PHARMACY UPDATE
ROLE OF THE SELECTIVE CYCLO-OXYGENASE-2 (COX-2) INHIBITORS IN CHILDREN

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There has been a great deal written about the use of selective cyclo-oxygenase-2 (COX-2) inhibitors in the adult population. Yet despite this there is still controversy over their place in treatment and in the interpretation of evidence from the major clinical trials.[1] In the UK the National Institute for Clinical Excellence (NICE) recommended COX-2 inhibitors only be prescribed for osteoarthritis and rheumatoid arthritis patients at high risk of developing serious gastrointestinal adverse effects.[2]

Their role in children is even less well defined, with only a small number of published studies. Yet despite this lack of published evidence there is an undercurrent among paediatric practitioners to prescribe these agents. The aim of this review is to highlight the current published literature on the use of COX-2 inhibitors in children.

BACKGROUND
The major mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs) is inhibition of cyclo-oxygenase (COX) enzymes, which catalyse prostaglandin synthesis from arachidonic acid. There are at least two isoforms of cyclo-oxygenase: COX-1 is found in high concentrations in platelets, vascular endothelial cells, stomach, and in the kidney. It is accountable for the production of prostaglandins necessary for the maintenance of normal endocrine and renal function, gastric mucosal integrity, and haemostasis. The COX-2 isoform, under normal physiological conditions, is almost undetectable in most tissues; however, it increases up to 20 fold at the site of tissue damage.

It is suggested that COX-2 plays a role in the inflammation process, while inhibition of COX-1 is responsible for the adverse effects of NSAIDs. Based on this hypothesis, drugs that selectively inhibit COX-2 enzymes should have the beneficial anti-inflammatory activity of traditional NSAIDs without the toxicity.

Available COX-2 inhibitors
NSAIDs may be classified in terms of their COX-2 selectivity. However, there are international differences regarding COX-2 classification. The Food and Drug Administration in the USA classifies meloxicam and etodolac as ''preferential'' COX-2 inhibitors; however, in the UK they are classified as selective COX-2 inhibitors. For the purposes of this review we chose to follow the categorisation of selective COX-2 inhibitors as outlined in the British National Formulary[3] and included all agents shown in table 1.

The selective COX-2 inhibitors are approved for a range of different indications. These include the treatment of acute pain, osteoarthritis, rheumatoid arthritis, acute gout, and dysmenorrhoea. The indication varies with the individual product licence and also between countries. However there are currently no COX-2 inhibitors approved for use in children in the UK, USA, or Australia.

At this time there are no trials favouring any particular selective COX-2 inhibitor. The choice of agent has largely been dependent on other factors such as whether the drug is marketed in a particular country and the availability of a suitable formulation.

For example, in Australia, rofecoxib is available as an oral suspension. This, combined with a once daily dosing regimen, has led to its increased use in children, despite it not being licensed for this age group.

Similarly, until recently the only available parenteral NSAID in Australia was ketorolac. Parecoxib, an injectable selective COX-2 inhibitor, has recently become available and is being increasingly used intraoperatively, in paediatric patients requiring an NSAID.

All other selective COX-2 inhibitors are only marketed as tablets or capsules.

USE IN CHILDREN
Pharmacokinetics
In 2002 Stempak[4] published information on the pharmacokinetics of celecoxib in children. This study involved 10 patients aged 6–16 years who received 250 mg/m^2 orally twice daily for the

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Table 1 Marketed selective COX-2 inhibitors

COX-2 inhibitor	Brand	Marketed in		
		UK	USA	Australia
Celecoxib	Celebrex	Yes	Yes	Yes
Etodolac	Lodine SR	Yes	Yes	No
Rofecoxib	Vioxx	Yes	Yes	Yes
Parecoxib	Dynastat	Yes	No	Yes
Etoricoxib	Arcoxia	Yes	No	No
Valdecoxib	Bextra	Yes	Yes	No
Meloxicam	Mobic	Yes	Yes	Yes
Lumiracoxib	Prexige	Yes	No	No

Lumiracoxib (Prexige) is not in the British National Formulary 47th edition[3]; however it was first marketed in the UK in September 2003.

treatment of solid tumours. Celecoxib was found to be cleared approximately twice as fast in children than in adults and had a half-life that was approximately half as long.

