Prospective observational study of adverse drug reactions to diclofenac in children

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Diclofenac is frequently used off-label in children for acute pain, but little information is available on diclofenac adverse drug reactions in this population.

WHAT THIS STUDY ADDS

- The common adverse drug reactions of diclofenac for acute pain in children are of a similar type to those seen in adults.
- Serious adverse reactions occur in <0.8% of children and the incidence of diclofenac-induced bronchospasm in asthmatic children is <2.7%.

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AIM

The aim of this study was to investigate the type of common (occurring in >1% of patients) adverse reactions caused by diclofenac when given to children for acute pain.

METHODS

A prospective observational study was undertaken on paediatric surgical patients aged ≤12 years at Great Ormond Street and University College London Hospitals. All adverse events were recorded, and causality assessment used to judge the likelihood of them being due to diclofenac. Prospective recruitment meant not all patients were prescribed diclofenac, allowing an analysis of utilization. Causality of all serious adverse events was reviewed by an expert panel.

RESULTS

Children prescribed diclofenac were significantly older, and stayed in hospital for shorter periods than those who were not. Diclofenac was not avoided in asthmatic patients. Data on 380 children showed they suffer similar types of nonserious adverse reactions to adults. The incidence (95% confidence interval) of rash was 0.8% (0.016, 2.3); minor central nervous system disturbance 0.5% (0.06, 1.9); rectal irritation with suppositories 0.3% (0.009, 1.9); and diarrhoea 0.3% (0.007, 1.5). No serious adverse event was judged to be caused by diclofenac, meaning the incidence of serious adverse reactions to diclofenac in children is <0.8%.

CONCLUSION

Children given diclofenac for acute pain appeared to suffer similar types of adverse reactions to adults; the incidence of serious adverse reaction is <0.8%.

Introduction

Diclofenac was found to be one of the most commonly used off-label medicines on UK paediatric surgical wards [1, 2]. The term off-label refers to diclofenac being unlicensed for use in acute pain in children, although while this study was being undertaken the suppositories were licensed for those aged ≥ 6 years. This still leaves children < 6 years, who are treated off-label, and as there is no licensed paediatric oral formulation, oral treatment is unlicensed either due to the need for modifying adult formulations (usually taking a proportion of a dispersible tablet) or using an unlicensed suspension. It is thought children treated with off-label and unlicensed medicines may be at higher risk of adverse reactions [3,4], and the propensity for medication errors due to manipulation of adult formulations is also increased [5]. Furthermore, developmental differences in drug handling [6] may lead to different incidence and types of adverse reactions in children and adults.

In recent years, governments have realised that children are disadvantaged by not having access to licensed medicines. Legislation in the USA was first enacted with the 1997 Food and Drug Administration Modernisation Act, giving financial incentives for paediatric medication research in the form of extended patents [7]. Similar legislation has now been implemented across Europe, a particular feature of which allows for the licensing of old, off-patent medicines [8].

This study formed part of an investigation to address the lack of information on diclofenac off-label use in children, which also included a pharmacokinetic study [9] and systematic literature review [10]. The aims of the present study were to ascertain the types of common (occurring in $>1\%$ of patients) adverse drug reactions caused by diclofenac in children treated for acute pain, and to report all serious adverse events regardless of their cause. The importance of reporting all serious adverse events is highlighted by the practolol disaster; the ocular manifestations of practolol toxicity went unrecognized for several years due to it being an unexpected response to a β -blocker [11]. Reporting all serious adverse events aims to provide timely pattern recognition in order to identify unexpected adverse reactions, which in this study may include unexpected serious adverse reactions to diclofenac seen in children but not adults.

Methods

Study type and recruitment

A prospective observational study was undertaken on the paediatric surgical wards at Great Ormond Street Hospital for Children and University College London Hospital. The study was approved by independent research ethics committees at each hospital. Parents of children aged ≤ 12

years were approached to provide written informed consent prior to surgery. The exclusion criteria were:

- 1 Patients admitted for emergency surgery, as prospective recruitment would not be possible.
- 2 Patients scheduled for high-risk surgery defined as those requiring an intensive care stay in the postoperative period. These patients were likely to have multiple interventions, meaning determining a single cause of any adverse events would be difficult.
- 3 Any patient already enrolled in more than one other study.

The decision to prescribe diclofenac rested solely with the anaesthetic and surgical teams caring for the patient.

