Ibuprofen for Pain Control in Children

New Value for an Old Molecule

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Background: Acute pain is one of the major complaints reported in pediatric emergency departments and general wards. Recently, both the US Food and Drug Administration and European Medicine Agency emitted some warnings regarding the use of opioids, including codeine, in children.

Objective: The aims of this study were summarizing the main pharmacological aspects of ibuprofen, discussing the current evidence about the use of ibuprofen in different and specific clinical settings, and providing a comparison with acetaminophen and/or codeine, according to available studies.

Study Design and Methods: Studies evaluating ibuprofen for the management of acute pain in children were extracted from the PubMed and MEDLINE database within the period ranging from 1985 through 2017. After discussing safety of ibuprofen and its concomitant use with acetaminophen, the specific indications for the clinical practice were considered.

Results: Ibuprofen resulted to be more effective than acetaminophen, and comparable to the combination acetaminophen-codeine, for the control of acute pain related to musculoskeletal pain. Moreover, similar results have been reported also in the management of toothache and inflammatory diseases of the oral cavity and pharynx. Ibuprofen resulted to be useful as a first approach to episodic headache. Finally, the role of ibuprofen in the management of postoperative pain and, particularly, after tonsillectomy and/or adenoidectomy has been reconsidered recently.

Conclusions: Ibuprofen resulted to be the most studied nonsteroidal anti-inflammatory drug in the management of acute pain in children; in general, it showed a good safety profile and provided evidence of effectiveness, despite some differences according to the specific clinical context.

Key Words: acetaminophen, acute pain, codeine, ibuprofen

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According to the definition provided by the International Association for the Study of Pain, pain is “an unpleasant sensory and emotional experience associated to actual or potential tissue damage, or described in terms of such damage.” Pain is a multidimensional clinical phenomenon, as several components (sensory, physiological, cognitive, emotional, behavioral, spiritual) contribute all together to determine how the pain experience is really perceived by the individual.1

Pain evaluation is the first step for an appropriate clinical approach to pain management in pediatrics, and age-related communicative issues are the first barrier to be overcome for a successful treatment. Thus, specific tools have been coined to assess acute pain in children of different ages and in different clinical settings. Of course, the second step is pain relief, and currently, both nonpharmacological and pharmacological methods are available.2

In this narrative review, we aimed at providing the current evidence about the usefulness of ibuprofen in the pharmacological treatment of acute pain in children. Indeed, whereas acetaminophen has been the fundamental therapeutic resource for pediatric pain probably, nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, have been frequently spared because of the fear of some adverse effects, which might be related to an inappropriate use that is medically unsupervised too often.3 Actually, in several clinical settings, ibuprofen resulted to be superior to acetaminophen alone, and its use is getting larger and larger, considering also that several scientific organizations have made statements discouraging the use of “mild opioids,” such as codeine and tramadol, for the treatment of acute pain in children. Indeed, the combined use of acetaminophen and codeine has been associated to some adverse events in children (such as respiratory depression, sedation, nausea and vomiting, constipation).4–8 Moreover, recent studies showed that the administration of codeine in children being “rapid metabolizers,” is associated to respiratory complications, according to the warming first dispatched by the US Food and Drug Administration; eventually, the European Medicine Agency has limited the use of codeine to children older than 12 years, because of the description of several cases of obstructive sleep apnea in children who had undergone tonsillectomy.5

