion studies were carried out with this technique and showed that the amount recovered after the passage through the tube was greater than 95% and consistent with appropriate drug delivery to the gastrointestinal tract (5). A syringe was used to deliver the drug to orally fed patients. The IV acetaminophen

treatment was dosed according to the Dutch Pediatric Handbook: 20 mg/kg loading dose, followed by 10 mg/kg q6h (< 1 mo old) or 15 mg/kg q6h (≥ 1 mo old) (19). The IV acetaminophen dose in mg was rounded to the nearest integer, and it was prepared and double-checked in the pharmacy. Some children had already received multiple doses before the microtracer dose was given and information on these doses was included in the pharmacokinetic analysis.

Blood samples (1 mL) were drawn from the indwelling catheter just before administration of the acetaminophen microtracer dose and at 10 and 30 minutes, and 1, 2, 4, 6, 12, 24 hours after administration. After centrifugation, plasma was stored at –80°C.

Measurements

[^{14}C] acetaminophen plasma concentrations were measured by liquid chromatography-accelerator mass spectrometry (LC + AMS) as previously described (5, 20). The LC + AMS qualification was performed in accordance with the recommendation of the European Bioanalytical Forum (21). Three quality control (QC) concentration levels were included as follows: QC high 145 mBq/mL, QC medium 14.5 mBq/ mL, and QC low 2.4 mBq/mL. The accuracy of QC high, medium, and low analysis corresponded to 104%, 103%, and 90%, respectively. The precisions, defined by a coefficient of variation (CV) of 9.1%, 6.7%, and 6.9%, respectively, were within the requirements for LC + AMS analysis (21). The lower limit of quantification (LLOQ) of the method was 0.58 mBq/mL (5). Treatment acetaminophen plasma concentrations were measured by liquid chromatography-mass spectrometry. The LLOQ for cold (nonradioactive) acetaminophen was 0.05 mg/L. Mean intra- and inter-assay accuracy ranged from 85% to 111%, and intra- and inter-assay imprecision did not exceed 15% CV.

DATA ANALYSIS

Pharmacokinetic Analysis

Population pharmacokinetic analysis was performed using the nonlinear mixed-effect modeling NONMEM 7.3.0 software (Icon Development Solutions, Ellicott City, MD). Log transformed treatment and [^{14}C] acetaminophen concentrations were modeled simultaneously. A structural pharmacokinetic model was developed to describe the typical pharmacokinetic variables, including F (oral bioavailability), together with a statistical model providing for the unexplained interindividual variability. Then, potential covariates were tested for statistical significance. These covariates are clinical characteristics to be taken into account for individualized dosing. In pediatrics, weight is included in most models, and therefore, doses are calculated per kilograms. Other patient characteristics (described in **Table 1**) that significantly decreased the interindividual variability of pharmacokinetic variables were included in the model to target dosing to these characteristics. To account for exposure from the rectal doses given prior to inclusion, the absorption rate, and lag time for this administration route were fixed to literature values (22) and bioavailability was estimated. One, two, and three compartment models, first and zero order oral absorption and an oral absorption lag time were tested. The details of the analysis are provided in the **eMethods** (Supplemental Digital Content 1, http://links.lww.com/CCM/E943).

Dosing Simulations

To compare systemic exposure (plasma concentrations) after oral and IV administration, the concentration-time profiles until 24 hours after administration and mean steady-state concentrations (Css) were simulated based on Monte-Carlo simulations using the validated pharmacokinetic model estimates from the current analysis. The average concentration at steady state was calculated by dividing the AUC over the dosing interval by the dosing time interval.