Adverse event monitoring

The medical notes, with clarification from clinical staff where necessary, were used to compile demographic and medical histories. The presence of pre-existing asthma was recorded according to the British Thoracic Society guidelines: 'mild asthma' meaning that asthma was mentioned in the past medical history and/or was being treated with bronchodilators only (step one), and asthma requiring at least regular inhaled steroid treatment (step two or above) [12].

For patients prescribed diclofenac, any adverse events reported in the medical or nursing notes, by clinical staff or by patients/parents were recorded. Adverse event reporting was specifically sought from inpatients and their parents, who were approached on the day after the operation (before discharge for day-case patients), on day 3 after the operation, and 1 week later. A single open question was asked:

'Have you/your child experienced any problems?'

Medicines prescribed on discharge were recorded and patients/parents were telephoned approximately 1 week after discharge to check for adverse events since leaving hospital.

Definition of terms

Adverse drug reaction definitions [13] are often long and contain terms open to ambiguity, so the following simple definition was used:

'An adverse event caused by a medicinal product'

This contains three terms requiring clarification, namely 'adverse event', 'caused' and 'medicinal product'.

An adverse event was defined as any untoward occurrence that presents during the study period, regardless of its cause. An adapted from a common definition [14] was used:

Table 1

World Health Organization causality categories [13]

Very likely/certain:
A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
Probable/likely:
A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
Possible:
A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by current disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unlikely:
A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanation.
Unrelated:
A clinical event, including laboratory test abnormality, with an incompatible time relationship to drug administration, and which could be explained by underlying disease or other drugs or chemical.
Unclassifiable:
A clinical event, including laboratory test abnormality, with insufficient information to permit assessment and identification of the cause.

‘Any new diagnosis, reason for referral to a doctor, unexpected deterioration in a concurrent illness, any suspected adverse drug reaction, or any other complaint considered to be of sufficient importance to enter in the patient’s medical/nursing notes. Any laboratory test result outside the usual reference range and any complaint from the patient or parent was also classified an adverse event’.

The second term requiring clarification is the word ‘caused’. The World Health Organization (WHO) has produced a series of definitions of terms used in causality assessment, the details of which are given in Table 1, and final adverse event categorization was based on this. In order to guide this assessment process, a scoring system by Naranjo [15] and an algorithm based on yes/no questions [16] were used, taking a similar approach to a previous prospective observational study [17].

The final term to be defined is ‘medicinal product’. A medicinal product is defined in the UK Medicines Act 1968 as being:

‘Any substance or article (not being an instrument, apparatus or appliance) which is being manufactured,

sold, supplied, imported or exported for use wholly or mainly in either or both of the following ways, that is to say:

- 1 use by being administered to one or more human beings or animals for a medicinal purpose;
- 2 use as an ingredient, by a practitioner or in a pharmacy or in a hospital or in a business comprising the sale of herbal remedies, in the preparation of a substance or article which is to be administered to one or more human beings or animals for a medicinal purpose’ [18].

In order to determine the potential for morbidity and mortality of adverse events, each one was given a measure of seriousness, the definition of which is given in Figure 1 [13].

Sample size

When n is the number of patients, events that are not seen must have an overall population frequency of $<3/n$ patients with a confidence of 95% [19]. Therefore, in order to be 95% confident of seeing at least one reaction whose population frequency is $>1\%$, a minimum sample of 300 patients was required.

Causality assessment

Each adverse event was given a measure of causality using the WHO definitions (Table 1). In addition, causality of all serious adverse events was assessed by an expert panel consisting of: a paediatric anaesthetist, a paediatric clinical pharmacologist, and a paediatric pharmacist.

Data analysis

Data from the case report forms were entered into a demographic and adverse events database using the statistical package SPSS (version 13; SPSS Inc., Chicago, IL, USA). Adverse reaction incidence 95% confidence intervals (95% CI) were calculated according to the Poisson distribution.