SAFETY PROFILE

Ibuprofen has been indicated for the treatment of mild to moderate acute pain both in children and adults. Analgesic properties of ibuprofen have been linked to its anti-inflammatory activity, through the inhibition of the inducible isoform of the enzyme cyclooxygenase 2 (COX-2), converting arachidonic acid to prostaglandin H2. Importantly, ibuprofen is not a selective COX inhibitor, and therefore, it is not devoid of potential adverse effects deriving from the interference with the activity of non-inducible COX isoform (COX-1). However, as regards the risk of gastrointestinal adverse events (eg, vomiting, gastritis, gastrointestinal bleeding, etc), ibuprofen resulted to be the least toxic NSAIDs in adults, and this finding has been confirmed in children, too.9–8 An important study of pharmacological surveillance by Lesko and Mitchell9 provided fundamental insights into the safety profile of ibuprofen: indeed, they carried out a double-blind randomized clinical trial (DB-RCT) evaluating the risk of hospitalization because of major adverse events related to the use of ibuprofen to control fever, compared with a group receiving acetaminophen. Among 84,192 children (aged 6 months to 12 years) included in this study, only 1% (n = 795) was admitted to the hospital, and actually, almost all developed complications because of the infection causing the febrile disease; indeed, there was no difference between the 2 groups (ibuprofen vs. acetaminophen). As regards very few cases of gastrointestinal bleeding in the ibuprofen group (n = 4, of whom 3 were aged <2 years), the estimated risk resulted to be 7.2 per 100,000 (95% confidence interval [CI], 2–18 per 100,000), which was not statistically different from the acetaminophen group. The risk of gastrointestinal bleeding during therapy with ibuprofen may be caused also by the inhibition of
platelet aggregation, in addition to a direct effect on the gastric mucosa, which probably has discouraged its use in surgical settings. Importantly, in the study by Lesko and Mitchell, among 55,785 children randomized to receive ibuprofen, no cases of anaphylaxis, Reye syndrome, or acute kidney failure were reported.

As regards potential concerns about negative effects of ibuprofen on kidney function, nonselective NSAIDs may inhibit the local prostaglandin production, leading to some hemodynamic consequences; indeed, there could be a constriction of the afferent arteriole of the renal glomerulus, which might promote renal ischemia up to acute tubular necrosis in some circumstances, such as a pronounced hypovolemic status. Thus, based on the medical literature, in children with normal kidney function and effective circulating volume, it is very unlikely that ibuprofen by itself leads to acute kidney injuries. However, the over-the-counter and inappropriate use of NSAIDs can expose pediatric patients to a greater risk of renal complications, as reported by Schaller and Kaplan several years ago. Moreover, an important factor to be considered in the clinical practice is also the combination of ibuprofen with other drugs, including acetaminophen. Actually, the current evidence indicated a relative safety of the acetaminophen + ibuprofen combination therapy for short treatments, but some points must be highlighted in this regard. Both ibuprofen and acetaminophen are known to be metabolized in the liver, but pass through different metabolic pathways, as described below. Five to ten percent of acetaminophen is oxidized to N-acetyl-p-benzoquinoneimine, which resulted to be toxic to both liver and kidney; this compound is detoxified through the conjugation with glutathione and, thus, is excreted by the kidney. However, the inhibition of prostaglandin synthesis by ibuprofen could result also in a reduction of glutathione production, in addition to reducing renal perfusion during hypovolemic conditions, which might lead to an impairment of the detoxification capacity of N-acetyl-p-benzoquinoneimine. Thus, the combination of all these pathophysiological aspects (Fig. 1) could lead to an increased risk of renal toxicity, during the combined use of acetaminophen and ibuprofen. Actually, recent studies showed a reversible reduction of renal function during the combination therapy in dehydrated patients. In conclusion, as the volume depletion resulted to be a recurrent occurrence in patients developing NSAIDs-related nephropathy, caution is recommended with the use of ibuprofen (particularly in combination with acetaminophen) in children with preexisting renal disease and/or at risk of dehydration, as it occurs in respiratory febrile illnesses with increased perspiration and gastrointestinal diseases with increased water loss or impairment of water intake.