The simulated dosing regimen was as follows: similar oral and IV doses of 15 mg/kg per dose every 6 hr (60 mg/kg/d) (23). The highest recommended oral dosing regimen of 22.5 mg/kg/dose every 6 hours (90 mg/kg/d) was also simulated (19). Simulations were performed for four age groups: 1 month, 6 months, 1 year, and 5 years, assuming a typical weight of 4.5, 8, 10, and 18 kg, respectively, according to the Centers for Disease Control and Prevention growth charts. For each dosing regimen and age group, 1,000 simulations were performed taking into account interindividual variability in the model variables. For each simulation, the mean Css was computed based on the dose and the sampled individual clearance variable, as well as the sampled individual bioavailability variable for oral administration. The median as well as the 5th and 95th percentiles of the concentration-time profiles and of the mean Css were plotted for each dosing and age group.

A mean Css of 10 mg/L (± 20% SD) was targeted. This threshold is based on two studies by Anderson et al (24, 25) on a total of 220 children who received acetaminophen after tonsillectomy (with or without adenoidectomy). They showed adequate analgesia with a steep decrease in pain scores when concentrations increased up to 10 mg/mL and only a marginal decrease in pain scores at higher concentrations. Despite scarce data, dosing regimens in children are generally designed to reach an average Css of 10 mg/L (26, 27). Based on the Monte-Carlo simulations, the percentage of patients reaching the targeted mean Css of 10 mg/L ± 20% (8–12 mg/L) in the IV acetaminophen group and in the enteral acetaminophen group was computed for the four age groups.

RESULTS

Population

As depicted in **Supplemental Figure 1** (Supplemental Digital Content 2, http://links.lww.com/CCM/E944; **legend**, Supplemental Digital Content 5, http://links.lww.com/CCM/E947), among 232 eligible patients, a total of 118 were excluded, of whom 60 on the basis of exclusion criteria; for 21 patients the study drug was unavailable (outside office hours of pharmacy) and 37 patients participated in another clinical trial (6). Of the 114 parents/carers approached, 64 declined participation of their child and thus 50 patients were enrolled. Two patients were excluded after inclusion as they vomited shortly after

TABLE 1. Covariates Tested for Their Influence on Pharmacokinetics Variables

Type of Data Collected	Reason for Collection	Potential Covariates
Weight	Weight is often found a major predictor of pharmacokinetics variability in pediatric patients	Weight at study day
		Weight SD from 50th percentile for age and sex
Maturation	Age often found a major predictor of pharmacokinetics variability in pediatric patients	Postnatal age
		Postmenstrual age
		Gestational age
Diagnostic	Surgery and associated opioid use induce ileus that may influence oral absorption	Surgery
	Abdominal surgery induces gut edema and alters intestinal perfusion	Abdominal surgery
Severity of disease	Severity of disease is associated to ileus, gut edema, and altered gut perfusion	Severity scores: PELOD score, Pediatric Risk of Mortality, Pediatric Index of Mortality
Organ function	Organ failure may influence pharmacokinetics	Renal function: urea, creatinine *z* score adjusted for gender and age
		Liver function tests: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, gamma-glutamyltransferase
		Number of organ dysfunction: defined as the number of organ with a positive PELOD score
		Other: albumin, lactate
Inflammation	Inflammation may have a major impact on pharmacokinetics	C-reactive protein
		Leucocytes
Way of oral dose administration	Enteral drug absorption is influenced by the location of administration within the gastrointestinal tract	Oral, nasogastric tube, gastrostomy, duodenal tube
Oral feeding status	Critical illness is associated to gastrointestinal dysmotility and food intolerance	Oral feeding status within the 24 hr prior to microtracer
Comedication	Slowing absorption	Opioids
	Increasing absorption	Prokinetics
	Influences absorption	Vasopressor and inotropic drugs

PELOD = pediatric logistic organ dysfunction.

administration of the microtracer and for one patient treatment acetaminophen dosing information was missing, leaving 47 evaluable patients with a median age of 6.1 months (interquartile range [IQR], 1.8–20 mo) and a median bodyweight of 7.4 kg (Q1–Q3, 4.3–10.5 kg). Patient characteristics and treatment are described in **Table 2.** Thirty-seven patients (78.7%) had been admitted for postoperative care. The median Pediatric Risk of Mortality score was 16 (Q1–Q3, 5–29).

