CURRENT MEDICAL RESEARCH AND OPINION®
VOL. 25, NO. 9, 2009, 2207–2222

0300-7995
doi:10.1185/03007990903116255




REVIEW ARTICLE

# Systematic review and meta-analysis of the clinical safety and tolerability of ibuprofen compared with paracetamol in paediatric pain and fever

Elizabeth R. Southey[a], Karla Soares-Weiser[b] and Jos Kleijnen[c,d]

[a]*Watermeadow Medical, Witney, Oxfordshire, UK*

[b]*Enhance Reviews, Kfar-Saba, Israel*

[c]*Kleijnen Systematic Reviews Ltd, York, UK*

[d]*Care and Public Health Research Institute (CAPHRI), University of Maastricht, The Netherlands*

***Corresponding author:*** **Elizabeth R. Southey, Watermeadow Medical, Range Road, Witney, Oxfordshire, OX29 0YN, UK; liz.southey@watermeadow.com**

***Keywords:*** **Adolescent – Child – Fever – Ibuprofen – Infant – Pain – Paracetamol**



## ABSTRACT

*Objective*: The main aim of this review was to compare the tolerability and safety between ibuprofen and paracetamol when used as anti-pyretic and analgesic agents in children up to 18 years of age.

*Methods*: MEDLINE (1950 to November 2008), EMBASE (1980 to November 2008), The Cochrane Library (2007, Issue 3), ACP Journal Club (1991 to November 2007) and Pascal (1987 to November 2007) were searched for randomised controlled trails (RCTs) (comparing ibuprofen and/or paracetamol with placebo), controlled observational studies and large case series comprised more than 1000 participants.

*Main outcome measures*: Adverse events (AEs) requiring discontinuation of medication; systemic reactions related to ibuprofen or paracetamol; serious AEs that are fatal, life-threatening or require hospitalisation; and serious AEs not requiring hospitalisation.

*Results*: A total of 24 RCTs examined either ibuprofen and/or paracetamol versus placebo for AE data. Twelve other studies meeting our criteria were also included for AE data. Meta-analysis of systemic reactions demonstrated that tolerability and safety of ibuprofen was similar to placebo, as was paracetamol: ibuprofen versus placebo relative risk (RR) 1.39 (95% CI: 0.92, 2.10); paracetamol versus placebo RR 1.57 (95% CI 0.74, 3.33). A total of 2937 systemic AEs occurred in 21 305 patients taking ibuprofen compared with 1466 systemic AEs in 11 164 patients taking paracetamol: RR 1.03 (95% CI 0.98, 1.10). There was no significant difference between the two groups. Narrative analysis of AE data identified conflicting evidence regarding hepatic injury with paracetamol and group A streptococcal infections with ibuprofen or paracetamol treatment.

*Conclusions*: Ibuprofen, paracetamol and placebo have similar tolerability and safety profiles in terms of gastrointestinal symptoms, asthma and renal adverse effects. While the study data investigated here may not reflect over-the-counter use, these results are still relevant in the context of any safety concerns relating to general ibuprofen or paracetamol treatment in children.

## Introduction

Fever and pain in children, especially associated with infections such as acute otitis media, is very common[1]. While only being a sign or symptom of other illness or disease, an elevated body temperature is associated with discomfort, and an increased risk of dehydration and seizures[2]. Naturally, parental concern of these effects leads to fever being one of the most commonly-treated paediatric conditions; fever and pain can be treated easily with over-the-counter antipyretic/analgesic drugs such as ibuprofen and paracetamol. Widespread use of these medications has shown that they are effective and generally well-tolerated in the reduction of paediatric fever and pain, although surprisingly optimal doses, dosing regimens and choice of medication are not clearly described in the scientific literature[3,4].

Despite the extensive administration of ibuprofen and paracetamol, adverse events (AEs) with the therapeutic use of these drugs seem to be uncommon. Ibuprofen is better tolerated than other non-steroidal anti-inflammatory drugs (NSAIDs), although it has previously been associated with renal toxicity, allergic reactions and gastrointestinal (GI) adverse effects[5–7]. It has also been documented in the literature that ibuprofen use could lead to exacerbation of symptoms in febrile children with a past medical history of asthma[8,9]. This association has been investigated in clinical trials but has not been confirmed[10,11].

Hepatotoxicity appears to be the most serious and well-documented AE associated with paracetamol use in children. Case reports have suggested that liver failure can occur with chronic treatment with doses just above the recommended maximum dose[12,13]. Urticaria and maculopapular rashes have been attributed to paracetamol use[14] along with rare dermatological AEs such as acute generalised exanthematous pustulosis (AGEP)[15]. Hypersensitivity reactions (including skin reactions) have resulted in reports of bronchospasm, vasculitis and Stevens–Johnson syndrome[14]. These often occur within the first hour of dosing, although these could also occur 4–5 hours after initial treatment[16,17]. Allergic rhinitis may also be linked with paracetamol use[18].

While randomised controlled trials (RCTs) are continuously being published on the efficacy of ibuprofen and paracetamol use in children[19,20], and systematic reviews in this area have previously been conducted[21,22], it appears that no systematic review has specifically and comprehensively investigated the safety of both these agents in paediatric pain and fever. Rare AEs are infrequently identified through randomised trials, and this review sought well-designed observational studies that might lead to the identification of serious AEs that are fatal, life threatening or required hospitalisation, other serious AEs such as asthma, cardiovascular AEs, abdominal pain, gastrointestinal bleeding, renal failure of any cause (i.e., interstitial nephritis), hepatotoxicity, dermatological reactions, hypersensitivity or haematological reactions or AEs that required discontinuation of medication and systemic reactions such as nausea, sweating, or cutaneous rash more accurately. Consequently, the main aim of this review was to compare the tolerability and safety between ibuprofen and paracetamol when used as antipyretic and analgesic agents in children from 0 to 18 years of age.

## Methods

This systematic review followed the Centre for Reviews and Dissemination guidelines for undertaking systematic reviews (CRD 2001[23]) and The Cochrane Collaboration Handbook[24].

### Data sources and searches

The search strategies were developed specifically for each database (the search strategy for MEDLINE is presented in the Appendix; details of similar strategies for the other databases can be provided from the authors upon request).

The following databases were searched: MEDLINE (1950 to November 2008)[25]; EMBASE (1980 to November 2008)[26]; CDSR, CENTRAL, and DARE published in The Cochrane Library (2007, Issue 3)[27]; ACP Journal Club (1991 to November 2007)[28]; Pascal (1987 to November 2007)[29].

### Study selection

Inclusion criteria were: RCTs comparing the efficacy and tolerability and safety of ibuprofen or paracetamol with placebo; controlled observational studies for rare AEs; case series with more than 1000 participants; children up to 18 years of age, who have pain and/or fever. These broad entry criteria were applied to capture the literature and routine use of these drugs in clinical practice; however, such criteria were expected to identify studies differing widely in quality and design.

Two reviewers independently inspected the abstract of each reference identified by the search and determined the potential relevance of each article. For potentially relevant articles, or in cases of disagreement, the full article was obtained, independently inspected, and inclusion criteria applied. Any disagreement was resolved through discussion and was checked by a

third reviewer. Justification for excluding studies from the review was documented. Studies were excluded if they did not meet the inclusion criteria, if no relevant data could be extracted/estimated, or if the paper was not in English, French, Spanish, Dutch, German or Portuguese.

Outcome measures included: serious AEs that were fatal, life threatening, or required hospitalisation; serious AEs that did not require hospitalisation (e.g., asthma, cardiovascular AEs, abdominal pain, gastrointestinal bleeding, renal failure of any cause (specifically interstitial nephritis), hepatotoxicity, dermatological reactions, hypersensitivity or haematological reactions); AEs that required discontinuation of medication; systemic reactions related to the use of ibuprofen or paracetamol (e.g., nausea, sweating, cutaneous rash).

### Data extraction and quality assessment

Data extraction forms were developed using SRS (www.srsnexus.com), piloted independently on a small selection of studies varying in quality and adjusted as necessary. For each study, data were extracted independently by two reviewers. Any disagreements were resolved by consensus. Data extraction was discussed and decisions documented.

