

## Base the short-term use of ibuprofen in infants aged 3–6 months on body weight and administer via the oral route if possible

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**Abstract** Ibuprofen is the NSAID most commonly used to treat mild-moderate pain, fever and inflammation in children, although dosage recommendations in infants aged 3–6 months still differ between countries. Based on the available evidence, the short-term use of ibuprofen to manage pain and fever appears to be effective and safe in infants aged 3–6 months who weigh  $\geq 5$ –6 kg. The dosage should be weight-based, with preference given to oral preparations. To minimize the risk of renal toxicity, it is important to ensure that the infant is adequately hydrated.

### Paediatric use of ibuprofen is well established

The efficacy and safety of ibuprofen in children and adults is well-established [1, 2]. Ibuprofen is approved as an over-the-counter medication in many countries and is the most commonly used NSAID for the treatment of mild-moderate pain, fever and inflammation in children [1, 2]. Table 1 presents an overview of the use of ibuprofen in infants aged 3–6 months. Of note, the use of ibuprofen in infants aged 3–6 months is approved in some countries (e.g. the UK and Australia), but not elsewhere (e.g. the USA and several EU countries). A weight-based approach should be employed first to determine whether the use of ibuprofen is appropriate, and then to calculate the appropriate dosage for the individual (Table 1). Maximum daily doses should not be

exceeded and the history of the patient and contraindications to the use of ibuprofen should be carefully considered (Table 1)

This article provides a brief overview of the available evidence on the efficacy and safety of the short-term use of ibuprofen in infants aged 3–6 months for the relief of pain and fever, as reviewed by Ziesenitz et al. [2]. The use of ibuprofen in the treatment of patent ductus arteriosus in infants is well established [3] and is not discussed further.

### No correlation between age and ibuprofen pharmacokinetics ...

No associations between age and ibuprofen pharmacokinetics were found in clinical studies of oral, rectal or intravenous ibuprofen across a range of indications (Table 2) [2].

For example, in a study investigating the effect of age on the pharmacokinetic properties and antipyretic effects of oral ibuprofen 8 mg/kg in 49 infants and children aged 3 months to 10.4 years (median 2.5 years), there was no meaningful relationship between age and ibuprofen pharmacokinetics [4]; however, clearance appeared to be enhanced in children aged up to 5 years. Notably, some efficacy parameters (e.g. a rapid onset of antipyresis and a greater maximum antipyretic effect) were more favourable in younger children than in those who were older; the relatively greater body surface area of younger patients may contribute to more efficient dissipation of heat [4]. The mean change in temperature was  $-0.24$  °C per mg/L of ibuprofen in the plasma (effect compartment concentration) [4].

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**Table 1** Overview of the use of ibuprofen in infants aged 3–6 months, as reviewed by Ziesenitz et al. [2] and de Martino et al. [1]

<b>Pharmacological properties</b>	
Mechanism of action	NSAID: inhibits cyclooxygenase isoforms 1 and 2; improves synthesis of endocannabinoids
Interactions (pharmacodynamic)	Interferes with platelet aggregation; should not be administered with ASA (may be relevant in infants with congenital heart disease, such as those with stents or vascular grafts)
Pharmacokinetic profile	High oral bioavailability, time to maximum plasma concentration $\approx$ 90 min; highly (90–99%) protein bound
	Metabolized to inactive metabolites by CYP2C8 and CYP2C9, and excreted into urine
<b>Approved use in infants</b>	
Indication	To treat pain, fever, inflammation, patent ductus arteriosus
Approved infant group	USA and several EU countries: age > 6 months and weight $\geq$ 5 kg
	UK and Australia: age > 3 months and weight $\geq$ 5 or 6 kg; not suitable for infants aged < 3 months unless advised by a physician
<b>Dosage and administration</b>	
Route	Oral: preferred route; infant suspensions generally contain ibuprofen 20 or 40 mg/mL; administer with or after food
	Rectal: use only if the oral route is unavailable (orifice rejection may occur leading to variable absorption and poor effectiveness); infant suppositories generally contain 60 or 75 mg ibuprofen
	Intravenous: for use under close monitoring in a hospital setting; appropriately hydrate patients before commencing intravenous treatment
Usual dosage	Suspension and suppositories: 5–10 mg/kg 3 or 4 times daily
	Intravenous: 10 mg/kg infused over 10 min
Maximum cumulative dose	30–40 mg/kg/24 h (may $\uparrow$ the risk of serious AEs, such as acute renal failure, gastrointestinal ulcers and/or bleeding)
<b>Contraindications</b>	
	Neonates/infants with wheeze, bronchospasm, persistent asthma, and/or varicella infection
	Infants at risk of dehydration <sup>a</sup> (e.g. those with profuse vomiting and/or diarrhoea $\pm$ fever)
	Infants with pre-diagnosed kidney disease <sup>a</sup> or chronic inflammatory bowel disease
	Infants receiving nephrotoxic substances ( $\uparrow$ risk of kidney damage because of $\downarrow$ nephron mass)
	Infants receiving concomitant antiplatelet agents/anticoagulants
	Infants with hypersensitivity to NSAIDs
<b>Warnings and precautions</b>	
	Avoid use during treatment with ASA for Kawasaki syndrome
	Use carefully in infants who are premature or have a low birth weight ( $\uparrow$ risk of kidney damage because of their $\downarrow$ nephron mass)
	Exercise care in children with severe respiratory tract infections to avoid septic complications
	Use carefully in children with asthma; advise immediate use of salbutamol if exacerbation occurs
	When initiating ibuprofen therapy, prevent/treat dehydration, hypovolaemia and hypotension
<b>Tolerability profile</b>	
Common AEs (reported in $\geq$ 1 and < 10% of patients)	Gastrointestinal AEs: nausea, dyspepsia, abdominal pain, diarrhoea, constipation, flatulence, vomiting
Potentially life-threatening AEs	Peptic ulcers, gastric haemorrhage, gastric perforation, acute renal failure, interstitial nephritis, papillary necrosis (associated with long-term use)
	Very rare (reported in < 0.01% of patients)
Hypersensitivity-related AEs	Allergic reactions, skin reactions, angioedema, anaphylaxis, respiratory tract reactivity
Unspecific AEs	Dizziness, headache