A secondary objective of the study was to determine the safety of the use of celecoxib in this population group. They concluded that the drug was well tolerated by children and appeared safe for long term treatment, with one patient receiving celecoxib for a period of 16 months.

An abstract by St Rose outlines a study investigating the pharmacokinetics of rofecoxib in children aged 2–5 years with juvenile rheumatoid arthritis.[5] The investigators gave two different dosing regimens of 0.32 and 0.7 mg/kg/day rofecoxib. They concluded that rofecoxib 0.6 mg/kg/day in children aged 2–5 years should approximate exposure to 25 mg in adults.

In another abstract, Edwards studied the pharmacokinetics of rofecoxib in children with sickle cell haemoglobinopathy admitted for pain episodes.[6] Eight patients aged 3–14 years received an oral dose of rofecoxib of 1 mg/kg. Rofecoxib clearance and half life were similar in children compared to adults.

Boni published a single centre, open label, single dose pharmacokinetic study of etodolac in paediatric and adolescent patients with stable rheumatoid arthritis.[7] The study involved 11 patients aged 8–14 years. Clearance values for paediatric and adolescent patients were comparable to those of adults and were independent of age.

Review of usage
One of the first reports of celecoxib use in children was a review of its use over a 12 month period in a tertiary paediatric hospital.[8] Twelve patients, aged 6–17 years, received celecoxib over this time period. These patients either had existing haematological disorders, such as von Willebrand's disease with coexisting morbidities of joint swelling and pain, or had previously reported adverse events to non-selective NSAIDs. This second group of patients had a range of chronic underlying conditions such as cerebral palsy and arthritis. Dosing was empiric and based on the recommended adult regimen. In all patients celecoxib was well tolerated.

Tonsillectomy
Tonsillectomies are one of the most common surgical procedures performed in children. Despite this, providing safe and effective analgesia is still very challenging. While opioids can provide sufficient analgesia they may cause respiratory depression which can be detrimental, particularly in patients with obstructive airway disease. They are also associated with postoperative nausea and vomiting. NSAIDs, which are without these effects, have the potential to cause bleeding which has limited their use. The selective COX-2 inhibitors do not affect platelet function nor increase the risk of bleeding, and this has led to their use in this patient group.

However, it is important to look at the evidence of bleeding in tonsillectomy patients with traditional NSAIDs. A recent systematic review by Møiniche[9] looked at the risk of operative site bleeding after tonsillectomy with NSAIDs and concluded that the evidence for NSAIDs to increase the incidence of bleeding after tonsillectomy remains ambiguous. The cautious clinical message was that there is some evidence from randomised, controlled trials that NSAIDs may increase the likelihood of re-operation because of bleeding, particularly when NSAIDs are given in the postoperative period. However, there is a lack of evidence for NSAIDs to increase intraoperative blood loss or to increase the incidence of postoperative bleeding or readmission because of bleeding. The authors suggested that the COX-2 inhibitors may have advantages compared with traditional NSAIDs, their COX-2 selectivity producing minimal effect on platelet aggregation.

Despite the limited evidence against the use of non-selective NSAIDs there has been much focus on tonsillectomies as an indication for the use of selective COX-2 inhibitors.

In a UK study by Pickering[10] the authors assessed the analgesic effectiveness of combining paracetamol (acetaminophen) (20 mg/kg) with rofecoxib (0.625 mg/kg), ibuprofen (5 mg/kg), or placebo as premedication for adenotonsillectomy in 98 children aged 3–15 years. The primary outcome measure was the need for early supplementary analgesia (within two hours). The interim blind analysis found that significantly more children required early analgesia in the rofecoxib group compared with the ibuprofen group. This study failed to show any analgesic effect of rofecoxib in combination with paracetamol. The authors also studied operative blood loss and complications and found no difference between the three groups.

Joshi studied the use of a single dose of rofecoxib 1 mg/kg before tonsillectomy.[11] They investigated 66 patients aged 3–11 years who were to undergo tonsillectomies. They received either placebo or rofecoxib. They found that there were no differences in blood loss but found that pain scores were significantly lower in the rofecoxib group. The incidence of nausea and vomiting in the control group post-discharge was also significantly higher.