Dataset

Supplemental Figure 2 (Supplemental Digital Content 3, http://links.lww.com/CCM/E945; legend, Supplemental Digital Content 5, http://links.lww.com/CCM/E947) shows the concentration-time profile of the complete dataset including 250 and 314 radiolabeled and treatment acetaminophen concentrations, respectively. Twenty-three measurements below the limit of quantification (BLOQ) and two upper the limit of quantification for radiolabeled and treatment acetaminophen, respectively, were excluded from the dataset as these measurements represented less than 10% of the total number of available measurements (8.4% and 0.6% for [^{14}C] acetaminophen and treatment acetaminophen, respectively). The median numbers of concentrations per patient included in the analysis were six (Q1–Q3, 5–6) and seven (Q1–Q3, 6–8) for [^{14}C] acetaminophen and treatment acetaminophen, respectively.

Pharmacokinetics Model

A two-compartment model best described the time course of oral ^{14}C microtracer and IV treatment acetaminophen blood concentrations. The mean oral bioavailability in the population

TABLE 2. Patients' Characteristics and Treatment ($n = 47$)

Patients' Characteristics and Treatments	Values
Patient characteristics	
Age (mo)	6.1 (1.8–20)
Weight (kg)	7.4 (4.3–10.5)
Normalized weight for age (*z* score), mean (SD)	−0.7 (1.2)
Sex, male, *n* (%)	38 (80.9)
Gestational age (wk)	39.9 (38–40)
Mortality rate, *n* (%)	0 (0)
Mechanical ventilation on study day, *n* (%)	20 (42.6)
Duration of PICU stay, d	3.8 (0.9–9.2)
Severity scores	
Pediatric logistic organ dysfunction (on study day)	10 (1–11)
Pediatric Index of Mortality II score	0.92 (0.2–3.88)
Pediatric Risk of Mortality	16 (5–29)
Diagnostic, *n* (%)	
Surgical (total)	37 (78.7)
Of which abdominal surgery	12 (25.5)
Medical	10 (21.3)
Way of oral acetaminophen administration, *n* (%)	
Oral	14 (29.8)
Nasogastric tube	22 (46.8)
Duodenal	8 (17.0)
Gastrostomy	3 (6.4)
Orally fed patients[a], *n* (%)	23 (48.9)
Comedications, *n* (%)	
Prokinetics	0 (0)
Opioids	43 (91.5)
Vasoactive-inotropic drugs	13 (27.7)
Laboratory values at infusion start	
Urea (mmol/L)	3.5 (2.3–4.9)
Creatinine (μmol/L)	23 (18–34)
Alanine aminotransferase (U/L)	16 (10–24)
Gamma-glutamyltransferase (U/L)	20 (10–71)
Alkaline phosphatase (U/L)	151 (127–197)
Leucocyte count (10^9 per L)	10.6 (8.1–13.8)
C-reactive protein (mg/L)	5.9 (1.2–22)

[a]Feeding status was defined as oral feeding until 24 hr before microtracer dose. Values are expressed as median and (Q1–Q3) unless specified otherwise.

TABLE 3. Variable Estimates From the Structural and Final Model With Bootstrap Results

