

# Ketoprofen Pharmacokinetics, Efficacy, and Tolerability in Pediatric Patients

Hannu Kokki

Department of Anesthesiology and Intensive Care, Kuopio University Hospital, University of Eastern Finland, Kuopio, Finland

## Contents

|                                                                          |     |
|--------------------------------------------------------------------------|-----|
| Abstract . . . . .                                                       | 313 |
| 1. Pharmacokinetics . . . . .                                            | 315 |
| 1.1 Adults . . . . .                                                     | 315 |
| 1.2 Children . . . . .                                                   | 315 |
| 1.3 CNS Pharmacokinetics . . . . .                                       | 316 |
| 1.4 Drug-Drug Interactions . . . . .                                     | 317 |
| 2. Efficacy . . . . .                                                    | 317 |
| 2.1 Fever . . . . .                                                      | 317 |
| 2.1.1 Oral Administration . . . . .                                      | 317 |
| 2.1.2 Rectal Administration . . . . .                                    | 317 |
| 2.2 Perioperative Use . . . . .                                          | 318 |
| 2.2.1 Intravenous Administration . . . . .                               | 318 |
| 2.2.2 Intramuscular Administration . . . . .                             | 322 |
| 2.2.3 Rectal Administration . . . . .                                    | 322 |
| 2.2.4 Oral Administration . . . . .                                      | 322 |
| 2.3 Inflammatory Conditions . . . . .                                    | 323 |
| 2.3.1 Oral Administration . . . . .                                      | 323 |
| 2.3.2 Topical Administration . . . . .                                   | 323 |
| 3. Safety/Tolerability Issues . . . . .                                  | 323 |
| 3.1 Effects on Opioid-Related Adverse Events . . . . .                   | 325 |
| 3.2 Intra- and Postoperative Bleeding . . . . .                          | 325 |
| 3.3 Renal Effects . . . . .                                              | 326 |
| 3.4 Bone Healing . . . . .                                               | 326 |
| 3.5 Summary . . . . .                                                    | 326 |
| 3.6 Long-Term Tolerability . . . . .                                     | 326 |
| 4. Evidence-Based Pediatric Ketoprofen Dosing: Recommendations . . . . . | 327 |
| 5. Conclusions . . . . .                                                 | 327 |

## Abstract

The NSAID ketoprofen is used widely in the management of inflammatory and musculoskeletal conditions, pain, and fever in children and adults. Pharmacokinetic studies show that drug exposure after a single intravenous dose is similar in children and adults (after dose normalization), and thus similar mg/kg bodyweight dosing may be used in children and adults. Ketoprofen crosses the blood-brain barrier and therefore has the potential to cause central analgesic effects.

Ketoprofen has been investigated in children for the treatment of pain and fever, peri- and postoperative pain, and inflammatory pain conditions. The results of four clinical trials in febrile conditions with the oral syrup formulation indicate that ketoprofen is as effective as acetaminophen (paracetamol) and ibuprofen,

allowing children to rapidly return to daily activities with improvements in sleep quality and appetite. Studies of ketoprofen in the management of postoperative pain indicate that ketoprofen is a highly effective analgesic when administered perioperatively for a variety of surgical types, by a variety of routes, and whether given preoperatively or postoperatively. For adenoidectomy, intravenous ketoprofen provided superior postoperative analgesic efficacy compared with placebo. Analgesic efficacy was similar with intravenous, intramuscular, or rectal routes of administration, but oral administration just before surgery was inferior to intravenous administration in this setting. In patients undergoing a tonsillectomy, intravenous ketoprofen was superior to intravenous tramadol in terms of the need for postoperative rescue analgesia, but did not remove the need for rescue opioid therapy in these patients. Intravenous ketoprofen had superior postoperative analgesic efficacy to placebo when given as an adjuvant to epidural sufentanil analgesia after major surgery. Oral ketoprofen has shown efficacy in the treatment of juvenile rheumatoid arthritis.

Ketoprofen is generally well tolerated in pediatric patients. Most of the adverse events reported are mild and transient, and are similar to those observed with other NSAIDs. Long-term tolerability has not yet been fully established in children, but data from three studies in >900 children indicate that oral ketoprofen is well tolerated when administered for up to 3 weeks after surgery.

In conclusion, ketoprofen is effective and well tolerated in children for the control of post-surgical pain and for the control of pain and fever in inflammatory conditions.

The NSAIDs are used increasingly in multimodal management of pain and fever.<sup>[1]</sup> Ketoprofen has been in use in Europe since 1974<sup>[2]</sup> and in the US since the 1980s. Ketoprofen is a potent, classical NSAID of the arylpropionic acid class.<sup>[3]</sup> Classical NSAIDs inhibit prostaglandin synthesis by inhibiting the cyclo-oxygenase (COX) enzyme.<sup>[3]</sup> Ketoprofen exhibits analgesic, antipyretic, and anti-inflammatory properties through non-specific COX-1 and COX-2 inhibition,<sup>[3]</sup> thought to occur mainly in peripheral sites, although recent studies indicate that ketoprofen also appears to have central effects.<sup>[4]</sup> Ketoprofen is a chiral molecule and only the *S*-enantiomer has beneficial biological activity.<sup>[5]</sup>

Conditions causing elevated body temperature and acute pain (e.g. injury, illness, or medical procedures) are common in children, with NSAIDs frequently being used in children for the symptomatic treatment of fever and for pain management.<sup>[3,6]</sup> Acute pediatric pain causes increased anxiety, avoidance behavior, somatic symptoms, and distress in both the child and caregiver, and could cause long-lasting untoward effects on both the growing body and the mind of the child.<sup>[6]</sup> Pain in infants, children, and adolescents is often poorly assessed and managed.<sup>[6]</sup> One of the main reasons for this is a lack of knowledge of the dosages and formulations of analgesics that are appropriate for this patient population.<sup>[6]</sup> Other contributing factors include inappropriate recognition and evaluation of pain in children, and fear of adverse effects of the analgesics.<sup>[6]</sup> Fever in children is a source of great concern to caregivers, and the primary method of body temperature control is the appropriate use of antipyretic drugs.<sup>[7]</sup>

Currently approved indications for ketoprofen in adults include pain, fever, and certain inflammatory and musculoskeletal conditions.<sup>[8]</sup> Ketoprofen is available in intravenous, intramuscular, oral (tablet and syrup), rectal, and topical formulations. In children, ketoprofen has been investigated in postsurgical pain, predominantly in an intravenous formulation, although the oral, intramuscular, and rectal formulations have also been investigated. The oral tablet and syrup formulations have been assessed for use in fever and/or pain, and in inflammatory conditions. In pediatric patients, ketoprofen is used for symptomatic relief of fever and management of pain in infants and children aged 6 months to 11 years (up to 35 kg). Ketoprofen syrup has been approved for use in children in various countries. In addition, ketoprofen is currently approved worldwide for use in adolescents (aged 12 years or older with a bodyweight 35 kg or over) and in adults. It is available in a variety of dosage forms, including tablets (25 mg, 50 mg, 100 mg, 150 mg, 200 mg), capsules (50 mg, 100 mg, 150 mg, 200 mg), solutions for intramuscular route (50 mg, 100 mg), suppository 100 mg, syrup 1 mg/mL, skin patches and gels (1%, 2.5%, 5%), and oral soluble film (12.5 mg). Ketoprofen is not approved for use in infants aged <6 months.

This paper reviews the current evidence supporting the use of ketoprofen in children for pain management and antipyresis. For this review, available literature was searched using MEDLINE and EMBASE databases limited to English abstracts, and using the search terms 'ketoprofen' ('ketoprofene'), 'NSAID use', 'pain relief' ('analgesia'), and 'children'; the results were deduplicated (no date restrictions were applied). Specific publications

included in this review were then selected manually from the search results for their relevance to this topic.

## 1. Pharmacokinetics

A brief overview of the pharmacokinetics of ketoprofen in adults is provided for reference and completeness where information in the pediatric population is not available or is sparse.

### 1.1 Adults

Generally, in adult populations (patients and healthy volunteers), ketoprofen administered as a regular-release oral tablet 50–200 mg is rapidly absorbed and peak plasma concentrations ( $C_{\max}$ ) of 2.6–23.0 mg/L occur between 0.8 and 2.4 hours after a dose ( $t_{\max}$ ).<sup>[5]</sup> The absorption rate of an oral dose of ketoprofen 50 mg syrup was found to be faster than that of the regular-release tablet formulation ( $t_{\max}$  0.35 vs 1.2 hours), but the area under the plasma concentration-time curve (AUC) values did not differ between these two oral formulations.<sup>[5]</sup> Sustained-release preparations of ketoprofen 150–200 mg provided lower  $C_{\max}$  values (2.8–5.6 mg/L) and longer  $t_{\max}$  values (3.5–10.1 hours) than regular-release preparations, but AUC values for both formulations were similar (8.2–70.4 and 22.1–81.0 mg • h/L, for regular- and sustained-release, respectively).<sup>[5]</sup> Administration with food decreases the rate, but not the extent, of absorption of ketoprofen.<sup>[5]</sup>

Oral ketoprofen 100 mg has a bioavailability of  $\geq 92\%$ , based on reported AUC values and assuming that individuals are closely matched for bodyweight.<sup>[5]</sup> Ketoprofen is highly protein bound ( $>95\%$ ) and, therefore, is primarily confined to the plasma compartment.<sup>[5]</sup>

The bioavailability of ketoprofen following rectal administration is slightly lower (70–90%) than that of oral administration.<sup>[9]</sup> Rectal ketoprofen 75–100 mg resulted in a  $C_{\max}$  of 2.2–7.5 mg/L,  $t_{\max}$  of 1.1–2.1 hours, and AUC from time zero to infinity ( $AUC_{\infty}$ ) of 12.9–17.2 mg • h/L.<sup>[5,9]</sup> Pharmacokinetic parameters in adults administered intramuscular ketoprofen 100 mg are similar, with a  $C_{\max}$  of 10.1 mg/L,  $t_{\max}$  of 1.2 hours and  $AUC_{\infty}$  of 21.1 mg • h/L.<sup>[5]</sup>

After a single intravenous dose of ketoprofen, and following dose normalization to 1 mg/kg of bodyweight, the mean  $C_{\max}$  was 13.2 mg/L and the mean  $AUC_{\infty}$  was 14.0 mg • h/L in adults.<sup>[9,10]</sup>

Ketoprofen is extensively metabolized by hepatic enzymes to form unstable acylglucuronide conjugates; minimal quantities of unchanged drug are detected in the urine and bile, regardless of the patient's age or renal function.<sup>[5,11]</sup> A reduction in the renal clearance of ketoprofen in elderly patients, relative to

healthy adults, has been attributed to the higher concentrations of conjugates found in the plasma. However, the potential for accumulation is low because the elimination half-life ( $t_{1/2}$ ) is short. The terminal elimination  $t_{1/2}$  of ketoprofen is 1.5–2 hours for the oral formulation, 2.2 hours for rectal administration, and 2 hours for intravenous administration.<sup>[11]</sup>

### 1.2 Children

The pharmacokinetic properties of ketoprofen have been studied in children and infants, administered as a single intravenous,<sup>[11]</sup> intramuscular,<sup>[12]</sup> or rectal dose;<sup>[9]</sup> as a continuous 24-hour intravenous infusion;<sup>[13]</sup> or orally, either as tablet<sup>[12]</sup> or syrup<sup>[14]</sup> formulations (see table I for dosages). Among these pediatric patients, 38 were aged 6–23 months and 22 were aged 6–11 months. The numbers of children aged 6–23 months and 6–11 months, respectively, receiving ketoprofen formulations were as follows: syrup, 10 and 7; single intravenous dose, 8 and 5; rectal, 0 and 0; oral tablet, 1 and 0; intramuscular injection, 3 and 1; and 24-hour intravenous infusion, 8 and 5 (Kokki H, unpublished observations).

