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Oral Ibuprofen Is More Effective than Intravenous Ibuprofen for Closure of a Patent Ductus Arteriosus: Can Pharmacokinetic Modeling Help Us to Understand Why?

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Keywords
Pharmacokinetics · Ibuprofen · Neonates · Patent ductus arteriosus · Pharmacology

Abstract
Introduction: Oral ibuprofen is more effective than intravenous (IV) ibuprofen for closure of a patent ductus arteriosus (PDA). This study explored whether higher concentrations of the biologically active S-enantiomer or increased R- to S-conversion following oral dosing could explain this finding. ***Methods:*** Two datasets containing 370 S- and R-ibuprofen concentrations from 95 neonates with PDA treated with oral (n = 27, 28%) or IV ibuprofen were analyzed using nonlinear mixed effects modeling. Concentration-time profiles in typical neonates were explored and compared in different dosing or R- to S-conversion scenarios. ***Results:*** Postnatal age (PNA), gestational age (GA), and being small for GA impacted S- and R-ibuprofen clearance. Upon oral dosing, S-ibuprofen concentrations were lower compared to IV ibuprofen for a large part of the dosing interval. We could show that R- to S-conversion will not exceed 45%. Exploration of a 30% presystemic R- to S-conversion resulted in a 25–32% increase in S-ibuprofen exposure following oral administration with AUC_{72h} values varying between 700–2,213 mg*h/L (oral) and 531–1,762 (IV) for the standard or 1,704–2,893 (oral) and 1,295–2,271 mg*h/L (IV) for PNA-based dosing. ***Discussion:*** The absence of higher S-ibuprofen concentrations does not support a beneficial concentration-time profile after oral dosing. While a fraction of up to 45% presystemic R- to S-conversion could not be ruled out, the impact of such a low conversion might be only relevant for the standard but not high dosing regimens, considering reported exposure-re-

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sponse targets. Perhaps, the lack of high peak concentrations observed following IV dosing may play a role in the observed effects upon oral dosing.

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Introduction

A hemodynamically significant patent ductus arteriosus (PDA) is currently treated with one or more courses of ibuprofen [1, 2]. Several studies have shown a higher efficacy of oral versus intravenous (IV) ibuprofen following standard dosing (10, 5, and 5 mg/kg with 24 h intervals), a finding that was recently confirmed in two meta-analyses [2, 3].

Ibuprofen is administered as a racemic mixture consisting of two mirrored, nonidentical enantiomers. S-ibuprofen is biologically active, whereas R-ibuprofen is considered to be biologically inactive. In vivo, the ratio between both enantiomers changes over time since elimination pathways differ between the enantiomers, and, in addition, R-ibuprofen is partly converted unidirectionally into the biologically active S-ibuprofen [4, 5].

A beneficial concentration-time profile of orally administered ibuprofen, where the absorption phase is expected to lead to a prolonged "effective" S-ibuprofen exposure, might be a possible reason for the reported higher efficacy of oral ibuprofen [6–8]. A direct comparison of S-ibuprofen concentration-time profiles after oral and IV administration could substantiate this theory but has not been conducted to date. Although the enantiomer-specific pharmacokinetics of IV ibuprofen in neonates have been fairly studied [9–11], most pharmacokinetic studies of oral ibuprofen are only of a descriptive nature [12–14]. Therefore, the available information cannot be used directly for dose simulations and comparison of these two administration routes.

A second explanation for the higher efficacy of oral ibuprofen assumes a higher enantiomeric R- to S-ibuprofen conversion after oral administration [15]. Assuming that enantiomeric conversion occurs primarily in the liver, this could be increased when ibuprofen is given orally as a result of first-pass metabolism. However, the evidence on enantiomeric conversion in neonates is rather weak. While numerous studies report fractions of the dose undergoing enantiomeric conversion of around 60% in adults [16–19], conflicting results are reported for conversion in neonates with fractions varying from 0 to 61% [9–11, 20].