In order to complete the discussion on the potential complications of ibuprofen in children, some authors reported its association to the development of necrotizing fasciitis caused by group A Streptococcus pyogenes in children with varicella. Although available studies provided discordant conclusions in this regard, a case-control study supported an increased risk of necrotizing fasciitis in children with varicella receiving ibuprofen (odds ratio [OR], 11.5; 95% CI, 1.4–96.9); moreover, among these complicated cases, an increased prevalence of toxic shock syndrome and acute kidney injury was reported (overall OR, 16; 95% CI, 1.0–825.0). Another perspective study showed an increased risk of any invasive group A streptococcus infection among children receiving ibuprofen (OR, 3.9; 95% CI, 1.3–12), but not acetaminophen (OR, 1.2; 95% CI, 0.50–3.0). Therefore, caution is recommended for the use of ibuprofen to treat pain and fever in children with varicella and impetigo.

Finally, although hypersensitivity cross-reactions to ibuprofen are seen in children with aspirin-sensitive asthma, the use of ibuprofen is considered generally safe in children with asthma.

**CLINICAL USE**

The clinical management of acute pain in children can be summarized through the “3-step” analgesic scale proposed by the World Health Organization: each step corresponds to mild, moderate, and severe pain, respectively. In general, each step is associated to the most appropriate pain drug, as regards analgesic potency: a specific drug therapy is started and, based upon the pain control and the clinical setting, the therapy can be increased.

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**FIGURE 1.** Schematic overview: mechanisms of renal toxicity due to the combined therapy with acetaminophen and ibuprofen.
and safety is quite heterogeneous and is different according to the acute pain in children, actually the current evidence on its efficacy management through ibuprofen-based regimens.6,24,25

Mit physicians to establish the most appropriate pharmacological after the last dose. The knowledge of all these aspects should per-

plished in the liver through P450 cytochrome enzymatic complex; (90% of ibuprofen is 2 to 4 hours, and protein binding is very high is achieved between 90 minutes and 3 hours. Plasmatic half-life tion is slower and variable, as the peak of plasma concentration after 45 to 60 minutes; if ibuprofen is taken after meal, the absorp-

the stomach is empty: the plasma concentration peak is reached

Because of the growing evidence of potential adverse events related to mild opioids in children, as previously described, the combination of acetaminophen and ibuprofen has been consid-

ered for the management of moderate pain. This clinical approach has been used also in children with mild pain being un-

responsive to the monotherapy, and actually, the combination of acetaminophen and ibuprofen could have a role even in the manage-

ment of severe pain with the aim of reducing the dosage of opi-

oids and, as a consequence, the occurrence of adverse events.22,23

The therapeutic scheme of ibuprofen for pain management is

summarized in Table 1, through a comparison with acetaminophen. The recommended dosage of ibuprofen for acute pain is 5 to 10 mg/kg, every 6 to 8 hours; the daily dose must not be greater than 40 mg/kg, regardless of the association to acetaminophen. Ibuprofen must not be administered to infants younger than 3 months; at this age, acetaminophen is the only allowed analgesic.

Indeed, although ibuprofen has been safely used to treat patent ductus arteriosus in preterm and/or low-birth-weight infants, the administration of ibuprofen to infants younger than 3 months to treat inflammatory/febrile illnesses has not been approved, because of lack of enough clinical data and to avoid the risk of masking and/or delaying the diagnosis of serious infections and sepsis (Table 2).

The oral absorption of ibuprofen is rapid, if it is taken when the stomach is empty: the plasma concentration peak is reached after 45 to 60 minutes; if ibuprofen is taken after meal, the absorption is slower and variable, as the peak of plasma concentration is achieved between 90 minutes and 3 hours. Plasmatic half-life of ibuprofen is 2 to 4 hours, and protein binding is very high (90%–99%). The metabolism of ibuprofen is mostly accomplished in the liver through P450 cytochrome enzymatic complex; then, metabolites are cleared through the kidney within 24 hours after the last dose. The knowledge of all these aspects should permit physicians to establish the most appropriate pharmacological management through ibuprofen-based regimens.6,24,25

**MAIN INDICATIONS**

Although ibuprofen is considered an effective drug to treat acute pain in children, actually the current evidence on its efficacy and safety is quite heterogeneous and is different according to the clinical setting. Therefore, in the following paragraphs, a specific discussion for the most common pain syndromes in children, where ibuprofen is found to have a clinical indication, is provided to the reader.