A 24-hour intravenous ketoprofen infusion in children<sup>[13]</sup> displayed a pharmacokinetic profile that was similar to that seen in an early study in adults<sup>[10]</sup> (table I). Steady-state concentrations were 1.3–2.7 mg/L in children ( $n=18$ ) receiving a 1 mg/kg loading dose of ketoprofen followed by 4 mg/kg as a continuous 24-hour infusion,<sup>[13]</sup> and 3.6–4.8 mg/L in adults ( $n=10$ ) receiving a ketoprofen 35 mg loading dose followed by 600 mg as a continuous 24-hour infusion.<sup>[10]</sup> These data indicate that the between-subject variability is relatively low in children aged 6 months or older. The bodyweight-based infusion rate of ketoprofen administered to children was half that of adults and, consequently, the plateau concentrations observed were approximately halved.<sup>[10]</sup> Moreover, after a single intravenous dose of ketoprofen and following dose normalization to 1 mg/kg of bodyweight, the pharmacokinetic profile in children was very similar to that observed in adults, with mean values for  $C_{\max}$  of 15.5 mg/L and for  $AUC_{\infty}$  of 15.4 mg • h/L.<sup>[9,10]</sup> The bioavailability of ketoprofen following rectal administration in children is 73% (versus 70–90% in adults using a comparable mg/kg dose).<sup>[9]</sup> These pharmacokinetic results suggest that the same mg/kg bodyweight dose of the rectal and intravenous formulations of ketoprofen may be used in both children and adults.<sup>[9]</sup>

The absolute bioavailability of oral ketoprofen (*S*-enantiomer) 12.5–50 mg is approximately 70–80%.<sup>[16]</sup> Moreover, there is no difference in the bioavailability of a single intramuscular and oral ketoprofen dose.<sup>[12]</sup> In children aged 10–69 months who

**Table 1.** Ketoprofen pharmacokinetic parameters in pediatric patients. Results from four open-label, prospective studies<sup>[9,12,13,15]</sup> involving patients aged 7 months to 16 years who received oral (tablet or syrup), rectal, intravenous (IV), or intramuscular (IM) formulations of ketoprofen prior to surgical procedures

| Study (y)                           | No. of patients (age [mo]) | Route; dose                                     | C <sub>ss</sub> (μg/mL) <sup>a</sup> | C <sub>max</sub> (μg/mL) <sup>a</sup> | t <sub>max</sub> (h) <sup>b</sup> | AUC (μg•h/mL) <sup>a</sup> | CL (L/h/kg) <sup>a</sup>   | V <sub>d</sub> (L/kg) <sup>a</sup> | t <sub>1/2</sub> (h) <sup>a</sup> |
|-------------------------------------|----------------------------|-------------------------------------------------|--------------------------------------|---------------------------------------|-----------------------------------|----------------------------|----------------------------|------------------------------------|-----------------------------------|
| Kokki et al. <sup>[13]</sup> (2002) | 18 (7–193)                 | IV; 1 mg/kg loading dose and 4 mg/kg/24 h       | 2.0 (0.5)<br>[1.3–2.7]               |                                       |                                   | 47.6 (1.11)<br>[31.1–65.4] | 0.09 (0.02)<br>[0.06–0.13] | 0.16 (0.03)<br>[0.12–0.21]         | 1.3 (0.22)<br>[0.12–0.21]         |
| Kokki et al. <sup>[9]</sup> (2003)  | 18 (7–93)                  | IV; 1 mg/kg over 2 min                          |                                      | 15.5 (3.5)<br>[10.5–22.2]             |                                   | 15.4 (4.4)<br>[9.2–23.5]   | 0.07 (0.02)                | 0.07 (0.01)                        | 1.5 (0.5)                         |
|                                     | 10 (33–79)                 | Rectal; 25 mg suppository                       |                                      | 5.3 (1.3)<br>[3.8–7.4]                | <1                                | 11.2 (1.4)<br>[8.8–12.9]   | 0.09 (0.01)<br>[0.07–0.11] | 0.12 (0.03)<br>[0.08–0.16]         | 1.8 (0.6)<br>[1.2–2.9]            |
| Kokki et al. <sup>[12]</sup> (2001) | 10 (16–69)                 | Oral; 12.5 mg or 25 mg tablet = 0.74–1.39 mg/kg |                                      | 5.4 (1.6)<br>[2.8–8.2]                | 0.5<br>[0.5–1.0]                  | 11.4 (1.9)<br>[8.7–14.1]   | 0.09 (0.02)<br>[0.07–0.12] |                                    | 1.3 (0.3)<br>[0.9–2.1]            |
|                                     | 10 (10–77)                 | IM; 1 mg/kg                                     |                                      | 5.7 (1.2)<br>[3.6–7.4]                | 0.5<br>[0.25–1]                   | 11.6 (2.0)<br>[8.8–14.6]   | 0.09 (0.02)<br>[0.07–0.11] |                                    | 1.6 (0.4)<br>[0.84–2.2]           |
| Kokki et al. <sup>[15]</sup> (2000) | 10 (6–24)                  | Oral syrup; 0.5 mg/kg                           |                                      | 3.0 (0.7)                             | 0.5                               | 5.6 (1.1)                  |                            |                                    | 2.0 (0.7)                         |
|                                     | 10 (>2–7 y)                |                                                 |                                      | 3.1 (0.6)                             | 0.5                               | 4.9 (0.9)                  |                            |                                    | 1.9 (0.6)                         |

<sup>a</sup> Data are presented as mean (SD) and [range].<sup>b</sup> Data are presented as mean [range].**AUC** = area under the plasma concentration-time curve; **CL** = apparent clearance; **C<sub>max</sub>** = peak plasma concentration; **C<sub>ss</sub>** = steady-state concentration; **t<sub>1/2</sub>** = elimination half-life; **t<sub>max</sub>** = time to C<sub>max</sub>; **V<sub>d</sub>** = volume of distribution.

received either a single intramuscular or oral dose of ketoprofen, pharmacokinetic parameters were similar (table I), indicating that there is no justification for the use of intramuscular ketoprofen in preference to oral ketoprofen in awake children.<sup>[12]</sup> The pharmacokinetic profile of a ketoprofen syrup formulation was similar in children aged 6 months to 2 years to that in children aged >2–7 years (table I).<sup>[15]</sup> There were no between-group differences in values for C<sub>max</sub>, t<sub>1/2</sub>, or AUC.<sup>[15]</sup> Although the mean residence time was longer in the younger children (2.0 vs 1.7 hours; p=0.05), no relationship was observed between AUC and age.<sup>[15]</sup> Again, when compared with pharmacokinetic data previously reported in adult populations, these results in pediatric patients were similar.<sup>[10,15,17]</sup>

In general, weight-normalized clearance (CL) and volume of distribution (V<sub>d</sub>) values for NSAIDs (including ketoprofen) in children are greater than those in adults, but observed t<sub>1/2</sub> values are similar.<sup>[18]</sup> In contrast, the weight-normalized CL for NSAIDs in neonates is less than that in infants, children, and adults.<sup>[18]</sup> There are no specific data for ketoprofen in neonates.

In conclusion, pharmacokinetic data indicate that the weight-based dosing of ketoprofen used in children aged 6 months or older may be the same as that used in adults. There are no pharmacokinetic data in younger infants, and thus great caution is necessary if using ketoprofen in neonates or young infants.

### 1.3 CNS Pharmacokinetics

Because NSAIDs have significant central effects, the CNS pharmacokinetics of different compounds has been of interest. Ketoprofen has a small (254 g/mol) molecular weight, and is highly lipophilic in an un-ionized form (pK<sub>a</sub> 4.2) and, as such, could pass through the blood-brain and blood-cerebrospinal fluid (CSF) barrier.<sup>[4]</sup>

Ketoprofen has been detected in the CSF of adults<sup>[19]</sup> and children.<sup>[14]</sup> In the latter study, of the ten children included, four were aged 6–11 months. Thirty minutes after a single oral dose of ketoprofen syrup 1 mg/kg, ketoprofen was detectable in the CSF only in one child; this child had the highest plasma concentration (7.4 ng/mL), and the CSF/plasma ratio was 0.008.<sup>[14]</sup> However, the detection limit in the study was relatively high, and with the more sensitive assay method used in the study by Mannila et al.,<sup>[4]</sup> some of the CSF samples from the other children in this study were shown to contain low amounts of ketoprofen (Kokki H, unpublished observations). To better characterize the potential for ketoprofen to cross the blood-CSF barrier, the CSF distribution of ketoprofen after intravenous administration in young children was investigated.<sup>[4]</sup>

Following intravenous administration of ketoprofen 1 mg/kg prior to inguinal surgery and lumbar puncture performed for spinal anesthesia in 21 children aged 12–94 months (four were aged 12–23 months), ketoprofen was detectable at 1.4–24.0 ng/mL in all CSF samples assayed at 7 minutes through to 1 hour after administration. Furthermore, CSF ketoprofen concentrations increased with increasing time ( $p=0.026$ ). This indicates that ketoprofen has a high potential to have central analgesic effects.<sup>[4,16]</sup>

#### 1.4 Drug-Drug Interactions

Drug-drug interactions with NSAIDs have been reported.<sup>[11]</sup> NSAIDs are highly protein-bound and may increase plasma levels of other protein-binding drugs such as anticoagulants, antihypertensives, diuretics, cardiac glycosides, lithium, ciclosporin, corticosteroids, or quinolone antibacterials.<sup>[11]</sup> Ketoprofen should not be used in conjunction with other NSAIDs because the potential for adverse reactions is increased if administered with similar-acting drugs (including aspirin [acetylsalicylic acid]).