A combined population pharmacokinetic analysis of existing S- and R-ibuprofen data following both IV and oral administration would not only allow dose simulations and comparison of concentration-time profiles following both routes but could also be the best approach to explore the presence and magnitude of enantiomeric conversion given the currently available data. Moreover, it could reveal whether the beneficial effect of oral dosing also applies to the novel, higher dose regimens such as a recently proposed postnatal age (PNA)-based dose regimen [1, 11]. A better understanding of the underlying mechanisms on the observed beneficial effect of oral ibuprofen is crucial to guide future research and improve the efficacy of ibuprofen in closing PDA. This study was conducted with this purpose by (1) performing an enantiomer-specific characterization of the population pharmacokinetics of S- and R-ibuprofen in neonates with PDA following oral and IV administration, (2) exploring the presence of enantiomeric R- to S-ibuprofen conversion in the population pharmacokinetic model, and (3) comparing S-ibuprofen concentration-time profiles following oral and IV ibuprofen administration with standard and PNA-based dose regimens.

Methods

Data

Pharmacokinetic data from two independent studies conducted in neonates receiving ibuprofen for closure of a PDA were combined for the current analysis [9, 11]. Study A (Engbers et al. [11]) consisted of 72 neonates, mostly treated intravenously (n = 68, 94%), while study B (Samiee-Zafarghandy et al. [9]) consisted of 23 neonates, all treated with oral ibuprofen via nasogastric tube. PK samples were collected following a (semi-)opportunistic sparse sampling design, and S- and R-ibuprofen concentrations were measured using validated chromatography methods with a lower limit of quantification (LLOQ) of 1 μg/mL (study A) or 0.01 μg/mL (study B) [9, 11]. Covariates were collected for all individuals, including PNA, birth weight, body weight, gestational age (GA), or small for GA. For more details, we refer to the original publications [9, 11]. Baseline characteristics were analyzed by the Mann-Whitney U test or Fisher's exact test for continuous and binary data, respectively, performed using R (v4.0.2), where a p value < 0.05 was considered statistically significant.

Population Pharmacokinetic Analysis

Concentration-time data were analyzed using nonlinear mixed effects modeling (NONMEM v7.4.1; ICON Development Solutions, Ellicott City, MD, USA). LLOQ data were included in the analysis using the M3 method [21]. Both enantiomers (S-ibuprofen and R-ibuprofen) were first modeled separately, assuming an equal amount of both enantiomers in each ibuprofen dose. One- and two-compartment models were explored, with different absorption models (with and without lag time or a number of transit

Table 1. Baseline characteristics of included neonates

	IV group (*n* = 68)	Oral group (*n* = 27)	*p* value	Total (*n* = 95)
Sex, *n* females (%)	33 (49)	13 (48)	1	46 (48)
Birth weight, g	868 (465–1,450)	750 (540–1,270)	0.020	860 (465–1,450)
PNA at the start of treatment, days	3.0 (1.0–12)	3.7 (1.2–31)	0.522	3.0 (1.0–31)
GA, weeks	26.1 (24.0–30.1)	25.9 (23.4–27.3)	0.079	25.9 (23.4–30.1)
Small for GA, *n* (%)	7 (10)	6 (22)	0.183	13 (14)

Shown as median (range) unless otherwise specified.

Table 2. Overview of pharmacokinetic data

	IV group (*n* = 68)	Oral group (*n* = 27)	Total (*n* = 95)
Number of doses per neonate, *n*	3 (1–9)	3 (1–4)	3 (1–9)
Loading dose, mg/kg	10.8 (5.4–22.7)	18.9 (9.9–20.4)	10.9 (5.4–22.7)
Maintenance dose, mg/kg	7.3 (4.5–20.5)	9.9 (4.4–10.6)	7.8 (4.4–20.5)
R-/S-Ibuprofen plasma concentrations, *n*	211	159	370
R-/S-ibuprofen plasma concentrations per neonate, *n*	3 (1–9)	7 (1–9)	3 (1–9)
Time after dose of measurements, h	15.9 (0.1–113)	8.0 (0.02–46)	11.1 (0.02–113)
R-/S-ibuprofen concentrations under LLOQ, *n* (%)	S-ibuprofen: 4 (2) R-ibuprofen: 145 (69)	S-ibuprofen: 0 (0) R-ibuprofen: 5 (3)	S-ibuprofen: 4 (1) R-ibuprofen: 150 (41)