Quality assessment forms were developed based on Oxman's checklist for systematic reviews[30], and checklists for randomised clinical trials and other checklists relevant for different study designs from CRD report 4 (CRD 2001) (http://www.york.ac.uk/inst/crd/CRD_Reports/crdreport4_app3.pdf). Quality assessment was carried out independently by two reviewers. Any disagreements were resolved by consensus. It was planned, if enough data were available (ten studies/factor), to include each of the quality components from the studies as explanatory variables in a meta-regression analysis to explain possible heterogeneity; unfortunately, however, there were not enough data to do this.

### Statistical analysis

Statistical analyses were performed using the RevMan (version 5.0.10) software.

Dichotomous data were analysed by calculating the relative risk (RR) for each trial using the Mantel–Haenszel method and the correspondent 95% confidence intervals (CIs)[24]. Continuous data were analysed by calculating the weighted mean difference (WMD) between groups and the correspondent 95% CI[24]. For continuous data, standard deviations and means should be reported in the paper or obtainable from authors. If they could not be obtained by these means, they were estimated from the data that were provided or a representative value was taken from other studies. Data were only pooled if it was felt that the studies were measuring the same effects and if the studies had the same study design; if this was not the case, a narrative synthesis was used. Therefore, the fixed-effects model was used for the calculation of odds ratio (OR) or WMDs. Heterogeneity was initially assessed by measuring the degree of inconsistency in the studies' results ($I^2$)[31].

In order to allow the reader to consider outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed, and where meta-analysis was considered unsuitable for some or all of the data that were identified (e.g., due to the heterogeneity of the studies, or no reliable data were presented in the report), a narrative synthesis method was employed. This involved organising the studies by (as appropriate) intervention, population, outcomes assessed, summarising the results of the studies, summarising the range and size of the associations that these studies report, and describing the most important characteristics of the included studies.

## Results

Following two levels of screening of 5517 identified references, 462 articles were ordered and the full text screened once more independently by two reviewers for inclusion and exclusion. Of these, 36 studies fulfilled the inclusion criteria, and 426 references were excluded. The study flowchart, including reasons for exclusion, is presented in Figure 1. Twenty-four RCTs compared ibuprofen to paracetamol or one of both versus placebo and reported AEs (Table 1[5,10,19,32–64]). Twelve studies that were not RCTs met the study inclusion criteria for AEs (Table 1).

Of the 24 RCTs identified, the allocation generation sequence was unclear in seven studies. Likewise, the allocation concealment was unclear in 12 studies. Information on who was blinded was included in 15 studies. An ITT analysis was carried out in 17 studies. Eight of the 23 studies were reported as having been funded by the pharmaceutical industry.

### Serious AEs that are fatal, life threatening, or require hospitalisation

#### *Acute gastrointestinal (GI) bleeding, renal failure and anaphylaxis*

The risk of hospitalisation from acute GI bleeding, renal failure or anaphylaxis was measured in a randomised control trial of 84 192 children receiving either ibuprofen (5 or 10 mg/kg) or paracetamol (12 mg/kg)[40].

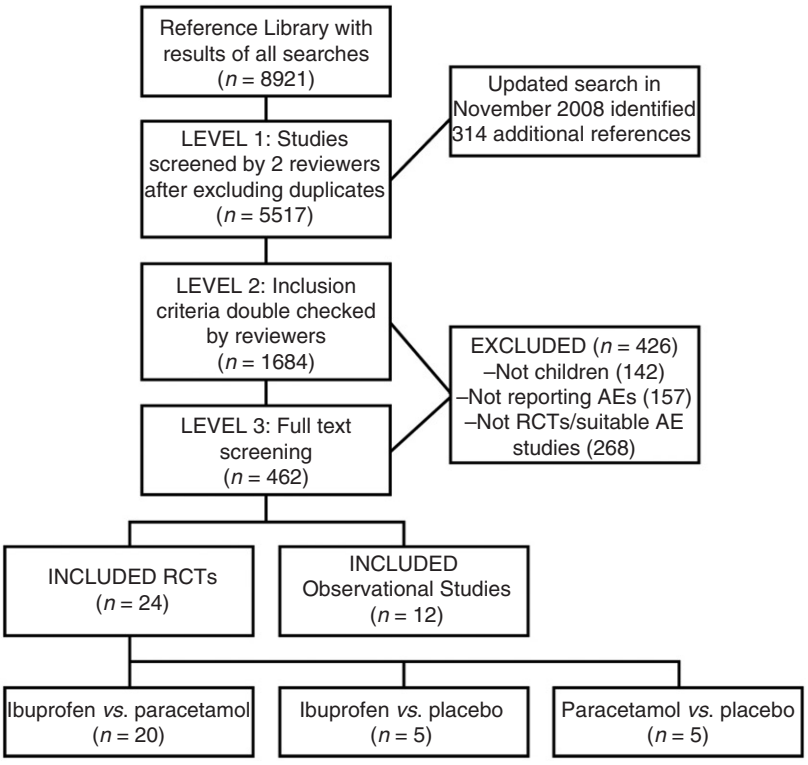


***Figure 1.*** *Study flow. AE, adverse event; RCTs, randomised controlled trials*

Overall, there was no difference in serious AEs that were life threatening or required hospitalisation (OR 1.31 [95% CI: 0.87, 1.97]).

All-cause hospitalisation rates between the two treatment groups were comparable, and there was no evidence of an increased risk of acute GI bleeding, acute renal failure, anaphylaxis or Reye's syndrome with ibuprofen treatment compared with paracetamol. Four children were diagnosed with acute non-major GI bleeding (two each in the ibuprofen dose groups); however, this risk 7.2/100 000 (95% CI: 2, 18/100 000) was not increased compared with paracetamol treatment ($p = 0.31$). Due to the low incidence of GI bleeding, no potential risk differences between ibuprofen doses could be identified. No cases of renal failure, anaphylaxis or Reye's syndrome were observed in either treatment group.

No other studies were identified that reported any risk of renal AEs with the use of ibuprofen or paracetamol.

### *Reye's syndrome*

In support of the RCT outlined above, two case-control studies[54,55] examining pre-admission use of aspirin or paracetamol and the incidence of Reye's syndrome, observed no epidemiological link between paracetamol use and subsequent development of the syndrome. The association between aspirin use and Reye's syndrome is already acknowledged and has led to the contraindication of aspirin use in children. No case-control studies were identified that investigated ibuprofen use and development of Reye's syndrome.

Reassuringly, a large study[32] did not record any incidence of Reye's syndrome, renal failure, anaphylaxis or necrotising fasciitis (NF) in 41 810 children treated with ibuprofen or paracetamol. Furthermore, this study observed no cases of GI bleeding.

### *Group A streptococcal (GAS) infections*

Four case control studies examining the risk of group A streptococcal infections (in particular necrotising fasciitis/necrotising soft tissue infection) associated with non-steroidal inflammatory use during primary varicella infection in children were identified by this review[53,56,58,59]. The studies report conflicting results. Lesko and colleagues[56] found no evidence in a study with 52 cases of GAS infections and 172 controls with uncomplicated primary varicella infections: no association was found between ibuprofen use and necrotising soft tissue infections (OR 1.3 [95% CI: 0.33, 5.3]), although, overall there was an association between ibuprofen use and invasive GAS infections (OR 3.9 [95% CI: 1.3, 12]). However, the authors state that there was no evidence of a dose–response relationship and this was based on the inability to control totally for confounding factors such as indication/severity of the varicella illness, including the height and duration of the fever. Furthermore, this association was