## 2. Efficacy

### 2.1 Fever

#### 2.1.1 Oral Administration

The antipyretic effect of oral ketoprofen syrup was investigated in five randomized, blinded, clinical studies in pediatric patients with fever.<sup>[20–22]</sup>

A significant dose response (primary endpoint: maximum reduction in temperature before remedication within the first 6 hours) was observed between the three ketoprofen doses studied (0.25, 0.5, and 1.0 mg/kg) in two dose-ranging studies of ketoprofen syrup in children aged 6–24 months ( $n=165$ ) and in children aged 2–6 years ( $n=164$ ) with a fever of  $\geq 39^\circ\text{C}$ .<sup>[21]</sup> The best efficacy/safety ratio after a single oral dose was observed with the 0.5 mg/kg dose in both studies, and this dose yielded similar efficacy to oral acetaminophen (paracetamol) 15 mg/kg. The adverse event profiles of ketoprofen and acetaminophen were as expected, with most adverse events being non-serious; diarrhea and vomiting were the most commonly reported adverse events, and were probably due to the underlying diseases.<sup>[21]</sup>

These preliminary results were reinforced in two phase III comparative clinical studies;<sup>[22]</sup> data were reported in a single publication. In one study involving 275 infants and children (aged 6 months to 6 years) with a fever of  $39.5^\circ\text{C}$  at baseline, ketoprofen 0.5 mg/kg syrup and acetaminophen 15 mg/kg sus-

pension reduced temperature (primary endpoint) to a similar extent at 3 hours post-dose ( $-1.5$  vs  $-1.4^\circ\text{C}$ , respectively). A significant antipyretic activity was sustained after 6-hourly repeated ketoprofen dosing. In a second study in 272 infants and children with a baseline fever of  $39.2^\circ\text{C}$ , ketoprofen 0.5 mg/kg syrup was as effective as ibuprofen 5 mg/kg suspension in reducing the temperature profile over 3 hours.<sup>[22]</sup> The mean treatment duration was 1.6 days in both studies. Similar antipyretic efficacy was observed in a comparative trial ( $n=301$ ) that investigated the antipyretic effect of oral syrup formulations of ketoprofen 0.5 mg/kg, ibuprofen 5 mg/kg, and acetaminophen 15 mg/kg in children aged 1–14 years with a baseline temperature of  $38^\circ\text{C}$  (axillary) or  $39^\circ\text{C}$  (rectal).<sup>[20]</sup> Following a single dose, each of the three medications provided a reduction in body temperature at 30, 60, and 120 minutes ( $p<0.001$  vs baseline), but there were no significant between-group differences. In these studies, there was no difference in AUC values between ketoprofen 0.5 mg/kg and ibuprofen 5 mg/kg. In the AUC from 0 to 6 hours comparisons, oral (syrup) ketoprofen 0.25 mg/kg appeared to be inferior to oral acetaminophen 15 mg/kg, but oral (syrup) ketoprofen doses of 0.5 mg/kg and 1 mg/kg were superior to oral acetaminophen both in infants and children.<sup>[20,21]</sup>

Furthermore, in the phase III studies,<sup>[20,22]</sup> with respect to quality of life (QOL), a numerical difference between the ketoprofen 0.5 mg/kg and ibuprofen groups was seen in the recovery of normal play; more children (71%) in the ketoprofen group were reported to play normally at 48 hours compared with the ibuprofen group (61%). There was also a numerical difference between the ketoprofen 0.5 mg/kg and acetaminophen 15 mg/kg groups; the proportion of children reported to have normal sleep, appetite, and play activities at 48 hours was 65%, 46%, and 76%, respectively, with ketoprofen, and 57%, 35%, and 57%, respectively, with acetaminophen. Most caregivers (approximately 90% in both studies) stated that they would use ketoprofen syrup again based on the rapid onset of action, palatability, and QOL improvements.<sup>[22]</sup>

In summary, the available pediatric data indicate that in infants (aged  $\geq 6$  months) and children, the antipyretic effect of ketoprofen syrup administered at a dose of 0.5 mg/kg is similar to that observed with ibuprofen 5 mg/kg and acetaminophen 15 mg/kg.

#### 2.1.2 Rectal Administration

Ketoprofen was an effective antipyretic and analgesic when administered as a single rectal dose to infants, children, or adolescents with fever and pain in two randomized, double-blind, dose-ranging studies; data were reported in a single publication.<sup>[23]</sup> Patients with fever (rectal body temperature

38°C) associated with an acute inflammatory disease of the respiratory system or urinary tract were enrolled.<sup>[23]</sup> In the first study, ketoprofen was administered rectally as a single dose of either 20, 30, or 40 mg to infants and children aged 6–36 months ( $n=53$ ) and, in the second study, at 40, 60, or 80 mg to children and adolescents aged 3–13 years ( $n=54$ ).<sup>[23]</sup>

Ketoprofen (all doses) reduced body temperature from baseline at 1, 2, 3, 4, 6, and 8 hours after administration ( $p=0.007$ ). Observer-rated pain (measured using the Maunuksele pain scale<sup>[24]</sup> [an observational behavioral scale based on facial expression, limb, and trunk responses, and measured cardiorespiratory variables, also referred to as the Objective Pain Scale]) was significantly reduced from baseline in children and adolescents ( $p=0.001$ ) treated with ketoprofen 80 mg. Decreases in pain scores were noted for the other dosages in this study and for all dosage groups in infants.<sup>[23]</sup> The single dosages associated with the best risk: benefit ratio for the treatment of pain and fever were 30 mg in infants and younger children, and 60 mg in older children.<sup>[23]</sup>

## 2.2 Perioperative Use

The analgesic efficacy of ketoprofen in the perioperative setting in children has been evaluated in several clinical studies and has shown efficacy in many types of surgery.

Where reported, patients belonged to the American Society of Anesthesiologists (ASA) physical status classification of 1 or 2, and, in comparative studies, patients in different treatment groups were generally well matched in terms of baseline characteristics (age, sex, bodyweight, type and duration of surgery). In three studies in which patients received preoperative ketoprofen, a second dose of ketoprofen was given 2–6 hours postoperatively.<sup>[25–27]</sup>

Where specified, the primary study efficacy endpoint was either the proportion of patients who received an opioid for rescue analgesia or the mean number of doses of rescue analgesia administered during the postoperative period. The reduction in pain intensity was also measured. Generally, pain was assessed using the validated Maunuksele pain scale<sup>[24]</sup> or the modification of this scale by Nikanne et al.<sup>[28]</sup> In some studies, and generally in those involving older children, pain was assessed using a visual analog scale (VAS) in addition to, or instead, of the Maunuksele scale.<sup>[25,27,29–33]</sup>

### 2.2.1 Intravenous Administration

Early studies established the efficacy of intravenous ketoprofen in children in several surgical settings. As is the case with

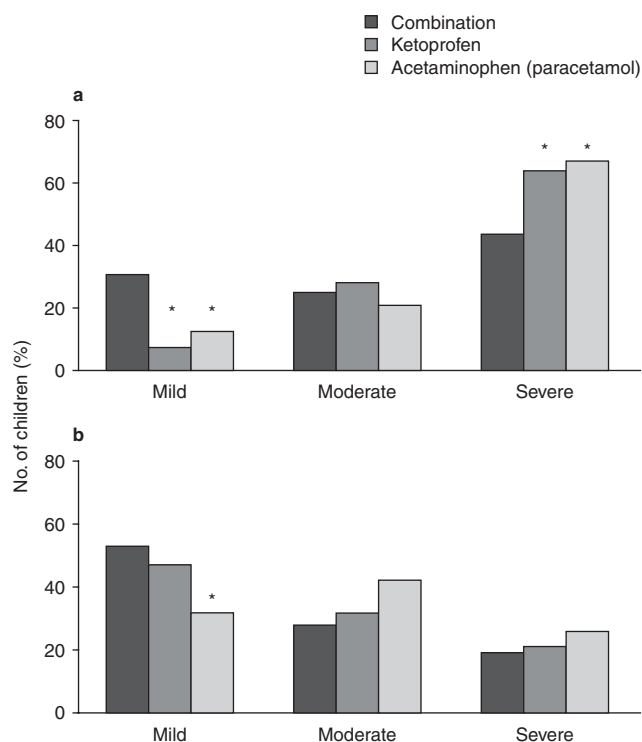
other NSAIDs, ketoprofen is not approved for intravenous administration in children aged <12 years; however, despite this restriction, it is often used in children at a dosage of 1 mg/kg three times daily for up to 48–72 hours.<sup>[34]</sup> In some of the injectable formulations of ketoprofen, benzyl alcohol is used as a preservative and it may cause toxic or allergic reactions in neonates and younger infants.<sup>[35]</sup> Therefore, all preparations containing benzyl alcohol should be used with great caution; intravenous ketoprofen containing benzyl alcohol is contraindicated in preterm infants and neonates. However, single doses of intravenous ketoprofen containing low amounts of benzyl alcohol have been used in the management of acute pain in older infants (aged  $\geq 3$  months) without any apparent harm.<sup>[36]</sup>

#### Soft Tissue or Orthopedic Surgery

Postoperative pain relief with intravenous ketoprofen 2 mg/kg administered initially as a single dose after the induction of anesthesia and again 8 hours later ( $n=39$ ) was similar to that with oral plus rectal acetaminophen ( $n=39$ ) in a randomized, double-blind, triple treatment arm study in children (mean age 4 years; range 1–9 years) undergoing orthopedic or soft tissue surgery.<sup>[26]</sup> Acetaminophen was given as a rectal 60 mg/kg dose after the induction of anesthesia plus an oral 40 mg/kg dose 8 hours later. A combination of intravenous ketoprofen and oral plus rectal acetaminophen offered no further advantage over intravenous ketoprofen monotherapy; however, in a subgroup of patients who had orthopedic surgery ( $n=61$ ), combination treatment provided pain relief that was superior to that with monotherapy with acetaminophen or ketoprofen (figure 1).<sup>[26]</sup> The mean number of rescue doses of intravenous morphine 0.05 mg/kg required during the 24-hour postoperative period was similar in the group receiving intravenous ketoprofen 4 mg/kg (total dose) plus acetaminophen 100 mg/kg (total dose) to that in the group receiving intravenous ketoprofen monotherapy (4.1 vs 5.4 doses), but was less than that in the group receiving acetaminophen monotherapy (5.9 doses;  $p<0.05$ ).<sup>[26]</sup> The study was not sufficiently powered to show a difference between ketoprofen monotherapy and combination therapy. However, at 30 and 90 minutes after the end of anesthesia, the cumulative number of rescue analgesic doses was lower ( $p<0.05$ ) with the ketoprofen plus acetaminophen combination treatment than with either agent administered as monotherapy.