A conference abstract by Vallee reported similar findings.[12] This study involved 80 patients aged 5–17 years undergoing tonsillectomy. They found that rofecoxib (1 mg/kg) with morphine was a better postoperative combination in the treatment of pain, following tonsillectomy in children, than a combination of paracetamol and morphine. Rofecoxib had a morphine sparing effect and led to faster recovery in terms of time to normal diet and normal activities.

In summary, the two published studies have shown that rofecoxib is a superior analgesic compared to placebo in patients undergoing tonsillectomy, although it has not been shown to be more effective than ibuprofen or paracetamol. Further studies in this patient group are necessary.

Rheumatology
There have been two recent reviews of NSAID use in children with musculoskeletal disorders. While not presenting any new evidence, the authors discuss the potential role of

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selective COX-2 inhibitors.[13] [14] Munro suggested that selective COX-2 inhibitors may confer some benefit to those at risk of gastrointestinal side effects from non-selective NSAIDs.[13] However, the indications and efficacy are less clear for children who would be considered low risk, due to the lower rate of co-morbidities for gastrointestinal disease among the paediatric population. They concluded that the traditional NSAIDs remain the first choice agents in Australia, with COX-2 inhibitors probably reserved for patients with gastrointestinal co-morbidities or severe gastrointestinal intolerance to a traditional NSAID. Fahey, while discussing the potential benefits of the selective COX-2 inhibitors, concluded that further investigation in children was required.[14]

Kiss recently presented an abstract demonstrating the efficacy and tolerability of rofecoxib in children and adolescents in a 12 week randomised study.[15] Three hundred and ten patients aged 2–17 years were randomised to receive either rofecoxib (0.3 mg/kg, maximum 12.5 mg daily), rofecoxib (0.6 mg/kg, maximum 25 mg/daily), or naproxen (7.5 mg/kg twice daily). Rofecoxib and naproxen demonstrated similar efficacy, with a trend towards greater efficacy in the high dose rofecoxib group compared to lower dose rofecoxib. Rofecoxib was generally well tolerated with significantly fewer gastrointestinal adverse effects in patients taking the lower dose relative to naproxen.

Foeldvari investigated the use of meloxicam in juvenile rheumatoid arthritis (JRA).[16] This was a 12 week phase I/II study with an additional open extension lasting up to 52 weeks which investigated the safety, efficacy, and pharmacokinetics of meloxicam in JRA. Thirty six patients aged 2–16 years were enrolled. A dose of 0.25 mg/kg once daily was used. The authors concluded that meloxicam 0.25 mg/kg once daily seemed to be effective and safe for treating active JRA over a period of 52 weeks.

The same author, in a letter to the editor,[17] described the use of meloxicam in juvenile idiopathic arthritis in naproxen intolerant children or in patients who preferred the convenience of a once daily preparation. Over two years, meloxicam was used in 45 patients at a mean dose of 0.24 mg/kg/day. Meloxicam was well tolerated and effective in 73% of patients.

In summary, there is some evidence demonstrating that selective COX-2 inhibitors are safe and effective in patients with musculoskeletal disorders. However, until further information is available, COX-2 inhibitors, in accordance with Munro, should be reserved for patients with gastrointestinal co-morbidities or severe gastrointestinal intolerance to a traditional NSAID.

OTHER USES
Treatment of solid tumours
Over expression of the inducible isoform COX-2 has been discovered in a variety of adult solid tumours, and COX-2 inhibitors have been shown to have antiproliferative effects. Celecoxib has been shown to be anti-angiogenic, interfering with the tumour's ability to make blood vessels and therefore affecting the growth of the tumour. Dickens et al investigated the expression of COX-2 in rhabdomyosarcoma, osteosarcoma, and Ewing sarcoma.[18] They found that the majority of these tumours expressed COX-2 to varying degrees and suggested that the efficacy of COX-2 inhibitors in the treatment of paediatric sarcomas warranted studying.

The use of COX-2 inhibitors, as an adjunct in the treatment of tumours, is an area generating much interest. This

has led to the incorporation of celecoxib into one arm of the Children's Oncology Group Protocol investigating the treatment of Ewing's sarcoma.[19] In this study a dose of 250 mg/m^2 twice daily celecoxib is recommended.

