**Ibuprofen Dosing in Obese Children: A Systematic Review**

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**ABSTRACT**

***Objective:***

Childhood obesity can affect drug disposition and efficacy of ibuprofen. The primary objective was to assess efficacy of ibuprofen in obese children.

***Design:***

A systematic review was registered with PROSPERO (CRD42021213500) and undertaken following PRISMA methodology. Studies were identified from 12 databases. Two independent reviewers evaluated studies against the inclusion criteria and assessed for methodological quality.

***Setting:*** Any clinical setting

***Patients:*** Patients under 18 years who were overweight/obese.

***Interventions:*** Patients taking ibuprofen for any indication, dose or regime.

***Main Outcome Measures:*** The efficacy and tolerability of ibuprofen treatment in obese children and presence of any adverse drug reactions.

***Results:*** Searches identified 1305 studies. Fourstudies met inclusion criteria: three retrospective cohort studies (*n*=583, median age: 6 years, range: 1-18 years, *n*=200, median age: 11 years, range: 3-18 years, *n*= 358 median age: 3.1 years, range: 1.2–8.5 years respectively) and one case study. Each study differed in their method of dosing ibuprofen (weight-based, age-based and adjusted-body-weight dosing). Various doses were used: 5 mg/kg every 6 hours, 400 mg three times daily, 120 mg/dose and a dose calculated using adjusted body weight. One study reported efficacy (obese *n*=189, non-obese, *n*=394), where adequate pain control was achieved using 5mg/kg. The other three studies did not determine if efficacy differed between obese or non-obese children.

One study described adverse effects. An increased risk of bleeding with ibuprofen was noted, but did not differentiate between obese and non-obese children.

***Conclusion:***

There is little published data to guide clinicians prescribing ibuprofen in obese children.

WHAT THIS STUDY ADDS

* Ibuprofen had similar effectiveness for pain in children who were obese or non-obese but these data were from only two publications, with limited numbers of patients, using different dosing strategies
* Beyond efficacy, there is insufficient published information on the tolerability and safety of ibuprofen in obese children and young people.
* The optimal dosing regimen of ibuprofen for an obese child is not clear.

WHAT IS ALREADY KNOWN

* Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that is widely used for its anti-inflammatory, analgesic and anti-pyretic properties in children
* As the prevalence of childhood obesity has increased, so has the need for clinicians to treat comorbidities in these individuals.
* Dosing guidelines for obese children are often extrapolated from data in obese adults.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY:

* Further research is required to establish the efficacy, tolerability and safety profile of ibuprofen in obese children.
* Prescribers lack adequate information to optimise use of ibuprofen in obese children.
* Without this, obese children risk potential therapeutic failure or increased adverse effects.

**INTRODUCTION**

Obesity represents a threat to the health and wellbeing of children, with nearly 1 in 3 children aged 2-15 being classed as overweight or obese in the UK (1,2). As rates of childhood obesity have risen, so has the need for clinicians to treat comorbidities in these individuals (3). Dosing medications in children is frequently based on age, allometric scaling, body surface area or weight, where weight-based dosing is the most commonly used method (4). The pharmacokinetics for many drugs can be influenced by excess body weight, hence overweight and obese children could be at risk of drug toxicity or a minimised therapeutic effect (5).

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that acts as a non-specific inhibitor of the cyclo-oxygenase enzymes, and is widely used for its anti-inflammatory, analgesic and anti-pyretic properties in children (6,7). In the UK, it is licensed from 3 months of age (7), and available as an “over the counter” medicine families can purchase directly. However, ibuprofen also has well recognised adverse effects, including gastrointestinal bleeding, rash, and acute kidney injury (8,9).

The British National Formulary of Children (BNFc) does not contain any guidance on dose alterations for ibuprofen in children who are overweight or obese (7). Ibuprofen is a polar molecule with a small volume of distribution (10,11). In children, there are considerable physiological changes that could affect the circulating drug concentration including: the proportionally increased circulating blood volume in younger children; decreased renal clearance in the youngest; altered hepatic enzyme expression; variations in albumin and other serum proteins (5). Currently, the clinical concern would therefore be that either obese children and young people are not receiving adequate analgesia if using an age-based dosing strategy or are at increased risk of adverse effects due to larger doses prescribed in a weight-based dosing strategy.

