Pediatr Drugs (2017) 19:277–290
DOI 10.1007/s40272-017-0235-3

CURRENT OPINION

Efficacy and Safety of Ibuprofen in Infants Aged Between 3 and 6 Months

Victoria C. Ziesenitz[1,2] · Andreas Zutter[3] · Thomas O. Erb[3] · Johannes N. van den Anker[1,4]

Published online: 17 May 2017

Abstract Ibuprofen is a non-steroidal anti-inflammatory drug frequently administered to children of various ages for relief of fever and pain and is approved as an over-the-counter medication in many countries worldwide. Although there are extensive data on its efficacy and safety in children and adults, there are divergent dosing recommendations for analgesia and treatment of fever in infants, especially in the age group between 3 and 6 months of age. In this article, we have assessed the safety and efficacy of ibuprofen use in infants in an attempt to find the optimal method of pain and fever management in this specific age group. Based on the current evidence, short-term use of ibuprofen is considered safe in infants older than 3 months of age having a body weight above 5–6 kg when special attention is given to the hydration of the patient. Ibuprofen should be prescribed based on body weight using a dose of 5–10 mg/kg. This dose can be administered 3–4 times a day resulting in a maximum total daily dose of 30–40 mg/kg. The rectal route has been shown to be less reliable because of erratic absorption, especially in young infants. Since most efficacy and safety data have been derived from trials in infants with fever, future studies should focus on the efficacy of ibuprofen in young infants with pain.

Key Points

There are currently conflicting dosing recommendations regarding ibuprofen in infants between 3 and 6 months of age.

We reviewed the currently available data on the safety and efficacy of ibuprofen in an attempt to find the optimal method of pain and fever management in this specific age group.

Based on our assessment, the short-term use (up to 3 days) of ibuprofen for relief of fever or pain is safe in infants older than 3 months with a body weight above 5–6 kg when special attention is given to the hydration of the patient. We suggest using oral preparations whenever possible because the rectal route has been shown to be less reliable, especially in young infants.

✉ Victoria C. Ziesenitz
Ziesenitz.md@gmail.com

1 Division of Paediatric Pharmacology and Pharmacometrics, University of Basel Children's Hospital, Spitalstrasse 33, 4056 Basel, Switzerland

2 Department of Paediatric Cardiology, University Children's Hospital, Heidelberg, Germany

3 Division of Paediatric Anaesthesiology, University of Basel Children's Hospital, Basel, Switzerland

4 Division of Clinical Pharmacology, Children's National Health System, Washington, DC, USA

1 Introduction

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) frequently administered to children for relief of fever and pain and is approved as an over-the-counter (OTC) medication in many countries worldwide. Although there are extensive data on its efficacy and safety in children and adults, there are divergent dosing recommendations in infants, especially between the ages of 3 and

6 months. In the US and several European countries, ibuprofen suspension is approved for use in children older than 6 months with a body weight of at least 5 kg. Ibuprofen has been approved in other countries (Australia and the UK) for children older than 3 months weighing at least 5 or 6 kg, but is not considered suitable for children younger than 3 months unless advised by a physician.

In neonates and young infants, renal function is still impaired and renal elimination processes (glomerular filtration and active tubular secretion) mature during the first months of life until both reach adult activity by 6–12 months [1]. Since prostaglandins promote renal development and function, the inhibition of the renal prostaglandin synthesis by NSAIDS may cause renal vasoconstriction and temporary reduction of kidney function [2, 3]. Current evidence, especially from studies in preterm infants with a patent ductus arteriosus, has shown that ibuprofen was associated with fewer renal side effects than indomethacin [4–6].

In an attempt to harmonize dosing recommendations, a recent public assessment report at the European Medicines Agency [7] proposed to dose based on body weight and not to define a lower age limit, but a lower limit of body weight (5 kg). Unfortunately, due to different regulatory requirements in the EU member states, a harmonization of dose recommendations (solely based on weight) was not possible, resulting in the current situation where diverging dose recommendations still exist.

The currently recommended dosing regimen of ibuprofen in children is 20–30 mg/kg per 24 h divided in 3–4 doses, resulting in 5–10 mg/kg per dose. Doses exceeding the maximum daily dose of 40 mg/kg/day may increase the risk of serious adverse events, such as acute renal failure, gastrointestinal (GI) ulcers, and/or bleeding [8]. Ibuprofen is usually used as a 20- or 40-mg/mL suspension [9–11]. Suppositories are available in several countries, such as Germany, France, Austria, Sweden, Portugal, and Israel.

Considering these variable recommendations based on patients' age or weight, we reviewed the currently available data on the safety and efficacy of ibuprofen in infants aged 3–6 months in an attempt to find the optimal method of pain and fever management in this specific age group. Studies investigating ibuprofen for the treatment of patent ductus arteriosus in preterm or term neonates were excluded from the review, although ibuprofen has been shown to be effective and safe for this indication [12].

2 Ibuprofen Pharmacokinetics in Children

Ibuprofen is a racemic mixture of two enantiomers [R(−)-ibuprofen and S(+)-ibuprofen]. The inactive R(−) isomer is unidirectionally converted into the active S(+) isomer, which is responsible for the therapeutic effects of ibuprofen [13, 14]. Ibuprofen has a high oral bioavailability [15, 16]. Peak plasma concentrations are usually reached within 90 min after administration. Ibuprofen is highly bound to plasma proteins (90–99%), and mainly metabolized by CYP2C8 and CYP2C9 to inactive metabolites, which are excreted into the urine [15–17].

The plasma concentrations of S(+) ibuprofen have been found to be lower in infants 6–18 months old due to either a slower conversion rate of R(−)- to S(+)-ibuprofen, or an increased clearance of S(+)-ibuprofen, indicating that infants might need higher doses for achieving analgesia compared with adults [18, 19]. This phenomenon, however, has not been confirmed in older or in younger children. Enantiomer-specific effects of genetic polymorphisms of CYP2C9 on the clearance of S(+)- and CYP2C8 on the R(−)-ibuprofen clearance have been reported in adults [20, 21]. In contrast, Garcia-Martin et al. found a non-enantioselective influence of CYP2C8 (CYP2C8*3) and CYP2C9 (CYP2C9*3) polymorphisms [22].

Pharmacokinetics (PK) studies of ibuprofen in 254 children are described in Table 1a–c. Five studies included at least 18 infants younger than 6 months.

2.1 Ibuprofen Pharmacokinetics in Infants Younger Than 6 Months

Only two studies reported PK separately for children under 6 months of age [23, 24], and one of these studies included only one patient in that age group [23]. Kyllonen et al. demonstrated that there is no difference in the PK of ibuprofen suppositories between different age subgroups of infants in their first year of life [24]. Kauffman and Nelson found no correlation between age and PK in children aged 3 months to 10 years [25].