***Table 1.*** *Studies included for adverse event outcomes*

| Type of study | Lead author | Country | Time period | No. of patients | Events investigated |
|---|---|---|---|---|---|
| RCT | Ashraf (1999)[32] | USA | March 1993 – July 1995 | 20111 (ibuprofen) 10033 (paracetamol) | Any |
| RCT | Autret (1994)[33] | France | Not stated | 77 (ibuprofen), 77 (paracetamol) | Systemic reactions: dermatological, GI disturbances, epistaxis |
| RCT | Autret (1997)[34] | France | Not stated | 116 (ibuprofen), 116 (paracetamol) | Systemic reactions: dermatological, GI disturbances, others |
| RCT | Autret-Leca (2007)[35] | France | Not stated | 151(ibuprofen), 150 (paracetamol) | Systemic reactions: infections, GI disturbances, respiratory reactions |
| RCT | Bertin (1996)[36] | France | Nov 1988 – Mar 1990 | 71 (ibuprofen), 73 (paracetamol), 75 (placebo) | Systemic reactions |
| RCT | Bertin (1991)[37] | France | May 1988 – June 1989 | 77 (ibuprofen), 78 (paracetamol), 76 (placebo) | Systemic reactions: nausea, abdominal pain, cutaneous rash |
| RCT | Gupta (2007)[38] | India | Not stated | 103 (paracetamol), 107 (placebo) | Systemic reactions: GI disturbances, headaches |
| RCT | Hay (2008)[19] | UK | Jan 2005 – May 2007 | 52 (paracetamol), 52 (ibuprofen), 52 (paracetamol + ibuprofen) | Systemic reactions: diarrhoea and vomiting; serious AEs with hospital admission |
| RCT | Khubchandani (1995)[39] | India | Jan 1993 – May 1993 | 29 (ibuprofen), 29 (paracetamol) | No AEs reported |
| RCT | Lesko (1995)[40] | USA | Feb 1991 – June 1993 | 28130 (paracetamol), 27948 (ibuprofen 5 mg/kg), 27837 (ibuprofen 10 mg/kg) | Rare but serious AEs |
| RCT | Lesko (2002)[10] | USA | Feb 1991 – June 1993 | 632 (paracetamol), 636 (ibuprofen 5 mg/kg), 611 (ibuprofen 10 mg/kg) | Asthma morbidity |
| RCT | Lands (2007)[41] | USA | Sept 1998 – Aug 2000 | 142 (70 ibuprofen; 72 placebo) | Systemic reactions (with ibuprofen): conjunctivitis; abdominal cramps, nausea, diarrhoea; nausea, vomiting, tinnitus; and, GI bleeding |
| RCT | Lewis (2002)[5] | USA | Not stated | 45 (ibuprofen), 39 (placebo) | Systemic reactions (no AEs were reported). |
| RCT | McGaw (1987)[42] | Canada | Not stated | 41 (ibuprofen), 43 (paracetamol), 39 (placebo) | Systemic reactions (mild GI disturbance) |

(*continued*)

***Table 1.*** *Continued*

| Type of study | Lead author | Country | Time period | No. of patients | Events investigated |
|---|---|---|---|---|---|
| RCT | McIntyre (1996)[43] | UK | Not stated | 76 (ibuprofen), 74 (paracetamol) | Systemic reactions: dermatological, GI disturbances, respiratory distress, epistaxis, cough, asthma, convulsion |
| RCT | Mercan (2007)[44] | Turkey | Not stated | Children in the control group ($n = 59$) received no analgesia until they had a pain score >5; children in group 2 ($n = 65$) were given rectal paracetamol (20–25 mg/kg) 3 h after caudal injection; and those in group 3 ($n = 78$) were given rectal paracetamol 20–25 mg/kg) 4 h after caudal injection | Laryngospasm |
| RCT | Moore (1985)[45] | Canada and USA | Not stated | 14 (ibuprofen), 12 (paracetamol), 11 (placebo) | Systemic reactions (no AEs reported) |
| RCT | Sidler (1990)[46] | Switzerland | Not stated | 30 (ibuprofen 7 mg/kg); 30 (ibuprofen 10 mg/kg); 30 (paracetamol 10 mg/kg) | Systemic reactions: dermatological, GI disturbances |
| RCT | Van Esch (1995)[47] | Netherlands | June 1992 – October 1993 | 34 (ibuprofen), 36 (paracetamol) | Systemic reactions: GI disturbances, febrile seizures, dermatological |
| RCT | Vauzelle-Kervroedan (1997)[48] | France | October 1992 – Dec 1993 | 60 (ibuprofen), 56 (paracetamol) | Systemic reaction: vomiting |
| RCT | Viitanen (2003)[49] | Finland | Not stated | 41 (ibuprofen), 40 (paracetamol), 38 (placebo) | Systemic reactions: vomiting |
| RCT | Vinh (2004)[50] | Vietnam | 1995 – 1998 | 40 (ibuprofen), 40 (paracetamol) | Systemic reactions: GI disturbances, sweating, head cold, epistaxis |
| RCT | Walson (1992)[51] | US | Not stated | 15 (ibuprofen 5 mg/kg), 15 (ibuprofen 10 mg/kg), 15 (paracetamol) | Systemic reactions: respiratory, headache, GI disturbances |
| RCT | Wong (2001)[52] | Central/South America | May 1998 – Dec 1998 | 209 (ibuprofen), 210 (paracetamol) | Systemic reactions: respiratory, GI disturbances, ear/nose/throat, dermatological |

| | | | | | |
|---|---|---|---|---|---|
| Controlled observational (case-control) | Dubos (2008)[53] | France | 2003 | 21 cases of severe bacterial skin complications and 138 controls (paracetamol, NSAIDs) | Severe varicella-related bacterial skin complications |
| Controlled observational (case-control) | Hall (1988)[54] | UK | Aug 1981 – July 1985 | 106 cases of Reye's syndrome and 185 controls with acute febrile illnesses (aspirin, paracetamol) | Reye's syndrome |
| Controlled observational (case-control) | Hurwitz (1985)[55] | USA | Feb 1984 – May 1984 | 30 cases with Reye's syndrome and 145 matched controls (paracetamol, salicylates) | Reye's syndrome |
| Controlled observational (case-control) | Lesko (2001)[56] | USA | June 1996 – Sept 1998 | 52 cases with invasive GAS and 172 controls with uncomplicated primary varicella infection (paracetamol, ibuprofen) | Invasive group A streptococcal (GAS) infections in children with primary varicella infection |
| Controlled observational (case-control) | Ranganathan (2006)[57] | Sri Lanka | Jan 2001 – Mar 2001 | 25 cases with a history of exposure to a supratherapeutic dose (>60 mg/kg/day) of paracetamol and 33 matched controls | Fulminant hepatic failure |
| Controlled observational (case-control) | Souryi (2008)[58] | France | Jan 2000 – Dec 2004 | 38 cases of necrotising soft-tissue infection and 228 matched controls (NSAIDs, paracetamol) | Severe necrotising soft-tissue infection |
| Controlled observational (case-control) | Zerr (1999)[59] | USA | Dec 1993 – May 1994 | 19 cases of NF and 29 controls with a soft-tissue infection (not NF) within 3 weeks of primary varicella infection (ibuprofen, paracetamol) | NF during primary varicella infection |
| Cohort/cross-sectional study | Beasley (2008)[60] | Europe | Not stated | 205 487 (paracetamol) | Asthma, rhinoconjunctivitis, eczema |
| Cohort study | Ludvigsson (2006)[61] | Sweden | Oct 1997 – Oct 1999 | 8341 (paracetamol) | GI symptoms |
| Case series | Hawton (1992)[62] | UK | 1976 – 1989 | 2282 (paracetamol) | Deliberate self-harm/poisoning |
| Case series | Mohler (2000)[63] | USA | Mar 1996 – Mar 1998 | 1039 (paracetamol) | Hepatic injury with paracetamol |
| Case series | Wong (2007)[64] | China | Not stated | 3089 (paracetamol) | Asthma and atopic disorders |

RCT, randomised controlled trial; GI, gastrointestinal; AE, adverse events; GAS, group A streptococcal infections; NF, necrotising fasciitis

confined to children who had taken both ibuprofen and paracetamol in the 7 days before presenting. Paracetamol use was associated with an increased risk of necrotising soft-tissue infection (OR 3.8 [95% CI: 0.92, 16]) compared with ibuprofen (OR 1.3 [95% CI: 0.33, 5.3]), but it did not cross the cut-off for significance.

In contrast, Zerr *et al*. 1999[59] observed an association between NF and ibuprofen use in primary varicella infections (OR 10.2 [95% CI: 1.3, 79.5]). The multivariate analysis for paracetamol (after adjustment for GAS isolation, age and gender) demonstrated an OR of 0.6 (95% CI: 0.1, 3.9). This study was retrospective and with a small sample size (only 19 cases were compared with 29 controls), and therefore no strong conclusions can be drawn from the results. Furthermore, causality could not be demonstrated.