There is evidence of altered pharmacokinetics in obese adults, where a case-control study investigating ibuprofen disposition between the obese and non-obese identified decreased peak concentrations of ibuprofen in obese individuals (12).

We therefore aimed to systematically review the published literature regarding ibuprofen for dosing regimens used in obese children and young people. As a secondary outcome, we aimed to examine the efficacy, tolerability and safety of ibuprofen in obese children and young people dosed in these studies.

**METHODS**

The systematic review was registered on the PROPSERO website (CRD42021213500).

**Study Inclusion Criteria**

Journals were identified through literature searches (from inception until January 2021) on the following databases: Allied and Complementary Medicine Database (AMED), CINAHL Plus, Cochrane Reviews, MEDLINE, NHS Evidence, PsycARTICLES, PsycINFO, PsycTESTS, PubMed, SAGE Journals, Scopus and Web of Science. We included studies reporting the administration of ibuprofen to children (aged <18 years), where the authors also reported use in overweight or obese children (see supplementary data, Table 1, for full inclusion and exclusion criteria). All study designs involving primary research that met the inclusion criteria were included, hence reviews, editorials or letters were excluded. The search did not impose any language or date restrictions. Any references cited in the papers were also searched.

**Search Strategy**

The search strategy was developed by two reviewers (E.S. and A.H.) collectively and the search was then executed independently. The search terms, outlined in Table 1, were used to ensure papers relating to children, dosing regimens, overweight/obese subjects and the use of ibuprofen were identified.

**Data Extraction**

All search results obtained from the databases were exported (Microsoft Excel) and de-duplicated. Titles and abstracts from the retrieved articles were screened independently by the two reviewers (E.S. and A.H.). For the remaining articles, the full-text articles were then reviewed and excluded if any exclusion criteria (see Supplementary Data, Table 1) were met. Where discrepancies were noted, consensus regarding the final inclusion or exclusion was reached following discussion between the two reviewers (E.S. and A.H.). If this remained unresolved, the paper was assessed by a third reviewer (D.H.). Information regarding study demographics and characteristics (e.g. obese status, ibuprofen efficacy, tolerability and adverse events) were extracted using a bespoke data extraction tool.

**Quality Assessment**

Papers were quality assessed using the Critical Appraisal Skills Programme (CASP) checklists independently by the two reviewers (E.S. and A.H.) (13), generating a quality assessment score (*QAS*) (see Supplementary Data Table 2 for full quality assessment protocol).

**RESULTS**

**Flow of Articles**

After deduplication, the search strategy retrieved 1305 potentially relevant articles from the databases: CINAHL Plus, *n*=6; Cochrane Reviews, *n*=25; MEDLINE, *n*=4; NHS Evidence, *n*=182; PubMed, *n*=2; Scopus, *n*=1019; Web of Science, *n*=1 (see Figure 1 for PRISMA chart). Of these, 1279 articles were excluded based on irrelevant titles and abstracts. From the 26 full text reviews, four met the study inclusion criteria (three retrospective cohort studies and one case report).

**Quality Assessment**

To assess quality, papers were scored against a set of 12 questions (see supplementary data, Table 2, for full quality assessment details). Three of the four studies exhibited high methodological quality, with the remaining paper classed as moderate quality.

**Study Demographics**

Table 2 shows the individual study demographics for each paper. Three of the four studies in children were carried out in the United States and one in Denmark. All studies were performed in a single hospital or clinical setting.

The four included studies involved 1141 children and young people. 583 participants (median age: 6 years, range: 1-18 years) were included in the first cohort study (14), 200 children (median age: 11 years, range: 11-18 years) in the second cohort study (15), and 358 participants (median age: 3.1, range: 1.2 – 8.5 years) in the third cohort study (16). Of the 200 children in the second cohort study, there were only 11 prescriptions for ibuprofen. The fourth study was a case study evaluating prescriptions of critically ill infants and children (age <18 years) but did not state the number of participants in their sample size or their age distribution (17). There were a relatively even distribution of males and females in the three retrospective cohorts (14,15), but the case study did not state the gender distribution in their sample.