AEs adverse events, ASA acetylsalicylic acid (aspirin), CYP cytochrome P450 enzymes,  $\uparrow$  increase(d),  $\downarrow$  decreased

<sup>a</sup>Risk factor for renal toxicity; NSAIDs should only be used if there are no alternatives at the lowest effective dose

### ...but route of administration affects efficacy

The pharmacokinetic parameters of rectally administered ibuprofen did not differ between various age subgroups in paediatric patients aged < 1 year [5]. However, orifice

rejection is as a clinically relevant concern, as it leads to incomplete delivery of the dose and poor efficacy [2]. Moreover, in a pharmacokinetic comparison of oral versus rectal ibuprofen in adults, rectal administration was associated with lower absorption, with a resulting relative

**Table 2** Overview of key findings from clinical studies assessing the pharmacokinetics, efficacy and safety of oral, rectal or intravenous ibuprofen in infants and children, including those aged < 6 months, as reviewed by Ziesenitz et al. [4]

<b>Oral</b>
No correlation between PK parameters and age in children aged 3 months to 10 years [4]
PK parameters were not dose-linear in children aged 3 months to 12 years [7]
No reports of ALT and AST abnormalities [8, 9]
In children aged 0–12 years, concomitant use of ibuprofen + paracetamol (acetaminophen) may ↑ the risk of acute kidney injury [10]
No reports of serious AEs (e.g. anaphylaxis, Reye’s syndrome, renal failure, GI bleeding/perforation or necrotizing fasciitis) [11–13]
<b>Rectal</b>
No correlation between PK parameters and age in infants during the first year of life [5]
No difference between rectal ibuprofen and placebo with regard to the incidence of AEs in children aged 4–12 years undergoing ophthalmic, orthopaedic or general surgery [14, 15]
Rectal ibuprofen (40 mg/kg/day) ↓ postoperative pain without ↑ the risk of bleeding in patients aged 1–4 years in the perioperative setting [14, 16]
No significant difference between ibuprofen and codeine with regard to post-tonsillectomy bleeding events in children [17]
<b>Intravenous</b> (hospitalized paediatric patients; no patients were aged ≥ 2 and < 6 months, and only one patient was aged < 2 months) [18]
Slight ↑ in exposure with age
Effectively normalized temperature (clinically relevant ↓)
No reports of serious AEs

AEs adverse events, PK pharmacokinetic, ↑ increase(d/ing), ↓ decrease(d/ing)

bioequivalence of 63% [6]. These results suggest that ibuprofen should be administered orally whenever possible, with the rectal route being reserved for when the oral route cannot be used.

In cases where the use of rectal ibuprofen is warranted, consider using higher dosages (e.g. 10 mg/kg) than those used with orally administered ibuprofen (e.g. 7 mg/kg) to compensate for the variability in bioequivalence, being careful to ensure the maximum recommended daily dose is not exceeded [2].

