REVIEW ARTICLE

Drug Saf 2012; 35 (12): 1119-1125
0114-5916/12/0012-1119/$49.95/0

Balancing the Risks and Benefits of the Use of Over-the-Counter Pain Medications in Children

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Contents

Abstract

Paracetamol (acetaminophen) and ibuprofen are the most frequently purchased over-the-counter (OTC) medicines for children. Parents purchase these medicines for the treatment of fever and pain. In some countries other NSAIDs such as aspirin (acetylsalicylic acid) and dipyrone are available.

We aimed to perform a narrative review of the efficacy and toxicity of OTC analgesic medicines for children in order to give guidance to health professionals and parents regarding the treatment of pain in a child.

Neither aspirin nor dipyrone are recommended for OTC use because of the association with Reye's syndrome for the former and the risk of agranulocytosis for the latter. Both paracetamol and ibuprofen are effective for the treatment of mild pain in children. Adverse effects with both medicines are infrequent. Ibuprofen is an NSAID and therefore there is a greater risk of gastrointestinal adverse effects and hypersensitivity.

Aspirin and dipyrone should be avoided. Paracetamol is the drug of first choice for mild pain in children because of its favourable safety profile. For the treatment of significant musculoskeletal pain, ibuprofen is the drug of first choice.

Over-the-counter (OTC) medicines are widely used in children of all ages. Studies in both Europe and Australia have shown that paracetamol (acetaminophen) and NSAIDs are the most frequently purchased OTC medicines.[1,2] Parents purchase these medicines for the treatment of fever and pain. Ibuprofen is the most frequently purchased NSAID OTC. It is important to recognize, however, that in some countries other NSAIDs, such as aspirin (acetylsalicylic acid) and dipyrone are still available.[3,4]

The management of pain in children is important. Historically, children have been undertreated for pain but there is now widespread recognition within high-income countries that children should be given analgesia to treat pain. Most studies on OTC use of medicines comment on the medicines purchased. There have been relatively few studies evaluating why parents have chosen to purchase particular medicines.[5] This is of major relevance in relation to paracetamol and NSAIDs, which can be used for the treatment of fever as well as pain. A British study identified that fever and pain were the two main reasons for purchasing an OTC medicine.[5] Fever was the most frequent indication and pain was the second most frequent. Fever is an extremely common symptom in children and many parents will automatically give their child an antipyretic if they have the slightest temperature. The need for a more rational management of fever in children focusing on the comfort of the child has recently been highlighted.[6] Within hospitals it has become standard practice to treat febrile children with a combination of paracetamol and ibuprofen. A recent systematic review has highlighted that the advantages of using combined drug therapy are insignificant and that it would be more rational to treat children with a single antipyretic alone.[7] Fortunately most parents who treat their children at home will use one antipyretic agent only.

The aim of this narrative review was to review both the efficacy and safety of OTC analgesic medicines used in children.

1. Efficacy of NSAIDs

There are many different NSAIDs. They all inhibit the conversion of arachidonic acid to cyclic endoperoxides by the inhibition of the enzyme cyclooxygenase. This results in reduced production of prostaglandins such as PGE_2 and prostacyclin. The NSAIDs most likely to be used by parents for their children as OTC medicines are ibuprofen, dipyrone and salicylates. The availability and use of each of these NSAIDs is determined by geographical and socioeconomic factors.

1.1 Ibuprofen

Ibuprofen is a derivative of propionic acid and was initially marketed in the UK in 1969 as a prescription-only medicine for the treatment of rheumatoid arthritis. In the 1980s it became available both in Europe and the US as a suspension and as an OTC medicine.[8] Ibuprofen has been shown to be effective in the treatment of pain in children of all ages. A study in children under the age of 5 years showed that ibuprofen was effective as a pre-emptive analgesic for postoperative pain.[9] In 2004, a meta-analysis showed that single doses of ibuprofen (4–10 mg/kg) were effective for relieving moderate to severe pain in children.[10] More recent clinical trials have confirmed that ibuprofen is effective for musculoskeletal trauma and orthodontic pain in paediatric patients.[11,12]

