Safe use of NSAIDs in infants and children

MADLEN GAZARIAN MB BS, MSc(ClinEpi), FRACP **LINDA V. GRAUDINS** BPharm, DipHospPharm, FSHP

NSAIDs are effective in alleviating pain and inflammation in infants and children. They are generally well tolerated when used for appropriate indications, in recommended paediatric doses, and with consideration of relevant precautions.

NSAIDs have well known analgesic, antipyretic and anti-inflammatory effects. This article discusses the main indications for their use in infants (excluding neonates) and children, adverse effects that occur in this age group and the principles guiding the choice of NSAID.

NSAIDs for pain and inflammation

The main indication for NSAIDs in children is the treatment of inflammatory pain. This includes a variety of chronic inflammatory conditions, most often juvenile idiopathic arthritis (JIA), where NSAIDs are used for both their analgesic and anti-inflammatory properties. Onset of the analgesic effect of NSAIDs is relatively rapid but the anti-inflammatory effects may take longer (up to six to eight weeks for optimal relief of chronic inflammation) and require higher doses than those used for analgesia (see Table).

NSAIDs are also effective analgesics for the treatment of mild to moderate acute pain where inflammation may be the principle underlying mechanism. In single doses they have analgesic efficacy comparable to that of paracetamol, which is the preferred first line agent because of its superior tolerability profile. NSAIDs, such as ibuprofen, are used for analgesia in the postoperative period, either to decrease opioid requirements or to provide adjunctive analgesia with regular paracetamol.

Dr Gazarian is Senior Lecturer, School of Women's and Children's Health, University of NSW, and Paediatric Clinical Pharmacologist and Rheumatologist, Sydney Children's Hospital, Randwick.

Ms Graudins is Quality Use of Medicines Pharmacist, Sydney Children's Hospital, Randwick, and Conjoint Lecturer, School of Women's and Children's Health, University of NSW, Sydney, NSW.

NSAIDs for fever?

The role of NSAIDs in the treatment of febrile illness in children is more controversial. Most children tolerate low grade fever (less than 38.5°C) well and do not require pharmacological treatment for fever. Antipyretic therapy does not prevent febrile convulsions, and there is some evidence that such therapy may prolong the course of some infections.[1]

If antipyretic therapy is needed (e.g. for a symptomatic child with high fever), paracetamol is the preferred pharmacotherapy.[2] Ibuprofen has equivalent antipyretic efficacy to paracetamol when used at recommended doses, but it is unclear whether ibuprofen is equally effective in relieving important clinical outcomes, such as the child's discomfort and symptoms (a Cochrane review is currently investigating this question). It is also unclear whether ibuprofen has any safety advantage. Although short term use of ibuprofen for fever control appears to be relatively safe, the comparative safety of longer term and more widespread use for febrile illness in young children with typical underlying comorbidities (e.g. dehydration, mild renal impairment) has not been clearly established. Known toxicities of NSAIDs include gastrointestinal and renal adverse effects, with the latter more likely to manifest in those with recognised risk factors, such as volume depletion or borderline renal function. Most trials of ibuprofen have not evaluated these outcomes systematically in febrile illness, but there are case reports of such toxicities occurring in children.[2]

The use of ibuprofen and paracetamol in combination or in an alternating regimen in the setting of febrile illness is discouraged.[3] The physiological effects of the combination may potentiate the risk of toxicity with each agent, and the efficacy and safety of this practice have not been well evaluated.[4] The combined use of these antipyretics needs further investigation, as there is evidence that it may also lead to an increased incidence of adverse effects as a result of parental confusion about correct dosing.[1,5]

Adverse effects and precautions

Serious toxicity associated with NSAIDs appears to be rare in children. The spectrum of adverse effects that occur in adults may also occur in children, although there are some differences.

Gastrointestinal effects

Adverse gastrointestinal effects related to the use of NSAIDs are a significant problem in adults. Although the magnitude of this problem in children is poorly documented, it is thought to be considerably less. Mild gastrointestinal symptoms (e.g. abdominal pain) are commonly reported in children receiving NSAIDs, but clinically significant gastroduodenal pathology is uncommon. In many children who develop gastrointestinal symptoms, underlying disease, psychosocial factors and concomitant medication may account for these effects.

To minimise gastrointestinal effects, NSAIDs should always be given with food. Concurrent treatment with gastroprotective drugs is generally not necessary. NSAIDs should be used with caution (and at the lowest effective dose) in children who have underlying gut pathology (e.g. inflammatory bowel disease).