Variable	Model Variables Estimates (RSE %) (Shrinkage %)	Bootstrap Mean (Bootstrap RSE %)
Bioavailability		
F	0.718 (6)	0.718 (6)
Absorption rate constant		
ka (h^{-1})	2.15 (27)	2.25 (32)
Clearance		
CL	$CL = TVCL \times (BW/7.4)\ \Theta_{CL}$	
TVCL ($L{\cdot}h^{-1}{\cdot}7.4{\cdot}kg^{-1}$)	1.95 (6)	1.94 (7)
Θ_{CL}	1.05 (12)	1.06 (12)
Inter-compartmental clearance		
Q	$Q = TVQ \times (BQ/7.4)$	
TVQ ($L{\cdot}h^{-1}{\cdot}8.6\,kg^{-1}$)	0.346 (12)	0.372 (44)
Volumes of distribution		
V1	$V1 = TVV1 \times (BW/7.4)\Theta_{V1}$	
TVV1 ($L{\cdot}8.6\,kg^{-1}$)	6.67 (5)	6.62 (6)
Θ_{V1}	0.702 (15)	0.715 (16)
V2	$V2 = V1 \times \Theta_{V2}$	
Θ_{V2} ($L{\cdot}8.6\,kg^{-1}$)	0.502 (21)	0.549 (30)
Inter-individual variability		
ω CL	0.114 (23) (7)	0.109 (24)
ω ka	2.45 (30) (20)	2.44 (32)
ω F	1.31 (35) (22)	1.28 (37)
Residual error		
Exponential error therapeutic acetaminophen	0.224 (16) (5)	0.218 (16)
Exponential error radiolabeled acetaminophen	0.102 (19) (16)	0.101 (18)

ω = interindividual variability, Θ_{CL} = estimated allometric exponent for clearance, Θ_{V1} = estimated allometric exponent for the central volume of distribution, Θ_{V2} = fraction of the population central volume of distribution representing the population peripheral volume of distribution, BW = body weight, CL = population clearance, F = oral bioavailability, Q = population inter-compartmental clearance, RSE = residual SE, TVCL = typical population clearance for a 7.4 kg child, TVQ = typical population inter-compartmental clearance, TVV1 = typical population central volume of distribution, V1 = population central volume of distribution, V2 = population peripheral volume of distribution.

Typical population values correspond to the population variable for a child of 7.4 kg.

was 72% (bootstrap 95% CI, 64–79%) with a high interindividual variability: individual bioavailability estimates ranged from 11% to 91%, implying that some patients absorbed only around 10% of the oral doses while in others the absorption

was almost complete. The other pharmacokinetics variables are provided in **Table 3**. The IV data were similar as previously reported (26), including similar pharmacokinetics variable relationship with weight over the first and third IQR. Detailed comparison of the model variables with literature values can be found in eMethods (Supplemental Digital Content 1, http://links.lww.com/CCM/E943) and **eResults** (Supplemental Digital Content 4, http://links.lww.com/CCM/E946).

Bodyweight was the best predictor of clearance and volume of distribution. After inclusion of bodyweight in the model, age and other potential covariates tested were not found to be significant.

The interindividual variability in bioavailability could not be explained by any patient characteristic. The minimum, 5th, 50th, and 95th percentile and the maximum individual enteral bioavailability estimates in our analysis were 0.11, 0.34, 0.72, 0.90, and 0.91 respectively. As illustrated in supplementary 1 in the eResults (Supplemental Digital Content 4, http://links.lww.com/CCM/E946), feeding status and the characteristics of the route of enteral administration (oral, nasogastric, duodenal, and gastrostomy) did not significantly impact bioavailability. Moreover, abdominal surgery was also not a significant explanatory variable for bioavailability. Table 3 describes variable estimates of the final model. All internal validation presented in the eResults (Supplemental Digital Content 4, http://links.lww.com/CCM/E946) shows that the model described the data accurately and precisely.