Shown as median (range) unless otherwise specified.

compartments). Development of a structural and statistical model was followed by a covariate analysis. Both enantiomer covariate models were then combined and modeled simultaneously. Next, enantiomeric R- to S-ibuprofen conversion was investigated by introducing a rate parameter between the R-ibuprofen and S-ibuprofen central compartments (K_{42}, for systemic conversion) or between the R-ibuprofen depot compartment and the S-ibuprofen central compartment (K_{32}, for presystemic conversion) as shown in online supplementary Figure S1 (for all online suppl. materials, see www.karger.com/doi/10.1159/000526210). The fraction of the dose that undergoes R- to S-ibuprofen conversion for systemic ($R_{systemic}$) and presystemic ($R_{presystemic}$) conversion was defined using online supplementary equations S1 and S2. For more details regarding the modeling of R- to S-ibuprofen conversion, we refer to the online supplementary file. A post hoc power analysis (details in the online suppl. file, Table S3) indicated that the current dataset, study design, and analysis method yielded sufficient power to detect at least a 45% fraction of the S-ibuprofen doses to be converted (power of 80% and 86% for presystemic or systemic conversion, respectively). In all steps of the modeling process, the nested models were compared using the objection function value (OFV, where a reduction of 3.8, 6.6, or 10.8 points corresponds to significance levels of $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively). In addition, goodness of fit plots, such as observation versus predictions or conditional weighted residuals versus predictions or time after dose, was assessed. The internal validity of the final model was evaluated by normalized prediction distribution errors and a bootstrap resampling analysis (n = 1,000 datasets).

Comparison of Concentration-Time Profiles following Different Administration Routes

To explore differences in concentration-time profiles between administration routes, the final pharmacokinetic model was used to simulate S-ibuprofen concentrations in five typical neonates with PDA representative of the range in PNA and GA of the population. Ibuprofen was administered either IV or oral with a dose based on (1) the drug label, i.e., 10-5-5 mg/kg at 0, 24, and 48 h ("standard dosing") [22] and (2) the recently proposed optimal PNA-based dosing regimen by Engbers et al. [11] with doses ranging from 10-5-6 mg/kg to 24-12-13 mg/kg at 0, 24, and 48 h ("PNA-based dosing"), respectively. Details of the PNA-based dosing regimen are shown in online supplementary Table S1. For each neonate, plots of S-ibuprofen concentrations versus time and the exposure over the first 72 h (AUC_{72h}) were compared, keeping in mind the exposure-response target of >900 mg*h/L as proposed by Hirt et al. [23]. Based on the population pharmacokinetic analysis and a post hoc power analysis presented in this study, we could show that a presystemic R- to S-ibuprofen conversion will not exceed 45%. Therefore, we additionally assessed the influence of a hypothetical 30% presystemic R- to S-ibuprofen conversion fraction upon oral administration by repeating the simulations with the same model but with 30% of the R-ibuprofen being converted to S-ibuprofen presystemically ($R_{presystemic}$ = 30%, see online suppl. Fig. S1).