Results

Demographics and diclofenac utilization

A total of 385 patients were recruited to the main study, and four were recruited at pre-admission but excluded (two had their operations at a different hospital, two had their operations cancelled). A further eight patients recruited during a pilot of the case report form, and 71 patients taking part in a pharmacokinetic study of a new diclofenac oral suspension at Great Ormond Street Hospital [9], were also included for the analysis of adverse events. Table 2 gives the demographic details of the 385 patients recruited to the main adverse drug reaction study; 301 of

A serious adverse event is:
1. **Fatal.**
2. **Life-threatening.**
3. **Prolongs hospitalisation.**
4. **Causes persistent or significant disability or incapacity**
5. **Requires medical or surgical intervention to prevent the above (1-4)**

Figure 1
Definition of a serious adverse event. Adapted from: Edwards IR and Aronson JK, 2000 [13]

Table 2
Demographic details of patients recruited to the adverse event monitoring study

	Frequency given as number (percentage) or mean (range) as appropriate			Mann-Whitney test
	All Patients	Received diclofenac Yes	No	
Age (years)	6.0 (0.3–12.9)	6.3 (0.9–12.9)	4.7 (0.3–12.6)	$P < 0.001$
Weight (kg)	22.7 (5.3–80)	23.9 (7.6–80)	18.9 (5.3–54.4)	$P < 0.001$
Stay length (days)	3.1 (1–117)	2.6 (1–26)	4.9 (1–117)	$P = 0.004$
Male	221 (57%)	177 (59%)	44 (52%)	χ^2 test $P = 0.17$
Female	164 (43%)	124 (41%)	40 (48%)	
No known allergies	314	249 (79%)	65 (21%)	
At least one known allergy	71	52 (73%)	19 (27%)	
No asthma	336	261 (78%)	75 (23%)	
Mild asthma	30	27 (90%)	3 (10%)	χ^2 test $P = 0.17$
Asthma	19	13 (68%)	6 (32%)	
Surgery type:				
Dental	137	119 (87%)	18 (13%)	
Ear, nose and throat	12	12 (100%)	0 (0%)	
* General	69	48 (70%)	21 (30%)	
Orthopaedic	49	44 (90%)	5 (10%)	
Plastic/craniofacial	56	45 (80%)	11 (20%)	
* Urology	62	33 (53%)	29 (47%)	

*Certain procedures (hernia repair, circumcision, orchidopexy) carried out by general surgeons and urologists – classification made by surgeon specialty.

these received diclofenac. The median number of doses per patient was one (range one to 22).

Adverse events
Adverse event data from the main, pilot and pharmacokinetic [9] studies were collected from 380 patients. A total of 224 adverse events were recorded in 130 patients, eight of which were unclassifiable (laboratory abnormalities with no temporal information) and 35 unrelated events that occurred before diclofenac was administered. Table 3 gives details of all adverse events with a possible or probable/likely causality classification. No events were classified as very likely/certain.

Probable/possible adverse drug reactions
Two adverse events were classified as being probable/likely adverse drug reactions. The first was a 7-year-old boy who suffered a single episode of diarrhoea, the second was a case of rectal irritation in a 5-year-old girl. In total, 99 patients suffered at least one adverse event classified as probable/likely or possible. Median number of doses (1 vs.

1), mean age (6.6 vs. 5.6 years) and proportion receiving $>1\text{ mg kg}^{-1}$ (15 vs. 16%) and formulation received did not differ between these patients and those with no probable/likely or possible adverse events, respectively.

Serious adverse events
Twenty-three adverse events were classified as serious and were reviewed by the expert panel. Tables 4–6 give details of each event according to their causality.

Discussion
Diclofenac utilization
Patients who received diclofenac were significantly older and spent less time in hospital than those who did not (Table 2). We found that diclofenac was avoided in younger children, possibly due to worries about renal function maturation, and in patients who stayed for longer and underwent more complex surgery. Diclofenac is an effective, opiate-sparing analgesic and most patients received a

Table 3

Detailed listing of adverse events occurring with a reasonable temporal relationship to diclofenac administration (possible and probable/likely classifications)

Event type	Number of events	Details (number of events)
Cardiac	1	Tachycardia (1)
Central nervous system	2	Dizziness (1), drowsiness (1)
Dermatological	5	Itchy back (1), rash – generalized (2), rash – hands (2)
Gastrointestinal	67	Abdominal pain (5), constipation (1), diarrhoea (1), nausea (2), occult blood aspirated from nasogastric tube (1), rectal irritation (1), vomited (56)
Haematological	34	Excessive blood loss from drains (2), excessive ooze from wound (4), laboratory values outside range (26), nosebleed (1), re-admitted to theatre due to bleeding (1)
Infection	7	Bacterial culture from swabs (3), laboratory values outside range (2), pyrexia (2)
Muscular	1	Muscle spasm (1)
Respiratory	4	Hyperventilation (1), laryngospasm (2), wheeziness (1)
Urological	1	Catheter blocked (1)
Total	122	