2.2 Pharmacokinetics of Rectal Ibuprofen

Orifice rejection of drugs is rather the rule than the exception in pediatric drug therapy, which poses a clinically relevant problem, as seen in the study by Kyllonen et al., since several young infants expelled the suppository [24]. Expulsion of the suppository resulted in incomplete dosing and consecutively poor analgesic efficacy of the drug (Table 1c). Kyllonen et al. found similar AUC (area under the concentration–time curve) values in all age groups, suggesting that ibuprofen can be given according to the above-mentioned weight-based dosing scheme to infants between 1 week and 12 months of age and AUC ratios of R(−)- and S(+)-ibuprofen did not differ significantly in these young infants. This was in contrast to Rey et al., who found a lower exposure towards S(+)-ibuprofen after oral dosing [18]. In adults, considerably lower

Table 1 Clinical studies assessing the pharmacokinetics (PK) of oral, rectal, and intravenous ibuprofen that include children younger than 6 months of age. Data are given as mean ± SD if not stated otherwise in the table [18, 23–25, 65–69]

Reference	No. of patients	Age (range if not stated otherwise)	Clinical setting and duration of follow-up	Dose and route	Pharmacokinetics	Efficacy/safety/remarks	Main results/conclusion
(a) Studies investigating the pharmacokinetics of oral ibuprofen							
Nahata et al. [65]	17	3.1–9.6 y	Fever, PK until 8 h	Oral	*See below*	No adverse event	Ibuprofen PK not affected by dose of 5–10 mg/kg or age 3–10 y
	9	Mean 6.7 ± 2.5 y		5 mg/kg	C_{max} 28.4 ± 7.5 mg/L		
				Oral	t_{max} 1.1 ± 0.3 h		
					Cl/*F* 1.2 ± 0.4 mL/min/kg		
					$t_{½}$ 1.6 ± 0.6 h		
	8	Mean 6.2 ± 2.1 y		10 mg/kg	C_{max} 43.6 ± 18.6 mg/L		
				Oral	t_{max} 1.2 ± 0.6 h		
					Cl/*F* 1.4 ± 0.5 mL/min/kg		
					$t_{½}$ 1.6 ± 0.5 h		
Kelley et al. [66]	17	Mean 5.8 ± 2.8 y	Fever, PK until 8 h	6 mg/kg	*Measured*	Safety not studied	Ibuprofen 6 mg/kg is effective in reducing childhood fever. Its effect lasts longer than that of paracetamol. Peak effects are delayed until 2.5–3 h after administration
				Oral	C_{max} 33.5 ± 14.7 mg/L		
					t_{max} 1.0 ± 0.3 h		
					Estimated		
					V_d 0.164 L/kg		
					Cl 0.96 mL/min/kg		
					$t_{½}$ 1.97 h		
					t_{max} 0.90 h		
					C_{max} 26.67 mg/L		
Kauffman and Nelson [25]	49 (14 aged <12 mo)	Median 2.5 y (3 mo–10.4 y)	Fever, PK until 8 h	8 mg/kg	(n = 38)	Mean temperature drop −0.24 °C per mg/L ibuprofen effect compartment concentration	Age had no significant effect on the rate of absorption, plasma concentration, rate of elimination, or the time course of ibuprofen concentration in the effect compartment
				Oral	C_{max} 35.8 ± 16.7 mg/L	No adverse event	
					t_{max} 0.7 ± 0.5 h		More efficient dissipation of heat in younger children due to the relative greater body surface area
					$t_{½absorb}$ 0.3 ± 0.3 h		
					$t_{½elim}$ 1.6 ± 0.7 h		
					AUC 102.6 ± 35.2 mg*h/L		

Table 1 continued

Reference	No. of patients	Age (range if not stated otherwise)	Clinical setting and duration of follow-up	Dose and route	Pharmacokinetics	Efficacy/safety/remarks	Main results/conclusion
Brown et al. [67]	49	3 mo–12 y	Fever, PK until 6 h	5 mg/kg Oral	($n = 44$)[a] C_{max} 19.03 ± 1.37 mg/L t_{max} 1.60 ± 0.13 h ($n = 38$) $t_{½}$ 1.65 ± 0.22 h AUC 71.12 ± 5.94 mg*h/L V_d/F 0.182 ± 0.017 L/kg Cl_p/F 1.48 ± 0.15 mL/min/kg	Maximum fever relief 2.5 h after C_{max} Safety not studied	Ibuprofen AUC higher and V_d and Cl_p lower in children aged ≥2.5 y. PK not dose-linear, thus the observed dose dependency of AUC and the effect of age on ibuprofen disposition must be considered if PK interpretations are used to optimize the antipyretic dose of ibuprofen in children
	50			10 mg/kg Oral	($n = 49$)[a] C_{max} 34.35 ± 2.18 mg/L t_{max} 1.54 ± 0.12 h ($n = 46$) $t_{½}$ 1.48 ± 0.11 h AUC 115.76 ± 5.55 mg*h/L V_d/F 0.217 ± 0.026 L/kg Cl_p/F 1.65 ± 0.12 mL/min/kg		
Rey et al. [18]	11	6–8 mo	Postoperative pain	7.6 ± 0.3 mg/kg Oral	*R(−) and S(+) enantiomers* C_{max} 24.4 ± 6.6 mg/L t_{max} 2–4.1 h $t_{½}$ 1.6 ± 0.4 h AUC 78.1 ± 28.1 mg*h/L Cl/F 1.83 ± 0.17 mL/min/kg V_z/F 0.2 ± 0.09 L/kg	Plasma concentrations of the active S(+)–isomer were lower than those reported in adults Safety not studied	Infants might require a higher dose because of lower S(+) ibuprofen plasma concentrations
Har-Even et al. [68]	28	Mean 58.2 ± 51.3 mo (5.0–180.5 mo)	Fever, PK: one plasma vs one CSF sample	Mean 9.5 ± 1.6 mg/kg median 10.0 mg/kg range (3.4–11.4 mg/kg) Oral	(*data given as estimates with % rel. SE*) *from PK model* V/F 0.418 (36) L/kg Cl/F 1.72 (19) L/kg/h	PK-PD modeling analysis CSF ibuprofen concentrations were approx. 100-fold lower than plasma concentrations (C_{CSF}/C_{plasma} 0.011 ± 0.007) Safety not studied	A single 10-mg/kg dose of ibuprofen was able to induce a gradual decrease in body temperature by almost 1 °C Following a lag time of approx. 25 min, ibuprofen is rapidly absorbed to the central compartment and rapidly equilibrates with the CSF