#### Adenoidectomy and Tonsillectomy

Eight studies evaluated the use of intravenous ketoprofen in two of the most common and painful surgical procedures in children: day-case adenoidectomy in patients aged 1–9



**Fig. 1.** Analgesic effect of intravenous ketoprofen (2 mg/kg administered as a single dose after the induction of anesthesia and again 8 hours later), acetaminophen (paracetamol) [60 mg/kg rectally after the induction of anesthesia plus an oral 40 mg/kg dose 8 hours later] or a combination of both for pediatric soft tissue or orthopedic surgery. The figure presents the percentage of children whose maximal pain scores in (a) the post-anesthesia care unit (n = 117) and (b) on the postoperative ward (n = 109) were mild, moderate, or severe (reproduced from Hiller et al.,<sup>[26]</sup> with permission). See section 2.2.1 for further regimen details. \*  $p < 0.05$  vs combination group.

years<sup>[28,37–42]</sup> (tables II and III), and tonsillectomy in children and adolescents aged 3–16 years.<sup>[25,30]</sup> Most of the studies were placebo-controlled. Opioid analgesics were given as rescue analgesia in all studies.<sup>[28,30,38,41,42]</sup>

When administered perioperatively to children undergoing adenoidectomy, intravenous ketoprofen 0.3–3.0 mg/kg, compared with placebo, resulted in a reduction in the need for rescue opioid analgesia (tables II and III).<sup>[28,38,39,41]</sup> In the key study, fewer ketoprofen recipients than placebo recipients required fentanyl rescue analgesia (64% vs 77%;  $p = 0.0006$ ); of note, two doses of ketoprofen were administered in this study (tables II and III).<sup>[28]</sup> In the dose-finding study by Kokki et al.,<sup>[38]</sup> the number of fentanyl doses needed in the post-anesthesia care unit (PACU) was less in all ketoprofen groups compared with placebo ( $p = 0.01–0.001$ ) [tables II and III].

Pre-emptive analgesia compared with postoperative administration of the first dose of ketoprofen had no effect on pain at home in patients who underwent day-case surgery. A follow-up study of 611 children (aged 1–7 years) who un-

derwent adenoidectomy found that the patients who received a higher number of fentanyl doses in hospital experienced greater pain intensity at home ( $p < 0.001$ ); no such association existed for administration of pre-emptive intravenous ketoprofen and the duration of pain at home, or the number of oral ketoprofen doses needed at home.<sup>[43]</sup> A study in tonsillectomy patients aged 3–16 years found no difference in postoperative analgesic efficacy between preoperative and postoperative low dose (0.5 mg/kg) intravenous ketoprofen administration.<sup>[30]</sup> Intravenous ketoprofen was administered on induction (preoperative group,  $n = 47$ ) or immediately postoperatively ( $n = 42$ ); a placebo group ( $n = 20$ ) was also included. All patients also received three doses of intravenous ketoprofen 1 mg/kg over the first 24 hours after surgery, i.e. a total dose of 3 mg/kg/24 hours in the placebo group and 3.5 mg/kg/24 hours in the active groups.<sup>[30]</sup> In the preoperative, postoperative, and placebo groups, rescue analgesia was required in 89%, 86%, and 95% of patients.<sup>[30]</sup>

In three placebo-controlled studies in children undergoing adenoidectomy,<sup>[39,41,42]</sup> similar postoperative pain relief with ketoprofen was observed in the intravenous and intramuscular routes of administration<sup>[41]</sup> and in the intravenous and rectal routes,<sup>[39]</sup> and diminished postoperative pain scores were observed with an intravenous formulation compared with an oral syrup formulation.<sup>[42]</sup> Two<sup>[39,42]</sup> of these studies confirmed that intravenous ketoprofen provided greater pain relief compared with placebo (tables II and III).

In children undergoing tonsillectomy, there was a trend toward superior analgesic efficacy with intravenous ketoprofen 2 mg/kg (administered after induction of anesthesia) compared with placebo during the first 6 hours after tonsillectomy in children and adolescents aged 9–15 years in a randomized, double-blind, active- and placebo-controlled study ( $n = 45$ ).<sup>[25]</sup> The number of patient-administered fentanyl doses was less in the ketoprofen-treated children ( $n = 15$ ) than in the placebo recipients ( $n = 15$ ) during the first 6 hours after surgery (10 vs 14 doses;  $p = 0.049$ ) [primary endpoint].<sup>[25]</sup> VAS pain scores were also lower with ketoprofen during the first 6 hours after surgery ( $p < 0.05$  vs placebo). Between 6 and 24 hours postoperatively, ketoprofen was no more effective in pain relief than placebo. In this study, intravenous ketoprofen provided better postoperative analgesia than intravenous tramadol 1 mg/kg (as a preoperative loading dose then again postoperatively as a 6-hour infusion at the same dose) [ $n = 15$ ]; the mean number of patient-administered fentanyl doses was 22 for the tramadol group compared with 10 for the ketoprofen group ( $p = 0.035$ ).<sup>[25]</sup> VAS pain scores were also lower ( $p < 0.05$ ) in the intravenous ketoprofen group compared with the intravenous tramadol group during the first 6 postoperative hours. In fact, relative to

**Table II.** Study design and dose and administration details for studies of intravenous (IV) ketoprofen (KET) as a postoperative analgesic in children undergoing an adenoidectomy

| Study (y)                                   | Study design  | No. of patients (age range [y])                              | Treatment and dosage                                                | Administration                                                                              | Timing of administration                    |
|---------------------------------------------|---------------|--------------------------------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------|
| Kokki et al. <sup>[38]</sup> (1998)         | r, db, pc     | 55 (1.3–6.6)<br>55 (1.5–6.2)<br>55 (1.3–7.1)<br>55 (1.3–6.0) | IV KET 0.3 mg/kg<br>IV KET 1.0 mg/kg<br>IV KET 3.0 mg/kg<br>Placebo | 5-min injection in 10 mL NaCl 0.9%                                                          | Preoperatively, postinduction               |
| Nikanne et al. <sup>[40]</sup> (1997)       | r, db         | 54 (1.0–7.6)<br>53 (1.2–7.3)                                 | IV KET 2.0 mg/kg<br>IV KET 0.5 mg/kg                                | 10-min injection in 10 mL NaCl 0.9%                                                         | Preoperatively, postinduction               |
| Nikanne et al. <sup>[28]</sup> (1997)       | r, db, pc     | 80 (1.0–9.3)<br>84 (0.8–7.9)                                 | IV KET 2.0 mg/kg<br>Placebo                                         | Loading dose 5-min injection in 10 mL NaCl 0.9% followed by 2-h infusion in 40 mL NaCl 0.9% | Loading dose: preoperatively, postinduction |
| Kokki et al. <sup>[39]</sup> (2000)         | r, db, dd, pc | 42 (1.3–8.1)<br>42 (1.4–7.5)<br>39 (1.2–6.1)                 | IV KET 25 mg<br>PR KET 25 mg<br>Placebo                             | 5-min injection in 10 mL NaCl 0.9%<br>Suppository, buttocks taped                           | Preoperatively, postinduction               |
| Tuomilehto and Kokki <sup>[41]</sup> (2002) | r, db, dd, pc | 40 (1.3–6.3)<br>40 (1.0–8.3)<br>40 (1.3–7.1)                 | IV KET 2 mg/kg<br>IM KET 2 mg/kg<br>Placebo                         | 5-min injection in 10 mL NaCl 0.9%<br>IM injection in left deltoid muscle                   | Preoperatively, postinduction               |
| Tuomilehto et al. <sup>[42]</sup> (2000)    | r, db, dd, pc | 40 (1.3–6.8)<br>40 (1.7–8.4)<br>20 (1.3–8.4)                 | IV KET 1.0 mg/kg<br>PO KET 1.0 mg/kg<br>Placebo                     | 5-min injection in 10 mL NaCl 0.9%<br>1 mg/mL syrup                                         | Postinduction, preoperatively               |

**db** = double-blind; **dd** = double-dummy; **IM** = intramuscular; **NaCl** = sodium chloride; **pc** = placebo-controlled; **PO** = oral; **PR** = rectal; **r** = randomized.

placebo and in contrast to ketoprofen, intravenous tramadol had no analgesic efficacy at any timepoint (0–6 hours, 6–12 hours, 12–18 hours, or 18–24 hours postoperatively).<sup>[25]</sup>

In summary, the available pediatric data indicate that intravenous ketoprofen doses of  $\geq 0.3$  mg/kg and enteral ketoprofen doses of 1 mg/kg provide sufficient analgesia in children undergoing adenoidectomy, but in children with tonsillectomy, higher doses of intravenous ketoprofen and rescue analgesia with opioid analgesics (in addition to ketoprofen) are often needed to provide sufficient analgesia. No ceiling effect has been shown with ketoprofen at a single dose of up to 3 mg/kg.<sup>[38]</sup>

#### Ocular Surgery

Two randomized, double-blind, placebo-controlled studies evaluated intravenous ketoprofen in children and adolescents aged 1–15 years undergoing strabismus surgery.<sup>[27,29]</sup> The worst postoperative pain (assessed using the Maunukela scale<sup>[24]</sup>) was less severe with intravenous ketoprofen 2 mg/kg compared with placebo (3/10 vs 5/10;  $p=0.035$ ), and ketoprofen provided a small advantage in terms of the use of rescue analgesia (number of fentanyl doses: 1 vs 2;  $p=0.047$ ) in one study.<sup>[29]</sup> In the second study, no additional postoperative pain relief

was achieved with add-on intravenous ketoprofen 1 mg/kg (an initial dose administered at induction of anesthesia and a second dose 3 hours later) to preoperative oral acetaminophen (24 mg/kg).<sup>[27]</sup> However, the worst pain experienced by patients in the PACU (assessed using the Maunukela scale<sup>[24]</sup>) was less severe in the ketoprofen ( $n=30$ ) than the placebo ( $n=29$ ) recipients ( $p=0.035$ ).<sup>[27]</sup> There was a trend toward less use of rescue fentanyl in the first 2 hours after surgery in the group receiving ketoprofen (1 vs 2 doses;  $p=0.047$ ).