**Sore Throat**

As well as acetaminophen, ibuprofen has been used to treat sore throat in children. Two DB-RCTs (by Bertin et al26 and Schlachtel and Thoden27) evaluated the efficacy of ibuprofen (compared with placebo and acetaminophen), and both drugs were found to be equally effective. Similar conclusions emerged from a recent meta-analysis23 assessing safety and efficacy of ibuprofen and acetaminophen, both in children and adults. Indeed, both drugs were recommended to control this form of pain in several guidelines; however, a routine approach with the combined therapy has not been supported yet, and in those cases with a major exudative component and/or local adenitis, ibuprofen could be preferred because of its inflammatory properties. Moreover, no evidence against the use of ibuprofen during group A streptococcus pharyngitis has emerged so far.28

**Ear Pain**

Ibuprofen has been used to control ear pain in children. Bertin et al29 carried out a DB-RCT including 219 children (aged 1–6 years) with otitis media, and they assessed the outcome after the systematic treatment with ibuprofen for 48 hours. Ibuprofen was compared with acetaminophen, and both showed an equivalent control of ear pain; moreover, in this study, the authors aimed at assessing also the potential impact of ibuprofen on the natural

**TABLE 1. Non-opioid Pharmacological Management of Acute Pain in Children**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ibuprofen</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended dose</strong></td>
<td>5–10 mg/kg</td>
<td>10–15 mg/kg</td>
</tr>
<tr>
<td><strong>Dosing interval</strong></td>
<td>Every 8 h</td>
<td>Every 6 h</td>
</tr>
<tr>
<td>If needed, every 6 h</td>
<td>If needed, every 4 h, in children having weight &gt;20 kg</td>
<td></td>
</tr>
<tr>
<td><strong>Daily maximum dose</strong></td>
<td>30–40 mg/kg per day</td>
<td>60 mg/kg per day (weight &lt;20 kg or if risk factors) 90 mg/kg per day (weight &gt;20 kg)</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Oral</td>
<td>Oral, intravenous, rectal</td>
</tr>
</tbody>
</table>

(step-up) or reduced (step-down). Mild pain is usually treated with non-opioid drugs, such as acetaminophen and/or NSAIDs (in particular, ibuprofen); moderate pain requires mild opioids, which can be associated to acetaminophen or NSAIDs; finally, severe pain is treated with morphine and, if needed, adjuvant drugs (eg, steroids, anticonvulsants, etc) and/or anesthetics.1

<table>
<thead>
<tr>
<th><strong>Clinical Setting</strong></th>
<th>Ibuprofen</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sore throat</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>(Probably, &gt; in exudative forms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear pain</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Toothache</td>
<td>&gt;</td>
<td>&lt;</td>
</tr>
<tr>
<td>Headache</td>
<td>= or &gt;</td>
<td>&lt; or =</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>&gt;</td>
<td>&lt;</td>
</tr>
<tr>
<td>(Minor) surgery pain</td>
<td>= or &gt;</td>
<td>&lt; or =</td>
</tr>
<tr>
<td>Adenoid-tonsillectomy pain</td>
<td>&gt;</td>
<td>&lt;</td>
</tr>
<tr>
<td>(Bleeding risk under evaluation)</td>
<td></td>
<td></td>
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</tbody>
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Post-surgical Pain

The inappropriate management of pain after surgical procedures has been linked to negative and long-term effects on several physical and psychological aspects in children. Unfortunately, it is estimated that 40% to 60% of pediatric cases of pain syndromes after surgery are still undertreated. Indeed, in pediatrics, the use of analgesic drugs is still too low for several reasons, such as an incomplete knowledge of pain pathophysiology, the difficulties in estimating precisely pain intensity in children (especially in newborns and infants), the fear of potential iatrogenic adverse effects, and the fewer pain drugs approved for pediatric use.1,44 However, several NSAIDs have been approved in pediatrics, and importantly, ibuprofen was shown to be the most studied and to have, probably, the best safety profile in children, in addition to several evidence of efficacy.17,23