Table 1 continued

Reference	No. of patients	Age (range if not stated otherwise)	Clinical setting and duration of follow-up	Dose and route	Pharmacokinetics	Efficacy/safety/remarks	Main results/conclusion
(b) Studies investigating the pharmacokinetics of rectal ibuprofen							
Pharmacia AB [69]	18	Mean 6.2 y (0.6–15.3 y)	Fever, PK until 8 h	5–10 mg/kg (single doses of 60, 125, and 250 mg) Rectal	C_{max} 23.3 mg/L t_{max} 1.3 h (range 0.3–2.1) *60-mg dose:* AUC_{∞} 57 mg*h/L Cl/*F* 1.90 mL/min/kg *125-mg dose:* AUC_{∞} 122 mg*h/L Cl/*F* 0.97 mL/min/kg *250-mg dose:* AUC_{∞} 90 mg*h/L Cl/*F* 1.35 mL/min/kg	Maximum observed decrease of body temperature was about 2 °C (range 0.6–3.5) for all dose groups and was observed after 2–8 h (mean 3.9). The effect on temperature was higher in the oldest children compared with the youngest children Three adverse events, all moderate and judged not to be related to the study medication. No patient discontinued treatment due to adverse events	C_{max} and AUC increased slightly with increasing doses per body weight and BSA, respectively. t_{max} appeared to occur earlier with lower body weights (i.e., in younger children). The AUC appeared to be lower and the Cl/F higher for the youngest children The maximum decrease of body temperature appeared to be largest in the oldest children Treatment was safe
Kyllonen et al. [24]	9	Mean 4.2 ± 1.9 wk (1–7 wk)	Perioperative pain, PK until 10 h	19.0 ± 1.6 mg/kg Rectal	(*n* = 5), *R(−) and S(+) enantiomers:* C_{max} 49.2 ± 20.7 mg/L t_{max} 1.9 ± 1.2 h $t_{½}$ 4.6 ± 5.1 h AUC 299 ± 69 mg*h/L	Efficacy/safety not studied *PK in infants who expelled the suppository (n = 4):* C_{max} 25.7 ± 14.2 mg/L t_{max} 1.9 ± 0.9 h $t_{½}$ 2.9 ± 2.1 h AUC 108 ± 83 mg*h/L	Single ibuprofen dose of approx. 20 mg/kg provided analgesic plasma concentrations in the early postoperative period. No major PK differences observed between groups when the suppositories were retained. In case of expelled suppositories, t_{max} was comparable, but C_{max} was only 50% and AUC only 36% of the values in the retained suppository group
	8	Mean 16.1 ± 6.9 wk (8–25 wk)		19.2 ± 1.1 mg/kg Rectal	*R(−) and S(+) enantiomers:* C_{max} 75.6 ± 44.6 mg/L t_{max} 1.6 ± 0.7 h $t_{½}$ 1.9 ± 0.5 h AUC 248 ± 153 mg*h/L	Efficacy/safety not studied	
	7	Mean 41.4 ± 7.8 wk (26–52 wk)		19.8 ± 1.1 mg/kg Rectal	*R(−) and S(+) enantiomers*: C_{max} 87.9 ± 36.6 mg/L t_{max} 1.6 ± 0.3 h $t_{½}$ 2.1 ± 0.7 h AUC 339 ± 136 mg*h/L	Efficacy/safety not studied	

Table 1 continued

Reference	No. of patients	Age (range if not stated otherwise)	Clinical setting and duration of follow-up	Dose and route	Pharmacokinetics	Efficacy/safety/remarks	Main results/conclusion
(c) Studies investigating the pharmacokinetics of IV ibuprofen							
Cumberland Pharmaceuticals [23]	1	<2 mo	Fever, PK until 4 h	10 mg/kg 10-min infusion IV	AUC_{0-t} 51.18 mg*h/L AUC_{0-4} 69.14 mg*h/L C_{max} 49.83 mg/L t_{max} 10 min $t_{½}$ 1.18 h Cl 2.15 mL/min/kg V_z 0.220 L/kg	IV Ibuprofen provided clinically meaningful temperature reduction/normalization in treating fever in hospitalized pediatric patients. The commonly reported adverse events were GI symptoms and laboratory test abnormalities. No serious adverse events	The mean AUC_{0-4} increased slightly with age. The mean $t_{½}$ values were similar among age categories. The body weight normalized Cl and V_z values appear to be similar in all age groups. Elimination half-life ranged from 0.79 to 2.87 h with a mean of 1.55 h Only one subject was recruited from age group birth to <2 mo, and no subject was recruited from 2–6 mo. Short-term use of IV ibuprofen 10-min infusion at 10 mg/kg in pediatric patients closely monitored in a hospital setting appears to be reasonably safe. Patients should be well hydrated before receiving IV ibuprofen to minimize the risks for acute renal toxicities
	5	6 mo to <2 y			AUC_{0-t} 71.15 mg*h/L AUC_{0-4} 70.92 mg*h/L C_{max} 59.24 mg/L t_{max} 10 (10–30) min $t_{½}$ 1.78 h Cl 2.23 mL/min/kg V_z 0.311 L/kg		
	12	2 to <6 y			AUC_{0-t} 79.19 mg*h/L AUC_{0-4} 80.25 mg*h/L C_{max} 64.18 mg/L t_{max} 12 (10–46) min $t_{½}$ 1.48 h Cl 2.17 mL/min/kg V_z 0.227 L/kg		
	25	6 to <16 y			AUC_{0-t} 80.67 mg*h/L AUC_{0-4} 85.73 mg*h/L C_{max} 61.89 mg/L t_{max} 10 (10–40) min $t_{½}$ 1.55 h Cl 1.82 mL/min/kg V_z 0.227 L/kg		

AUC area under the concentration-time curve, *BSA* body surface area, *Cl* clearance, *Cl/F* apparent clearance after non-intravenous administration, Cl_p/F apparent plasma clearance after non-intravenous administration, C_{max} maximum plasma concentration, *CSF* cerebrospinal fluid, *GI* gastrointestinal, *IV* intravenous, *PK* pharmacokinetics, *SEM* standard error of the mean, t_{max} time of the maximum plasma concentration, $t_{½}$ elimination half-life, V_d volume of distribution, V_d/F apparent volume of distribution after non-intravenous administration, V_z volume of distribution during terminal phase, V_z/F apparent volume of distribution during terminal phase after non-intravenous administration, *mo* months, *y* years, *wk* weeks

[a] Data given as mean ± SEM

ibuprofen plasma concentrations were observed after rectal administration of a suppository (maximum concentration [C_{max}] 22.6 ± 5.6 mg/L, time to maximum concentration [t_{max}] 1.85 ± 0.34 h, half-life [$t_{½}$] 1.88 ± 0.51 h, AUC 86.9 ± 28.9 mg*h/L) versus oral administration of diluted ibuprofen syrup (C_{max} 48.4 ± 15.9 mg/L, t_{max} 0.67 ± 0.29 h, $t_{½}$ 1.80 ± 0.41 h, AUC 137.6 ± 52.0 mg*h/L, all except $t_{½}$, $p < 0.05$), resulting in a relative bioequivalence of 63% [26]. Thus, while ibuprofen suppositories can contribute to fever and pain management, they should ideally be administered only when the oral route is not available.

If the rectal route is the only available route of administration, a possible mitigation strategy could be administering a higher dose (e.g., 10 mg/kg) compared with the oral route (e.g. 7 mg/kg) to produce comparable ibuprofen plasma concentrations and clinical effects. This should, however, only be performed within the recommended maximum daily dose, since the unpredictability of the dose–concentration relationship after rectal administration warrants caution and an increase in dose might result in higher bioavailability.

It seems that above the age of 6 months, age does not have significant effects on absorption, plasma concentration, volume of distribution and elimination half-life of ibuprofen and PK is comparable to adults, but clearance is enhanced in children up to the age of 5 years [13, 15, 18, 25, 27, 28]. Also, the rectal route is less reliable than oral administration. Therefore, the oral route should be preferred for ibuprofen dosing.