Intravenous ketoprofen 2 mg/kg had similar analgesic efficacy to intravenous pethidine 1 mg/kg in a randomized, single-blind study in pediatric patients undergoing vitreoretinal surgery where the study drugs were administered before induction of anesthesia to provide intra- and postoperative analgesia.<sup>[44]</sup> Postoperatively, 6/44 (14%) children in the ketoprofen group had pain during the first 24 postoperative hours compared with 17/42 (40%) children in the pethidine group ( $p<0.01$ ). However, pain at 2, 6, and 24 hours and the need for rescue analgesia were no different between the two groups.<sup>[44]</sup>

#### Major Surgery

Intravenous ketoprofen 1 mg/kg (10-minute injection) as a loading dose after induction of anesthesia followed by a

4 mg/kg/24-hour infusion for up to 24–72 hours had superior postoperative analgesic efficacy to placebo when given as adjuvant treatment to epidural sufentanil analgesia after major surgery in two randomized, double-blind studies in children and adolescents aged 1–15 years (figure 2).<sup>[31,32]</sup> Patients had either major thoracic, abdominal, genitourinary, or orthopedic surgery.<sup>[31,32]</sup>

In the first study, fewer intravenous ketoprofen-treated children needed rescue analgesia than those receiving placebo for background analgesia (none of 29 patients vs 8 of 29 patients;  $p=0.0004$ ).<sup>[31]</sup> In the second study, the use of adjuvant ketoprofen ( $n=24$ ) significantly reduced the amount of epidural sufentanil needed for adequate analgesia; the mean total dose of sufentanil was 8.3  $\mu\text{g/kg}$  in the ketoprofen group compared with 12.5  $\mu\text{g/kg}$  in the placebo group ( $n=23$ ) [ $p=0.002$ ]. Twelve per cent of ketoprofen recipients and 17% of placebo recipients required rescue medication with epidural bupivacaine.<sup>[32]</sup> In the first study, the between-group difference for this

efficacy endpoint was not significant due to the low power of the study.<sup>[31]</sup> However, in both studies, more ( $p<0.05$ ) patients receiving ketoprofen than placebo met the criteria for termination of epidural sufentanil before the planned end of the 72-hour study period (figure 2).<sup>[31,32]</sup> In both studies, there was a good correlation between the observed (11-point Maunukela scale) and expressed (100 mm VAS) pain scores.<sup>[31,32]</sup> Where reported, pain at rest was not different between ketoprofen and placebo groups.<sup>[31,32]</sup> In fact, in one study, pain scores at rest were very low in both treatment groups (median score 0 for both groups at 24, 48, and 72 hours after surgery);<sup>[31]</sup> however, ketoprofen provided better pain relief than placebo during activity, and dynamic pain scores were lower at 24 hours ( $p=0.01$ ) and 72 hours ( $p=0.033$ ) after surgery.<sup>[31]</sup>

In another study evaluating the efficacy of intravenous ketoprofen in 31 children and adolescents (aged 10–15 years) undergoing chest-wall correction surgery,<sup>[45]</sup> ketoprofen (1 mg/kg at 0, 8, and 16 hours postoperatively) was shown to provide

**Table III.** Efficacy of intravenous (IV) ketoprofen (KET) as a postoperative analgesic in studies of children undergoing an adenoidectomy

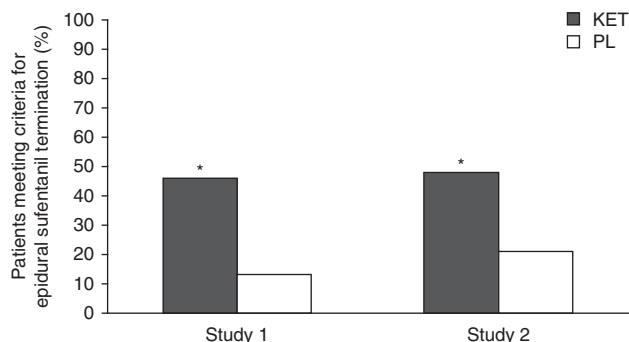
| Study (y)                                                | Treatment group <sup>a</sup> | Rescue analgesia |                           | Maunukela pain score <sup>[24]</sup><br>at rest/swallowing |                     | Overall efficacy                     |
|----------------------------------------------------------|------------------------------|------------------|---------------------------|------------------------------------------------------------|---------------------|--------------------------------------|
|                                                          |                              | % of patients    | no. of doses <sup>b</sup> | worst in PACU                                              | on discharge        |                                      |
| Kokki et al. <sup>[38]</sup> (1998), <sup>c</sup>        | IV KET 0.3                   | 65**             | 1.0 (1.1)                 | 3 (0–8)/4 (0–8)                                            | 0 (0–1)/0 (0–3)     | IV KET 0.1, 0.3, 3.0 > PL;           |
| Kokki H, personal observation                            | IV KET 1.0                   | 62***            | 0.9 (0.9)                 | 2 (0–8)/3 (0–8)                                            | 0 (0–1)/0 (0–2)     | IV KET 0.1 = IV KET 0.3 = IV KET 3.0 |
|                                                          | IV KET 3.0                   | 53***            | 0.7 (0.8)                 | 1* (0–8)/3 (0–8)                                           | 0 (0–0)/0 (0–1)     |                                      |
|                                                          | PL                           | 82               | 1.7 (1.1)                 | 4 (0–8)/5 (0–8)                                            | 0 (0–1)/0 (0–1)     |                                      |
| Nikanne et al. <sup>[40]</sup> (1997) <sup>b</sup>       | IV KET 2.0                   | 50               | 0.7 (0.8)                 | 2.5 (2.9)/3.1 (2.9)                                        | 0.2 (0.8)/0.2 (0.8) | KET 2.0 = KET 0.5                    |
|                                                          | IV KET 0.5                   | 47               | 0.7 (0.8)                 | 2.4 (2.6)/2.8 (2.9)                                        | 0.1 (0.4)/0.2 (0.5) |                                      |
| Nikanne et al. <sup>[28]</sup> (1997) <sup>b</sup>       | IV KET 2.0                   | 64**             | 1.0* (1.1)                | 1.9* (2.4)/2.9** (2.7)                                     | 0.2 (0.5)/0.4 (0.8) | KET > PL                             |
|                                                          | PL                           | 77               | 1.5 (1.1)                 | 2.9 (2.7)/4.5 (2.9)                                        | 0.3 (1.0)/0.6 (1.3) |                                      |
| Kokki et al. <sup>[39]</sup> (2000) <sup>a</sup>         | IV KET 25                    | 67               | 1.3 (1.2)                 | 4 (0–8)/5 (1–8)                                            | 0 (0–1)/0 (0–2)     | IV KET = PR KET > PL                 |
|                                                          | PR KET 25                    | 64               | 1.2* (1.2)                | 4 (1–8)/5 (1–8)                                            | 0 (0–1)/0 (0–2)     |                                      |
|                                                          | PL                           | 85               | 2.2 (1.4)                 | 5 (0–8)/6 (1–8)                                            | 0 (0–1)/1 (0–2)     |                                      |
| Tuomilehto and Kokki <sup>[41]</sup> (2002) <sup>a</sup> | IV KET 2.0                   | 63               | 1.3 (1.2)                 | 2 (0–6)/3* (0–7)                                           | 0 (0–1)/0 (0–1)     | IV KET = IM KET > PL                 |
|                                                          | IM KET 2.0                   | 68               | 1.2 (1.2)                 | 3 (0–6)/3 (0–7)                                            | 0 (0–2)/0 (0–2)     |                                      |
|                                                          | PL                           | 88               | 1.8* (1.2)                | 5 (0–7)/6 (0–8)                                            | 0 (0–1)/0 (0–2)     |                                      |
| Tuomilehto et al. <sup>[42]</sup> (2000) <sup>a</sup>    | IV KET 1.0                   | 75               | 1.1* (0.9)                | 4 (0–8)/5 (0–8)                                            | 0 (0–1)/0 (0–2)     | IV KET > PO KET = PL                 |
|                                                          | PO KET 1.0                   | 70               | 1.5 (1.2)                 | 5 (0–8)/7 (0–8)                                            | 0 (0–2)/0 (0–3)     |                                      |
|                                                          | PL                           | 75               | 1.7 (1.3)                 | 3 (0–9)/6 (0–9)                                            | 0 (0–2)/0 (0–3)     |                                      |

a See table II for dosage units and administration details.

b Data are mean values (SD) for number of rescue analgesia doses and pain scores.

c Data are median values (10th–90th percentiles) for pain scores.

**IM** = intramuscular; **PACU** = post-anesthesia care unit; **PL** = placebo; **PO** = oral; **PR** = rectal; = indicates similar efficacy; > indicates greater efficacy. \*  $p \leq 0.05$ , \*\*  $p \leq 0.01$ , \*\*\*  $p \leq 0.001$  vs PL; †  $p < 0.05$  vs active comparator.



**Fig. 2.** The proportion of patients who met the criteria for termination of epidural sufentanil in the 72-hour study period in two randomized, double-blind studies in patients aged 1–15 years undergoing major surgery.<sup>[31,32]</sup> Patients received intravenous ketoprofen (KET; 1 mg/kg in 10 mL of 0.9% saline loading dose, followed by an infusion of 4 mg/kg in 50 mL of 0.9% saline over 24 hours for up to 72 hours) or placebo (PL; similar volume of 0.9% saline for loading dose and infusion). The criterion for termination was a visual analog scale score of <30 mm (100 mm scale) for 6 hours with an epidural sufentanil infusion rate of 0.03 µg/kg/h. The number of evaluable patients in study 1 was 24 in the KET group and 23 in the PL group,<sup>[32]</sup> and in study 2 it was 29 in both groups.<sup>[31]</sup> See section 2.2.1 for further regimen details. \*  $p < 0.05$  vs PL.

an opioid-sparing effect and improved analgesia versus placebo. The mean cumulative 24-hour morphine dose used was 490 µg/kg with ketoprofen and 670 µg/kg with placebo ( $p = 0.03$ ) and the AUC for pain was lower with ketoprofen compared with placebo ( $p = 0.026$ ).