Table 4

Serious adverse events ‘unrelated’ to diclofenac

Background	Adverse event	Comments
Male 3 years, admitted for closure of ileostomy	Problems re-establishing feeding postoperatively leading to prolonged hospital admission and the requirement for total parenteral nutrition	Diclofenac was not given intra-operatively and was started on day 2 post surgery when poor feeding had already been noted. Furthermore, feeding problems continued for over a week after the last diclofenac dose
Male 1 year, admitted for cranial vault re-modelling	Massive intra-operative bleed requiring fluid, red blood cell and plasma replacement	Diclofenac was not given until the evening, after the operation
Male 4 years, admitted for cranial vault expansion	Intra-operative bleed requiring fluid, red blood cell and whole blood replacement	Diclofenac was not given until the day after the operation
Female 1 year, admitted for cranial fronto-orbital re-modelling	Very low haemoglobin (7 g dl ⁻¹) noted in theatre, required overnight blood transfusion	Onset before diclofenac was given (at the end of the operation)
Male 11 years, admitted for bladder neck reconstruction and closure	Intra-operative complications – blood and urine leaking from incision, re-explored and sealed hole	Diclofenac was not given until day 3 after the operation

dose of 1 mg kg⁻¹, which gives a similar exposure to 50 mg in adults [9]. While many patients in this study received a single dose, this reflects how diclofenac is used in practice, meaning the results should be relevant to health professionals treating children with acute pain.

There was no significant difference in the frequency of diclofenac prescribing between asthmatic and non-asthmatic children. It seems that prescribers in this study did not avoid diclofenac in asthmatic children, probably due to a combination of factors. First, a large randomized trial in febrile children, where 1879 asthmatics received ibuprofen or paracetamol, resulted in a paradoxical significant decrease in asthma morbidity in the ibuprofen group [20], so concerns of nonsteroidal anti-inflammatory drug (NSAID)-induced bronchospasm in asthmatics may be unwarranted. Second, as diclofenac is an effective opioid-sparing analgesic, the first dose of which is being given in a hospital, the potential benefit to the patient is probably greater than the risk of harm due to bronchospasm.

This study included 40 asthmatic children, none of whom experienced bronchospasm with diclofenac; the

same was also found in a published bronchoprovocation challenge in 70 asthmatic children given oral diclofenac 1–1.5 mg kg⁻¹ [21]. Combining these groups gives a total of 110 asthmatic children in whom diclofenac did not induce bronchospasm, making the maximum incidence of diclofenac-induced bronchospasm 2.7% with a confidence of 95% [19]. NSAID-induced bronchospasm in asthmatics is thought to occur in approximately 11% of asthmatics and its mechanism is probably through inhibition of cyclooxygenase (COX)-1 mediated leukotriene production [22]. As diclofenac is a more potent inhibitor of COX-2 than of COX-1 [23], this may explain the lower incidence of bronchospasm than would be expected with other NSAIDs.

Diclofenac adverse drug reactions

In total, 122 adverse events occurred within a reasonable time relating to diclofenac administration, and were therefore classified as ‘possible’ or ‘probable/likely’ (Table 1). There follows a discussion of these grouped by body system. Due to the relatively small number of children included, the precision of adverse drug reaction rates is