### Short-term treatment with ibuprofen is effective...

The efficacy of ibuprofen for the management of pain following musculoskeletal trauma has been established in patients aged 6–17 years, as has been its superiority to codeine or paracetamol (acetaminophen) [19]. Moreover, in children of all age groups, including those aged < 6 months, the antipyretic effects of ibuprofen have been demonstrated in studies and confirmed in meta-analyses, some of which suggest that ibuprofen has additional antipyretic benefits relative to paracetamol (Table 2) [2].

### ...and safe

The safety of oral ibuprofen as an antipyretic was compared with that of oral paracetamol in a large practitioner-based, randomized, double-blind trial in 84,192 febrile children aged < 12 years [20]. In the subgroup of 319 children aged < 6 months and a reported weight of

between the 5th and 95th sex-specific percentile for their reported month of age, 111 received ibuprofen 5 mg/kg, 96 received ibuprofen 10 mg/kg and 112 received paracetamol 12 mg/kg [11]. Over a follow-up period of 4 weeks, the risk of serious adverse events (AEs) in children aged < 6 months was low; 1.4% of children were hospitalized for any cause with no significant difference between ibuprofen and paracetamol with regard to absolute risk of hospitalization (0.63%; 95% CI 0.08–2.2%) [11]. There were no hospitalizations for gastrointestinal bleeding, acute renal failure, Reye’s syndrome, anaphylaxis, asthma, bronchiolitis or vomiting/gastritis (all serious AEs) [11]. These results indicate that short-term treatment with ibuprofen is safe in children aged < 6 months, although it must be noted that this trial was not sufficiently powered to detect serious AEs and that study results were not representative of all patients presenting to hospital (due to the exclusion criteria) [2].

The safety of ibuprofen suspension in infants was demonstrated in the Children’s Analgesic Medicine Project, which enrolled children aged 1 month to 18 years [12]. The safety profile of ibuprofen in 7381 children aged < 2 years was consistent with that in 12,730 children aged ≥ 2 years [12]. AEs reported in > 1% of the younger children included fever, vomiting, diarrhoea, rhinitis, rash and otitis media [14]. The safety profile of ibuprofen was similar to that of paracetamol in the same age groups.

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### *Rectal route: low risk of severe gastrointestinal events*

Rectally-administered ibuprofen is well tolerated and associated with a low risk of gastrointestinal AEs when used within the recommended dosages [2]. For example, in a study investigating parental satisfaction and possible AEs in 490 children (aged 3 months to 10 years) receiving ibuprofen 60 or 125 mg suppositories at a dosage of 5–10 mg/kg up to four times daily for 3–7 days, AEs occurred in 1.6% of patients and were short in duration, mild, self-limiting and did not cause permanent damage [21]. Diarrhoea was the most common AE (0.8% of patients), which occurred immediately after suppository administration; other AEs reported following rectal ibuprofen were rash (0.4%), shivering and rectal burning (0.2% each). Although subjective inconvenience was reported by parents in 8.5% of cases because of the suppository's texture, satisfaction was high, as was the likelihood of repeated expected use [21].

### *Pay special attention to hydration*

Special attention should be given to hydration of infants aged < 6 months prior to commencing ibuprofen therapy (Table 1). Dehydration increases the risk of ibuprofen-related renal toxicity and dehydration may be more severe in this age group [1]. Paracetamol is the primary drug of choice in febrile infants with dehydration [2].

In a trial that assessed the impact of ibuprofen exposure on renal function in 105 dehydrated children (aged 1 month to 18 years) with acute gastroenteritis [22], ibuprofen exposure was a risk factor for the development of acute kidney injury independent of the extent of dehydration (HR 2.47; 95% CI 1.78–3.42;  $p < 0.001$ ). Children who developed acute kidney injury were younger and had more frequently received ibuprofen than those who did not ( $p \leq 0.01$ ) [22].

### **Educate parents and caregivers**

Parents and caregivers of children receiving ibuprofen should be thoroughly educated about the following [2, 21]:

- *Avoiding accidental overdose* If multiple dose forms of ibuprofen are to be used (e.g. suspension and suppositories), the maximum daily cumulative dose of 40 mg/kg must be emphasised.
- *Ensuring accurate doses* For oral formulations, the dose-measuring device supplied with the suspension should be used. Suppositories must not be divided/broken before administration, to avoid uneven distribution of active drug.

- *Preventing melting of the suppository* Advise parent to store the suppositories at 4 °C, and unwrap individual suppositories as close as possible to insertion.