Three papers shared the Centres for Disease Control and Prevention’s definition of obesity: obesity as a BMI above the 95th percentile (14,16,17), whereas as one paper defined obesity based on a BMI z score (15). Two cohort studies clearly differentiated the numbers of obese and non-obese children in their sample with the first having 189 obese and 394 non-obese participants (14). The second cohort study had a total of 366 obese and 2975 non-obese participants, of which 38 obese (10.6%) and 320 non-obese individuals (89.4%) were on ibuprofen (16). Another cohort study had a mean BMI z-score of 2.95 (*n*=200, range: 1.28-9.72) of its total sample, but did not clearly distinguish the numbers of obese and non-obese children (15). The case study did not provide numbers of obese and non-obese children (17).

The use of ibuprofen differed amongst the four papers; one retrospective cohort study investigated the pain relief from ibuprofen post-tonsillectomy (14), the second retrospective cohort study investigated the currently applied dosage strategies in overweight or obese children by looking at their prescriptions (15), the third retrospective cohort study assessed the antipyretic efficacy in critically ill paediatric patients (16) and the case study investigated prescriptions for commonly prescribed drugs to aid in the development of a decision support tool (17).

**Ibuprofen Dosing Regimens (Primary Outcome)**

All studies had differing methods of dosing ibuprofen in children (see Table 3). One retrospective study used a weight-based dosing regimen where ibuprofen was given at 5 mg/kg every 6 hours, alongside an alternating dose of paracetamol in children (14). Another retrospective study used a fixed age-band dosage of 400 mg taken three times daily for 11-18 year olds (15). The third cohort study used a 120 mg/dose ibuprofen regime and stated a mean mg/kg/dose of 8.2 ± SD 1.7 (16). The ibuprofen dosing regimen in the case study, however, suggested the use of adjusted body weight (AjBW) when dosing ibuprofen to obese children (17).

**Efficacy and Tolerability of Ibuprofen in Obese Children**

With regards to ibuprofen efficacy, two retrospective studies clearly differentiated obese and non-obese children allowing comparison of the groups. One study showed adequate pain control (90%) being achieved by both obese and non-obese children. Following multivariable analysis, the second cohort study found that enteral ibuprofen was significantly greater at reducing fever in children than paracetamol. Interestingly, the study also found that obese individuals took longer to defervesce, possibly due to increased oxidative metabolism. However, neither study specified the number of obese individuals on an ibuprofen regime to allow for further comparison. The efficacy of ibuprofen was not explicitly mentioned in the other two papers and hence could not be assessed. There is insufficient data to ascertain which, if any, ibuprofen dosing method is most efficacious in obese children.

Ibuprofen tolerability was not directly measured in any of the retrieved studies, hence cannot be accurately assessed.

**Safety of Ibuprofen**

Similarly, the safety profile of ibuprofen, including reported adverse drug reactions, were not explicitly reported in any of the retrieved studies. A cohort study stated that no adverse events had been identified in most of their participants, however the details of this were not provided (14). It did later discuss that individuals who had taken ibuprofen had a greater rate of bleeding (4.1%) post-tonsillectomy than those who had taken paracetamol (3.6%) (14), but this did not differentiate between obese and non-obese patients. Another cohort study was the only article to specifically refer to gastrointestinal bleeding as a common severe adverse drug reaction of ibuprofen but did not specify the prevalence in their sample. Acute kidney injury was identified as a known risk of ibuprofen in the third cohort study, but the prevalence in their sample was not mentioned. The case study compiled safety information on ibuprofen, including adverse events and its tolerability profile, from other papers. Reports of other adverse drug reactions including; rash, angioedema, headache or agranulocytosis, were not included in any of the papers.

DISCUSSION

To our knowledge, this is the first systematic review to examine the dosing strategies used for ibuprofen in obese children and young people. There is very limited published data regarding either dosing strategies used, or the efficacy and safety profile of ibuprofen doses used in obese children and young people.

 Each study differed in their method of dosing ibuprofen from weight-based (14,16), age-based (15) to adjusted-body-weight dosing (17). Various specific doses were used in each study: 5 mg/kg every 6 hours, fixed dose of 400 mg three times daily, 120 mg/dose and a dose calculated using adjusted body weight. Consequently, this could mean that the same child in each study could be given a different dose, potentially exposing them to therapeutic failure or higher doses unnecessarily and hence the increasing the risk of adverse drug reactions (ADRs).