Kokki45 evaluated the effectiveness of ibuprofen in preventing pain after minor surgical procedures to correct hernias, phimosis, hydrocele, mild hypospadia, and so on. They randomized 81 children aged 1 to 4 years to receive rectal ibuprofen or placebo during narcosis. Ibuprofen significantly reduced pain experience in the first hours after the procedure and, importantly, spared the use of morphine.45 Similar results were obtained by another study by Stewart et al.46 Therefore, ibuprofen could find a place in the management of pain after minor surgery in pediatrics, maybe in addition to acetaminophen, too. Of course, the unavailability of parenteral formulations of ibuprofen limits its use after major surgery. Actually, ibuprofen has been considered in the treatment of pain after tonsillectomy and/or adenoidectomy in last few years, as results from several clinical researches. Indeed, despite some concerns related to the bleeding risk, the recent limitations to the use of opioids in such a surgical context prompted the search of different analgesics, including ibuprofen.

Two RCTs compared ibuprofen and the combination acetaminophen-codeine after tonsillectomy and/or adenoidectomy in 1990s. Harley and Dattolo32 carried out a DB-RCT including 27 patients aged 6 to 16 years; the combination acetaminophen-codeine resulted to be more effective in pain control, both at the first day and the third day after surgery. Moreover, 12.5% of patients treated with ibuprofen showed post-surgical bleeding, compared with none in the combination therapy group.47 St Charles et al48 carried out an open RCT including 110 children aged 2 to 16 years, by using ibuprofen (5–10 mg/kg) or the combination acetaminophen-codeine (15 + 1 mg/kg): 22% of children treated with ibuprofen needed an additional treatment with acetaminophen (alone or combined with codeine), whereas only 4% of children receiving the acetaminophen-codeine combination requested an additional treatment with ibuprofen to control the pain; however, no differences in bleeding events were reported between the groups, and actually, children receiving the pharmacologic combination including codeine complained of nausea and vomiting more than patients treated with ibuprofen.48 Therefore, these old studies have not supported the use of ibuprofen, but several studies have been published in the last few years. Some retrospective researches agreed on the efficacy of ibuprofen to control pain in children after this kind of surgery, but have not been concordant as concerns the risk of bleeding.49–52 However, at least 3 prospective studies have been carried out to investigate these aspects. Merry et al53 published a multicenter DB-RCT with 154 children aged 6 to 14 years undergoing tonsillectomy: they were randomized to receive ibuprofen (24 mg/kg per day) or acetaminophen (48 mg/kg per day) or a combination alternating both drugs, for 48 hours after surgery. Here, the equivalence among all 3 therapeutic regimens was reported. Moss et al54 carried out a DB-RCT with 161 pediatric patients aged 6 to 17 years.

History of otitis media, but no differences on the clinical course or the aspect of tympanic membrane were noticed.39 A recent systematic review of the medical literature analyzed the use of acetaminophen and NSAIDs, including ibuprofen, to treat otitis media; both drugs were equivalent in the control of ear pain at 24 and 48 hours and showed no differences as regards the rate of adverse events; interestingly, no advantage emerged from the combination compared with the monotherapy.30

Toothache

Ibuprofen was very useful in children with dental caries and for the control of toothache after dental procedures.31 Importantly, several placebo-controlled studies demonstrated the efficacy of ibuprofen to provide pain relief within 2 hours.25,34 Few studies compared ibuprofen with other drugs. The study by Hämäläinen et al35 compared both acetaminophen (15 mg/kg) and ibuprofen (10 mg/kg) with placebo; both drugs were 2 folds more effective than placebo within 2 hours. Actually, through an intention-to-treat analysis, this study suggested that the therapeutic success of ibuprofen would be greater than acetaminophen.35 On the contrary, a recent systematic review and a meta-analysis showed no significant differences between acetaminophen and ibuprofen, although the latter drug might provide a faster relief.36,37