### **Data are still limited/lacking**

Further studies that examine the use of ibuprofen exclusively in patients aged 3–6 months are needed to determine the efficacy and optimal dosage of ibuprofen in this age group. Other areas that require study in children include the effect of ibuprofen administration with or after food on gastrointestinal AEs, the co-administration of proton pump inhibitors and ibuprofen during long-term NSAID therapy, the safety of prolonged usage of ibuprofen in children aged < 2 years, and the safety of ibuprofen in combination with paracetamol for any duration of time,

### **Take home messages**

The short-term (i.e. up to 3 days) use of ibuprofen to treat pain and fever in infants aged between 3 and 6 months who weigh 5–6 kg appears to be effective and safe. When using ibuprofen to treat this paediatric age group, it is important to:

- Base the dosage on weight rather than age
- Not exceed a maximum cumulative daily dosage of 30–40 mg/kg (administered as single doses of 5–10 mg/kg three to four times a day)
- Use the oral route preferentially over the rectal route, whenever possible
- Ensure infants are adequately hydrated
- Carefully consider the patient's history/contraindications, particularly those associated with an increased risk of renal function impairment (e.g. hypovolaemia)
- Educate parents and caregivers about maximum daily doses, especially when different dose forms (e.g. suspension and suppositories) and/or formulation (e.g. ibuprofen and paracetamol) are being used concomitantly

### **Compliance with ethical standards**

**Conflict of interest** The article was adapted from *Pediatric Drugs* 2017;19(4):277–20 [2] by employees of Adis/Springer, who are responsible for the article content and declare no conflicts of interest.

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## References

1. de Martino M, Chiarugi A, Boner A, et al. Working towards an appropriate use of ibuprofen in children: an evidence-based appraisal. *Drugs*. 2017;77(12):1295–311.
2. Ziesenitz VC, Zutter A, Erb TO, et al. Efficacy and safety of ibuprofen in infants aged between 3 and 6 months. *Paediatr Drugs*. 2017;19(4):277–90.
3. Adis Medical Writers. Consider pharmacological treatment to close patent ductus arteriosus in preterm infants when the condition is haematologically significant. *Drugs Ther Perspect*. 2017;33(1):22–5.
4. Kauffman RE, Nelson MV. Effect of age on ibuprofen pharmacokinetics and antipyretic response. *J Pediatr*. 1992;121(6):969–73.
5. Kyllonen M, Olkkola KT, Seppala T, et al. Perioperative pharmacokinetics of ibuprofen enantiomers after rectal administration. *Paediatr Anaesth*. 2005;15(7):566–73.
6. Vilenchik R, Berkovitch M, Jossifoff A, et al. Oral versus rectal ibuprofen in healthy volunteers. *J Popul Ther Clin*. 2012;19(2):e179–86.
7. Brown RD, Wilson JT, Kearns GL, et al. Single-dose pharmacokinetics of ibuprofen enantiomers in febrile children. *J Clin Pharmacol*. 1992;32(3):231–41.
8. Simila S, Kouvalainen K, Keinänen S. Oral antipyretic therapy. *Scand J Rheumatol*. 1976;5(2):81–3.
9. 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.
10. Yue Z, Jiang P, Sun H, et al. 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.
11. Lesko SM, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. *Pediatrics*. 1999;104(4):e39.
12. Ashraf E, Ford L, Geetha R, Cooper S. Safety profile of ibuprofen suspension in young children. *Inflammopharmacology*. 1999;7(3):219–25.
13. Joshi YM, Sovani VB, Joshi VV, et al. Comparative evaluation of the antipyretic efficacy of ibuprofen and paracetamol. *Indian Pediatr*. 1990;27(8):803–6.
14. 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.
15. Maunuksela EL, Ryhanen P, Janhunen L. Efficacy of rectal ibuprofen in controlling postoperative pain in children. *Can J Anaesth*. 1992;39(3):226–30.
16. Kokki H, Hendolin H, Maunuksela EL, et al. 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.
17. Pfaff JA, Hsu K, Chennupati SK. The use of ibuprofen in posttonsillectomy analgesia and its effect on posttonsillectomy hemorrhage rate. *Otolaryngol Head Neck Surg*. 2016;155(3):508–13.
18. Summary review for regulatory action. *Caldolor injection/ibuprofen intravenous injection (NDA 22348, Supplement 005)*. Silver Spring: US Food and Drug Administration; 2015.
19. Clark E, Plint AC, Correll R, et al. A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. *Pediatrics*. 2007;119(3):460–7.
20. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen: a practitioner-based randomized clinical trial. *JAMA*. 1995;273(12):929–33.
21. Hadas D, Youngster I, Cohen A, et al. Premarketing surveillance of ibuprofen suppositories in febrile children. *Clin Pediatr*. 2011;50(3):196–9.
22. Balestracci A, Ezquer M, Elmo ME, et al. Ibuprofen-associated acute kidney injury in dehydrated children with acute gastroenteritis. *Pediatr Nephrol*. 2015;30:1873–8.