Table. NSAIDs available for use in children

Drug	Main uses	Total dose/day (mg/kg/day)*	Number of doses/day	Comments
Naproxen†,‡,§	Chronic inflammation	10 to 15	2	Most frequently used initial NSAID for JIA Favourable toxicity profile overall (note pseudoporphyria, particularly in fair children)
Ibuprofen†	Chronic inflammation Acute pain Fever	30 to 40 15 to 40 15 to 40	3 to 4 3 to 4 3 to 4	Weaker anti-inflammatory NSAID Most favourable toxicity profile (note association with aseptic meningitis in systemic lupus erythematosus) Combined use with paracetamol should be avoided in treating fever Can be used in infants and children older than 6 months (note that infant drops are double the concentration of the suspension formulation)
Indomethacin‡,§	Chronic inflammation	1 to 4	2 to 4	Useful in treating spondyloarthropathies or pericarditis in systemic onset JIA Less favourable toxicity profile (cases of severe liver toxicity reported)
Diclofenac‡,§	Chronic inflammation Acute pain	1 to 3	2 to 3	Similar potency to indomethacin Reports of significant liver toxicity Suppositories not recommended for patients less than 12 months old
Piroxicam§	Chronic inflammation	0.2 to 0.3	1	Once daily dosing may be useful in older children and adolescents Less favourable toxicity profile
Aspirin	Rheumatic fever Kawasaki disease: – anti-inflammatory (acute phase) – antiplatelet (convalescent phase)	80 to 100 Refer to specialist centre 3 to 5	4 Refer to specialist centre 1	Least favourable toxicity profile generally (liver function abnormalities common; monitor salicylate levels at high dose) Do not use in children with febrile viral illnesses because of the risk of Reye's syndrome

*** Do not exceed the maximum daily dose recommended for adults.**
† Available in liquid form. ‡ Available as a suppository suitable for some children (suppositories should not be cut). § Listed on the PBS.

Hepatotoxicity

Hepatitis with elevated transaminase levels can occur during treatment with any NSAID but is most common with aspirin. In some patients, elevated transaminase levels may be due to the underlying disease (e.g. intercurrent viral illness, systemic onset JIA) or concomitant therapy (e.g. methotrexate). These are rarely of clinical significance and often resolve spontaneously or with dose adjustment. However, rare cases of severe hepatotoxicity have been reported.[2] Liver function should be monitored periodically (e.g. about six monthly) in children receiving long term NSAID treatment, especially those with systemic onset JIA in whom more frequent monitoring may be required.

Renal toxicity

Several types of renal toxicity may occur with NSAID treatment, including reversible renal insufficiency, acute renal failure, acute interstitial nephritis, nephrotic syndrome, papillary necrosis, and salt and water retention. The frequency of these adverse effects is lower in the paediatric age group than in adults, with a reported prevalence of 0.2 to 0.4% in studies of children with JIA.[6,7]

Renal impairment has, however, been reported in children with risk factors, such as dehydration, hypovolaemia, hypotension, pre-existing renal disease or concomitant therapy with nephrotoxic drugs.[2] Renal function should be monitored in these at-risk children and in children receiving long term therapy (e.g. about six-monthly routinely, with more frequent monitoring in those with risk factors).

Asthma

Aspirin-induced asthma is a distinct syndrome affecting some adults with asthma. There is high cross-sensitivity to other NSAIDs such as ibuprofen, naproxen and diclofenac. NSAID-induced bronchospasm occurs much less commonly in children with asthma, with reported rates of between 2 and 5%.[8,9]

NSAIDs should be avoided in any patient who has a positive history of NSAID-induced asthma or has high risk features (severe asthma, nasal polyps, urticaria or chronic rhinitis);[8] they may

be used with caution in other asthmatic patients. If safety concerns exist and NSAIDs are definitely needed in a child with asthma, the first dose should be administered under medical supervision.

Skin reactions

A variety of skin reactions including pruritis, urticaria, erythema multiforme and phototoxic reactions have been described. Pseudoporphyria is a distinctive type of photodermatitis that occurs fairly commonly in children with JIA receiving naproxen (prevalence of 12%);[2] individuals with fair skin are particularly susceptible. All signs except scarring resolve with discontinuation of therapy, so early recognition is important.