Table 5

Serious adverse events 'unlikely' to be diclofenac adverse drug reactions

Background	Adverse event	Comments
Female 3 years, admitted for cranial fronto-orbital re-modelling	Re-hospitalized 1 week post discharge due to wound infection requiring debridement and intravenous antibiotics	Received a single dose of diclofenac in theatre. Time of onset of infection unclear but showing no signs of infection on discharge (5 days after the dose of diclofenac)
Female 4 years, admitted for insertion of gastric feeding tube. Type 1 diabetes	Loss of glycaemic control, prolonged hospitalization in the postoperative period	Received a single dose of diclofenac in theatre, problems with blood sugars started 36 h later and continued until day 7, during which time the patient did not receive any diclofenac
Male 2 years, admitted for Nissens fundoplication and gastrostomy formation	Patient was unable to tolerate feeding for 3 weeks after the operation, prolonging hospitalization. Received 16 doses of diclofenac in the first 6 days postoperatively	Feeding problems did not resolve for 2 weeks after the last dose of diclofenac, unlikely that gastric irritation leading to anorexia would be this prolonged. No drops in haemoglobin, red blood cells or any other markers that would suggest a gastrointestinal bleed
Male 1 year, admitted for cranial vault re-modelling	Developed rash and pyrexia on day 4 post operation, which prolonged hospitalization. Had four doses of diclofenac, the last one was the day after the operation. Mother was breast feeding and started a course of flucloxacillin on day 3 post operation. Cultures of <i>Staphylococcus aureus</i> were grown from femoral line samples. Diclofenac re-started on day 6 post operation with no recurrence of rash	The temporal relationship to the onset of the rash and pyrexia was poor, and rechallenge with diclofenac did not cause a rash/pyrexia. This reaction was thought to be probably a combination of femoral line infection and possible flucloxacillin allergy from breast milk
Male 10 years, admitted for posterior spinal fusion	Wound did not heal and continued to ooze for 8 days, prolonging hospitalization. Received seven doses of diclofenac in the first 3 days postoperatively. Cultured <i>Staphylococcus epidermidis</i> from wound swabs and clinical impression was wound infection	Poor temporal relationship as wound continued to ooze after diclofenac stopped. Diclofenac inhibition of COX-1 is reversible, so would expect platelet aggregation to normalize on withdrawal. No clotting times measured, but wound infection provides compelling causative factor
Male 7 years, admitted for Nissens fundoplication. History of recurrent respiratory tract infections	Suffered a collapsed lung and pneumonia on the day after the operation, requiring a week-long stay in the intensive care unit. Received a single dose of diclofenac in theatre	Respiratory complications liable to be either COX-1 mediated or allergic-type reactions, neither of which have a temporal association that would be likely to extend to the day after a single dose of diclofenac. Patient's medical history provides more compelling contributing factor
Female 1 year, admitted for removal of cystic hygroma	Admitted to local hospital 6 days post discharge with wound infection	Received a single dose of diclofenac in theatre. Time of onset of infection unclear but showing no signs of infection on discharge (2 days after the dose of diclofenac)
Male 11 years, admitted for circumcision	Developed a wound infection 1 week after discharge, which required treatment with oral antibiotics. Received a single dose of diclofenac in the operating theatre	Poor temporal relationship, onset was a week after diclofenac dosing
Male 4 years, admitted for circumcision	Developed a wound infection 3 days after discharge, which cleared with oral antibiotics. Received a single dose of diclofenac in the operating theatre	Poor temporal relationship, onset was 3 days after diclofenac dosing
Male 9 years, admitted for dental extractions	Developed a throat infection 4 days after discharge, which cleared with oral antibiotics. Received a single dose of diclofenac in the operating theatre	Poor temporal relationship, onset was 4 days after diclofenac dosing
Male 9 years, admitted for dental extractions	Developed a throat infection 3 days after discharge, which cleared with oral antibiotics prescribed by dentist. Received a single dose of diclofenac in the operating theatre	Poor temporal relationship, onset was 3 days after diclofenac dosing

poor, but rates have been included with 95% CI for some of the more likely adverse reactions.

Bleeding Nine patients had elevated activated partial thromboplastin times (aPTT) compared with baseline preoperative values; of these, seven had undergone craniofacial vault remodelling, and two had spinal fusions. Procedures in the craniofacial region have a high risk of bleeding complications due to disseminated intravascular coagulation, where the high thromboplastin levels in the brain cortex increase in response to trauma, causing extensive clotting in the microcirculation. Consequently, clotting factors become depleted, which can result in elevated aPTT [24]. Spinal fusion surgery is also a major operation with a high degree of blood loss; in these patients depletion of clotting factors would also elevate aPTT. None of the 112 other patients, some of whom had minor procedures, had elevations in laboratory clotting times with a reasonable temporal relationship to diclofenac. Of the four patients with subjectively excessive wound ooze, two were dental patients having had multiple teeth removed, one had a revision of cleft palate scar and the final patient had an alveolar bone graft. No pathology results were available for these patients. The patient with nosebleed after dental surgery reported suffering from regular nosebleeds. Finally, a patient had to be taken back to the operating theatre for wound re-stitching due to bleeding, but had pulled the stitches out through overactivity.