Simulation

Figure 1 shows the median and the 90% prediction intervals of the simulated plasma concentrations over 24 hours after acetaminophen administration. Exposure after standard similar IV and oral doses (15 mg/kg every 6 hr) led to adequate Css with the IV route (median mean Css corresponded to the targeted mean Css of 10 mg/L). Nevertheless, most patients were below the targeted blood concentrations with the same oral standard doses (median mean Css around 6.5 mg/L). Patients were 2.5 times more likely to reach targeted blood concentrations with IV than with oral administration. The highest oral dosing of 90 mg/kg/d potentially leads to adequate Css, but patients with bioavailability

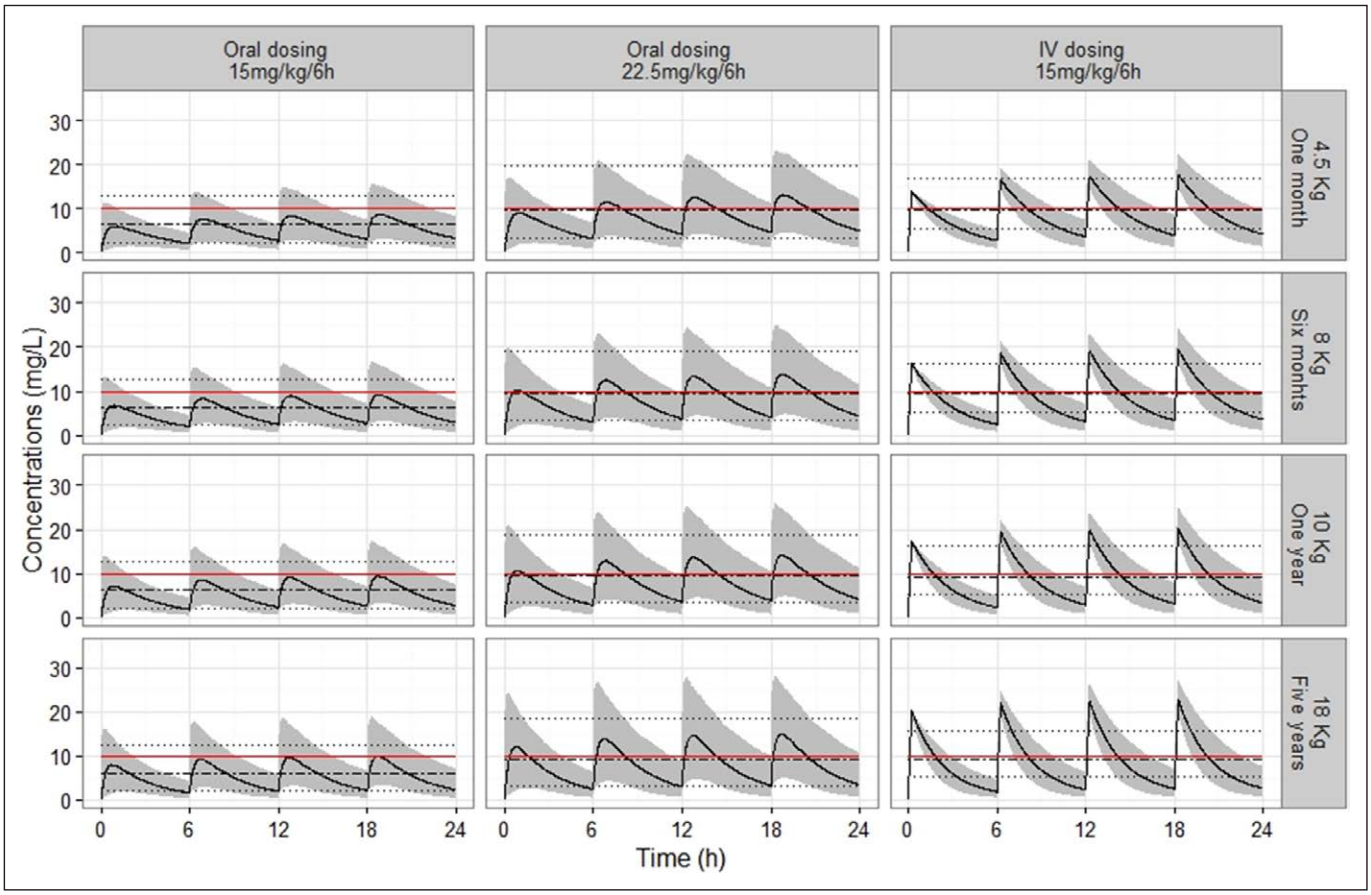

Figure 1. Simulated acetaminophen concentration-time profiles over 24 hr after standard oral dose (60 mg/kg/d—*left*), high oral doses (90 mg/kg/d—*middle*), and IV dosing (*right*) in four age groups, that is, 1 mo, 6 mo, 1 yr, and 5 yr of 4.5, 8, 10, and 18 kg. The *dashed line* shows the median of the mean steady-state concentration and the *lower* and *upper dotted lines* indicate the 5th and the 95th percentiles of the mean steady-state concentration, respectively. The *red line* represents the targeted steady-state concentrations. Doses recommended by the Lexicomp Pediatric and Neonatal Handbook (23) were used for the oral and IV standard doses and the Dutch Pediatric Drug Handbook (19) for the high oral dose (90 mg/kg/d). Wide variability is seen with oral dosing while IV dosing leads to less variable steady-state concentrations. The mean targeted steady-state concentrations of 10 mg/L are not reached with an oral dosing of 60 mg/kg/d while the same IV dosing allows reaching adequate systemic exposure. With the highest recommended oral dose, the mean targeted steady-state concentrations are reached, but the important interindividual variability implies that some patients are underexposed and other overexposed.

in the upper range have higher exposure than with 60 mg/kg/d IV, and similarly, patients with bioavailability in the lower range would not reach targeted level. With 90 mg/kg/d dosing, patients are still 1.4 times more likely to be within the targeted range after IV administration than after high oral administration.

DISCUSSION