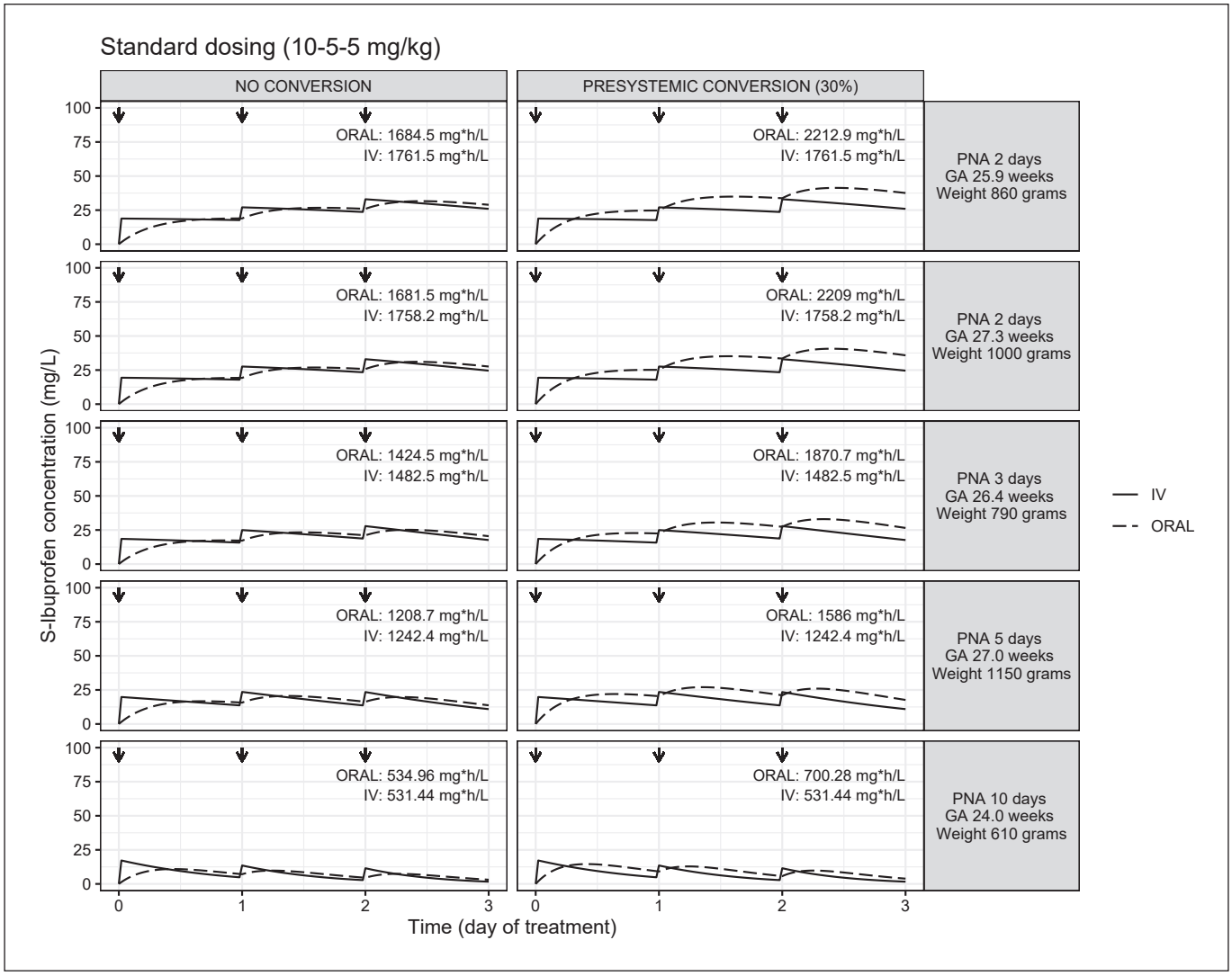

Fig. 1. S-ibuprofen concentrations versus time and AUC_{72h} following the standard dose of 10-5-5 mg/kg on time 0, 24, and 48 h, respectively, given either oral or IV (indicated by the black arrows) in five typical neonates derived from the original dataset. The left panel shows expected concentration-time profiles and AUC_{72h} based on the final PK model (without R- to S-conversion). The right panel shows the results when a hypothetical 30% fraction of the S-ibuprofen dose being converted presystemically. The lines represent the population-predicted ibuprofen concentrations with administration route depicted by the line type (solid line for IV and dashed line for oral administration). AUC_{72h} values are shown as inset in each figure. GA, gestational age; PNA, postnatal age.

