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Adverse drug reactions to nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and paracetamol in a paediatric hospital

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Aims
The use of nonsteroidal anti-inflammatory drugs (NSAIDs) in children has rapidly escalated over the last 5 years in Australia. This is primarily as a result of the availability of ibuprofen as an over-the-counter preparation. Several recent, significant adverse drug reactions (ADRs) to NSAIDs, at the Royal Children's Hospital (RCH) in Melbourne, Australia prompted review of all of the RCH reactions reported to these agents over 5 years.

Methods
The ADR programme documents both spontaneously reported ADRs and ADRs identified by discharge coding. For this study, reported reactions to aspirin, celecoxib, ibuprofen, indomethacin, naproxen, paracetamol and rofecoxib, for the previous 5-year period, were retrieved from the hospital ADR database.

Results
Nineteen reports of ADRs to NSAIDs and six to paracetamol, in patients aged from 4 months to 22 years (median 10 years) were identified. Reactions were predominantly rash (n = 10), gastrointestinal (n = 5) and respiratory (n = 4) side-effects. These included reports of haematemesis with both celecoxib and ibuprofen. One patient died of severe acute exacerbation of asthma following initiation of rofecoxib.

Conclusion
NSAID exposures are a significant cause of morbidity in children. Both nonselective NSAIDs and the newer COX-2 inhibitors were associated with significant drug reactions. The overall severity of these ADRs highlights the need for vigilant surveillance of ADRs in paediatrics, including both established and newer agents.

Introduction

Several recent, significant adverse drug reactions (ADRs) to nonsteroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase-2 (COX-2) selective inhibitors raised the awareness of the Royal Children's Hospital (RCH) ADR committee to side-effects of these agents in children. Simultaneously, it was noted that the use of NSAIDs, in particular ibuprofen, at the RCH was steadily increasing [1]. As ADRs experienced in children may differ from those reported in adults, and may not be recognized for many years [2], a review of ADRs detected at RCH was undertaken, to determine the range and preventability in our paediatric population.

A comprehensive ADR monitoring system was established at the RCH in November 1998. A multidisciplinary ADR committee regularly reviews ADRs reported spontaneously and identified through medical records coding reports. ADRs are then entered into a Microsoft Access-based database. ADRs to NSAIDs, COX-2 selective inhibitors and paracetamol, detected at RCH over a 5-year period, were reviewed.

Methods

All ADRs to aspirin, celecoxib, ibuprofen, indomethacin, naproxen and rofecoxib from January 1999 to December 2003 inclusive, were retrieved from the ADR database. These drugs incorporate all the NSAIDs and COX-2 inhibitors in use at the hospital over this period. ADRs to paracetamol for the same period were also retrieved. Each ADR retrieved was rated for likelihood of the drug causing the reaction, based on information from the ADR report. Patient medical records were reviewed for missing information when necessary. Likelihood rating was performed using the Naranjo ADR Probability Scale [3]. An assessment of preventability of each ADR was made using previously published criteria [4]. These criteria included consideration of appropriateness of drug use, dose, patient monitoring, history of drug reactions, drug interactions, serum drug concentration and compliance.

Results

Nineteen reports implicating NSAIDs and COX-2 selective inhibitors were retrieved from the database and a further six reports implicating paracetamol. The combined 25 ADRs reviewed represent 3.3% of the total ADR database of 754 reports for the 5-year period. Table 1 groups these reactions and Table 2 summarizes each ADR. Patient age ranged from 4 months to 22 years (median 10 years, mean 10 years), 12 reactions occurred in boys, 13 in girls. The 22-year-old patient was included as he was extremely underweight for age and is still being treated for complicated cerebral palsy at RCH. The patient population was diverse, ranging from children with complex chronic disease treated with multiple medications at risk of ADRs, to otherwise well children with a simple viral infection, on no regular medications.

Reports for NSAIDs and COX-2 selective inhibitors included 17 ADRs that took place while children were inpatients, in 10 of these 17 cases the ADR contributed to the hospital admission. A further of these reactions occurred while an outpatient and another one was the cause of an Emergency Department attendance.

It is not possible to determine the proportion of NSAID doses administered compared with other drugs. However, in the 5-year period covered by this review, there was a sevenfold increase in use of ibuprofen at RCH; 1806 packs of ibuprofen were purchased in 2003 [1]. Use of other NSAIDs is relatively limited as 146 packs of aspirin, 26 packs of rofecoxib, 25 packs of indomethacin and 10 packs each of celecoxib and naproxen were purchased in 2003. Paracetamol is used extensively at RCH – in 2003 over 9100 packs were purchased.