Another study identified, in the French Pharmacovigilance database, 38 cases of necrotising soft tissue infection: 12 infants (age 0–23 months), 16 children (age 2–15 years) and ten adults (>15 years), and these were matched with 228 controls[58]. Of the 24 infants and children diagnosed with varicella infection, 22 had taken NSAIDs: of these, 18 had taken ibuprofen, two had taken niflumic acid, and two had taken both ibuprofen and niflumic acid concomitantly. The numbers of children who had taken paracetamol, as above for ibuprofen or niflumic acid, was not reported. The study does not actually report OR for sole ibuprofen use and risk of necrotising soft tissue infection (NSTI), but instead reports the OR for NSAID use: 64.76 (95% CI: 16.00, 284.20); and the OR for paracetamol use and risk of NSTI: 5.69 (95% CI: 2.34, 13.80). This increased risk of NSTI with paracetamol use is in conflict with findings from the other case control studies above[56,59].

The authors, similarly to the Zerr *et al*. 1999 study[59], acknowledge the limitation of confounding factors such as the viral infection itself, noting that NSAID use had 'occurred after the onset of symptoms of secondary infection'. The authors also put the numbers of cases identified into context: the 38 cases included comprise only 1.9% of all serious skin reactions reported in the database.

The most recent case-control study investigating risk of severe bacterial skin complications identified in this review also implicated paracetamol (OR 4.3 [95% CI: 0.9, 28; $p = 0.04$]), but this association disappeared when adjusted for factors such as other medications and duration and intensity of fever[53] (the author was contacted for clarification of the above result, since a lower 95% CI of 0.9 cannot be associated with a significant *p*-value, however, no response was received). NSAID use (duration and dose were not defined) continued to be associated with an increased risk of severe bacterial skin infections (which included cellulitis, staphylococcal epidermolytic toxin-mediated diseases, abscesses, ecthymas, varicella gangrenosa and scarlet fever) (adjusted OR 4.8 [95% CI: 1.6, 14.4]). Similarly to the other studies, the authors concede that potential confounding factors regarding the indications for using NSAIDs may have confounded their results.

### *Overdose*

A case series with 2282 participants[62] observed a significant increase in the use of paracetamol in suicide attempts by adolescents (10–19 years): in the period 1976–77, paracetamol was used in 23.4% of overdoses; from 1982 to 1983 it was used in 31.1%; and from 1988 to 1989 it was used in 48.3% ($p < 0.001$ in both males and females). The use of minor tranquillisers and sedatives was also recorded: they were used in 20% of the overdoses in 1976–77, 15.7% of cases in 1982–83 and in only 5.2% of suicide attempts in 1988–89.

No studies were identified in this review reporting suicide attempts with ibuprofen in children.

### *Hepatic injury*

A case-control study examined 25 children with febrile illness and fulminant hepatic failure and compared them with 33 age-matched hospital controls[57]. All 25 cases (100%) had ingested supratherapeutic doses of paracetamol (>60 mg/kg/day) compared with only 11 (33%) of the controls (OR was not presented in the publication). Conversely, a prospective observational study has shown that paediatric patients with acute exposure to paracetamol doses of up to 200 mg/kg and monitored at home do not develop signs or symptoms of hepatic injury[59].

## Serious AEs not requiring hospitalisation

### *Haematology*

One study[40] provided data on eight of 55 785 patients receiving ibuprofen versus none of 28 130 patients receiving paracetamol who had low white blood cell (WBC) count (OR 8.57 [95% CI: 0.49, 148.55]). All of these cases were transient and mild with a minimum count of $1.5 \times 10^9$ WBC, and the difference between treatments was not significant. No other haematological parameters were reported.

### *Asthma*

A post-hoc analysis[10] of a previously published RCT[40], investigated the use of ibuprofen (5 or 10 mg/kg) or

paracetamol (12 mg/kg) and any association between bronchospasm and other morbidity from asthma in 1879 children who met the authors' definition of treated asthma. This was those children who had received a $\beta$-agonist, theophylline, or an inhaled steroid on the day before enrolment in the clinical trial. Children were ineligible for the trial if they had known sensitivity to paracetamol, ibuprofen, aspirin or any NSAID, or suffered from nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other NSAIDs.

Also, in this publication there was no evidence to suggest that ibuprofen use compared with paracetamol use increased the risk of asthma in children. Indeed, the ibuprofen-treated children experienced lower rates of hospitalisation and outpatient visits concerning asthma in comparison with paracetamol-treated children: RR 0.63 (95% CI: 0.25, 1.6) and 0.56 (95% CI: 0.34, 0.95), respectively. The RR for outpatient visits was significantly lower for ibuprofen compared with paracetamol. Furthermore, the dose of ibuprofen administered did not affect this risk. The authors acknowledge that because a placebo control was not included it is not possible to say whether paracetamol increased or ibuprofen decreased short-term asthma morbidity.

Paracetamol use (at least once a year, or at least once monthly) has also been found to be a risk factor for wheeze in children aged 2–6 years[64]: use at least once a year resulted in an OR of 1.53 (95% CI: 1.04, 2.00), $p < 0.007$ for paracetamol, after adjusting for various demographic and familial factors, parental level of education, and parental asthma. For paracetamol use at least once monthly, a similar increase in risk was found, after adjusting for the above factors: 2.41 (95% CI: 1.50, 3.87) $p < 0.001$.

A large, global cross-sectional study also supports this finding, with the conclusions that paracetamol use for fever in the first year of life is associated with an increased risk of asthma symptoms at age 6–7 years (OR 1.46 [95% CI: 1.36, 1.56])[60]. In this publication, reporting results from the International Study of Asthma and Allergies in Childhood (ISAAC) study in 205 487 children aged 6–7 years, current use of paracetamol was associated with a dose-dependent increased risk of asthma symptoms (OR 1.61 [95% CI: 1.46, 1.77]) for medium use (paracetamol use once per year) versus no use; and OR 3.23 [95% CI: 2.91, 3.60] for high use (paracetamol use once per month) versus no use. Similar increases in risk were also reported for paracetamol use and other allergic symptoms, namely rhinoconjunctivitis and eczema. Ibuprofen use was not measured. While this was an extensive and multinational study, the authors do report limitations such as the retrospective recollection of paracetamol use. Confounding factors, such as region, indication, antibiotic use and maternal educational status were also controlled for as far as possible, but there is a chance that the results are subject to some residual confounding.

### *GI symptoms*

Ludvigsson *et al.* 2006[61] investigated in a cohort study the risk factors, including paracetamol or salicylate use, for GI symptoms in 8341 Swedish children. All mothers of children born between October 1997 and October 1999 in Southeast Sweden were invited to participate in a study of risk factors for future autoimmune and allergic diseases. Mothers completed questionnaires at age 1 and 2.5 years of age of their offspring: the study found that, following adjustment for confounding factors, paracetamol use was linked to a five-fold increase in the risk of anorexia (OR 5.07 [95% CI: 1.88, 13.65]). Ibuprofen use was not specified. In this study more than 99% of children with anorexia had received paracetamol, although because the study was observational a causal link cannot be assumed. There was no association between paracetamol use and abdominal pain.

## AEs that require discontinuation of medication

The RR of experiencing an AE requiring discontinuation of medication with ibuprofen/paracetamol was evaluated in two RCTs[51,52] and was 0.54 (95% CI: 0.17, 1.71; 483 patients) (Figure 2).

The RR of experiencing an AE requiring discontinuation of medication with ibuprofencompared with placebo was evaluated in one RCT in 142 children with