### 2.2.2 Intramuscular Administration

In a randomized, double-blind study (method of randomization not defined), a single dose of intramuscular ketoprofen 1 mg/kg administered after induction of anesthesia was a more effective analgesic in the early postoperative period (<1 hour after surgery) than placebo in children (mean age 8.5 years; range 4–12 years) undergoing ophthalmic surgery.<sup>[46]</sup> Objective pain scale scores<sup>[47]</sup> were lower ( $p < 0.05$ ) in the ketoprofen group ( $n = 61$ ) than in the placebo group ( $n = 10$ ) at all time-points up to 30 minutes after surgery, and were similar thereafter. In the same study, intramuscular pethidine 1 mg/kg ( $n = 20$ ) was no more effective than placebo during the first 30 minutes after surgery.<sup>[46]</sup> Median pain scores were the same (0) in the pethidine and placebo groups at 45 and 60 minutes. By 60 minutes after surgery, 75% of placebo-treated children had received rescue analgesia, compared with only 35% of ketoprofen-treated children ( $p < 0.01$ ).<sup>[46]</sup>

### 2.2.3 Rectal Administration

The efficacy of postoperative rectal ketoprofen ( $n = 42$ ) was compared with that of rectal acetaminophen ( $n = 41$ ) in con-

trolling postoperative pain in a randomized, single-blind, multicenter study in children and adolescents aged 6–14 years undergoing minor surgery requiring standard epidural anesthesia.<sup>[33]</sup> Ketoprofen was dosed by bodyweight, with patients <30 kg receiving 30 mg and those over 30 kg receiving 60 mg ketoprofen. Acetaminophen was given as a 500 mg rectal dose. Although the decrease from baseline in mean pain scores (measured using a 100 mm VAS) over the 8 hours post-dose was greater with rectal ketoprofen than rectal acetaminophen ( $p < 0.008$ ), no conclusion regarding the efficacy of rectal ketoprofen in this indication should be drawn from this study as there were several study protocol violations, an unclear description of evaluable patient numbers for which results were presented, and a lack of data on the use of rescue analgesia (a second dose of study drug).<sup>[33]</sup>

### 2.2.4 Oral Administration

Children often require pain management on their return home after common day-case surgical procedures such as adenoidectomy and tonsillectomy. The main problem after tonsillectomy is significant pain that may last 9 days or longer after surgery. The use of oral ketoprofen has been assessed in an ambulatory, post-surgical setting in open-label, prospective, noncomparative, follow-up studies of patients who had previously participated in intravenous ketoprofen studies involving patients undergoing adenoidectomy<sup>[37]</sup> or tonsillectomy<sup>[48]</sup> (see section 2.2.1).

Oral ketoprofen alone did not provide sufficient pain relief for most children during the first week after tonsillectomy.<sup>[48]</sup> Most patients required rescue analgesia with acetaminophen or acetaminophen-codeine (85% of 102 patients) in the first week (median number of doses of rescue analgesia was 10 [range 0–38 doses]). During most of that first week, patients experienced significant postoperative pain in the morning before the first ketoprofen dose (the VAS pain score at rest was >30 mm, and on swallowing was >50 mm). Although pain was less severe during the evening after drug administration, no statistical comparisons were made in this qualitative study.<sup>[48]</sup> Most patients took their medication as recommended by the study investigators for the first 5 days as follows: oral ketoprofen 25 mg tablets, or 50 or 100 mg capsules in divided doses, to a total dose of 3–5 mg/kg/day; the median number of ketoprofen doses during the first week was 21 (range 5–27). Thereafter, the study drug was given as required.<sup>[48]</sup> Most patients returned to normal daily activities and experienced pain cessation on postoperative day 9.

In the second follow-up study, the majority of caregivers (88% of 522) rated oral ketoprofen 5 mg/kg/day (median [range

10th and 90th percentiles] of 4 [1–10] doses) on an as needed basis as a ‘sufficient’ analgesic in the first week after an adenoidectomy.<sup>[37]</sup> Only 73 (14%) children received some other analgesic in addition to ketoprofen.

In summary, oral ketoprofen 5 mg/kg/day for 2–3 days provides sufficient analgesia in children after adenoidectomy, but in children undergoing tonsillectomy, rescue analgesia may be required, because, in most patients, oral ketoprofen alone does not provide sufficient analgesia.

## 2.3 Inflammatory Conditions

### 2.3.1 Oral Administration

Ketoprofen has been investigated for control of pain and inflammation in juvenile rheumatoid arthritis in a 4-week open-label study.<sup>[49]</sup> Children received oral ketoprofen 100 mg/m<sup>2</sup>/day (approximately 3 mg/kg/day) and increased as required up to 320 mg/m<sup>2</sup>/day. Improvements from baseline were observed in the number of joints with pain, the severity of joint pain on motion, the duration of morning stiffness, and the time required to walk 15 meters ( $p < 0.035$ ).<sup>[49]</sup>

### 2.3.2 Topical Administration

Ketoprofen is also available in topical form as a gel but is not approved for use in children. A case report has described the use of ketoprofen gel in an 8-year-old girl with Sever’s disease – an overuse syndrome affecting the heel.<sup>[50]</sup> Ketoprofen gel improved pain, function, and range of motion, and the girl was able to return to usual activities in a shorter time than was expected without the gel.<sup>[50]</sup> There are no data regarding the use of topical ketoprofen in juvenile rheumatoid arthritis or other indications.

## 3. Safety/Tolerability Issues

Since there are no pooled analyses of safety data or post-marketing surveillance studies, this section provides an overview of safety data reported in the clinical trials discussed in section 2. Some studies focused on the efficacy of ketoprofen and reported only a brief overview of adverse events, and most of the trials were of insufficient size to detect rare adverse events; however, postmarketing surveillance data indicate that ketoprofen has a favorable safety profile.<sup>[21,22]</sup>

Ketoprofen was generally well tolerated in infants and children receiving single doses of the drug for fever<sup>[20,21,23]</sup> and in those undergoing various surgical procedures.<sup>[15,25–33,38–40,42,44,46,51]</sup> No systemic adverse events were reported in two single-dose studies in patients with fever and pain associated with acute in-

flammatory conditions, and therefore these trials are not discussed further in this section.<sup>[23]</sup>

In the randomized, comparative, antipyretic efficacy trial involving 301 children and adolescents aged 1–14 years of age, no adverse event, other than vomiting, was reported. Vomiting after single, oral doses of ketoprofen 0.5 mg/kg, acetaminophen 15 mg/kg, or ibuprofen 10 mg/kg occurred early (<6 hours) in 14% (10/74), 4% (3/77), and 10% (5/52), and late (6–48 hours) in 3% (2/74), 1% (1/77), and 6% (3/52) of patients, respectively.<sup>[20]</sup> The differences between groups were not significant. With ketoprofen (but not acetaminophen or ibuprofen), there was a significantly greater incidence of vomiting in the early period than the late period (ten vs two patients;  $p < 0.021$ ), but the investigators could not discount the potential of underlying infection as a contributing factor.<sup>[20]</sup> The taste of the formulation is an important factor for compliance in pediatric pharmacotherapy, and the acceptability of the NSAID formulations could have affected the incidence of vomiting. Unfortunately, this was not reported in the article. In studies in children undergoing tonsillectomy or adenoidectomy, up to one-fifth of patients (20% of 522<sup>[37]</sup> and 15% of 102<sup>[48]</sup>) had difficulty in swallowing the oral ketoprofen tablet/capsule or found the taste to be unpleasant. This was more common in children under 48 months of age in the adenoidectomy study.<sup>[37]</sup> Alteration of taste perception has been reported with analgesic agents, but the specific mechanisms in NSAIDs (including ketoprofen) are unknown.

In studies involving postoperative pain management<sup>[15,42]</sup> and in phase III studies<sup>[21,22]</sup> in the management of fever, a high taste acceptability of ketoprofen syrup has been shown and this appears to persist with repeated dosing. In children undergoing adenoidectomy, 5% (27/555) reported ketoprofen tablets as bad-tasting during the first days after surgery.<sup>[37]</sup> No difference between ketoprofen, ibuprofen, or acetaminophen was observed in taste perception in the early (<6 hours) or late (6–48 hours) period following drug administration in an antipyretic study in children and adolescents.<sup>[20]</sup>

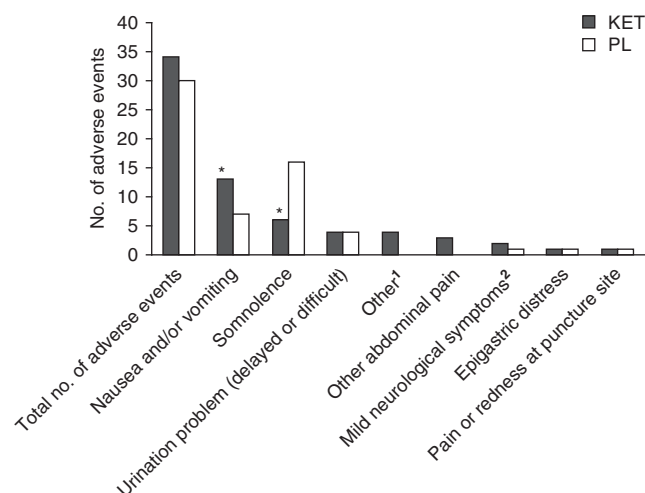
In the two dose-ranging studies on ketoprofen oral syrup in patients with fever, adverse events related to treatment were infrequent (5% and 2% of patients in the infant and children studies, respectively), mild to moderate, and transient.<sup>[21]</sup> There was no apparent dose response with respect to the incidence of adverse events. Adverse events included gastrointestinal disturbances (diarrhea in 6% [15/250] and vomiting in 6% [16/250]) and transient low body temperature measurements. There were no withdrawals due to adverse events.