Most ADRs were rated 'possible' (10 ADRs) or 'probable' (14 ADRs) according to the Naranjo scale, one was rated 'doubtful' and may have been caused by another drug. Drug dose and ADR outcome details were missing from some ADR reports and medical records.

The gastrointestinal reactions to celecoxib and ibuprofen were all described as haematemesis in the ADR reports. The three haematemesis reactions to ibuprofen were all in adolescents, the doses of 1600 mg to 1800 mg per day were at the higher end of the usual range. The 22-year-old, 29.5-kg patient who suffered haematemesis after celecoxib had been prescribed a large dose of 200 mg (6.8 mg kg^{-1}) twice daily.

All the respiratory ADRs required drug treatment; two of these patients were admitted. A 10-year-old girl who received a single rofecoxib tablet died of severe

Table 1
Summary of types of ADRs detected for each drug

Drug	Total	Gastrointestinal	Respiratory	Rash	Other
Aspirin	2		1		1
Celecoxib	2	1		1	
Ibuprofen	10	3	2	3	2
Indomethacin	1			1	
Naproxen	1			1	
Paracetamol	6			4	2
Rofecoxib	3	1	1		1

Table 2
Outline of each ADR

Age	Weight	Suspected drug, dose, indication	Reaction	Outcome and comments	Naranjo score*	Preventable?
6 years	21 kg	Aspirin 300 mg 'stat' dose, given at home for abdominal pain.	Allergic/anaphylactoid reaction, lip and eye swelling, shortness of breath, wheeze	Recovered	6	Yes
17 years	43.5 kg	Aspirin 900 mg 6 hourly	Hearing loss	Recovered partially, on other ototoxic drugs	4	Yes
10 years	34 kg	Celecoxib 100 mg twice daily, shoulder soreness	Extensive, red, macular, itchy rash, shoulder pain	Resolved	4	Yes
22 years	29.5 kg	Celecoxib 200 mg twice daily, pain associated with cerebral palsy	Haematemesis	Recovered, history of oesophagitis and haematemesis	5	Yes
13 years	70 kg	Ibuprofen 200–400 mg 6 hourly when required, fracture pain	'Coffee grounds' vomit	Recovered	5	No
2 years	13.8 kg	Ibuprofen at night, 2 doses, dose unknown	Wheeze	Recovered	6	Unable to assess
17 years	55 kg	Ibuprofen 400 mg four times a day, post orthopaedic surgery	Haematemesis	Recovered	6	No
14 years	75 kg	Ibuprofen 600 mg three times a day, chronic headache	Gastritis and haematemesis	Recovered. Used ~ 24 tablets/week last few months	6	Yes
10 years	39 kg	Ibuprofen 400 mg 6 hourly post orthopaedic surgery	Itchy rash	Unknown	5	No
10 years	41 kg	Ibuprofen 100 mg three times a day, given at home for viral infection	Acute renal failure, serum creatinine 0.4 mmol l^{-1} (range 0.03–0.08), dehydrated	Recovered, concurrent viral infection	5	Yes
17 years	47 kg	Ibuprofen 500 mg 'stat' dose, post operative analgesia	Exacerbation of asthma	Recovered, history of asthma	6	Yes
12 months	9.8 kg	Ibuprofen every 6–8 h when required, dose unknown, given at home, varicella infection	Streptococcal invasive disease secondary to ibuprofen use in varicella	Recovered	2	Yes
2 years	11.4 kg	Ibuprofen dose unknown, pain associated with cerebral palsy	Rash	Unknown	6	Unable to assess
11 years	37.4 kg	Ibuprofen dose unknown, given at home for viral infection	Swollen periorbital region, urticarial rash	Unknown	3	Unable to assess
11 years	53 kg	Indomethacin 100 mg one dose rectally, post-operative analgesia	Rash	Recovered	5	No
5 years	16.3 kg	Naproxen 75 mg three times a day, juvenile chronic arthritis	Generalized rash and itch	Not resolved at time of report	3	No
4 years	13.4 kg	Paracetamol mixture 192 mg, post-operative analgesia	Red macular rash, swollen red ears and mouth, cough, wheeze	Recovered. No reaction on rechallenge	3	No