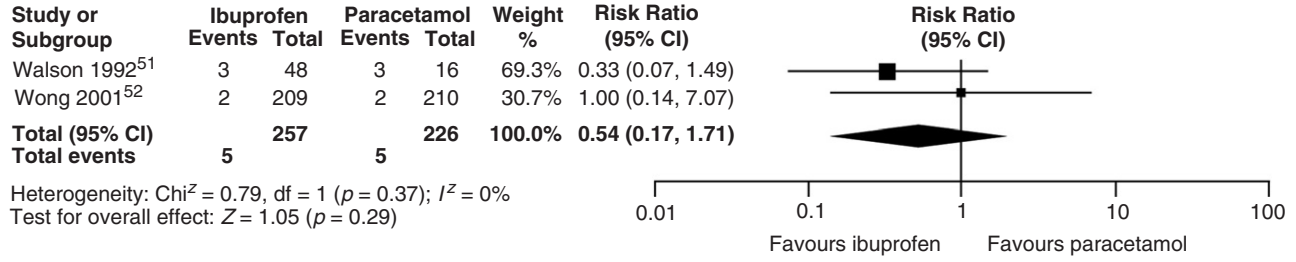


***Figure 2.*** *Adverse events that require discontinuation of medication*

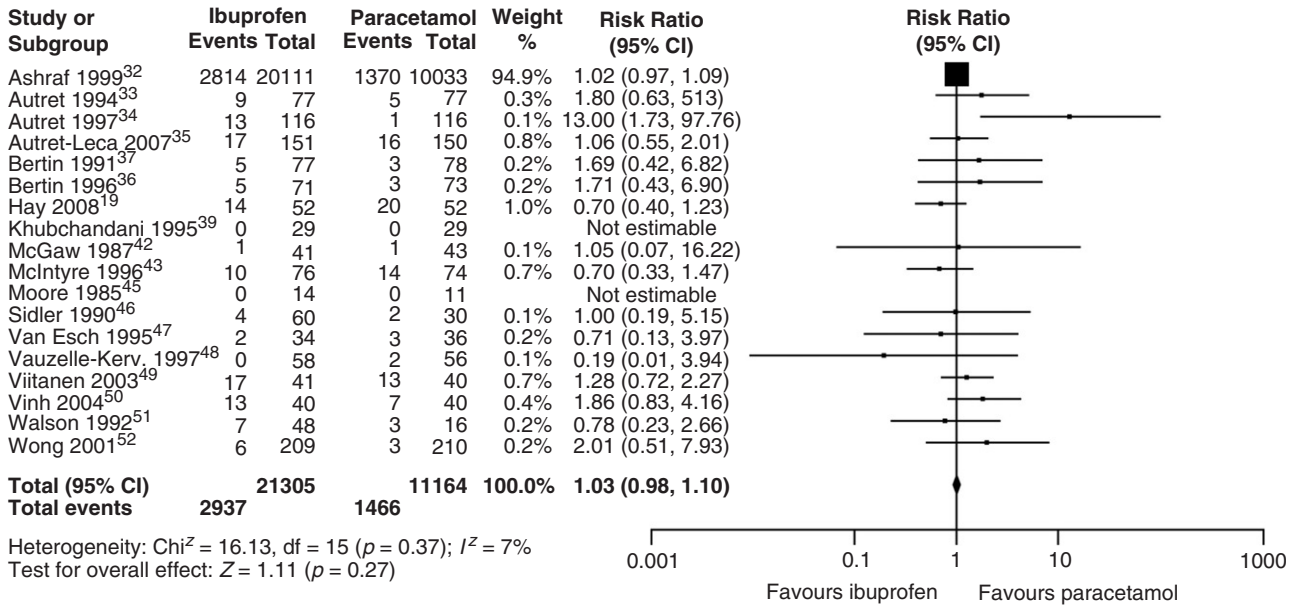


***Figure 3.*** *Systemic reactions with ibuprofen versus paracetamol*

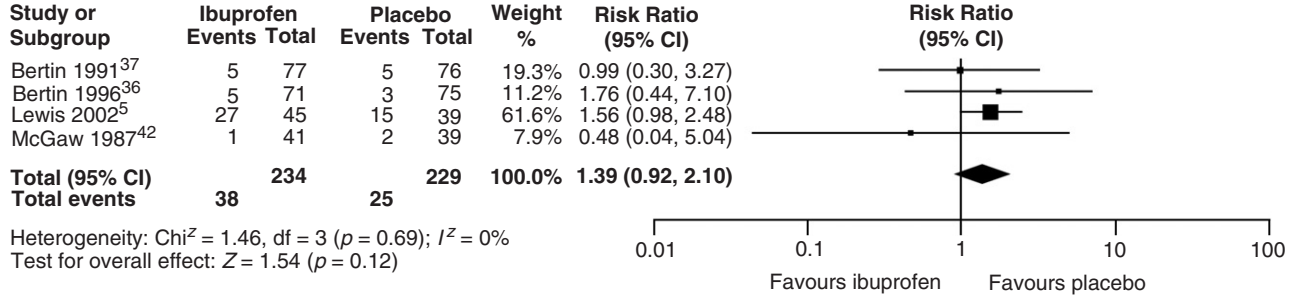


***Figure 4.*** *Systemic reactions with ibuprofen versus placebo*

cystic fibrosis given high dose ibuprofen (20–30 mg/kg/twice-daily)[41]. Treatment over 2 years with ibuprofen or placebo resulted in four patients withdrawing from the study due to ibuprofen treatment (conjunctivitis; abdominal cramps, nausea, diarrhoea; nausea, vomiting, tinnitus; and, gastrointestinal bleeding) and seven patients withdrawing from the study while on placebo (abdominal pain, gastritis; epigastric pain, diarrhoea, nausea; abdominal pain, reflux oesophagitis; abdominal pain admitted with hepatitis; reactive arthritis; elevated liver enzymes; abdominal pain). The RR was 0.59 (95% CI: 0.18, 1.92).

## Systemic reactions related to the use of ibuprofen or paracetamol

A total of 18 studies evaluated systemic reactions related to the use of either ibuprofen or paracetamol in 32 469 patients. Meta-analysis of these studies demonstrated that the RR for experiencing an AE (systemic reaction) with ibuprofen compared with paracetamol is 1.03 (95% CI: 0.98, 1.10) (Figure 3). The RR for experiencing an AE (systemic reaction) with ibuprofen versus placebo is 1.39 (95% CI: 0.92, 2.10) (Figure 4) and for experiencing an AE (systemic reaction) with paracetamol versus placebo is 1.57 (95% CI: 0.74, 3.33) (Figure 5).

The meta-analysis result for ibuprofen versus paracetamol is mainly derived from the Ashraf 1999 study; this was a large study in 20 111 children taking ibuprofen and 10 033 children taking paracetamol and reported the incidence of adverse effects in younger (<2 years) and older (≥2 and <12 years) children[33]. Significantly more AEs were recorded in patients taking ibuprofen versus paracetamol in both age groups (17.6 vs. 15.0%, $p<0.001$ for younger children and 11.9 vs. 10.7%, $p=0.040$ for older children). Fever, vomiting, diarrhoea, rhinitis, rash, and otitis media were the only AEs with an incidence rate of >1% in either treatment group for younger children. Rhinitis, pharyngitis and otitis media were the only AEs with incidence rates >1% in older children.

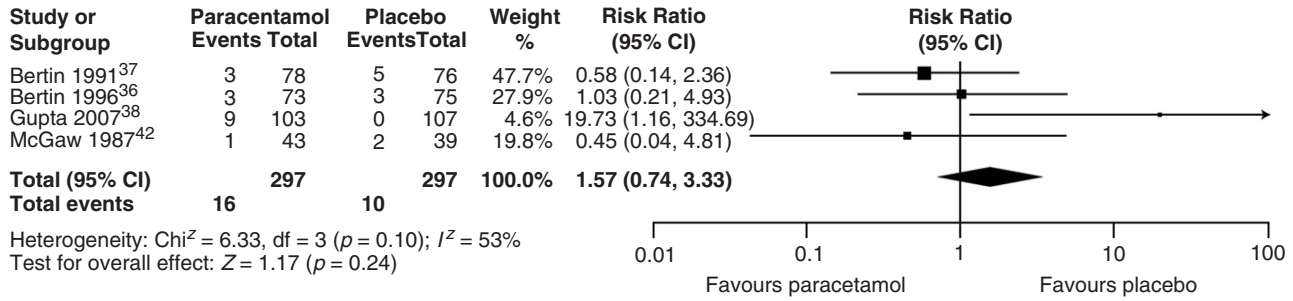


***Figure 5.*** *Systemic reactions with paracetamol versus placebo*

### Dosing

Study doses of ibuprofen or paracetamol are presented in Table 2. The majority of studies investigated ibuprofen doses of between 5 and 10 mg/kg in line with over-the-counter recommendation; likewise the majority of studies used paracetamol doses of between 10 and 15 mg/kg, also as recommended.

## Discussion

The tolerability and safety profile of both ibuprofen and paracetamol was investigated when used as antipyretic/analgesic agents in children up to 18 years. Overall, the results from this systematic review demonstrate that ibuprofen, paracetamol and placebo appear to have a similar tolerability and safety profile (in terms of GI symptoms, asthma and renal adverse effects), with serious AEs being rare occurrences. Conflicting evidence was found regarding hepatic injury with paracetamol and GAS infections with ibuprofen or paracetamol treatment.