The favorable safety profile of oral ketoprofen in the treatment of fever in infants and children was also seen in the two

phase III studies.<sup>[22]</sup> In one study involving infants and children aged 1–6 years, there were five severe adverse events (one in the ketoprofen 0.5 mg/kg group [0.7%] and four in the ibuprofen 5 mg/kg group [3%]). There were three adverse events reported as serious: one ketoprofen recipient developed facial edema and another presented with bloody diarrhea (later diagnosed to have *Salmonella typhi* gastroenteritis), and one ibuprofen recipient with erythema infectiosum developed dehydration due to protracted vomiting and thus required hospitalization (1.4% vs 0.7%). Ten patients withdrew due to adverse events (five from each group). Ten patients in the ketoprofen group (7%) and 11 patients in the ibuprofen group (8%) experienced drug-related adverse events. These were primarily gastrointestinal disturbances and all were transient and of mild to moderate intensity.<sup>[22]</sup> Similar data were observed in the second phase III study where the frequency and nature of drug-related adverse events was similar in the ketoprofen 0.5 mg/dose and acetaminophen 15 mg/dose groups (9% vs 9%, respectively). No cases of serious adverse events were reported in the ketoprofen group, but two children in the acetaminophen group had serious adverse events (one developed a febrile seizure and another developed acute pyelonephritis requiring hospitalization). Four patients in the ketoprofen group and two in the acetaminophen group withdrew due to adverse events.<sup>[22]</sup>

In studies in the postoperative setting, the most frequent adverse events in patients receiving ketoprofen perioperatively were postoperative nausea and vomiting (PONV), which affect up to 50% of patients taking ketoprofen.<sup>[25–32,38–40,42,51]</sup> Common adverse events from a trial in pediatric patients undergoing an adenoidectomy who received an intravenous bolus of ketoprofen 1 mg/kg followed by a 2-hour infusion of ketoprofen 1 mg/kg, or who received placebo are shown in figure 3.<sup>[28]</sup> Common systemic adverse events with ketoprofen are similar to those observed with other NSAIDs.<sup>[20]</sup> Major gastrointestinal effects, such as peptic ulceration or gastrointestinal hemorrhage, rarely occur with ketoprofen in the pediatric population.<sup>[17]</sup> The reasons for the lower risk of ketoprofen-related serious gastrointestinal events seen in infants and children, compared with adults, are not fully understood. In adults, the bleeding/perforation risk is highest during the first week of treatment, thus the duration of use is not likely to explain the difference in risk.<sup>[52]</sup> However, serious gastrointestinal complications have also been reported very rarely with other NSAIDs in the pediatric population. Clinicians and caregivers should be made aware of the risk of gastrointestinal bleeding so that prompt action can be taken should any suggestive symptoms arise.

The incidence of adverse events did not appear to be dose-related in single-dose studies investigating intravenous keto-



**Fig. 3.** Tolerability profile of intravenous ketoprofen (KET) compared with placebo (PL) [ $n=84$ ] in pediatric patients undergoing an adenoidectomy.<sup>[28]</sup> The frequency of adverse events occurring while patients were in the post-anesthesia care unit in a randomized, double-blind study in children aged 1–7 years are presented. In the KET group ( $n=80$ ), patients received a loading dose of intravenous KET 1 mg/kg injected over 10 minutes after the induction of anesthesia, followed by intravenous KET at the same dose given as a 2-hour infusion (total dose 2 mg/kg). <sup>1</sup> 'Other' adverse events were shivering, irritability, and breath weakness. <sup>2</sup> Mild neurological symptoms were cephalalgia, vertigo, and visual disturbance. \*  $p < 0.05$  vs PL.

profen doses between 0.3 and 3.0 mg/kg in the perioperative setting.<sup>[38,40]</sup> The route of administration did not influence the nature, severity, or incidence of adverse events; the tolerability of oral ketoprofen 1 mg/kg was similar to that of intravenous ketoprofen 1 mg/kg in patients undergoing an adenoidectomy,<sup>[42]</sup> and the tolerability of intravenous ketoprofen 2 mg/kg<sup>[51]</sup> or 25 mg<sup>[39]</sup> was considered to be similar to that of intramuscular ketoprofen 2 mg/kg<sup>[51]</sup> and that of rectal ketoprofen 25 mg.<sup>[39]</sup>

Adverse events occurred in 14–44% of ketoprofen recipients, compared with 16–40% of placebo recipients,<sup>[28,30,38,39,42,51]</sup> and, with a few minor exceptions (see also section 3.1), the type and incidence of adverse events were generally not different between treatment groups (figure 3). In one study in pediatric adenoidectomy patients, PONV occurred more frequently in intravenous ketoprofen 2 mg/kg than placebo recipients (16% vs 8%;  $p=0.018$ ), but somnolence occurred in more placebo than ketoprofen recipients (19% vs 7%;  $p=0.013$ ).<sup>[28]</sup> In a study in patients undergoing combined spinal-epidural anesthesia for major surgery, postoperative fever (a non-opioid adverse event) occurred in fewer intravenous ketoprofen than placebo recipients; this difference was attributed to the antipyretic effect of the drug.<sup>[32]</sup>

Where reported, there were no serious adverse events in the ketoprofen or comparator groups in the majority of studies

(data on intra- and postoperative bleeding are reported separately).<sup>[28,30,33,38,40]</sup> Discharge was delayed by 5–7 hours because of excessive sedation, severe pain, or protracted vomiting in seven<sup>[39]</sup> and six<sup>[41]</sup> ketoprofen recipients, and in one<sup>[39]</sup> and five<sup>[41]</sup> placebo recipients. However, in two studies, three children required hospitalization: one each from the rectal ketoprofen,<sup>[39]</sup> intramuscular ketoprofen, and placebo groups.<sup>[41]</sup> Postoperative adverse events requiring hospital admission in children undergoing strabismus surgery were vomiting in one patient and sedation in another; both patients had received combination therapy with ketoprofen and acetaminophen.<sup>[27]</sup> None of these adverse events requiring a delay in discharge or hospitalization were considered to be ketoprofen-related.<sup>[27,39,41]</sup>

There are no data on the use of ketoprofen in children with asthma, but this agent may be used if asthma is not severe.<sup>[36]</sup> Ketoprofen is contraindicated in patients who have a history of hypersensitivity reactions such as asthmatic attacks or other allergic-type reactions to ketoprofen, aspirin, or other NSAIDs.

### 3.1 Effects on Opioid-Related Adverse Events

NSAIDs may reduce or eliminate the need for opioids, and hence their relative positive impact on adverse events (such as PONV) after surgery in children.<sup>[52]</sup> Since patients consider nausea and vomiting to be among the most undesirable of postoperative outcomes,<sup>[53]</sup> an opioid-sparing regimen would be considered more favorable. A reduction in the incidence of opioid-related adverse events, associated with a reduced need for opioids, was demonstrated in some ketoprofen studies.

Opioid-associated adverse events occurred less often with perioperative intravenous ketoprofen than with placebo in a study in patients undergoing combined spinal-epidural anesthesia for major surgery.<sup>[31]</sup> Those receiving ketoprofen ( $n = 29$ ) received no rescue analgesia (bupivacaine) versus 8 of 29 children in the placebo group.<sup>[31]</sup> In patients receiving ketoprofen, there was a total of 16 opioid-associated adverse events (nausea/vomiting, oxygen desaturation [a measure of respiratory depression], low respiratory rate, difficulty in passing urine, and disturbed sleep) compared with 24 adverse events in the placebo group ( $p = 0.023$ ), and there was less pruritus in the ketoprofen group compared with the placebo group (4 vs 13 cases;  $p = 0.009$ ).<sup>[31]</sup> In a second, similarly designed study, the only opioid-related adverse event to occur less often with ketoprofen than with placebo ( $p = 0.035$ ) was oxygen desaturation, and this difference was attributed to the increased need for epidural sufentanil in the group receiving placebo;<sup>[32]</sup> however, ketoprofen may have also had direct protective effects on opioid-induced respiratory depression. In

a double-blind, randomized study in healthy male volunteers, respiratory depression was less marked with ketoprofen monotherapy, or ketoprofen plus morphine combination therapy than with morphine alone; thus ketoprofen was shown to have a direct protective effect on opioid-induced respiratory depression.<sup>[54]</sup>

Ophthalmologic surgery is associated with a high incidence of PONV, and opioids are often withheld for this reason.<sup>[36]</sup> PONV is very common in children having strabismus surgery. In studies that investigated the use of intramuscular or intravenous ketoprofen for pain relief following strabismus surgery, the incidence and frequency of PONV was lower among ketoprofen-treated children and thus their return to normal activities of daily living was enhanced compared with that of placebo-treated children. The reduction in PONV with ketoprofen was most likely attributable to an opioid-sparing effect.<sup>[27,29]</sup> In one study, fewer intravenous ketoprofen recipients experienced postoperative vomiting than placebo recipients (17% vs 41%;  $p = 0.036$ ).<sup>[29]</sup> In the other study, the rate of PONV was lower with ketoprofen and acetaminophen versus acetaminophen alone in the first 24 hours after surgery, but the power of the study was too low to show a significant difference (30% vs 48%;  $p = 0.15$ ).<sup>[27]</sup> Both of these studies were performed in patients undergoing strabismus surgery, a procedure associated with a high incidence of PONV.

Compared with intravenous pethidine, intravenous ketoprofen was associated with a lower ( $p < 0.05$ ) incidence of PONV up to 24 hours after vitreoretinal surgery when the drugs were administered perioperatively.<sup>[44]</sup> No such difference was observed when intramuscular pethidine was compared with intramuscular ketoprofen.<sup>[46]</sup>

The lack of difference in the incidence of PONV between active treatment and placebo in some studies was attributed to the multifactorial causes of PONV, and may have been confounded by the relatively high use of rescue opioids in the ketoprofen and active comparator groups (acetaminophen<sup>[26]</sup> and tramadol<sup>[25]</sup>).