Table 2
Continued

Age	Weight	Suspected drug, dose, indication	Reaction	Outcome and comments	Naranjo score*	Preventable?
4 months	4.48 kg	Paracetamol 40 mg every 6 h when required	Swollen eyelids, allergy?	Recovered	3	No
2 years	13.4 kg	Paracetamol 200 mg every 4 h	Red sore itchy eyes, urticarial rash right eyelid	Unknown	4	No
8 years	25 kg	Paracetamol dose unknown, abdominal pain	Itchy, widespread rash	No reaction on rechallenge with colourless paracetamol	3	No
15 years	50 kg	Paracetamol 500 mg–1 g 4–6 hourly when required, wound pain	Hot flushes	Recovered	6	No
12 years	35 kg	Paracetamol and codeine mixture once only dose unknown, abdominal pain	Fine red rash on lower limbs	Resolved	5	No
10 years	75 kg	Rofecoxib 25 mg daily, juvenile chronic arthritis	Severe muscle cramps	Unknown	0	Yes
10 years	50 kg	Rofecoxib 1 tablet daily dose unknown, joint pain	Severe acute exacerbation of asthma	Died, mild airway inflammation on autopsy	4	No
13 years	49 kg	Rofecoxib 25 mg daily, arthralgia	Nausea	Unknown	5	

**Naranjo score: 9 = highly probable; 5–8 = probable; 1–4 = possible; 0 = doubtful.*

acute exacerbation of asthma. She had a history of episodic asthma and multiple allergies to food, house dust mites and mould. She was prescribed rofecoxib by her local doctor, for joint aches and pains. She had no concurrent respiratory infection or symptoms. She collapsed at home, an ambulance report described swollen face and tongue, an autopsy report revealed mild airway inflammation.

In two instances, reactions to paracetamol may have been confounded by concurrent viral illness, a further paracetamol ADR was likely to have been caused by the colouring agent. It is unknown if excipients caused any other ADRs.

There were nine preventable ADRs (36%); in addition, three could not be assessed due to incomplete data (Table 2). The preventable ADRs included all of the reactions to aspirin and celecoxib, haematemesis with ibuprofen and the fatal exacerbation of asthma with rofecoxib.

Discussion

Several severe ADRs to NSAIDs were detected in this review in paediatric patients. A lack of clinical trials for medications in children, lack of paediatric dose forms, unique disease states, differences in pharmacokinetics and pharmacodyamics are some of the factors that place children at risk of ADRs and result in a different range of side-effects in children compared with adults [2, 4, 5]. Therefore ADRs reported in adults do not always predict ADRs in children. Children may be more susceptible to a particular ADR, for example aspirin causing Reye's syndrome, less susceptible, for example, to flucloxacillin causing hepatitis, or experience different ADRs such as dystonia caused by metoclopramide in adolescents. Ongoing, prospective surveillance in paediatrics is important to determine differences in ADRs in different age groups [2].

It has been determined that the paediatric population experiences a significant number of ADRs. A recent meta-analysis of prospective studies calculated an average ADR incidence of 9.5% ADRs for paediatric patients and an incidence of paediatric hospital admissions related to ADRs of 2.1%; contributing drugs were not listed [6]. A large ADR surveillance study from 1964 to 2000 in the UK found 331 suspected ADRs with a fatal outcome in children [5].

NSAIDs were associated with 12 of 196 fatalities in the UK study since 1990 [5]. No fatal respiratory ADRs were detected, but there were four ADR reports of gastrointestinal perforation, two suspected with ibuprofen, the others implicated diclofenac and mefenamic acid. The serious adverse events associated with ibuprofen in adults, e.g. gastrointestinal bleeding, are not well established in children [7, 8], with the possible exception of those with juvenile chronic arthritis [9]. Two large double-blind studies comparing the incidence of serious adverse events of ibuprofen and paracetamol in febrile children under 12 years and 2 years old, respectively, given ibuprofen (5 or 10 mg kg^{-1} $dose^{-1}$) or paracetamol (12 mg kg^{-1} $dose^{-1}$), reported the risk of hospitalization did not vary with antipyretic assignment [7, 8]. The risk of hospitalization with acute gastrointestinal bleeding did not vary significantly with ibuprofen dose and was not significantly greater than the risk among children randomized to paracetamol. In both studies, there were no hospitalizations for acute renal failure or anaphylaxis [7, 8]. A recent review of literature on efficacy and safety of these two agents concluded the risk of serious adverse events in children receiving short-term treatment with either ibuprofen or paracetamol was small and not influenced by choice of medication [10].