CNS effects

A substantial proportion of children receiving long term NSAID therapy may experience CNS effects, with headache being the most common. Less common symptoms include fatigue, sleep disturbance and hyperactivity. Ibuprofen has been reported to cause aseptic meningitis, particularly in patients with systemic lupus erythematosus.[2]

Platelets

NSAIDs inhibit platelet aggregation and may prolong bleeding time for some patients, especially with long term use. Clinically significant bleeding has not been associated with NSAIDs in children after tonsillectomy;[10] however, whether NSAIDs increase the risk of significant bleeding in the postoperative period generally remains controversial. Risk may vary with different procedures and so the management of an individual child should be discussed with the relevant surgeon or dentist.

Choosing an NSAID

Differences in anti-inflammatory activity between different NSAIDs are small, with unpredictable variability in individual patient response, but there are differences in the type and frequency of adverse effects (see Table). For an individual patient, the initial choice of NSAID should be based on which agent is likely to provide the most favourable benefit to risk ratio for the condition being treated. Additional considerations include the availability of a palatable paediatric formulation, convenience of dosing schedule and affordability. NSAID combinations should be avoided because toxicity is likely to be increased without a proven increase in benefit.

The NSAIDs currently available for use in children are listed in the Table. Only naproxen and ibuprofen are available in liquid form. Naproxen suspension is the only liquid NSAID listed on the PBS (authority required, for chronic inflammatory arthropathies where the patient is unable to take a solid dose form). [This suspension was temporarily unavailable in Australia from mid-2002, reinstated in the Australian market in late 2005, and relisted on the PBS in early 2006.] Naproxen suspension is the most widely used NSAID for treating chronic childhood arthropathies worldwide. It has a well established efficacy and safety profile in children, has a convenient dosing schedule and is affordable. Ibuprofen is somewhat less effective as an anti-inflammatory agent but has a more favourable toxicity profile. Aspirin is now used much less often in children because of its association with a greater frequency of adverse effects (including Reye's syndrome). Currently, the main role of aspirin is in the treatment of Kawasaki disease and rheumatic fever, and as an antiplatelet agent.

The COX-2 inhibitors currently marketed in Australia are not approved for use in children. Unlike adults, children have a negligible risk of significant gastropathy with NSAID therapy and so there is no good rationale for considering off-label use in the majority of children. The recent safety concerns with COX-2 inhibitors in the adult population and the lack of data from the paediatric population showing any advantage in efficacy or safety over currently available NSAIDs mean that the use of these agents in children outside a clinical trial setting is not recommended. MT

References

1. Knoebel EE, Narang AS, Ey JL. Fever: to treat or not to treat. Clin Pediatr (Phila) 2002; 41: 9-16.
2. Litalien C, Jacqz-Aigrain E. Risks and benefits of nonsteroidal anti-inflammatory drugs in children: a comparison with paracetamol. Paediatr Drugs 2001; 3: 817-858.
3. American Academy of Pediatrics, Committee on Drugs. Acetaminophen toxicity in children. Pediatrics 2001; 108: 1020-1024.
4. Carson SM. Alternating acetaminophen and ibuprofen in the febrile child: examination of the evidence regarding efficacy and safety. Pediatr Nurs 2003; 29: 379-382.
5. Li SF, Lacher B, Crain EF. Acetaminophen and ibuprofen dosing by parents. Pediatr Emerg Care 2000; 16: 394-397.
6. Szer IS, Goldstein-Schainberg C, Kurtin PS. Paucity of renal complications associated with nonsteroidal antiinflammatrory drugs in children with chronic arthritis. J Pediatr 1991; 119: 815-817.
7. Haftel HM, Mitchell JM, Adams BS. Incidence of renal toxicity from anti-inflammatory medications in a pediatric rheumatology population: role of routine screening of urine. J Rheumatol 2000; 27(suppl 58): 73.
8. Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. BMJ 2004; 328: 434-440.
9. Debley JS, Carter ER, Gibson RL, Rosenfeld M, Redding GJ. The prevalence of ibuprofen-sensitive asthma in children: a randomized controlled bronchoprovocation challenge study. J Pediatr 2005; 147: 233-238.
10. Cardwell M, Siviter G, Smith A. Non-steroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. Cochrane Database Syst Rev 2005; (2): CD003591.

This article is for general information purposes only. Both the full product information and the Australian Medicines Handbook should be consulted before prescribing the aforementioned medications.

DECLARATION OF INTEREST: None.