Microtracer studies offer a new opportunity to rationalize drug dosing and choice of route of administration in the critically ill patient. In this stable PICU population studied, the mean oral bioavailability of acetaminophen was 72% with a very wide interindividual variability. When compared to the reported therapeutic range, the current oral dosing guidelines potentially result in underexposure in most patients, in contrast to IV administration. The estimated oral and IV pharmacokinetics variables are in line with previous estimates in children (22, 26). Similar variability has been shown in infants younger than 3 months (22) and in adults undergoing surgery (28). In the latter, oral administration also led to more variable blood concentrations than IV administration (28).

The median bioavailability in the current study was 72%. Although the median enteral bioavailability in our analysis lies within the reported range in healthy adults of 60–97% as calculated by AUC (13–15), the range found in our analysis is much wider. Furthermore, the patients included in our analysis might present less pharmacokinetic variability than the overall PICU population due to inclusion criteria, meaning that an even higher variability in this population might be expected. Since the actual enteral bioavailability is not 100% but 72% or less in half of the patients included in our analysis, this can result in underexposure in a part of this population. We believe that dosing guidelines should actually reflect bioavailability. If only 72% of an oral dose reaches the systemic circulation, a one-third higher dose would be needed to reach the same blood level as with an IV dose. When simulating the plasma concentrations reached with different official dosing guidelines, we noticed that similar mean targeted Css were indeed reached with the highest recommended oral dose of 90 mg/kg/d and an IV dose of 60 mg/kg/d. But due to the high interindividual variability in oral bioavailability, a dose of 90 mg/kg can still potentially lead to underdosing in patients with low bioavailability and overdosing in patients with high oral bioavailability. This dosage is recommended for short-term use only (maximum 2–3 d) (19, 29). This seems a rational advice in the light of our findings suggesting that a patient with a bioavailability within the upper range may be at risk of overdosing. To date, there is no upper therapeutic range reported for acetaminophen in the pediatric population. Due to the lack of information on the upper therapeutic range, dosing guidelines should lead to a concentration-time profile the closest possible to the efficacious concentration, as an increased exposure might lead to toxicity. Acute liver failure in children receiving regular acetaminophen within the therapeutic dose range has been described (30, 31). Known risk factors for acetaminophen-induced liver failure are acute illness, fasting, and comedication with a CYP2E1 inducer (30, 32). Whether bioavailability in the upper range is a risk of acetaminophen toxicity remains to be determined.