This review identified a good number of RCTs comparing the tolerability and safety profile of ibuprofen and/or paracetamol with placebo, together with several observational studies, although results from these could not be included in any meta-analyses. Indeed, the comprehensive nature of this review can certainly be considered a strength. However, there are some limitations: while meta-analyses have been conducted where possible, the varied nature of the studies identified and the different reporting of AE outcomes meant that not all of the meta-analyses include all of the RCTs. Consequently, some caution may be required for drawing conclusions from endpoints based on results from a few small studies.

Other inconsistent variables for the studies consisted of sample size, length of follow up, dose and duration. Consequently, a degree of heterogeneity was found across the studies. Of course, this diversity does reflect the literature and the use of these drugs in routine clinical practice.

Additionally, not all RCTs employed ITT analyses and therefore reporting of AEs may not have been comprehensively captured in the per-protocol results, due to the exclusion of certain patients. Only three of the RCTs investigated safety as a primary outcome and it is therefore possible that the AE data collection in the remainder of the publications was inadequate.

Including data in a narrative synthesis method from observational studies does allow the capture of rare AEs, but of course these study designs are not as robust as RCTs. Case-series and retrospective data collection are subject to selection bias, confounding and measurement bias, and therefore results from these publications should be interpreted accordingly.

The narrative synthesis of the results from non-RCTs examining AEs includes conflicting studies with regards to hepatic injury (for paracetamol) and NF during primary varicella infection (for ibuprofen and paracetamol). It is difficult to draw firm conclusions from the studies identified here. The two studies concerning hepatic injury with paracetamol are quite different in nature, one being a large but observational study[63] with results that conflict with published case reports[12,13], the other being a small case-control study (25 cases and 33 matched controls) that does not report any ORs[57]. Likewise, interpreting the results from the four studies that investigated NF during primary varicella infection is also not straightforward[53,56,58,59]: small sample sizes, wide CIs, and confounding factors mean firm conclusions cannot be made. Certainly, other case-control studies have shown that general NSAID use is associated with severe necrotising tissue infections[65] however, like the Zerr study[59], Souryi and colleagues[58] state that the results might be confounded from '…''indication bias''…due to NSAIDs being given as a response to infection in patients with severe disease rather than being a cause of the severity of the illness'.

A review article by Leroy and colleagues[22] that reported AEs with ibuprofen compared with paracetamol in paediatric pain and fever, also commented on an increased risk of invasive GAS infection after chickenpox, and of acute renal failure in hypovolaemia after

***Table 2.*** *Doses of ibuprofen and paracetamol used in the randomised controlled trials*

| Reference | Ibuprofen (mg/kg) | | | | | | | Paracetamol (mg/kg) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5 | 7.5 | 10 | 12 | 15 | 20+ | Other (specified) | 5 | 7.5 | 10 | 12 | 15 | 20 | Other (specified) |
| Ashraf 1999[32] | | | | | | | Doses not specified | | | | | | | Doses not specified |
| Autret (1997)[34] | | x | | | | | | | | x | | | | |
| Autret (1994)[33] | | x | | | | | | | | x | | | | |
| Autret-Leca (2007)[35] | | | x | | | | | | | | | x | | |
| Bertin (1991)[37] | | | x | | | | | | | x | | | | |
| Bertin (1996)[36] | | | x | | | | | | | x | | | | |
| Gupta (2007)[38] | | | | | | | | | | | | x | | |
| Hay (2008)[19] | | | x | | | | | | | | | x | | |
| Khubchandani (1995)[39] | | | | | | | 7 mg/kg | | | x | | | | |
| Lands (2007)[41] | | | | | | x | 20–30 mg/kg | | | | | | | |
| Lesko (1995)[40] | x | | x | | | | | | | | x | | | |
| Lewis (2002)[5] | | x | | | | | | | | | | | | |
| McGaw (1987)[42] | | | | | | | Doses not specified | | | | | | | Doses not specified |
| McIntyre (1996)[43] | | | | | | x | up to 20 mg/kg/24 h | | | | | | x | up to 50 mg/kg/24 h |
| Mercan (2007)[44] | | | | | | | | | | | | | x | 20–25 mg/kg |
| Moore (1985)[45] | | | | | | | 200 mg | | | | | | | 240 mg for age 5–8 years<br>360 mg for 8–12 years |
| Sidler (1990)[46] | | | x | | | | 10 mg/kg and 7 mg/kg | | | x | | | | |
| Van Esch (1995)[47] | x | | | | | | | | | x | | | | |
| Vauzelle-Kervroedan (1997)[48] | | | | | | | ITT – 10 mg/kg average dose – 10.3 mg (1.19) | | | | | | | ITT – 10 mg/kg average dose – 9.8 mg (1.9) |
| Viitanen (2003)[49] | | | | x | | | | | | | | | x | 40 mg/kg |
| Vinh (2004)[50] | | | x | | | | | | | | x | | | |
| Walson (1992)[51] | x | | x | | | | | | | | | x | | |
| Wong (2001)[52] | x | | x | | | | | | | | x | | | |

ibuprofen treatment. However, none of the studies identified in this systematic review found any evidence to support acute renal failure in hypovolaemia following ibuprofen treatment. Furthermore, Leroy and colleagues[22] described the potential for gastroduodenal and haemorrhagic AEs with ibuprofen although causality could not be confirmed. Similarly, a recent review of the French Pharmacovigilance database of spontaneous reports of upper GI complications in children aged <15 being treated by NSAIDs for fever and pain did reveal 61 cases, including 23 cases with ibuprofen[66]. Paracetamol use did not appear to be investigated. The authors stated that such complications are rare in children as is supported by such a small case series of up to 9 years of reporting. Again, the current review did not find any increased risk of acute GI bleeding with ibuprofen from the studies identified: Lesko and colleagues[40] reported four children who were diagnosed with acute non-major GI bleeding (two each in the ibuprofen dose groups); however, this risk 7.2/100 000 (95% CI: 2, 18/100 000) was not increased compared with paracetamol treatment ($p = 0.31$). This finding is supported by similar results in adolescents and adults[67]: a randomised placebo-controlled trial in 1246 healthy non-prescription users of analgesics aged 12–83 years, the incidence of GI AEs were similar in the placebo and ibuprofen groups (16 vs. 19%), and GI bleeding was also comparable between the two groups, with an overall rate of 1.4% of patients testing positive at least once for an occult faecal blood test.

Owing to the association of aspirin-inducing asthma in susceptible adults, it is thought that due to the high prevalence of cross-sensitivity, NSAIDs affecting the cyclo-oxygenase pathway may also exacerbate asthma[68–70]. Both paracetamol and NSAIDs such as ibuprofen may also aggravate asthma in children, however, this association does not appear to be so well defined as it is in adults[8,9,70]. Similarly to a recent literature review[70], our systematic review found no increased risk of ibuprofen use associated with asthma-related morbidity, indeed there may even be a protective effect when compared with paracetamol[40]. Additionally, paracetamol use in children was found to be a risk factor for wheezing and asthma symptoms[60,64].

Another important observation from the systematic review was the finding that the tolerability and safety of ibuprofen was no different to that of paracetamol in terms of systemic reactions; meta-analyses demonstrated that the tolerability and safety of ibuprofen was no different to placebo in terms of systemic reactions, and neither was paracetamol: ibuprofen vs. placebo RR 1.39 (95% CI: 0.92, 2.10); paracetamol vs. placebo RR 1.57 (95% CI: 0.74, 3.33). A second meta-analysis demonstrated that a total of 2937 systemic AEs occurred in 21 305 patients taking ibuprofen compared with 1466 systemic AEs in 11 164 patients taking paracetamol: RR 1.03 (95% CI: 0.98, 1.10). There was no significant difference in systemic reactions between the two groups including fever, vomiting, diarrhoea, rhinitis, rash, otitis media and pharyngitis. While the studies identified were not necessarily performed in an 'over-the-counter' setting, this finding is still relevant for the safe general use of these drugs in children.