1.2 Salicylates

Aspirin has been used for many years as an analgesic and was introduced as a medicine prior to the necessity for clinical trials to prove efficacy. It has, however, been used for many years in children as an analgesic and antipyretic. In many low-income countries aspirin is still readily available as an OTC medicine.[3,4]

1.3 Dipyrone

Dipyrone (metamizole) is an analgesic that belongs to the pyrazolone group of drugs. Dipyrone is still widely used in many parts of the world, including the Far East, Africa and Latin America.[13]

2. Efficacy of Paracetamol (Acetaminophen)

The analgesic effect of paracetamol was first described in 1893, and since the 1960s it has been

widely available as an OTC medicine.[14] It has been the most widely used analgesic in children and is the most frequently used OTC medicine in young children. A meta-analysis of the efficacy of paracetamol showed that single doses ranging from 7–15 mg/kg were effective for relieving moderate to severe pain in children.[10] This meta-analysis compared the efficacy of paracetamol with ibuprofen and found that efficacy for pain for the two analgesics was similar. Subsequent clinical trials have suggested that paracetamol is less effective than ibuprofen following musculoskeletal trauma[11] and orthodontic pain.[12] In contrast, a study in children with acute limb fractures suggested that paracetamol and ibuprofen had equal analgesic efficacy.[15]

3. Safety of NSAIDs

Adverse effects of NSAIDs in children include hypersensitivity reactions,[16,17] gastrointestinal bleeding[18,19] and renal impairment.[20,21] The only group of medicines more likely to cause hypersensitivity reactions than NSAIDs are β-lactam antibiotics.[22] Although well recognized in adults, the prevalence in children is uncertain. One group with an interest in allergy has suggested that it is a significant problem in paediatric patients.[16] The most frequent hypersensitivity reactions are urticaria and angioedema. The NSAIDs most frequently reported as causes of skin hypersensitivity reactions in children were aspirin, ibuprofen and dipyrone.[16] A pharmacovigilance programme within a tertiary children's hospital in Australia reported 19 adverse drug reactions (ADRs) to NSAIDs over a 5-year period.[23] Ten of these involved ibuprofen and consisted of a rash in three children, bronchospasm in two, gastrointestinal bleeding in three, acute renal failure in one and streptococcal invasive disease in another.

A national study of upper gastrointestinal bleeding in children in France identified 177 children over a 2-year period.[18] Eighty-three children (47%) had taken at least one NSAID in the week prior to hospitalization. Fifty-eight of the children had taken ibuprofen, 26 had taken aspirin and nine had taken other NSAIDs. Odds ratios (ORs) were assessed by comparing exposure to NSAIDs in the week prior to hospitalization with exposure between day 21 and day 28 prior to hospitalization. The adjusted OR was 8.2 (95% CI 2.6, 26.0) for NSAIDs altogether. It was higher for ibuprofen [10.0 (95% CI 2.0, 51.0)] than for aspirin [7.3 (95% CI 0.9, 59.4)].[18]

Another study looking at spontaneous reports to the French Pharmacovigilance System reported serious upper gastrointestinal complications in 61 children.[24] The NSAIDs associated with toxicity were niflumic acid (27), ibuprofen (23) and tiaprofenic acid (11). A retrospective review of 570 children at an American paediatric rheumatology centre described a relative risk for gastroduodenal injury of 4.8 for patients taking NSAIDs.[19] They felt that the risk of gastroduodenal injury in children with arthritis was similar to that in adults but that hospitalization or death was uncommon. A review of fatalities reported to the regulatory agency in the UK that were thought to be associated with drug toxicity described four children who died from gastrointestinal perforation.[25] Two of these received ibuprofen, one mefenamic acid and one diclofenac. Additionally, there were two other children who died following cerebral and gastrointestinal haemorrhage. One had received indometacin and the other aspirin.

3.1 Ibuprofen

Ibuprofen is an extremely safe drug. A prospective, randomized clinical trial involving over 80 000 children in the US compared ibuprofen with paracetamol.[26] This clinical trial was funded by a pharmaceutical manufacturer of ibuprofen and paracetamol, and identified that in the vast majority of children ibuprofen did not have significant drug toxicity. Over 50 000 children received ibuprofen, and the significant drug toxicities identified were low white blood cell count (eight children – observed risk of 14 per 100 000; 95% CI 6.2, 28 per 100 000) and gastrointestinal bleeding resulting in admission to hospital (four children – risk of 7.2 per 100 000; 95% CI 2, 18 per 100 000). In contrast, there were no cases of low white blood cell count or gastrointestinal bleeding in the paracetamol group.