Results

Data

In total, 95 neonates were included for analysis with 27 (28%) being treated orally. Included neonates had a median PNA of 3.0 days (range 1–31) and GA of 25.9 weeks (range 23.4–30.1). Patient characteristics (Table 1) were similar between both administration routes, with the exception of a higher birth weight observed in the IV group. A total of 370 R- and S-ibuprofen plasma concentrations were available for analysis (online suppl. Fig. S2), with the most important details summarized in Table 2.

Population Pharmacokinetic Analysis

S-ibuprofen concentrations were best described using a one-compartment model with a proportional residual error model and inter-individual variability on S-ibuprofen clearance (CL_S) and volume of distribution (V_S) and

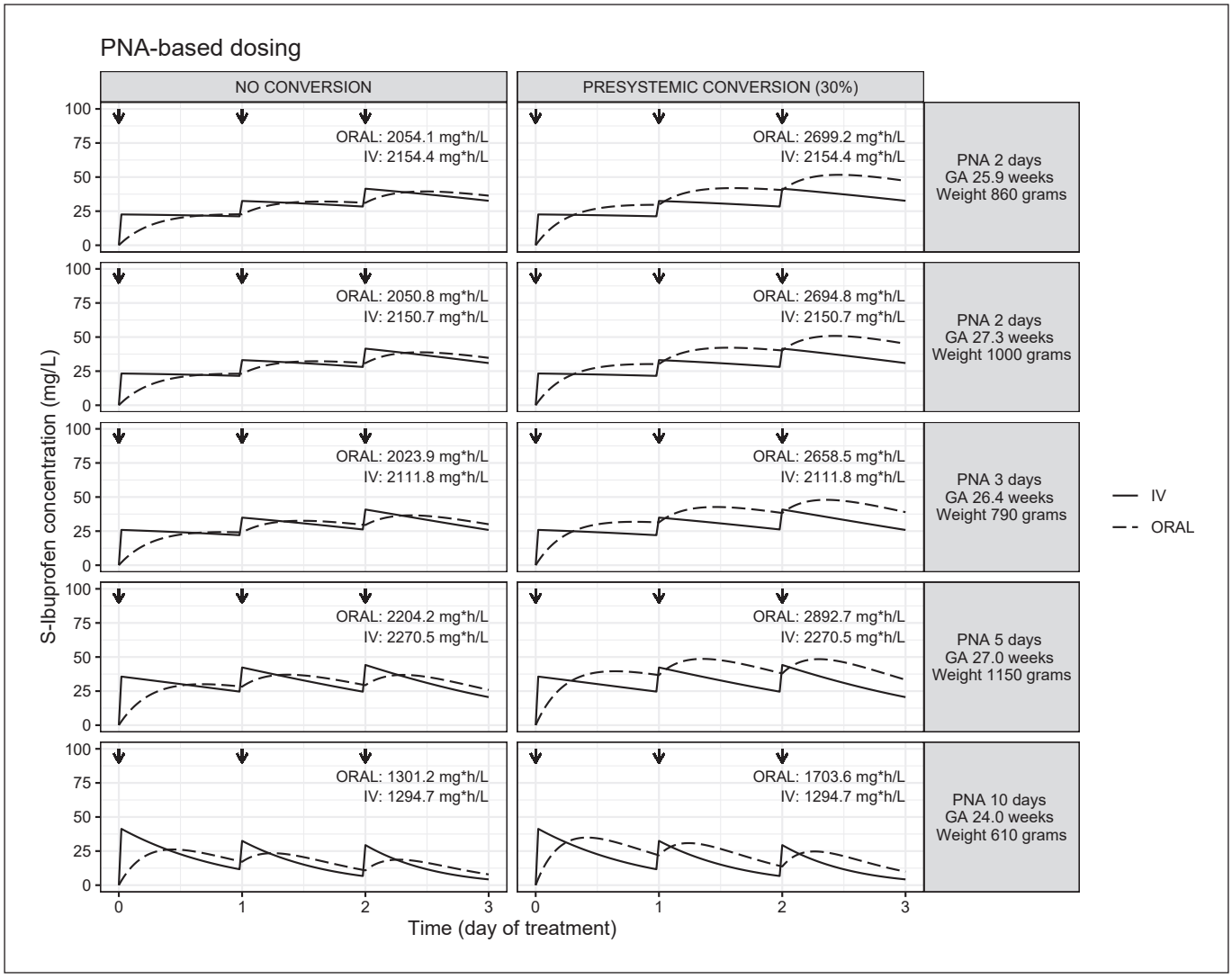

Fig. 2. S-ibuprofen concentrations versus time and AUC_{72h} following the recently proposed dosing regimen (Engbers et al. [11]) given either oral or IV on time 0, 24, and 48 h (indicated by the black arrows) in five typical neonates derived from the original dataset. The left panel shows expected concentration-time profiles and AUC_{72h} based on the final PK model (without R- to S-ibuprofen conversion). The right panel shows the results when a hypothetical 30% fraction of the S-ibuprofen dose being converted presystemically is introduced in this model. The lines represent the population-predicted ibuprofen concentrations with administration route depicted by the line type (solid line for IV and dashed line for oral administration). AUC_{72h} values are shown as inset in each figure. GA, gestational age; PNA, postnatal age.

absorption modeled using a standard first-order absorption model. CL_S increased significantly with PNA ($p < 0.001$) and GA ($p < 0.001$), while V_S increased with body weight ($p < 0.001$). R-ibuprofen concentrations could be best described using a one-compartment model with a proportional error model, a standard first-order absorption model, and inter-individual variability on R-ibuprofen clearance (CL_R) and volume of distribution (V_R). CL_R was found to increase significantly with PNA ($p < 0.001$), and no covariates could be identified for V_R. Lastly, both CL_S and