3 Efficacy and Safety of Ibuprofen in Children

Safety and efficacy of ibuprofen has been assessed in many pediatric clinical trials. The most common (≥1 and <10%) side effects occur in the GI tract and include nausea, dyspepsia, abdominal pain, diarrhea or constipation, flatulence, and vomiting. Very rare (<0.01%) in children, but potentially life-threatening adverse events are peptic ulcers, gastric hemorrhage or gastric perforation.

Acute renal failure, interstitial nephritis, and papillary necrosis, the latter especially with long-term use, are very rare (<0.01%) renal side effects of NSAIDs. Acute kidney failure may occur in children, as described in a series of seven children aged 4–15 years hospitalized for that complication after ibuprofen ($n = 6$) or ketoprofen ($n = 1$) for a maximum of 5 days [15, 29]. Five of these patients had risk factors predisposing them to renal toxicity, such as dehydration, pre-diagnosed kidney disease (renal transplantation), and concomitant therapy with other nephrotoxic drugs. The true incidence of renal adverse events in children has not been systematically investigated [30, 31].

Therefore, pre-diagnosed kidney disease is the most compelling contraindication, while the concomitant use of other nephrotoxic substances is a relative contraindication for ibuprofen therapy [19, 27, 28]. Special attention has to be paid to prevent and treat pathologic conditions such as dehydration, hypovolemia, and hypotension when initiating ibuprofen therapy. In dehydrated febrile infants, acetaminophen may be the primary drug of choice for antipyresis.

In addition, hypersensitivity reactions have been frequently reported and may consist of non-specific allergic reactions, various skin reactions, such as pruritus or urticaria, angioedema or anaphylaxis, and respiratory tract reactivity [11, 32]. Other unspecific side effects include dizziness and headache.

Ibuprofen should not be combined with acetyl salicylic acid because of interference with platelet aggregation. This pharmacodynamic interaction has only been observed in adults but might play a role in infants with congenital heart disease (e.g. with stents or vascular grafts) [33, 34].

In contrast to acetaminophen, ibuprofen was shown not to affect the immunogenicity of a 10-valent pneumococcal conjugated vaccine, and could therefore be considered as the primary antipyretic during vaccination courses [35].

A possible association between ibuprofen and invasive group A streptococcal infections in children with varicella was reported but there is a lack of data supporting a causal relationship [30].

3.1 Ibuprofen Efficacy and Safety in Infants Younger Than 6 Months

Eleven studies with a total of 39,293 patients, which included data from at least 207 children younger than 6 months, are summarized in Table 2a, b. The most common underlying pathological condition was fever treated in the outpatient setting. No studies were exclusively performed in children younger than 6 months. There were no efficacy studies investigating the analgesic effect conducted in children younger than 6 months. In older children (age 6–17 years), efficacy of ibuprofen has been proven for pain after musculoskeletal trauma and ibuprofen was superior to codeine or acetaminophen [36]. Efficacy has been proven for fever relief in children of several age groups, including infants younger than 6 months [37–40], in several studies and confirmed by meta-analyses [41–45]. Some studies attributed slightly more benefits in fever relief to ibuprofen than to acetaminophen [15, 27, 44, 45].

3.2 Safety of Oral Ibuprofen

The largest available safety study is the Boston University Fever Study, a randomized practitioner-based trial in

Table 2 Clinical studies assessing the safety and efficacy of ibuprofen in children. Data are given as mean ± SD if not stated otherwise in the table [37–40, 47, 48, 59, 70–73]

Reference	No. of patients	Age (range if not stated otherwise)	Design	Clinical setting and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
(a) Clinical studies assessing the safety and efficacy of oral ibuprofen							
Simila et al. [38]	11	3.3 y (0.3–11.4 y)	Open, controlled	Fever Follow-up 6 h	0.5 mg/kg Oral	Ibuprofen 0.5 mg/kg less effective than ibuprofen 6 mg/kg ALT and AST within normal limits	Ibuprofen 6 mg/kg, aspirin 10 mg/kg, aminophenazone 5 mg/kg, indomethacin 0.5 mg/kg and paracetamol 12.5 mg/kg had similar antipyretic effects
	13	2.4 y (0.7–7.8 y)	Open, controlled	Fever Follow-up 6 h	6 mg/kg Oral	Ibuprofen 6 mg/kg produced significant antipyresis ALT and AST within normal limits	
Wilson et al. [39]	16	2 mo–10 y	Open, controlled	Fever Follow-up 11 h	Irrespective of weight: *<12 mo (n = 6):* 50 mg every 8 h *12–59 mo (n = 5):* 100 mg every 8 h *60–120 mo (n = 5):* 200 mg every 8 h	Tests for hematuria, proteinuria and hematochezia carried out, but no results reported	Ibuprofen suspension produced a significantly greater reduction in temperature for a longer duration than paracetamol suppositories
Joshi et al. [70]	85	56 mo (3 mo–11 y)	Open, multi-center, controlled	Fever Follow-up 2 h	7 mg/kg Oral	No serious adverse events	Ibuprofen is safe and has an efficacy comparable to that of paracetamol
Sidler et al. [71]	30	5 mo–13 y	Multi-center, double-blind, randomized, controlled	Fever Follow-up 12–24 h	7 mg/kg Oral	Temperature reduction −1.64 °C. Three patients withdrew due to lack of response. Three adverse events (vomiting, abdominal pain, rash) in three patients	Ibuprofen more effective across the whole age range. Patients in ibuprofen group had lower overall mean temperature
	29				10 mg/kg Oral	Temperature reduction −2.09 °C. Four patients withdrew due to lack of response. One adverse event (hypothermia) in one patient	
Wilson et al. [40]	43	3.36 ± 0.22 y (3 mo–11 y 11 mo, for $n = 178$ patients in all treatment groups)	Double-blind, randomized, placebo-controlled	Fever Follow-up 6–12 h	5 mg/kg Oral	One child (aged 2.25 y) with transient hypothermia. Eight children needed rescue measures because of temperature non-response or increase	Ibuprofen 10 mg/kg preferred for children 3 mo to 12 y of age who have a rectally measured temperature of as much as 40.5 °C
	44				10 mg/kg Oral	One child (aged 4.5 y) with transient hypothermia. Four children needed rescue measures because of temperature non-response or increase	Ibuprofen 10 mg/kg significantly more effective than 5 mg/kg in fever reduction. Initial temperature and age influence the antipyretic response