Both ibuprofen and paracetamol are accepted to be effective in reducing fever and pain in children: recently published systematic reviews and meta-analyses have concluded that they are equivalent in their analgesic and antipyretic properties[21,22,71–73]. However, ibuprofen and paracetamol are different medications, and it is unclear if parents/caregivers are aware of distinctions between them, especially in terms of recommended doses and dosing intervals: two recently published cross-sectional studies aiming to identify the factors affecting antipyretic administration by caregivers to their febrile children in differing cultural-ethnic backgrounds showed that 35% administered a higher-than-recommended dose[74], 21% repeated the dose at intervals of $\leq 3$ h[74], and 66% of parents used over-the-counter medications unnecessarily to reduce mild fever (<38.5°C)[75], all of which have implications regarding the safe use of both drugs.

Guidelines from recognised bodies (NICE, ANZCA) do not report any concern regarding the tolerability or safety of either ibuprofen or paracetamol in the treatment of paediatric pain or fever (NICE guidelines 2007[76]; ANZCA guidelines 2007[77]). Interestingly, the NICE guidelines do highlight the lack of evidence supporting the need for antipyretic administration in managing childhood fever, but instead recommend ibuprofen or paracetamol to be administered to those who appear distressed or unwell due to a raised temperature[76]. The ANZCA guidelines do, however, state that 'safe dosing of paracetamol requires consideration of the age and body weight of the child, and the duration of therapy'. It appears that the dosages of ibuprofen (5–10 mg/kg) and paracetamol (10–15 mg/kg) used in the studies identified in this review are in accordance with recommended over-the-counter doses.

## Conclusion

It is the authors' recommendation that future RCTs should be rigorously designed to investigate as a primary endpoint the safety and tolerability of ibuprofen and paracetamol in managing paediatric pain and fever.

Long-term follow-up studies monitoring AEs for such regimens are also needed.

This systematic review has demonstrated that ibuprofen, paracetamol and placebo have similar tolerability and safety profiles, especially in terms of GI symptoms, asthma and renal adverse effects.

## Transparency

**Declaration of funding**

This review was funded by Reckitt Benckiser Plc. Reckitt Benckiser has had no role in creating, writing or reviewing this article. The authors take full responsibility for the contents and views expressed in the article, and have had full editorial control whilst preparing the article.

**Declaration of financial/other relationships**

K.S.W. is an employee of Enhance Reviews. J.K. is an employee of Kleijnen Systematic Reviews, E.S. is an employee of Watermeadow Medical. Enhance Reviews, Kleijnen Systematic Reviews and Watermeadow Medical have received funding from Reckitt Benckiser for the preparation of this article.

All peer reviewers receive honoraria from CMRO for their review work. Peer Reviewer 1 has disclosed that he/she has spoken at meetings on behalf of, and is an advisor on product development for, Reckitt Benckiser Plc, but has declared that this did not pose a conflict of interest in the peer review process. Peer Reviewer 2 has disclosed that he/she has no relevant financial relationships.

**Acknowledgements**

The authors would like to thank Willem Verberk (Kleijnen Systematic Reviews) and Elad Goldberg (Enhance Reviews) for their assistance with data collection and analysis, and Sheila Dunleavy (Watermeadow Medical) for her assistance with the manuscript preparation. Reckitt Benckiser sponsored the medical writing assistance provided by Watermeadow Medical.

## References

1. Hay AD, Heron J, Ness A; ALSPAC study team. The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC): a prospective cohort study. Fam Pract 2005;22:367-74
2. Gururaj AK, Bener A, Al-Suweidi EK, et al. Predictors of febrile seizure: a matched case-control study. J Trop Pediatr 2001;47:361-2
3. Meremikwu M, Oyo-Ita A. Paracetamol for treating fever in children. Cochrane Database Syst Rev 2002;CD003676
4. Hay AD, Redmond N, Fletcher M. Antipyretic drugs for children. BMJ 2006;333:4-5
5. Lewis DW, Kellstein D, Dahl G, et al. Children's ibuprofen suspension for the acute treatment of pediatric migraine. Headache 2002;42:780-6
6. Ulinski T, Bensman A. Renal complications of non-steroidal anti-inflammatories. Arch Pediatr 2004;11:885-8
7. Kang LW, Kidon MI, Chin CW, et al. Severe anaphylactic reaction to ibuprofen in a child with recurrent urticaria. Pediatrics 2007;120:e742-4
8. Palmer GM. A teenager with severe asthma exacerbation following ibuprofen. Anaesth Intensive Care 2005;33:261-5
9. Titchen T, Cranswick N, Beggs S. Adverse drug reactions to nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and paracetamol in a paediatric hospital. Br J Clin Pharmacol 2005;59:718-23
10. Lesko SM, Louik C, Vezina RM, et al. Asthma morbidity after the short-term use of ibuprofen in children. Pediatrics 2002;109:E20
11. Kader A, Hildebrandt T, Powell C. How safe is ibuprofen in febrile asthmatic children? Arch Dis Child 2004;89:885-6
12. Heubi JE, Barbacci MB, Zimmerman HJ. Therapeutic misadventures with acetaminophen: hepatoxicity after multiple doses in children. J Pediatr 1998;132:22-7
13. Hameleers-Snijders P, Hogeveen M, Smeitink JA, et al. [Risk of acute hepatic insufficiency in children due to chronic accidental overdose of paracetamol (acetaminophen)]. Ned Tijdschr Geneeskd 2007;151:897-900
14. Kvedariene V, Bencheriuoa AM, Messaad D, et al. The accuracy of the diagnosis of suspected paracetamol (acetaminophen) hypersensitivity: results of a single-blinded trial. Clin Exp Allergy 2002;32:1366-9
15. Sezer E, Sezer T, Koseoglu D, et al. Acute generalized exanthematous pustulosis in a child. Pediatr Dermatol 2007;24:93-5
16. Ayonrinde OT, Saker BM. Anaphylactoid reactions to paracetamol. Postgrad Med J 2000;76:501-2
17. Irion R, Gall H, Werfel T, et al. Delayed-type hypersensitivity rash from paracetamol. Contact Derm 2000;43:60-1
18. Del-Río-Navarro BE, Luna-Pech JA, Berber A, et al. Factors associated with allergic rhinitis in children from northern Mexico City. J Investig Allergol Clin Immunol 2007;17:77-84
19. Hay AD, Costelloe C, Redmond NM, et al. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trial. BMJ 2008;337:a1302
20. Bradley RL, Ellis PE, Thomas P, et al. A randomized clinical trial comparing the efficacy of ibuprofen and paracetamol in the control of orthodontic pain. Am J Orthod Dentofacial Orthop 2007;132:511-17
21. Perrott DA, Piira T, Goodenough B, et al. Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever: a meta-analysis. Arch Pediatr Adolesc Med 2004;158:521-6
22. Leroy S, Mosca A, Landre-Peigne C, et al. [Ibuprofen in childhood: evidence-based review of efficacy and safety]. Arch Pediatr 2007;14:477-84
23. Undertaking systematic reviews of research of effectiveness. CRD's Guidance for Those Carrying Out or Commissioning Reviews, 2nd edn. York, UK: Centre for Reviews and Dissemination, 2001
24. Higgins JPT, Green S (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008
25. MEDLINE (1950 to November 2008): http://www.ncbi.nlm.nih.gov/sites/entrez. Accessed 12.11.07 and 4.11.08
26. EMBASE (1980 to November 2008): http://www.embase.com/. Accessed 12.11.07 and 4.11.08
27. CDSR, CENTRAL, and DARE published in The Cochrane Library (2007, Issue 3): http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME?CRETRY=1&SRETRY=0. Accessed 12.11.07
28. ACP Journal Club (1991 to November 2007): http://www.acpjc.org/fcgi/imsearch.pl. Accessed 12.11.07
29. Pascal (1987 to November 2007): http://www.ovid.com/site/catalog/DataBase/214.jsp. Accessed 12.11.07
30. Oxman AD. Checklists for review articles. BMJ 1994;309:648-51
31. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60