CL_R were 2.16-fold higher in neonates being small for GA ($p < 0.01$). Introduction of presystemic or systemic R- to S-ibuprofen conversion (K_{32} and K_{42}, respectively, online suppl. Fig. S1) resulted in a decrease of OFV of 0.6 points for presystemic and an increase of 1.2 points for systemic conversion ($p > 0.05$ for both). Addi-

tional explorations with a separate K_{42} for both administration routes did not improve the model (ΔOFV of –0.3 points compared to a model without conversion, $p > 0.05$). Hence, neither presystemic nor systemic enantiomeric conversion could be identified. The model parameters for the final enantiomer-specific population PK model are shown in online supplementary Table S2. The goodness of fit plots for the final enantiomer-specific population pharmacokinetic model is shown in the online supplementary file (online suppl. Fig. S3). The internal validity of the final model was confirmed by normalized prediction distribution errors and bootstrap analysis (online suppl. Fig. S4; Table S2).

Comparison of Concentration-Time Profiles following Different Administration Routes

S-ibuprofen concentration-time profiles following the standard dosing regimen in five typical neonates are presented in Figure 1. In the final covariate model without enantiomeric conversion (Fig. 1, left panel), obtained exposures are similar between both administration routes, ranging between 531 and 1762 mg*h/L, while the concentration-time profiles show some marked differences. Upon oral dosing, S-ibuprofen concentrations are lower for a large part of the dosing interval (Fig. 1, left panel), which is most evident directly after the first dose. Similar S-ibuprofen concentrations could be observed shortly before redosing for both administration routes. Figure 2 (left panel) shows the results following simulations with a PNA-based dosing regimen [11] (online suppl. Table S1). Here, similar differences between the concentration-time profiles following oral and IV administration routes were obtained, although exposures, with values ranging 1,295–2,271 mg*h/L, were much higher compared to those observed following the standard dose regimen, often exceeding the reported exposure-response target [23].