Table 2 continued

Reference	No. of patients	Age (range if not stated otherwise)	Design	Clinical setting and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
McIntyre and Hull [37]	76 (20 aged <12 mo)	Median 1.8 y (0.4–11.6 y)	Double-blind, randomized	Fever Follow-up 36 h	5 mg/kg (max. 20 mg/kg/day) Oral	Seven patients withdrew due to adverse events (urticarial rash, vomiting, abdominal pain, sore throat, and hip surgery) and/or lack of efficacy Ten patients (13%) had 16 adverse events with possible (maculopapular rash, urticarial, diarrhea) or doubtful (maculopapular rash, sore throat, hyperactivity, vomiting, abdominal pain) relationship, most were mild. No asthma attack	Ibuprofen and paracetamol equally effective and well tolerated in the treatment of fever in young children
Díez-Domingo et al. [72]	256	3 mo ± 15 d	Open, multi-center	Prophylaxis for DTwP vaccine-related adverse reactions at age 3, 5, and 7 mo (follow-up for 4 mo)	Prophylaxis 20 mg/kg/day vs treatment 7.5 mg/kg as-needed Oral	No adverse events	Temperature increases after DTwP vaccination similar between prophylaxis and treatment group. Fewer systemic and local effects in prophylaxis group
Lesko and Mitchell [47]	17,938 (207 aged <6 mo)	1–23 mo	Randomized, controlled, multi-center	Fever Follow-up for 4 wk	Median treatment duration 3 d, median total doses: 6–10 Oral	No child <6 mo of age hospitalized due to adverse events. Overall risk of hospitalization with any diagnosis over 4 wk was 1.4%, did not vary by antipyretic assignment. No hospitalizations for acute renal failure, anaphylaxis, or Reye's syndrome. Three hospitalizations with GI bleeding during ibuprofen treatment (risk 17 per 100,000 [95% CI 3.5–49]), but not significantly greater than during paracetamol treatment. No difference in risk of hospitalization for asthma, bronchiolitis, or vomiting/gastritis between antipyretic assignments	Risk of serious adverse event in children <2 y during short-term treatment with paracetamol or ibuprofen suspension was small and did not vary by antipyretic treatment. No conclusions can be drawn on safety when used for prolonged periods or in combination, regardless of duration
	9159 (111 aged <6 m)	Median 13 mo			Planned: 5 mg/kg Median: 4.8 mg/kg		
	8779 (96 aged <6 mo)	Median 13 mo			Planned: 10 mg/kg Median: 9.6 mg/kg		

Table 2 continued

Reference	No. of patients	Age (range if not stated otherwise)	Design	Clinical setting and duration of follow-up	Dose and route	Efficacy/safety	Main result/conclusion
Ashraf et al. [48]	7381	>1 mo to <2 y	Open, multi-center	Fever/pain Follow-up 1–2 wk	Not reported Oral	1295 patients (17.6%) had one or more adverse events (total: 1860), of which 350 (18.8%) were mild, 238 (12.8%) were moderate and 231 (12.4%) were severe. Adverse events by body system: digestive (any 3%, abdominal pain 0.5%), nervous system (hyperkinesia 0.7%, insomnia 0.6%), respiratory (rhinitis 2.1%), skin (any 2.6%, sweat 0.05%), special senses (any 3.9%, otitis media 3.5%) and body as a whole (pain 0.4%)	In children <2 y, adverse events with an incidence rate >1% (including also paracetamol treatment group): fever, vomiting, diarrhea, rhinitis, rash, and otitis media; in children ≥2 y: rhinitis, pharyngitis, and otitis media. No serious adverse event, including anaphylaxis, Reye's syndrome, renal failure, GI bleeding/perforation or necrotizing fasciitis. Significantly more sick children received ibuprofen as the preferred treatment reflected in a slightly higher incidence of side effects in the ibuprofen group. Safety of ibuprofen in children <2 y was demonstrated, the safety profile is consistent with the excellent profile observed in children ≥2 y, which is similar to that of paracetamol in the same age groups
	12,730	≥2 y to ≤12 y				1515 patients (11.9%) had one or more adverse events (total 2019), of which 368 (18.2%) were mild, 225 (11.1%) were moderate and 183 (9.1%) were severe. Adverse events by body system: digestive (any 2.1%, abdominal pain 0.6%), nervous system (hyperkinesia 0.4%, insomnia 0.2%), respiratory (rhinitis 1.1%), skin (any 1.3%), special senses (any 2.0%, otitis media 1.7%) and body as a whole (pain 0.2%)	
Autret-Leca et al. [73]	151	Mean 3.84 ± 2.78 y (0.4–11 y)	Randomized, controlled, double-blind	Fever Follow-up 3 d	10 mg/kg Oral	Well tolerated	Ibuprofen (10 mg/kg) and paracetamol (15 mg/kg) have equivalent efficacy and tolerability
(b) Clinical studies assessing the safety and efficacy of rectal ibuprofen							
Hadas et al. [59]	490	1.95 ± 1.5 y (3 mo–10 y)	Open, multi-center	Fever Follow-up 1–8 d	5–10 mg/kg (max. 4 doses/d of a 60- or 125-mg single dose) Rectal	Eight patients (1.63%) had adverse events: 4 diarrhea (0.8%), 2 rash (0.4%), 1 shivering (0.2%) and 1 rectal burning (0.2%) after suppository administration	Rectal administration of ibuprofen suppositories was well tolerated and the adverse reactions following administration were few in frequency, mild, and self-limited

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *GI* gastrointestinal, *d* days, *mo* months, *y* years, *wk* weeks

84,192 febrile children younger than 12 years that compared ibuprofen and acetaminophen [46]. In this study, a total of 17,938 children younger than 2 years including 207 children younger than 6 months (1.2%) received ibuprofen (5 vs 10 mg/kg) suspension for fever relief [47]. No children were hospitalized for acute renal failure, anaphylaxis, or Reye's syndrome. Three children, who had all been treated with ibuprofen, were hospitalized with gastrointestinal bleeding. Although the risk of hospitalization with gastrointestinal bleeding during ibuprofen therapy was estimated at 17/100,000 (95% CI 3.5–49/100,000), it was not significantly greater than the risk in the control group who received acetaminophen. The study concluded that for short-term treatment with a median duration of 6–10 doses of ibuprofen over 3 days, the risk of serious adverse clinical events among children <2 years old is low. Although this study included the largest sample of children younger than 6 months ($n = 207$) and the safety results were reassuring in general, the power of this study to detect serious adverse events in this subgroup was limited.

The Boston University Fever Study [47] and an additional analysis in 1997 [31] assessed the renal side effects of short-term ibuprofen use in children younger than 12 years (median age 22 months, with a 5th to 95th percentile of 7–113 months in the 5-mg/kg dose group and with a 5th to 95th percentile of 6–105 months in the 10-mg/kg dose group). Children with severe dehydration (≥10% of body weight), or known chronic kidney, endocrine or neoplastic disease, however, were not eligible for participation. No differences in creatinine or blood urea nitrogen levels were seen between treatment groups, suggesting that the risk of severe renal impairment from short-term ibuprofen treatment in children without known renal disease is small. The study results, however, are not representative for all patients presenting to the hospital due to exclusion of patients at risk of renal side effects.

The second largest safety study that compared the safety of ibuprofen and actaminophen in children with fever and/or pain was the Children's Analgesic Medicine Project, an open-label, multi-center, prospective study that enrolled children between 1 month and 18 years of age [48]. There were 20,111 children treated with ibuprofen, of which 7381 (36.7%) were younger than 2 years and 12,730 (63.3%) were between 2 and 12 years old. Adverse events relating to the gastrointestinal tract comprised abdominal pain and others, which were not reported separately. There were no serious adverse events recorded, such as anaphylaxis, Reye's syndrome, renal failure, gastrointestinal bleeding or perforation, or necrotizing fasciitis.