Post-traumatic Musculoskeletal Pain

In childhood, ibuprofen is very useful in the relief of musculoskeletal pain after traumatic injuries.38 The most recent evidence suggested that ibuprofen should provide a better relief than acetaminophen and codeine and be equivalent to their combination and also morphine, but with fewer adverse events.39 The study by Clark et al40 compared single doses of acetaminophen (15 mg/kg), ibuprofen (10 mg/kg), and codeine (1 mg/kg) for the treatment of acute pain due to musculoskeletal trauma (54% cases being associated to bone fractures) in children and adolescents aged 6 to 17 years. The authors showed a greater improvement in pain score after ibuprofen than with the other 2 drugs.40 Another RCT including 336 children with musculoskeletal injuries and bone fractures of the limbs showed equivalent pain relief through ibuprofen and the combination acetaminophen-codeine, leading to more adverse effects.31 Recently, Poonai et al42 compared morphine and ibuprofen in 134 children with uncomplicated limb bone fractures, and those resulted to be equivalent. Actually, a less recent study has not shown any superiority of ibuprofen to acetaminophen in this clinical setting, but several factors, including the type of bone fracture and the techniques of limb immobilization, must be considered as potential sources of statistical bias affecting the final results.43 Finally, the more favorable pharmacological kinetics of ibuprofen, allowing longer time intervals of administration, could ameliorate the nocturnal rest and, as a consequence, the pain experience.
undergoing tonsillectomy; here, a single dose of intravenous ibuprofen (10 mg/kg) was compared with placebo. Interestingly, such a therapeutic approach resulted in significantly lower use of fentanyl without any increase in post-surgical complications, including bleeding.54 Again, Kelly et al55 randomized in double blindness 91 children (1–10 years), requiring tonsillectomy and/or adenoidectomy, to receive ibuprofen or the combination of acetaminophen and morphine. Interestingly, both regimens resulted to be equally effective, and no increase in bleeding complications was noticed in the ibuprofen group; actually, an increased and statistically significant risk of post-surgical oxygen desaturation episodes was found in the group receiving morphine.55

Therefore, the most recent evidence launched ibuprofen as a valid and potential alternative option to spare opioids for pain management after adenoidectomy and/or tonsillectomy.56,57 Indeed, in the aforementioned studies, a significant increase in bleeding risk was not evident and, very recently, a national DB-RCT has been opened in the United States, in order to recruit children undergoing tonsillectomy (with or without adenoidectomy): this trial aims at assessing the risk of post-surgical bleeding related to ibuprofen (compared with acetaminophen).58

CONCLUSIONS

Acute pain is a frequent symptom during pediatric illnesses and, probably, it is the most worrying both for children and parents. Despite the difficult assessment of pain in children and especially in newborns and infants, this symptom must be appropriately and timely treated, also because it is perceived more negatively and intensely in childhood compared to adults. The most common clinical settings of acute pain in children are sore throat, ear pain, headache, toothache, post-traumatic musculoskeletal pain, and postoperative pain. Ibuprofen resulted to be the most studied NSAID in the management of acute pain in children; in general, it showed a good safety profile and provided evidence of effectiveness, although it was variable according to the specific clinical context. Importantly, ibuprofen resulted to be more effective than acetaminophen, and as effective as the acetaminophen-codeine combination, for the control of acute injuries related to musculoskeletal injuries, including some limb fractures. Moreover, similar results have been reported also in the management of toothache and inflammatory diseases of the oral cavity and pharynx. Ibuprofen resulted to be useful as a first approach to episodic headache.

The role of ibuprofen in the management of postoperative pain and, particularly, after tonsillectomy and/or adenoidectomy has been reconsidered recently, because of European Medicine Agency and US Food and Drug Administration warnings regarding the use of opioids in those clinical settings. Recent studies seemed to show no clear and significant increase in bleeding complications in children receiving ibuprofen, but further studies are needed.

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