In the present study in 0 to 6-year-old children, we did not find a relationship between age and oral bioavailability. In most dosing guidelines, however, the ratio of advised oral to IV dosing guidelines increases with age (23, 33). Clinicians often assume that conditions for good oral drug absorption are met when critically ill patients tolerate oral feeds and are clinically stable (34). Interestingly, our study suggests that oral bioavailability of acetaminophen is independent of feeding status or disease severity, challenging this assumption.

The variable and unpredictable bioavailability of acetaminophen in critically ill children suggest that the IV route should be preferred for reliable and effective pain relief.

This study has several strengths. ^{14}C microtracer study design has been used in drug development in adults, but this is the first study in the PICU. This study design offers a new opportunity to study oral bioavailability in the PICU, where 15% of drugs are given enterally without bioavailability data (9). It presents also opportunities to study other patient populations for which the traditional crossover study design is not feasible for practical and/or ethical reasons (e.g., patients with quickly changing disease severity, pregnant women, and elderly). In addition, our study provides guidance for acetaminophen dosing in the pediatric intensive care. Similar studies on other analgesics and sedatives like morphine, clonidine, or benzodiazepines would provide useful information to rationalize dosing in the PICU, particularly when switching from IV to oral administration.

The following limitations should be addressed. First, we cannot exclude that the oral microtracer dose has contributed to the lower bioavailability and large interindividual variability observed. Such a low dose may contribute to more unexplained variability than does a treatment dose. However, incomplete oral drug administration is highly unlikely as recovery of the drug from the administration in the feeding tube was almost 100% (5). Also, saturation of intestinal drug metabolism with a treatment dose could have resulted in higher systemic exposure than with a microtracer dose alone. Both scenarios are unlikely, however, as our results are in line with an indirect marker of bioavailability, the oral to IV exposure ratio, that varies between 40% and 100% in different pediatric formularies (19, 23, 33, 35). Furthermore, similar pharmacokinetics results, that is, dose-linearity, have been obtained with acetaminophen oral microdose and therapeutic dose in adults (36, 37). Second, the current study was not designed to assess intra-individual variability in bioavailability that may influence acetaminophen exposure after multiple oral doses. Indeed, bioavailability was assessed on a single oral dose and then extrapolated to obtain Css. Third, it was not meant to assess the impact on acetaminophen effectiveness, and therefore, pharmacokinetics data should be seen as a surrogate endpoint. However, considering that a clear concentration-effect relationship has been established for acetaminophen (38), we believe that this study should motivate future studies comparing analgesic effect after oral and IV routes. A recent systematic review on the efficacy of oral versus IV acetaminophen in adults concluded that evidence is lacking to favor IV over oral

administration (12). This review included only three randomized efficacy trials in adults: that is, one open-label study, one underpowered study, and one in day-case surgery. In contrast, data from our group showed a very significant morphine sparing effect with IV acetaminophen (approximately 70% less) in neonates and infants after major surgery (10). The morphine sparing effect did not occur with the use of the rectal route, which resulted in the same variable absorption and bioavailability as with the oral route (39, 40).

CONCLUSIONS

Using a microtracer study design, an innovative approach to study oral drug disposition in the real-life clinical situation in the intensive care, we show that oral acetaminophen bioavailability is lower than generally assumed, with a large interindividual variability in stable pediatric intensive care patients until 6 years. Oral dosing will likely results in an unpredictable, likely lower systemic exposure that may lead to increased risks of therapeutic failure. These data suggest that for the treatment of acute pain in children in the PICU, IV administration of acetaminophen may be preferable. Analgesic effect of oral versus IV acetaminophen should be compared in future studies.

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