In the right panels of Figures 1 and 2 the impact of an assumed 30% presystemic R- to S-ibuprofen conversion on the S-ibuprofen concentration-time profile is shown. This hypothetical R- to S-ibuprofen conversion model reflects the maximum amount of conversion that, based on the current analysis, can be expected to occur. Here, the overall shape of the concentration-time profiles is similar to the situation without conversion (Fig. 1, 2, left panel). Yet, a pronounced increase in S-ibuprofen exposure and trough concentrations was found for orally compared to IV-administered ibuprofen: AUC_{72h} values increased by 25.6–31.8% following oral administration when using standard dosing (Fig. 1, right panel). Observed AUC_{72h} values ranged between 531 and 1762 mg*h/L and 700 and 2213 mg*h/L for IV and oral ibuprofen, respectively. Following PNA-based dosing (Fig. 2, right panel), the AUC_{72h} increased by 25.3–31.6% after oral administration. Here, values varied between 1,704–2,893 and 1,295–2,271 mg*h/L for oral and IV administration, respectively. In contrast to standard dosing, these exposures are well above 900 mg*h/L, which has been suggested as a possible exposure-response target for total (R- and S-) ibuprofen [23].

Discussion

In this study, we have successfully characterized the enantiomer-specific population pharmacokinetics of both oral and IV ibuprofen in neonates with PDA. Our study provides several new important insights from a mechanistic perspective to understand and put the higher observed efficacy of oral ibuprofen over IV ibuprofen in closure of PDA in neonates into perspective [2]. It underlines the importance of dose optimization in the pharmacological closure of PDA, especially when comparing different administration routes in clinical studies. This new knowledge could move the discussion of oral versus IV administration of ibuprofen for closure of a PDA forward and outlines several unanswered questions and knowledge gaps.

The analysis and model-informed simulations allow us to explore the validity of proposed explanations for higher observed efficacy of oral versus IV ibuprofen in PDA closure. Considering that COX-2 inhibition is a competitive, reversible process, slow oral absorption may result in superior COX-2 inhibition over the entire dose-interval [6, 24]. Model-informed dose simulations presented in this study make this explanation less plausible since slow absorption did not result in higher serum concentrations of S-ibuprofen, the active enantiomer. However, a higher peak concentration is visible following IV dosing. In theory, this could cause a transient reduction in glomerular filtration upon IV dosing. Subsequent fluid overload, a known risk factor for persistent PDA, might hamper PDA closure in the IV group [25]. More research is needed to further explore this potential harmful effect of IV ibuprofen on closing PDA. A second proposed explanation involves the first-pass presystemic R- to S-conversion leading to higher concentrations of the biologically effective S-ibuprofen after oral administration [15]. Our study shows no evidence for enantiomeric conversion, presystemically nor systemically, to occur in this population of neonates. Due to the sparsity of the data, a

low R- to S-ibuprofen conversion with 30% of the R-ibuprofen dose being converted could have remained undetected in our study. Therefore, we have additionally explored concentration-time profiles using a 30% R- to S-ibuprofen conversion fraction. In this hypothetical situation, presystemic conversion resulted in a 25–32% increased exposure when ibuprofen was administrated orally. We observed that the exposure was relatively low when employing the standard dose (10-5-5 mg/kg at 0, 24, and 48 h) with exposures in the range of the exposure-response target of 900 mg*h/L reported earlier [23]. A PNA-based dose regimen resulted in exposure well above this target for all neonates. Although to date, there is not much evidence to substantiate such an exposure-response target, this observation could be relevant since only the standard dose regimen was used in earlier studies that have demonstrated the benefit of oral ibuprofen [1, 2]. This implies that the increased S-ibuprofen exposure due to presystemic R- to S-conversion might only be clinically relevant for the standard dose regimen as opposed to higher dosing regimens. This suggestion is substantiated by the fact that a recent meta-analysis could not identify any difference in efficacy for oral ibuprofen versus IV ibuprofen when comparing only high-dose regimens, albeit with a large uncertainty due to lack of data [1]. We therefore recommend future research to focus on comparing the efficacy of oral versus IV ibuprofen for the novel tailored drug dosing regimens.