Despite its excellent safety, it is important that health professionals are aware of the toxicity.

An unfortunate association with availability of an OTC medicine is an overdose. This may be deliberate in the case of adolescents or accidental in the case of young children. In 1986 a report of 126 cases of ibuprofen overdose was described.[27] This included 88 paediatric patients (aged 8 months–5 years). Six of these 88 children (7%) became symptomatic. Symptoms in the paediatric patients included gastrointestinal upset, seizures, apnoea, hypotension, bradycardia, hepatomegaly and mild CNS depression. Two of the children had seizures or apnoea and one child died. Investigators from the same poison centre subsequently reported an additional 61 cases of ibuprofen overdose, including 39 paediatric patients aged 0.8–3 years.[28] On this occasion, five (13%) of the paediatric patients had symptoms. One of the children developed metabolic acidosis, which has also been reported by other investigators.[29,30]

It is well recognized in adults that NSAIDs can be associated with renal toxicity. Cases of children developing transient renal insufficiency in association with ibuprofen have also been reported. Precipitating factors were either an overdose of ibuprofen or the presence of hypovolaemia.[20,31,32] Many of the cases described were individual case reports. One centre in France, however, reported seven children (age range 4–15 years) who developed acute renal failure over a 20-month period.[21] Six of the children had received ibuprofen and one received ketoprofen. Four of the children had gastroenteritis.

3.2 Salicylates

In 1965, the possibility of an association between Reye's syndrome and salicylates was raised.[33] It had been noted that 15 out of 31 cases of Reye's syndrome reported had received aspirin prior to admission.[33] Subsequently, the association between the use of salicylates during a viral infection and the development of Reye's syndrome was confirmed following an outbreak of influenza A in a school.[34] The restriction on the use of salicylates as an OTC medicine led to a dramatic reduction in the incidence of Reye's syndrome.[35] Within the UK, the initial restriction was for children aged 12 years and under. Subsequently, Reye's syndrome was reported in children between the ages of 12 and 16 years; therefore salicylates are not recommended routinely as an OTC medicine for paediatric patients of all ages.

Acute salicylate poisoning can result in metabolic acidosis. A recent case series from South Africa described 22 children who were admitted to a single hospital over an 18-month period with varying degrees of salicylate poisoning, which in all cases was thought to be due to the use of OTC aspirin.[4]

3.3 Dipyrone

Agranulocytosis has been reported following the use of dipyrone.[13] This is not surprising as dipyrone is one of the pyrazolones, and other drugs within this group, such as phenylbutazone and amidopyrine, have been found to be associated with the development of agranulocytosis.[13] Dipyrone has been banned or withdrawn from the market in many high-income countries. Studies have confirmed that agranulocytosis is a rare but potentially lethal adverse effect of dipyrone.[36] The incidence of agranulocytosis in association with dipyrone in Sweden was found to be at least 1 in 1439 (95% CI 1 in 850, 1 in 4684) prescriptions.[36] A study in Latin America, however, suggested that the incidence of agranulocytosis was lower.[37] This study did, however, detect that the incidence rate of agranulocytosis was high in children between the ages of 1 and 9 years; therefore one would not recommend the use of dipyrone in children. Additionally, other studies where dipyrone is frequently used have shown that it is responsible for a greater proportion of ADRs than paracetamol.[38]