It would therefore seem that bleeding complications are multifactorial, and in most circumstances diclofenac

Table 6

Serious adverse events 'possibly' diclofenac adverse drug reactions

Background	Adverse event	Comments
Male 3 years, admitted for excision of naevus on his back	Had to return to theatre on day 1 post operation to re-stitch the wound as it re-opened. Diclofenac given in theatre on both occasions	Temporal relationship is reasonable, although no excessive oozing was noted on rechallenge with diclofenac. Furthermore, the likely cause was that the patient was very active and probably excessive movement caused the stitches to separate
Female 2 years, admitted for Nissens fundiplication, history of laryngomalacia and on regular nebulized salbutamol at home	Day 3 post operation developed polyphonic wheeze, treated with salbutamol, ipratropium and monteleukast and prolonged hospitalization. Received eight doses of diclofenac between day 1 and day 3	Reasonable temporal relationship for COX-1-mediated narrowing of airways. However, patient was on regular nebulized salbutamol at home, which was omitted after the operation due to an oversight. This provides an alternative plausible cause
Female 7 years, admitted for spinal fusion	Wound swab taken on day 3 post operation isolated a coagulase-negative Staphylococcus. Flucloxacillin restarted and hospitalization prolonged. Received nine doses of diclofenac during the first 4 days	Reasonable temporal relationship with diclofenac administration, but contamination either in theatre or on the ward provides a more plausible explanation
Male 11 years, admitted for revision of craniofacial re-modelling	Increased drainage of blood noted on the evening of the operation from the drains inserted, required blood transfusion. Received a single dose of diclofenac in theatre, aPTT elevated postoperatively but no preoperative samples available	Temporal relationship reasonable but unknown whether aPTT was elevated preoperatively. Also depletion of clotting factors and small quantities of heparin used to keep lines patent may affect aPTT
Male 1 year, admitted for hypospadias repair	Had an intra-operative laryngospasm, oxygen saturation dropped to 40% and developed bradycardia during the operation, required oxygen and brief cardiac massage. Received a dose of diclofenac at the start of the operation	There is a reasonable temporal relationship with diclofenac administration, but the patient also received propofol and fentanyl with a reasonable temporal relationship and was also intubated, which is the most likely cause as the patient showed no sign of allergic-type reaction
Male 3 years, admitted for hypospadias repair	Vomited several times after the operation despite use of anti-emetic (cyclizine) and prolonged hospitalization for a day. Received a single dose of diclofenac in the operating theatre	There is a reasonable temporal relationship with the onset of vomiting and diclofenac administration. The patient also received several other drugs, which provide other possible causes
Male 9 years, admitted for hypospadias repair	Urinary catheter would not drain so patient had to be re-admitted to theatre the following day for insertion of a suprapubic catheter under general anaesthetic. Received diclofenac on both occasions	Reasonable temporal relationship, but other possible causes include a blockage in the catheter or it becoming dislodged/misplaced

aPTT, activated partial thromboplastin time.

Table 7

Number of patients having at least one bleeding adverse event including elevated laboratory clotting times with a reasonable temporal relationship to diclofenac administration against surgery type

Surgery type	Number of patients prescribed diclofenac	Number having a bleeding adverse event with a reasonable temporal relationship to diclofenac administration (%)	Procedure undergone in patients experiencing bleeding/wound ooze/excessive loss from drains
Craniofacial	23	9 (39%)	Cranial remodelling
Dental	119	3 (3%)	Dental extractions
Ear, nose and throat	12	1 (8%)	Alveolar bone graft
General	48	0	
Orthopaedic	45	2 (4%)	Spinal fusion
Plastic	80	1 (1%)	Naevus excision – pulled stitches
Urology	53	0	
Total	380	16 (4%)	

seems a less plausible cause than other factors such as surgery type (Table 7). Further evidence for this is given in a systematic literature review, where 955 children undergoing tonsillectomy were randomized to receive either a NSAID or placebo/non-NSAID analgesic [25] and there was no significant increase in bleeding events in the NSAID group.