Based on the current analysis, we could show that a presystemic R- to S-conversion will not exceed 45%. This implies that if enantiomeric conversion in neonates occurs at all, and this is in a magnitude that is much lower than what is reported for adults, where its occurrence is relatively undebated with well-designed prospective studies having identified conversions up to 60% [16–19]. There is not much known about the maturation of key enzymes in enantiomeric conversion, such as 2-arylpropionyl-CoA epimerase or acyl-CoA synthetase [5], although the latter has been shown to mature in the first days after birth in developing rats [26]. In line with our results, there is not much evidence supporting R- to S-conversion in neonates. One PK study in 108 neonates treated with IV ibuprofen reported a low systemic R- to S-conversion rate of 17% [10]. A second study in 16 neonates where ibuprofen was administered IV in a 10-5-5 mg/kg dose schedule found evidence for enantiomeric conversion with a mean rate of 41%, albeit with a wide range (7–87%) [20].

Some limitations apply to our study. First, this pharmacokinetic analysis was done using a sparse dataset due to the opportunistic sampling scheme. As our post hoc power analysis showed, this hampered the potential of characterizing a low enantiomeric conversion rate. In addition, we were unable to separately quantify F_s and F_r. A second limitation is that in our study, we did not specifically sample shortly after dosing. Although our dataset contains relatively many samples in the first 8 h (online suppl. Fig. S2), more samples obtained shortly after dosing could have increased the power of our study to quantify the absorption profile and enantiomeric conversion. Lastly, the dataset consisted of two studies comparable in terms of patient characteristics and sampling design but with different analysis methods leading to more R-ibuprofen samples being under the LLOQ in study A (Table 2). By employing the M3 method, which is widely accepted as the most optimal method for analyzing LLOQ data, we were still able to include these data in the model building process. The model diagnostics split for administration route (online suppl. file) showed no bias for R-ibuprofen concentrations between different administration routes. Since most of the oral data were derived from study B, this also implies that there is no significant bias between both studies.

Conclusion

We have characterized the enantiomer-specific pharmacokinetics of both IV and orally administered ibuprofen simultaneously in neonates with PDA. We showed that the delayed absorption after orally administered ibuprofen does not result in higher S-ibuprofen concentrations and does not explain the higher efficacy observed for orally administered ibuprofen in recent meta-analyses. However, harmful effects of high peak concentrations following IV dosing could also play a role. We also could not identify enantiomeric conversion occurring in neonates. When exploring a scenario with a hypothetical presystemic R- to S-conversion fraction of 30%, reflecting a conversion fraction that we could not formally rule out in our study, S-ibuprofen exposures and trough concentrations increased in the oral group by 25–30%. In light of proposed target exposures for S-ibuprofen, this might only be relevant for the standard 10-5-5 mg/kg dose regimen as opposed to higher dosing regimens such as a PNA-based strategy. We recommend future research to focus on comparing the efficacy of oral versus IV ibuprofen, specifically for the novel PK model-informed drug dosing regimens.

Statement of Ethics

The research was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. For both studies, the Local Ethics Review Board approved the protocol (study A: Medical Research Ethics Committees United, reference MEC-2014-067 and study B: Hamilton Integrated Research Ethics Board, reference #4936-T). Written informed consent from the parents or legal guardians was obtained prior to study inclusion.

Conflict of Interest Statement

All the authors have no conflicts of interest to declare.

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Author Contributions

Robert B. Flint, Catherijne A.J. Knibbe, and Sinno H.P. Simons conceptualized and supervised study A. Samira Samiee-Zafarghandy and John N. van den Anker conceptualized and supervised study B. Cornelis Smit, Tamara van Donge, and Aline G.J. Engbers prepared the data. Cornelis Smit, Catherijne A.J.Knibbe, Marc Pfister, and John N. van den Anker analyzed the data. Cornelis Smit drafted the initial manuscript. All the authors provided input on the initial manuscript and approved the final version.

Data Availability Statement

The data that support the findings of this study are not publicly available since the authors do not have full ownership of the data but are available from the corresponding author upon reasonable request.

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