Dysmenorrhoea
In a recent review by Harel, the role of selective COX-2 inhibitors in the treatment of dysmenorrhoea in adolescents is discussed.[20] It suggests that COX-2 inhibitors should be considered in adolescents with a prior history of peptic ulcer who require high doses of traditional NSAIDs. However, while valdecoxib and rofecoxib are both listed in the table of suggested NSAIDs, the doses recommended for these agents are only for girls older than 18 years.

Bartter's syndrome
Kleta recently reported a single case of the use of rofecoxib in a 2 year old girl with Bartter's syndrome,[21] a group of related disorders characterised by congenital salt wasting as a result of abnormal salt reabsorption in the ascending loop of Henle. The clinical problems of Bartter's syndrome—prematurity, polyuria, dehydration, and growth retardation—are to a large extent caused by raised concentrations of prostaglandins. The authors suggest that the COX-2 isoenzyme appears to be responsible for the raised concentrations of inducible prostaglandins seen in this condition. In combination with a balanced sodium diet the authors gave a dose of rofecoxib 6.25 mg (0.8 mg/kg) once daily. The patient showed notable improvements in a range of clinical markers, as well as a reduction in volume of urine, and suggested that selected patients with Bartter's syndrome be treated with COX-2 inhibitors.

DISCUSSION
There are only a small number of published studies of COX-2 inhibitors in children and these are largely of low level evidence with some small pharmacokinetic studies, case reports, conference abstracts, usage reviews, open label studies, and only two randomised controlled trials. We found no published studies in children with parecoxib, valdecoxib, etoricoxib, or lumiracoxib.

Prescribers need to assess the risk:benefit of use before deciding to prescribe these drugs in children.

As a group the selective COX-2 inhibitors have not been shown to be any more effective than traditional NSAIDs.[2]

Although serious gastrointestinal perforations can occur in children with traditional NSAIDs[22] the risk for serious gastrointestinal adverse events is relatively low.[23] Therefore it would be hard to justify the routine use of selective COX-2 inhibitors in the paediatric population based on reduction in gastrointestinal adverse effects alone. While there may be certain paediatric patients who may benefit from the use of selective COX-2 inhibitors, it is important to remember that these drugs have been associated with serious gastrointestinal side effects in adults.[24]

While the minimal effect on platelet aggregation exhibited by the selective COX-2 inhibitors may make them useful as analgesics or anti-inflammatory agents in patients at increased risk of bleeding, such as pre-existing bleeding disorders and tonsillectomy patients, further studies are necessary to ensure safety and efficacy in these patient groups.

Any use of the selective COX-2 inhibitors has to be balanced against potential risk. Very few adverse events

experienced by children have been reported, reflecting the small number of children in which they have been studied. However, in adults a wide range of more serious adverse drug reactions have been reported including acute neuropsychiatric reactions (celecoxib, rofecoxib),[25] allergic vasculitis (celecoxib),[26] recurrent aseptic meningitis (rofecoxib),[27] temporary visual impairment,[28] toxic epidermal necrolysis (valdecoxib, rofecoxib),[29 30] and acute renal impairment (parecoxib).[31] There have been particular concerns about the increased risk of cardiovascular thrombotic events in patients taking COX-2 inhibitors compared with other NSAIDs.[32]

Another reason for caution is the consequence of selective blockage of COX-2 enzyme in developing human beings, particularly if these agents are going to be used for chronic treatment. Recently it has been revealed that the COX-2 isoenzyme is also expressed in kidney, brain, bone, ovaries, uterus, and normal non-inflammatory tissues. Therefore selective inhibition of the physiological or protective functions of the COX-2 enzyme may not prove to be as effective and safe as first thought.[33]

Choosing an appropriate dosing regimen of COX-2 inhibitors in children is difficult. While a number of published papers give suggested dosing regimens, many of these are not evidence based. The diverse outcomes from the four small pharmacokinetic studies, investigating three different agents in widely different population groups, do not clarify the situation. Large, consensus forming, pharmacokinetic studies in children are required.

CONCLUSION

None of the selective COX-2 inhibitors are approved for use in children and there is still a paucity of published information to support their use. While there may be specific patients who may benefit from their use, more studies are required before their widespread usage should be adopted.

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