32. Ashraf E, Ford L, Geetha R, et al. Safety profile of ibuprofen suspension in young children. Inflammopharmacology. 1999; 7:219-25
33. Autret E, Breart G, Jonville AP, et al. Comparative efficacy and tolerance of ibuprofen syrup and acetaminophen syrup in children with pyrexia associated with infectious diseases and treated with antibiotics. Eur J Clin Pharmacology 1994;46: 197-201
34. Autret E, Reboul-Marty J, Henry-Launois B, et al. Evaluation of ibuprofen versus aspirin and paracetamol on efficacy and comfort in children with fever. Eur J Clin Pharmacol 1997; 51:367-71
35. Autret-Leca E, Gibb IA, Goulder MA. Ibuprofen versus paracetamol in pediatric fever: objective and subjective findings from a randomized, blinded study. Curr Med Res Opin 2007; 23:2205-11
36. Bertin L, Pons G, D'Athis P, et al. A randomized, double-blind, multicentre controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis media in children. Fundam Clin Pharmacol 1996;10:387-92
37. Bertin L, Pons G, D'Athis P, et al. Randomized, double-blind, multicenter, controlled trial of ibuprofen versus acetaminophen (paracetamol) and placebo for treatment of symptoms of tonsillitis and pharyngitis in children. J Pediatr 1991;119:811-14
38. Gupta H, Shah D, Gupta P, et al. Role of paracetamol in treatment of childhood fever: a double-blind randomized placebo controlled trial. Indian Pediatr 2007;44:903-11
39. Khubchandani RP, Ghatikar KN, Keny S, et al. Choice of antipyretic in children. J Assoc Physicians India 1995; 43:614-16
40. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. JAMA 1995;273:929-33
41. Lands LC, Milner R, Cantin AM, et al. High-dose ibuprofen in cystic fibrosis: Canadian safety and effectiveness trial. J Pediatr 2007;151:249-54
42. McGaw T, Raborn W, Grace M. Analgesics in pediatric dental surgery: relative efficacy of aluminum ibuprofen suspension and acetaminophen elixir. J Dent Child 1987;54:106-9
43. McIntyre J, Hull D. Comparing efficacy and tolerability of ibuprofen and paracetamol in fever. Arch Dis Child 1996;74:164-7
44. Mercan A, Murat SM, Saydam S, et al. When to add supplemental rectal paracetamol for postoperative analgesia with caudal bupivacaine in children? A prospective, double-blind, randomized study. Paediatr Anaesth 2007;17:547-51
45. Moore PA, Acs G, Hargreaves JA. Postextraction pain relief in children: a clinical trial of liquid analgesics. Int J Clin Pharmacol Ther Toxicol 1985;23:573-7
46. Sidler J, Frey B, Baerlocher K. A double-blind comparison of ibuprofen and paracetamol in juvenile pyrexia. Br J Clin Pract 1990;44(8 Suppl 70):22-5
47. Van Esch A, Van Steensel-Moll HA, Steyerberg EW, et al. Antipyretic efficacy of ibuprofen and acetaminophen in children with febrile seizures. Arch Pediatr Adolesc Med 1995; 149:632-7
48. Vauzelle-Kervroedan F, D'Athis P, Pariente-Khayat A, et al. Equivalent antipyretic activity of ibuprofen and paracetamol in febrile children. J Pediatr 1997;131:683-7
49. Viitanen H, Tuominen N, Vaaraniemi H, et al. Analgesic efficacy of rectal acetaminophen and ibuprofen alone or in combination for paediatric day-case adenoidectomy. Br J Anaesth 2003;91:363-7
50. Vinh HA, Parry CM, Hanh VTN, et al. Double blind comparison of ibuprofen and paracetamol for adjunctive treatment of uncomplicated typhoid fever. Pediatr Infect Dis J 2004; 23:226-30
51. Walson PD, Galletta G, Chomilo F, et al. Comparison of multidose ibuprofen and acetaminophen therapy in febrile children. Am J Dis Child 1992;146:626-32
52. Wong A, Sibbald A, Ferrero F, et al. Antipyretic effects of dipyrone versus ibuprofen versus acetaminophen in children: results of a multinational, randomized, modified double-blind study. Clin Pediatr 2001;40:313-24
53. Dubos F, Hue V, Grandbastien B, et al. Bacterial skin infections in children hospitalized with varicella: a possible negative impact of non-steroidal anti-inflammatory drugs? Acta Derm Venereol 2008;88:26-30
54. Hall SM, Plaster PA, Glasgow JF, et al. Preadmission antipyretics in Reye's syndrome. Arch Dis Child 1988;63: 857-66
55. Hurwitz ES, Barrett MJ, Bregman D. Public health service study on Reye's syndrome and medications. Report of the pilot phase. N Engl J Med 1985;313:849-57
56. Lesko SM, O'Brien KL, Schwartz B, et al. Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella. Pediatrics 2001;107:1108-15
57. Ranganathan SS, Sathiadas MG, Sumanasena S, et al. Fulminant hepatic failure and paracetamol overuse with therapeutic intent in febrile children. Indian J Pediatr 2006; 73:871-5
58. Souyri C, Olivier P, Grolleau S, et al. Severe necrotizing soft-tissue infections and nonsteroidal anti-inflammatory drugs. Clin Exp Dermatol 2008;33:249-55
59. Zerr DM, Alexander ER, Duchin JS, et al. A case-control study of necrotizing fasciitis during primary varicella. Pediatrics 1999;103:783-90
60. Beasley R, Clayton T, Crane J, et al. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme. Lancet 2008; 9643:1039-48
61. Ludvigsson JF; Abis Study Group. Epidemiological study of constipation and other gastrointestinal symptoms in 8000 children. Acta Paediatr 2006;95:573-80
62. Hawton K, Fagg J. Deliberate self-poisoning and self-injury in adolescents. A study of characteristics and trends in Oxford, 1976-89. Br J Psychiatry 1992;161:816-23
63. Mohler CR, Nordt SP, Williams SR, et al. Prospective evaluation of mild to moderate pediatric acetaminophen exposures. Ann Emerg Med 2000;35:239-44
64. Wong GW, Leung TF, Ma Y, et al. Symptoms of asthma and atopic disorders in preschool children: prevalence and risk factors. Clin Exp Allergy 2007;37:174-9
65. Mikaeloff Y, Kezouh A, Suissa S. Nonsteroidal anti-inflammatory drug use and the risk of severe skin and soft tissue complications in patients with varicella or zoster disease. Br J Clin Pharmacol 2008;65:203-9
66. Autret-Leca E, Bensouda-Grimaldi L, Maurage C, Jonville-Bera AP. Upper gastrointestinal complications associated with NSAIDs in children. Therapie 2007;62:173-6
67. Doyle G, Furey S, Berlin R, et al. Gastrointestinal safety and tolerance of ibuprofen at maximum over-the-counter dose. Aliment Pharmacol Ther 1999;13:897-906
68. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G, et al. Aspirin-induced asthma. Hypersensitivity to fenoprofen and ibuprofen in relation to their inhibitory action on prostaglandin generation by different microsomal enzymic preparations. J Allergy Clin Immunol 1976;58:10-18
69. Stevenson DD. Aspirin and NSAID sensitivity. Immunol Allergy Clin North Am 2004;24:491-505
70. Kanabar D, Dale S, Rawat M. A review of ibuprofen and acetaminophen use in febrile children and the occurrence of asthma-related symptoms. Clin Ther 2007;29:2716-23
71. Purssell E. Treating fever in children: paracetamol or ibuprofen? Br J Community Nurs 2002;7:316-20
72. Goldman RD, Ko K, Linett LJ, et al. Antipyretic efficacy and safety of ibuprofen and acetaminophen in children. Ann Pharmacother 2004;38:146-50

73. Malaysian Health Technology Assessment Unit. Rational use of analgesics in paediatrics. Kuala Lumpur: Malaysian Health Technology Assessment Unit (MHTAU) 2006:34
74. Bilenko N, Tessler H, Okbe R, et al. Determinants of antipyretic misuse in children up to 5 years of age: a cross-sectional study. Clin Ther 2006;28:783-93
75. Walsh A, Edwards H, Fraser J. Over-the-counter medication use for childhood fever: a cross-sectional study of Australian parents. J Paediatr Child Health 2007;43:601-6
76. National Institute for Clinical Excellence Clinical Guideline 47. Feverish illness in children. May 2007 http://www.nice.org.uk/nicemedia/pdf/CG47Guidance.pdf. Accessed 01.04.09
77. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence, 2nd edn updates. December 2007. http://www.anzca.edu.au/resources/books-and-publications/acutepain_update.pdf. Accessed 27.11.08

## Appendix

A more detailed description of the search strategy used for this article is available as online supplementary material, published with the online version of this article.

CrossRef links are available in the online published version of this paper:
http://www.cmrojournal.com
Article CMRO-4925_4, *Accepted for publication:* 15 June 2009
*Published Online:* 16 July 2009
doi:10.1185/03007990903116255