Gastrointestinal There were no episodes of gastrointestinal bleeding that were attributed to diclofenac. Both adverse events classified as probable/likely to be diclofenac were gastrointestinal effects. One patient complained of rectal irritation and one of diarrhoea in the post-operative period after receiving a diclofenac suppository in the operating theatre. Rectal irritation is a known

adverse effect of diclofenac, which is a weak acid, and is mediated by either direct action of the drug on rectal mucosa or mechanical irritation caused by suppository insertion. The case of diarrhoea is less straightforward but still likely to be caused by diclofenac. This patient experienced a single episode of diarrhoea on the morning following surgery in which he received a diclofenac suppository. Diarrhoea is a known adverse effect of diclofenac and no other potential causes were obvious (no other medications received are known to cause diarrhoea, other family members were not affected). In total, 287 patients received at least one diclofenac suppository, making the incidence (95% CI) of rectal irritation 0.3% (0.009, 1.9). The incidence (95% CI) of diarrhoea associated with all forms of diclofenac in this study was 0.3% (0.007, 1.5).

Respiratory Four respiratory adverse events had a reasonable temporal onset compared with diclofenac administration, none of which was an allergic-type bronchospasm. Hyperventilation was recorded in the nursing notes for one patient who became extremely distressed after an operation for multiple dental extractions. The cause of this adverse event was most likely to be emotional rather than pharmacological. Two patients experienced laryngospasm in the operating theatre, and although the temporal relationship was reasonable with diclofenac administration, intubation is the most likely cause. The final respiratory adverse event was wheezing in a patient with pre-existing laryngomalacia who required regular nebulized salbutamol at home, which had been inadvertently omitted in the postoperative period. No respiratory adverse events could therefore reasonably be attributed to diclofenac.

Renal No patients had elevations in serum creatinine or urea in the postoperative period, but this is possibly a reflection of the fact that only 23 had samples taken for urea and electrolytes after the operation. In adults, a transient asymptomatic reduction in creatinine clearance occurred in the postoperative period when comparing NSAIDs with placebo [26]. Although in the present study no symptomatic reductions in renal function occurred, it was hoped that more patients would have undergone testing for urea and creatinine so that comparisons between ages could have been made.

Dermatological Five dermatological adverse events had a temporal relationship making them possibly related to diclofenac. Two were rashes on the hands where topical anaesthetic creams had been used. The three further reactions thought more likely to be diclofenac-related were: a macular patchy rash that developed on each limb within 30 min of diclofenac administration and resolved approximately 1 h later, an erythematous rash (may also have been caused by concomitant tonsillitis), and a patient who complained of an itchy back on day 3 of regular diclofenac

treatment for postoperative pain. The incidence (95% CI) of nonserious dermatological reaction caused by diclofenac was therefore 0.8% (0.016, 2.3).

Other events The only cardiovascular adverse event with a reasonable temporal relationship was an episode of postoperative tachycardia, which resolved within 6 h. This event had a reasonable temporal relationship with diclofenac administration, but the patient also received atracurium, which provides a more plausible cause. Two adverse events affecting the central nervous system (CNS) were recorded that had a reasonable temporal relationship with diclofenac. Dizziness and drowsiness are reported adverse effects of diclofenac [27], although in both cases the patients also received opioid analgesia (fentanyl and morphine) and propofol anaesthesia. If it were assumed that both were caused by diclofenac, this would give an incidence (95% CI) of minor CNS disturbance of 0.5% (0.06, 1.9). Seven patients had signs of infection with a reasonable temporal relationship to diclofenac administration. No mechanism from diclofenac's known pharmacology, such as immunosuppression, would make patients more susceptible to infection. The final 'possible' adverse drug reaction was a blocked urinary catheter. The temporal relationship made it a possible adverse drug reaction, but no pharmacological reason can be envisaged.

Serious adverse events No serious adverse events were recognized as diclofenac adverse drug reactions. This study took place in tertiary and secondary care settings, and included a range of procedures and diclofenac formulations. As most children in the UK undergo operations in similar settings, then these results should be transferable to the general paediatric population. This means that there is a 95% probability that serious adverse drug reactions such as acute renal failure, symptomatic gastrointestinal bleeding, bronchospasm and hepatotoxicity have an incidence of <0.8% in paediatric patients treated with diclofenac in the perioperative period.

Conclusions

The results of this study suggest that the common adverse drug reactions of diclofenac when used for acute pain in children are similar to those in adults. Serious adverse reactions occur in <0.8% of children and the incidence of diclofenac-induced bronchospasm in asthmatic children is <2.7%.

Competing interests

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