A recent retrospective analysis of the FDA's Adverse Event Reporting System database in 2014 concerning adverse event reports in children aged 0–12 years described an increased risk of acute kidney injury in children who were taking ibuprofen and acetaminophen simultaneously [49]. The reporting odds ratio (ROR) in this case was 4.01 (95% CI 2.96–5.43), compared with either acetaminophen alone (ROR 1.53, 95% CI 1.18–1.97) or ibuprofen alone (ROR 2.14, 95% CI 1.59–2.88). It was concluded that the concomitant use of these drugs might be associated with an increased risk of acute kidney injury.

While the relative risk (RR) of upper gastrointestinal complications during ibuprofen therapy has been reported as 1.84 (95% CI 1.54–2.20) in a meta-analysis in adults, besides case reports there are limited data available in children. The risk of upper gastrointestinal complications such as hematemesis, melena, or endoscopically confirmed gastroduodenal lesion during ibuprofen therapy was assessed in a case-control study in children aged 15–71 months [50]. An association between the short-term use (1–8 days) of NSAIDs, oral steroids, and antibiotics and an increased risk for upper gastrointestinal complications was found. The adjusted odds ratio (OR) for ibuprofen was 3.7 (95% CI 2.3–5.9) compared with acetaminophen (OR 2.0, 95% CI 1.5–2.6), NSAIDS overall (OR 2.9, 95% CI 2.1–4.0), and oral steroids (OR 2.9, 95% CI 1.7–4.8), which did not differ significantly. Due to the study design, an incidence of upper gastrointestinal complications could not be calculated, but the overall risk was low (estimated 2.4 per 10,000 children). The population investigated in this case-control study, however, did not reflect the typical pediatric patient population receiving NSAID treatment. There has been no study conducted in children assessing the influence of ibuprofen administration together with food on the gastrointestinal side effects of the drug.

While the concomitant use of proton pump inhibitors during long-term NSAID treatment in adults is established, there are no data on the efficacy and safety of this drug combination available in children.

Although it has been reported previously that ibuprofen might exacerbate asthma or bronchospasm [51–53], it has been shown in a recent multicenter, prospective, randomized, double-blind, parallel-group trial in young children [54] that there was no difference in incidence of asthma exacerbations or worse asthma control between patients taking as-needed ibuprofen or as-needed acetaminophen. The patients aged 12–59 months were pre-diagnosed with mild persistent asthma and assigned to receive either ibuprofen or acetaminophen for antipyresis or analgesia for a period of 48 weeks. The relative rate of asthma exacerbations between the acetaminophen and the ibuprofen group was 0.94 (95% CI 0.69–1.28; $p = 0.67$), but the study did not include a control group [55, 56]. Similar results have been found in earlier studies, such as the Boston University Fever Study, and reviews [57, 58].

3.3 Safety of Rectal Ibuprofen

One study described in Table 2b used the rectal route of drug administration in children between 3 months and 10 years of age and assessed tolerability and parents' satisfaction with ibuprofen suppositories [59]. Although the study lacked a control group with oral preparations or placebo suppositories, only a few mild and self-limited adverse events were reported. While rash and shivering do occur after oral ibuprofen administration, side effects such as diarrhea and rectal burning can probably be attributed to rectal rather than to oral dosing.

In children aged 4–12 years undergoing ophthalmic, orthopedic or general surgery, rectal ibuprofen was studied in the perioperative setting [60, 61]. There were no differences in incidence of side effects between ibuprofen and placebo groups. In particular, rectal ibuprofen has been shown in the perioperative setting to reduce postoperative pain scores in children aged 1–4 years using a maximum daily dose of 40 mg/kg without increasing the incidence of bleeding [60, 62]. Furthermore, a retrospective study in tonsillectomy patients did not show an increase in post-tonsillectomy bleeding events between children treated with ibuprofen versus a combination of acetaminophen and codeine (readmission: OR 0.932, 95% CI 0.707–1.228, $p = 0.617$; reoperation: OR 0.887, 95% CI 0.618–1.272, $p = 0.513$) [63].

In summary, when used within the recommended dose range, rectally administered ibuprofen has an excellent safety profile and a low risk of causing severe gastrointestinal adverse events [27, 64].

4 Discussion and Future Considerations

In this review, we tried to summarize the available knowledge and to offer an overview of PK, efficacy, safety, and dosing of ibuprofen in infants aged 3–6 months in a comprehensive manner. The use of ibuprofen in infants younger than 6 months is of great clinical relevance considering the frequency of conditions which can be treated with ibuprofen. In everyday clinical practice, many pediatricians already prescribe ibuprofen in infants aged between 3 and 6 months. Therefore, available data should be analyzed and further studies should be performed.

A limitation of this review is that the summarized studies on the use of ibuprofen in young infants are heterogeneous regarding population, study design, and endpoints. Unfortunately, currently available literature is limited and more data are undeniably needed.

The question of how to optimally dose ibuprofen in young infants (3–6 months old) for the purpose of fever and pain management still has to be answered, but more data have become available on ibuprofen safety and efficacy over recent years, suggesting that the current dosing recommendations can also be applied for this age group. Weight-based dosing should be preferred over age-based dosing, because efficacy and safety of the treatment may be increased due to a higher precision in drug dosing. While some studies suggested an optimum ibuprofen dose of 7–10 mg/kg [42], the current dosing guidelines should be followed that recommend a single dose of 5–10 mg/kg given 3–4 times a day and a maximum daily dose of 30–40 mg/kg.

Short-term use (up to 3 days) of ibuprofen for relief of fever or pain is safe in infants older than 3 months with a body weight above 5–6 kg when special attention is given to the hydration of the infant. Prevention or treatment of hypovolemia and hypotension will reduce the risk of renal function impairment. The rectal route has been shown to be less reliable, especially in young infants, therefore we suggest using oral preparations whenever possible. When using the rectal route, higher single doses per kg body weight may be administered (e.g., 10 mg/kg) compared with the oral route, but not exceeding the general dosing recommendations.

Compliance with Ethical Standards

Conflict of interest All authors (VCZ, AZ, TOE, JNvdA) declare that they have no conflict of interest.

Funding This work was supported by National Institutes of Health grants from the Eunice Shriver National Institute of Child Health and Human Development (5T32HD087969 & 5U54HD090254) to John van den Anker.