### 3.2 Intra- and Postoperative Bleeding

NSAIDs are contraindicated in children with bleeding disorders<sup>[3]</sup> because the suppression of prostaglandin synthesis can disrupt the cytoprotective effect of prostaglandins on the mucosal lining leading to gastrointestinal erosions and ulceration, and can also disrupt their involvement in normal platelet function and thus lead to abnormal bleeding.<sup>[3]</sup> Fears regarding an increased risk of blood loss during surgery and increased risk of postoperative bleeding because of NSAID-induced platelet

dysfunction have limited the use of NSAIDs,<sup>[36]</sup> particularly in surgeries such as tonsillectomy where hemorrhage is a serious potential complication.<sup>[52]</sup> Data on ketoprofen in patients who underwent a tonsillectomy are limited to two studies;<sup>[25,30]</sup> thus, the safety of ketoprofen for use as a post-tonsillectomy analgesic remains to be established. In one study, although intraoperative blood loss was greater in intravenous ketoprofen 2 mg/kg recipients ( $p=0.029$  vs placebo), none of the patients in the ketoprofen group required surgery due to postoperative bleeding,<sup>[27]</sup> whereas one patient each in the placebo and tramadol 1 mg/kg groups, respectively, required such surgery.<sup>[27]</sup> In the second study, the rate of perioperative bleeding was not increased in patients receiving intravenous ketoprofen 3 mg/kg, but two patients had prolonged bleeding that required electrocautery.<sup>[30]</sup>

With one exception (a child receiving intravenous ketoprofen 2 mg/kg),<sup>[40]</sup> no patients undergoing adenoidectomy experienced postoperative bleeding that required management by further surgery, or that necessitated a delay in discharge, hospitalization, or any other intervention.<sup>[28,38,39,42]</sup> A review of patients participating in studies investigating the efficacy of perioperative ketoprofen for analgesia after an adenoidectomy ( $n=335$ ) [see section 2.2] reported no clinically significant perioperative bleeding or other serious adverse events.<sup>[55]</sup>

### 3.3 Renal Effects

NSAIDs may have an adverse effect on renal function, which is thought to occur via inhibition of renal prostaglandin synthesis, although the exact mechanism is not well understood.<sup>[36]</sup> Administration of intravenous ketoprofen 1 mg/kg as a loading dose followed by a 24-hour infusion of 4 mg/kg over 24 hours in a pharmacokinetic study in children undergoing major surgery was not associated with any clinically significant change in urine output.<sup>[13]</sup>

### 3.4 Bone Healing

One of the concerns with NSAID use in trauma patients and in orthopedic surgery has been the effect of NSAIDs on bone and ligament healing after fractures, sprains, and surgery.<sup>[36]</sup> Experimental studies indicate that the risk for detrimental effects of ketoprofen on bone and ligament healing are unlikely.<sup>[56]</sup> However, there may be significant differences among NSAIDs, and data suggest that indomethacin,<sup>[57]</sup> ketorolac,<sup>[58]</sup> and COX-2 inhibitors<sup>[59]</sup> may adversely affect tissue healing more than other NSAIDs. Moreover, the dose used and the duration of administration may affect tissue healing.<sup>[56]</sup> Al-

though well designed human trials showing clinically important effects of ketoprofen on bone healing are lacking, the experimental data<sup>[56]</sup> suggest that the recommended doses of ketoprofen should not be withheld in children with fractures and bone surgery unless there are specific, proven contraindications.<sup>[36]</sup>

### 3.5 Summary

It is important to remember that the available evidence from the literature on ketoprofen use is generally from healthy pediatric populations, and ketoprofen has not been tested in high-risk patients. As with all NSAIDs, caution is needed in patients with severe concomitant medical conditions, in those with hypotension, hypovolemia, or congestive heart failure, and in those who are renally compromised. Thus, in these high-risk groups and in patients undergoing major surgery with an increased risk for hemorrhage, hypovolemia and hypotension should be corrected, and primary hemostasis should be achieved, before ketoprofen is administered.

### 3.6 Long-Term Tolerability

Follow-up safety/tolerability data on up to 3 weeks of ketoprofen administration are available on >900 children.<sup>[37,43,48,51]</sup> In three follow-up studies of patients enrolled in efficacy studies (see section 2), oral ketoprofen 3–5 mg/kg/day appeared to be well tolerated in patients for up to 3 weeks after adenoidectomy ( $n=822$ ),<sup>[37,43,51]</sup> and for up to 3 weeks after tonsillectomy ( $n=102$ );<sup>[48]</sup> however, further study is required before firm conclusions can be drawn.

The proportions of patients who experienced an adverse event were 63% and 72% in the two adenoidectomy open-label studies<sup>[37,51]</sup> and 47% in the tonsillectomy study.<sup>[48]</sup> In the latter study, most patients also received acetaminophen or acetaminophen-codeine during the first week after surgery (85% of patients).<sup>[48]</sup> The most frequent adverse events among the patients receiving ketoprofen on an as-needed basis during the first 3 weeks after a tonsillectomy (median of 25 doses) were minor bleeding (33 of 56 cases of adverse events), significant bleeding in the tonsillar bed (8 of 56), and excessive sedation (5 of 56). Five of the eight patients with significant bleeding needed electrocautery to stop the bleeding, and one required a blood transfusion. Vomiting and nausea were less common (one case each).<sup>[48]</sup> Somnolence and fever occurred more commonly than nausea or vomiting during the first week after an adenoidectomy (36–42% and 20–29% vs 9–15% of patients, respectively).<sup>[37,51]</sup> Postoperative minor bleeding occurred at home in 3–4% of patients (16 of 522 and 11 of 294); none

**Table IV.** Recommendations for the use of ketoprofen in children.<sup>a</sup> The dose can be repeated after 4–8 hours, up to a maximum dose of 5 mg/kg/24 hours. For severe pain, ketoprofen can be used as part of multimodal pain management in combination with paracetamol (acetaminophen) and/or an opioid and/or local anesthetics and/or other adjuvants

| Indication                                                                     | Route of administration  | Patient age        | Dose                                                           |
|--------------------------------------------------------------------------------|--------------------------|--------------------|----------------------------------------------------------------|
| <b>Pain and fever</b>                                                          | Oral (syrup or tablet)   | ≥6 mo              | 0.5–1 mg/kg                                                    |
|                                                                                | Intravenous              | ≥3 mo              | 0.5–1 mg/kg                                                    |
|                                                                                | Rectal                   | ≥6–36 mo<br>3–13 y | 12.5–25 mg<br>25–50 mg                                         |
| Muscle, joint, tendon pain due to overuse                                      | Topical gel <sup>b</sup> | ≥1 y               | Applied as required                                            |
| <b>Postoperative pain</b>                                                      |                          |                    |                                                                |
| Orthopedic or soft tissue surgery, ocular surgery, tonsillectomy/adenoidectomy | Intravenous              | ≥3 mo              | 1–2 mg/kg                                                      |
|                                                                                | Oral (syrup or tablet)   | ≥1 y               | 1–2 mg/kg                                                      |
|                                                                                | Rectal                   | ≥3 mo              | 5–10 kg bodyweight: 12.5 mg;<br>10–25 kg: 25 mg; >25 kg: 50 mg |
| Major thoracic, abdominal, genitourinary or orthopedic surgery                 | Intravenous              | ≥3 mo              | 1 mg/kg loading dose followed by 4 mg/kg/24 h for up to 72 h   |
| Postoperative pain after discharge from recovery room/hospital                 | Oral                     | ≥1 y               | 3–5 mg/kg/day for 2–5 days and then as required                |

a Also refer to local prescribing information.

b Ketoprofen gel is not indicated in children.

required further intervention, although caregivers of six of these children contacted a physician.

Bearing in mind the risks for postoperative hemorrhage after a tonsillectomy, overall these preliminary long-term data on the safety of oral ketoprofen to manage pain at home after soft tissue surgery are encouraging.

#### 4. Evidence-Based Pediatric Ketoprofen Dosing: Recommendations

Based on the available evidence discussed in the previous sections, recommendations for the use of ketoprofen in children are presented in table IV. Ketoprofen doses can be given every 4–8 hours, up to a maximum of 5 mg/kg over a 24-hour period. In patients with severe pain, ketoprofen can be used as part of a multimodal pain management strategy in combination with acetaminophen, opioids, local anesthetics, and/or other adjuvants.

#### 5. Conclusions

Ketoprofen has been shown to have predictable pharmacokinetics. Although data for ketoprofen use in children are limited, they show that pharmacokinetic characteristics in children can be reliably extrapolated from adult data. In children aged 10–69 months who received rectal, intramuscular,

or oral ketoprofen, pharmacokinetic parameters were similar between formulations. Importantly, studies show that ketoprofen has a favorable CNS pharmacokinetic profile as it passes readily through the blood-CSF barrier.

Pre-emptive administration of an analgesic is thought to limit the pain caused by the stimuli.<sup>[60]</sup> Although the theory of pre-emptive analgesic action of NSAIDs has not been confirmed, it is thought that, to be most effective, NSAIDs must be administered in advance, prior to the establishment of severe pain, to allow sufficient time for absorption and delivery to the peripheral tissues and across the blood-brain barrier to the CNS.<sup>[1,36]</sup> Current data support the use of pre-operative and/or pro-active ketoprofen in terms of pain relief and the need for rescue analgesia. In surgery in which there is an increased risk for bleeding, the first doses should be given only after the primary hemostasis has occurred.

Studies in children with fever aged ≥6 months show that ketoprofen syrup is as effective and well tolerated as acetaminophen and ibuprofen, allowing children a rapid return to daily activities with improvements in sleep quality and appetite.

Evidence shows that oral and parenteral ketoprofen are effective in children for the control of post-surgical pain after soft tissue surgery (tonsillectomy, adenoidectomy), ocular surgery, and after major surgery (genitourinary, thoracic, and orthopedic surgery), although higher doses and rescue medication are often required to achieve effective analgesia.

A consideration with ketoprofen therapy is the acceptability and palatability of oral ketoprofen preparations, specifically the unpleasant taste and the difficulty swallowing the tablets/capsules. Administration of a liquid formulation (syrup) of ketoprofen would overcome problems related to tablet/capsule formulation.

Studies on the overall tolerability of ketoprofen compared with other analgesics when used for postoperative pain control are limited (as are comparative data with other NSAIDs in children), and much of the data are available as data on file only. However, clinical trials in infants and children that involve inadequate pain control, including studies where rescue analgesia is withheld, pose significant ethical issues. In general, ketoprofen was well tolerated in infants and children receiving the drug for pain or fever management, and any adverse effects were of a mild and transient nature. A major tolerability benefit of ketoprofen use is the reduction or elimination of opioid requirement after surgery, resulting in a reduction in the incidence and/or severity of opioid-related adverse events such as PONV – a particular benefit in children. However, PONV remains the most common adverse event with ketoprofen treatment. Although in major ophthalmic surgery, ketoprofen use is associated with a high consumption of rescue analgesic opioids, overall, data suggest that ketoprofen can significantly reduce the intensity of severe pain experienced by patients in the PACU. The significant decrease in the incidence and frequency of PONV seen with ketoprofen even in this setting is considered to be a major health benefit for children. Furthermore, ketoprofen has been shown to have a direct protective effect on opioid-induced respiratory depression and has no adverse effect on tissue healing.

In conclusion, studies to date show that ketoprofen is a safe and effective anti-inflammatory treatment for management of fever and pain in children.

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Correspondence: Professor Hannu Kokki, Department of Anesthesiology and Intensive Care, Kuopio University Hospital, PO Box 1777, FI-70211 Kuopio, Finland.  
E-mail [hannu.kokki@kuh.fi](mailto:hannu.kokki@kuh.fi)