4. Safety of Paracetamol

Paracetamol has an excellent safety profile. The most serious adverse effect is hepatotoxicity, which is a major problem following deliberate poisoning in adolescents. Fortunately, hepatotoxicity in younger children following accidental poisoning is extremely uncommon. Rumack[39]

described 417 children aged 5 years or younger who had taken an overdose of paracetamol. Only three of the children had significantly raised plasma concentrations of liver enzymes.[39] A subsequent American study reviewed 322 paediatric patients.[40] Overall, 140 adolescents deliberately ingested paracetamol, of whom 26 developed liver toxicity. Only one of the 172 young children who accidentally ingested paracetamol developed problems and this consisted of elevated plasma concentrations of liver enzymes only. Additionally, dosing error was reported in ten patients, of whom one patient developed liver toxicity. It is thought that the altered metabolism of paracetamol in young children protects them from hepatotoxicity. The metabolism of paracetamol involves glucuronidation and sulphation. Infants and young children have a greater capacity for sulphation, which is the most likely explanation for the reduced hepatotoxicity of paracetamol in young children.[14]

More recently, however, there have been several case series describing young children who have received repeated doses of paracetamol over several days who have experienced hepatotoxicity.[41,42] Many of these children received overdoses of paracetamol following miscalculation by parents. The two large case series were from the US. In contrast, experience in Canada suggested that hepatotoxicity in young children following overdosing was extremely rare.[43] Individual case reports of young children receiving therapeutic doses of paracetamol resulting in liver failure have also been reported.[44] Unfortunately, in these cases either deliberate harm by parents or miscalculation of dosing cannot be excluded.

It is important to note that as well as inducing hepatotoxicity, paracetamol following an overdose can cause renal toxicity.[45] It is of interest that in several of the case reports that described renal damage following ibuprofen the children also received paracetamol.[46,47]

There is some evidence that paracetamol is a weak NSAID.[16,48] Hypersensitivity reactions to paracetamol are rare and those individuals who are hypersensitive to paracetamol are usually also hypersensitive to NSAIDs.[49]

More recently it has been suggested that ingestion of paracetamol in early life may be a predisposing factor for the development of atopy and asthma in particular. One large study suggested exposure to paracetamol in the first year of life increased the risk of asthma by the age of 6 years (OR 1.46; 95% CI 1.36, 1.56).[50] Other studies have also suggested that there is an association between the use of paracetamol and the subsequent development of asthma.[51] It is important to note that most of the studies asked parents about the use of paracetamol as an antipyretic not as an analgesic. Since the systematic review and meta-analysis,[51] there have been other articles published using a similar questionnaire design which have suggested an association between the use of paracetamol as an antipyretic and the subsequent development of asthma.[52,53] It has, however, been suggested that it was the viral respiratory infection and not its treatment with paracetamol that resulted in the increased risk for asthma.[54,55] It is well recognized that such infections are a risk factor for the development of asthma.[56,57] Others, by adjusting for the frequency of respiratory infections, found no association with the early use of paracetamol and the risk of asthma.[58] It is worth noting that it had previously been suggested that antibiotic use in early life resulted in asthma in children at a later age.[59] Subsequent prospective studies, however, showed that antibiotic use was not associated with the subsequent development of asthma in childhood but rather it was the presence of a lower respiratory tract infection that was associated with the development of asthma.[60]

5. Discussion

The two most widely used OTC analgesics are paracetamol and ibuprofen. Both of these medicines appear to be exceptionally safe; however, there is controversy regarding the role of paracetamol and the development of asthma.[61] The possible association with frequent paracetamol use and the development of asthma is in relation to its use as an antipyretic agent. It is important that parents and health professionals recognize that children should only be given antipyretics to improve their comfort.[6] As has recently been highlighted, fever is a symptom and not a disease.

In contrast, it is important to treat pain appropriately. This will usually involve administration of an analgesic but in other circumstances measures such as distraction or comforting a child are equally appropriate. The main concerns with ibuprofen relate to its associations with hypersensitivity reactions, gastrointestinal bleeding and renal impairment. These are all uncommon but are more likely in an NSAID than with paracetamol.

6. Conclusions

Salicylates and dipyrone, as OTC medicines, should not be used in children. Paediatric pharmacovigilance studies suggest that paracetamol is safer than the NSAID ibuprofen. One would therefore recommend paracetamol as the first-line analgesic for young children. However, for the treatment of significant musculoskeletal pain, ibuprofen would be the drug of choice because of its greater efficacy. It is important for parents to recognize that pyrexia is considerably over-treated and the routine administration of either analgesic is inappropriate.

Acknowledgements

No sources of funding were used to prepare this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

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