References

1. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology–drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349(12):1157–67.
2. Morris JL, Rosen DA, Rosen KR. Nonsteroidal anti-inflammatory agents in neonates. Paediatr Drugs. 2003;5(6):385–405.
3. Seyberth HW, Leonhardt A, Tonshoff B, Gordjani N. Prostanoids in paediatric kidney diseases. Pediatr Nephrol. 1991;5(5):639–49.
4. Aranda JV, Varvarigou A, Beharry K, Bansal R, Bardin C, Modanlou H, et al. Pharmacokinetics and protein binding of intravenous ibuprofen in the premature newborn infant. Acta Paediatr. 1997;86(3):289–93.
5. Varvarigou A, Bardin CL, Beharry K, Chemtob S, Papageorgiou A, Aranda JV. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. JAMA. 1996;275(7):539–44.
6. Van Overmeire B, Follens I, Hartmann S, Creten WL, Van Acker KJ. Treatment of patent ductus arteriosus with ibuprofen. Arch Dis Child Fetal Neonatal Ed. 1997;76(3):F179–84.
7. European Medicines Agency. Public Assessment Report for paediatric studies submitted in accordance with Article 45 of the

Regulation (EC) No 1901/2006, as amended—Ibuprofen—(DE/W/040/pdWS/001). 2014 April 4, 2014 December 23, 2016.
8. Fachinformation. PecFent® Nasenspray: Archimedes Pharma Germany GmbH; April 2011.
9. Reckitt Benckiser Deutschland GmbH. Fachinformation Nurofen Junior Fieber- und Schmerzsaft Erdbeer 40 mg/ml Suspension zum Einnehmen. 2015 January 2015 [cited 2016 December 21, 2016]; Available from: http://www.nurofen.de/media/922462/Nurofen-Junior-125-mg-Zaepfchen_Januar_2015.pdf.
10. Reckitt Benckiser Healthcare (UK) Ltd. Nurofen for Children Orange Baby/Nurofen for Children 3 months to 9 years. 2014 October 2, 2014 December 21, 2016. Available from: https://www.medicines.org.uk/emc/medicine/23381.
11. Reckitt Benckiser Healthcare (UK) Ltd. Nurofen for Children Strawberry/Nurofen Strawberry 3 months to 12 years. 2014 October 2, 2014 December 21, 2016. Available from: https://www.medicines.org.uk/emc/medicine/20096.
12. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. The Cochrane database of systematic reviews. 2015;18(2):CD003481.
13. Davies NM. Clinical pharmacokinetics of ibuprofen. The first 30 years. Clin Pharmacokinet. 1998;34(2):101–54.
14. Walson PD, Mortensen ME. Pharmacokinetics of common analgesics, anti-inflammatories and antipyretics in children. Clin Pharmacokinet. 1989;17(Suppl 1):116–37.
15. Leroy S, Mosca A, Landre-Peigne C, Cosson MA, Pons G. Ibuprofen in childhood: evidence-based review of efficacy and safety. Archives de pediatrie. 2007;14(5):477–84.
16. Halpern SM, Fitzpatrick R, Volans GN. Ibuprofen toxicity. A review of adverse reactions and overdose. Adverse drug reactions and toxicological reviews. 1993;12(2):107–28.
17. Tanaka E. In vivo age-related changes in hepatic drug-oxidizing capacity in humans. J Clin Pharm Ther. 1998;23(4):247–55.
18. Rey E, Pariente-Khayat A, Gouyet L, Vauzelle-Kervroedan F, Pons G, D'Athis P, et al. Stereoselective disposition of ibuprofen enantiomers in infants. Br J Clin Pharmacol. 1994;38(4):373–5.
19. Litalien C, Jacqz-Aigrain E. Risks and benefits of nonsteroidal anti-inflammatory drugs in children: a comparison with paracetamol. Paediatr Drugs. 2001;3(11):817–58.
20. Kirchheiner J, Meineke I, Freytag G, Meisel C, Roots I, Brockmoller J. Enantiospecific effects of cytochrome P450 2C9 amino acid variants on ibuprofen pharmacokinetics and on the inhibition of cyclooxygenases 1 and 2. Clin Pharmacol Ther. 2002;72(1):62–75.
21. Martinez C, Garcia-Martin E, Blanco G, Gamito FJ, Ladero JM, Agundez JA. The effect of the cytochrome P450 CYP2C8 polymorphism on the disposition of (R)-ibuprofen enantiomer in healthy subjects. Br J Clin Pharmacol. 2005;59(1):62–9.
22. Garcia-Martin E, Martinez C, Tabares B, Frias J, Agundez JA. Interindividual variability in ibuprofen pharmacokinetics is related to interaction of cytochrome P450 2C8 and 2C9 amino acid polymorphisms. Clin Pharmacol Ther. 2004;76(2):119–27.
23. Deputy Division Director Review—NDA 22348 Supplement 005—Caldolor pediatric indication—Reference ID: 3849398. 2015 November 19, 2015 [cited 2017 January 11, 2017]. Available from: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM480294.pdf.
24. Kyllonen M, Olkkola KT, Seppala T, Ryhanen P. Perioperative pharmacokinetics of ibuprofen enantiomers after rectal administration. Paediatr Anaesth. 2005;15(7):566–73.
25. Kauffman RE, Nelson MV. Effect of age on ibuprofen pharmacokinetics and antipyretic response. J Pediatr. 1992;121(6):969–73.
26. Vilenchik R, Berkovitch M, Jossifoff A, Ben-Zvi Z, Kozer E. Oral versus rectal ibuprofen in healthy volunteers. J Popul Ther Clin Pharmacol Journal de la therapeutique des populations et de la pharamcologie clinique. 2012;19(2):e179–86.
27. Rainsford KD. Ibuprofen: pharmacology, efficacy and safety. Inflammopharmacology. 2009;17(6):275–342.
28. Jacqz-Aigrain E, Anderson BJ. Pain control: non-steroidal anti-inflammatory agents. Semin Fetal Neonatal Med. 2006;11(4):251–9.
29. Ulinski T, Guigonis V, Dunan O, Bensman A. Acute renal failure after treatment with non-steroidal anti-inflammatory drugs. Eur J Pediatr. 2004;163(3):148–50.
30. Section on Clinical Pharmacology and Therapeutics, Committee on Drugs, Sullivan JE, Farrar HC. Fever and antipyretic use in children. Pediatrics. 2011;127(3):580–7.
31. Lesko SM, Mitchell AA. Renal function after short-term ibuprofen use in infants and children. Pediatrics. 1997;100(6):954–7.
32. Vifor Consumer Health SA. Fachinformation Algifor® Junior. 2012 August 2012 [cited 2016 December 21, 2016]. Available from: http://www.swissmedicinfo.ch.
33. Gladding PA, Webster MW, Farrell HB, Zeng IS, Park R, Ruijne N. The antiplatelet effect of six non-steroidal anti-inflammatory drugs and their pharmacodynamic interaction with aspirin in healthy volunteers. Am J Cardiol. 2008;101(7):1060–3.
34. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med. 2001;345(25):1809–17.
35. Falup-Pecurariu O, Man SC, Neamtu ML, Chicin G, Baciu G, Pitic C, et al. Effects of prophylactic ibuprofen and paracetamol administration on the immunogenicity and reactogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugated vaccine (PHiD-CV) co-administered with DTPa-combined vaccines in children: An open-label, randomized, controlled, non-inferiority trial. Hum Vaccin Immunother. 2017;13(3):649–60.
36. Clark E, Plint AC, Correll R, Gaboury I, Passi B. A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. Pediatrics. 2007;119(3):460–7.
37. McIntyre J, Hull D. Comparing efficacy and tolerability of ibuprofen and paracetamol in fever. Arch Dis Child. 1996;74(2):164–7.
38. Simila S, Kouvalainen K, Keinanen S. Oral antipyretic therapy. Scand J Rheumatol. 1976;5(2):81–3.
39. Wilson G, Guerra AJ, Santos NT. Comparative study of the antipyretic effect of ibuprofen (oral suspension) and paracetamol (suppositories) in paediatrics. J Int Med Res. 1984;12(4):250–4.
40. Wilson JT, Brown RD, Kearns GL, Eichler VF, Johnson VA, Bertrand KM, et al. Single-dose, placebo-controlled comparative study of ibuprofen and acetaminophen antipyresis in children. J Pediatr. 1991;119(5):803–11.
41. Eccles R. Efficacy and safety of over-the-counter analgesics in the treatment of common cold and flu. J Clin Pharm Ther. 2006;31(4):309–19.
42. Southey ER, Soares-Weiser K, Kleijnen J. Systematic review and meta-analysis of the clinical safety and tolerability of ibuprofen compared with paracetamol in paediatric pain and fever. Curr Med Res Opin. 2009;25(9):2207–22.
43. Pierce CA, Voss B. Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. Ann Pharmacother. 2010;44(3):489–506.
44. Goldman RD, Ko K, Linett LJ, Scolnik D. Antipyretic efficacy and safety of ibuprofen and acetaminophen in children. Ann Pharmacother. 2004;38(1):146–50.
45. Perrott DA, Piira T, Goodenough B, Champion GD. Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever: a meta-analysis. Arch Pediatr Adolesc Med. 2004;158(6):521–6.

46. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. JAMA. 1995;273(12):929–33.
47. Lesko SM, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. Pediatrics. 1999;104(4):e39.
48. Ashraf E, Ford L, Geetha R, Cooper S. Safety profile of ibuprofen suspension in young children. Inflammopharmacology. 1999;7(3):219–25.
49. Yue Z, Jiang P, Sun H, Wu J. Association between an excess risk of acute kidney injury and concomitant use of ibuprofen and acetaminophen in children, retrospective analysis of a spontaneous reporting system. Eur J Clin Pharmacol. 2014;70(4):479–82.
50. Bianciotto M, Chiappini E, Raffaldi I, Gabiano C, Tovo PA, Sollai S, et al. Drug use and upper gastrointestinal complications in children: a case-control study. Arch Dis Child. 2013;98(3):218–21.
51. Kauffman RE, Lieh-Lai M. Ibuprofen and increased morbidity in children with asthma: fact or fiction? Paediatr Drugs. 2004;6(5):267–72.
52. Goraya JS, Virdi VS. To the editor: exacerbation of asthma by ibuprofen in a very young child. Pediatr Pulmonol. 2001;32(3):262.
53. Menendez R, Venzor J, Ortiz G. Failure of zafirlukast to prevent ibuprofen-induced anaphylaxis. Ann Allergy Asthma Immunol. 1998;80(3):225–6.
54. Sheehan WJ, Mauger DT, Paul IM, Moy JN, Boehmer SJ, Szefler SJ, et al. Acetaminophen versus ibuprofen in young children with mild persistent asthma. N Engl J Med. 2016;375(7):619–30.
55. Sheehan WJ, Phipatanakul W. Acetaminophen versus ibuprofen in mild persistent asthma. N Engl J Med. 2016;375(21):2099–100.
56. Uzoigwe CE, Ali OH. Acetaminophen versus ibuprofen in mild persistent asthma. N Engl J Med. 2016;375(21):2099.
57. Kanabar D, Dale S, Rawat M. A review of ibuprofen and acetaminophen use in febrile children and the occurrence of asthma-related symptoms. Clin Ther. 2007;29(12):2716–23.
58. Lesko SM, Louik C, Vezina RM, Mitchell AA. Asthma morbidity after the short-term use of ibuprofen in children. Pediatrics. 2002;109(2):E20.
59. Hadas D, Youngster I, Cohen A, Leibovitch E, Shavit I, Erez I, et al. Premarketing surveillance of ibuprofen suppositories in febrile children. Clin Pediatr. 2011;50(3):196–9.
60. Romsing J, Walther-Larsen S. Peri-operative use of nonsteroidal anti-inflammatory drugs in children: analgesic efficacy and bleeding. Anaesthesia. 1997;52(7):673–83.
61. Maunuksela EL, Ryhanen P, Janhunen L. Efficacy of rectal ibuprofen in controlling postoperative pain in children. Can J Anaesth. 1992;39(3):226–30.
62. Kokki H, Hendolin H, Maunuksela EL, Vainio J, Nuutinen L. Ibuprofen in the treatment of postoperative pain in small children. A randomized double-blind-placebo controlled parallel group study. Acta Anaesthesiol Scand. 1994;38(5):467–72.
63. Pfaff JA, Hsu K, Chennupati SK. The use of ibuprofen in post-tonsillectomy analgesia and its effect on posttonsillectomy hemorrhage rate. Otolaryngol Head Neck Surg. 2016;155(3):508–13.
64. Rainsford KD, Roberts SC, Brown S. Ibuprofen and paracetamol: relative safety in non-prescription dosages. J Pharm Pharmacol. 1997;49(4):345–76.
65. Nahata MC, Durrell DE, Powell DA, Gupta N. Pharmacokinetics of ibuprofen in febrile children. Eur J Clin Pharmacol. 1991;40(4):427–8.
66. Kelley MT, Walson PD, Edge JH, Cox S, Mortensen ME. Pharmacokinetics and pharmacodynamics of ibuprofen isomers and acetaminophen in febrile children. Clin Pharmacol Ther. 1992;52(2):181–9.
67. Brown RD, Wilson JT, Kearns GL, Eichler VF, Johnson VA, Bertrand KM. Single-dose pharmacokinetics of ibuprofen and acetaminophen in febrile children. J Clin Pharmacol. 1992;32(3):231–41.
68. Har-Even R, Stepensky D, Britzi M, Soback S, Chaim AB, Brandriss N, et al. Plasma and cerebrospinal fluid concentrations of ibuprofen in pediatric patients and antipyretic effect: Pharmacokinetic-pharmacodynamic modeling analysis. J Clin Pharmacol. 2014;54(9):1023–30.
69. Study Report for Study 573-CHC-9127-001 - Open Label Pharmacokinetic Study of a Single Dose Ibuprofen Suppository in Children with Fever. 2003 December 05, 2003 [cited 2017 January 11, 2017]. Available from: http://art45-paediatric-studies-docs.ema.europa.eu/GROUP%20I/ibuprofen/ibuprofen%20573-CHC-9127-001.pdf.
70. Joshi YM, Sovani VB, Joshi VV, Navrange JR, Benakappa DG, Shivananda P, et al. Comparative evaluation of the antipyretic efficacy of ibuprofen and paracetamol. Indian Pediatr. 1990;27(8):803–6.
71. Sidler J, Frey B, Baerlocher K. A double-blind comparison of ibuprofen and paracetamol in juvenile pyrexia. Br J Clin Pract Suppl. 1990;70:22–5.
72. Díez-Domingo J, Planelles MV, Baldó JM, Ballester A, Núnez F, Jubert A, et al. Ibuprofen prophylaxis for adverse reactions to diphteria-tetanus-pertussis vaccination: a randomized trial. Curr Ther Res. 1998;59(8):579–88.
73. Autret-Leca E, Gibb IA, Goulder MA. Ibuprofen versus paracetamol in pediatric fever: objective and subjective findings from a randomized, blinded study. Curr Med Res Opin. 2007;23(9):2205–11.