Although the local prescribing of the COX-2 inhibitors is restricted and so use is infrequent, several serious reactions were reported to these drugs. The report of haematemesis seen with celecoxib may have been preventable if the dose had been 2 or 4 mg kg^{-1}, calculated on weight rather than age. On reviewing the literature, few reports published of ADRs to COX-2 inhibitors in children have been reported. Those reactions in the literature differed from the current study and included nausea with rofecoxib [11], pseudoporphyria induced by celecoxib in a 12-year-old, who had suffered the same reaction following naproxen [12], and a case report of aseptic meningitis associated with rofecoxib in a 16-year-old girl [13].

The severe asthma and subsequent death following a single dose of rofecoxib detected at RCH suggests caution with COX-2 selective inhibitors in patients with a history of asthma. Several small studies in adults suggest COX-2 selective inhibitors are unlikely to cause exacerbation of aspirin-induced asthma [14–18]. However, one case report describing acute exacerbation of asthma following three doses of rofecoxib 25 mg has been described in a 78-year-old woman with well-controlled asthma who had previously reacted to aspirin [19]. The product information for celecoxib and rofecoxib both list aspirin-induced asthma as a contraindication and state that these drugs should be used with caution in pre-existing asthma. Monitoring for ADRs with these newer agents is particularly important in children in view of these limited data.

The Australian Drug Reactions Advisory Committee (ADRAC) receives approximately 1000 ADR reports per month. Reports are voluntary but Australia has one of the highest reporting rates in the world. Nevertheless, it is well recognized that spontaneous monitoring grossly underestimates ADRs when compared with prospective intensive monitoring [20]. The reports detected at RCH may represent at best 10% of total ADRs in these patients. Maintenance of a nationwide ADR database plays a significant part in preventing their subsequent occurrence in both affected patients and others exposed in the community and in hospital. Establishing an extensive profile of side-effects to medications in children and adolescents provides ADRAC, and therefore health professionals in general, with data that help ensure the safe and appropriate use of medications in this age group.

The proportion of preventable ADRs (36%) was higher than 20.7% found in a large US evaluation of paediatric ADRs. However, numbers in the current study are small [4]. Prevention of ADRs in the community and individual patients is addressed by several approaches at a national, hospital and individual patient level.

Prescribing restrictions within an institution can limit use of certain medications and contribute to prevention of ADRs by avoiding inappropriate prescribing; these prescribing restrictions should be regularly reviewed. For example, prescribing of COX-2 inhibitors could require individual patient approval. Such restrictions may not extend to the community where several of the more severe, preventable ADRs in this review initiated. Regulatory changes in Australia have resulted in ibuprofen being readily available from supermarkets. The case of acute renal failure probably caused by ibuprofen may have been prevented if the drug had been avoided rather than administered for a viral infection in a setting of dehydration at home. It is well recognized that use of NSAIDs, even in moderate dehydration in children, is hazardous [9, 21]. Other preventable ADRs that initiated in the community included an allergic reaction subsequent to parent administration of aspirin to a 6-year-old, an age at which use of aspirin is contraindicated, exacerbation of asthma following rofecoxib and haematemesis following prolonged use of ibuprofen for headache.

Where possible, strategies should be developed to reduce preventable ADRs to targeted drugs, for example through educational intervention or guideline development. To prevent ADRs to NSAIDs, a minimum step

should be education to raise awareness of medical, nursing and pharmacy staff to the ADRs associated with NSAIDs in children and to ensure appropriate prescribing of NSAIDs for pain while discouraging use for fever. This has been an ongoing strategy employed through our ADR programme.

Our ADR committee has developed a number of strategies that have successfully prevented recurrence of the same ADR in individual patients. The committee reviews all ADRs reported, then informs patients or parents of the side-effect experienced, as appropriate, and whether future exposure to the medication should be avoided. This is achieved by sending a credit card-sized alert card to the patient or parent. In addition, an alert is placed in the medical history and in the pharmacy dispensing program, and a letter is sent to inform general practitioners and consultants. Referral to an allergist is made as required. Following a demonstrated allergic reaction to a NSAID, advice given to parents is to avoid aspirin and all NSAIDs in the child.

Conclusion

NSAID exposures are a significant cause of morbidity in children. Both nonselective NSAIDs and the newer COX-2 inhibitors were associated with significant drug reactions. The reactions reported to COX-2 selective inhibitors have not been well documented in paediatrics. A substantial proportion of ADRs reported were preventable, illustrating the difficulty in ensuring appropriate use of drugs readily available over the counter and the care that needs to be taken with paediatric drug selection. The overall severity of these ADRs highlights the need for ongoing, prospective ADR surveillance in paediatrics, including both established and newer agents.

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