It was however reassuring to note that the efficacy of ibuprofen was not noted to differ between obese and non-obese children and young people in the single study that examined this. It was also noteworthy that while ADRs were not extensively collected, an increased rate of bleeding post-tonsillectomy was described in one study (14).

Ibuprofen is well known to have a diverse therapeutic index in children including fever, post-operative pain and inflammatory disorders (18,19). Like other NSAIDs, it acts by inhibiting prostaglandin synthesis through blocking cyclooxygenases I and II (20). This stimulates vasoconstriction, resulting in decreased renal perfusion and can therefore increase the risk of prerenal acute kidney injury (AKI) (18). Interestingly, ibuprofen drug exposure has been found to increase the risk of developing an AKI by more than twofold in children (19) and the long-term consequences of NSAID-associated AKI are becoming increasingly recognised, such as the development of chronic kidney disease, with younger children more susceptible to more severe disease (20). In addition, a study by Nelson et al. found that young and middle-aged adults with an overweight or obese status significantly increased the hazard of developing AKI and chronic kidney disease (21). It is important to consider that NSAID-associated AKI is an avoidable risk to which children are regularly exposed. Should a child be overweight or obese, this can increase the risk considerably.

With the rise in childhood obesity, it is important for health services to deliver evidence-based dosing recommendations for obese children and young people. Future studies are needed to develop clear evidence based guidance regarding the prescription of ibuprofen in overweight and obese children. In the first instance, use of physiologically-based pharmacokinetic models, similar to ones used when doses of paediatric medicines have been introduced, would provide additional information to base rational dosing decisions on (22).

There is little published data to guide clinicians prescribing ibuprofen in obese children, and without this, these children risk therapeutic failure or increased risk of ADRs.

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FIGURES AND TABLES

**Table 1** Search terms used to identify relevant papers in this systematic review

|  |  |
| --- | --- |
| Theme | Search Terms |
| Children | (Infant\* OR infancy OR Newborn\* OR Baby\* OR Babies OR Neonat\* OR Preterm\* OR Prematur\* OR Postmatur\* OR Child\* OR Schoolchild\* OR School age\* OR Preschool\* OR Kid OR Kids OR Toddler\* OR Adoles\* OR Teen\* OR Boy\* OR Girl\* OR Minors\* OR Pubert\* OR Pubescen\* OR Prepubescen\* OR Paediatric\* OR Peadiatric\* OR Pediatric\* OR School\* OR Nursery school\* OR Kindergar\* OR Primary school\* OR Secondary school\* OR Elementary school\* OR High school\* OR Highschool\*) |
| Obesity | (Obes\* OR Overweight) |
| Dosing | (Prescribing OR Dosage OR Dosing OR Dose OR Prescribe) |
| Ibuprofen | (Ibuprofen) |



**Figure 1** PRISMA flow of articles through different phases of the selection process

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Paper No. | Age | Gender | Study Design and Sample Size Receiving Ibuprofen | Obesity Measure | No. of Obese Participants | No. of Non-Obese Participants | Ibuprofen Dose | Ibuprofen Tolerability | Ref. |
| 1 | 1-18 years | M: 304 (52%)F: 279 (48%) | Retrospective cohort study*N =* 583 | BMI >95th percentile | 189 (32.4%) | 394 (67.6%) | 5 mg/kgevery 6 hours (not to exceed 2.4 g/day) | No side-effects or adverse events in majority of children | (14) |
| 2 | 11-18 years | M: 126 (63%)F: 74 (37%) | Retrospective cohort study*N =* 11 | BMI z scoreBMI >90th percentile | Not specified for those taking ibuprofen. | Not specified for those taking ibuprofen. | Fixed dose 400 mg three times daily | Not stated | (15) |
| 3 | 1.2 – 8.5 years | M: 202 (56.4%)F: 156 (43.6%) | Retrospective cohort study*N* = 358 | BMI >95th percentile | 366 (11.0%)Out of which 38 (10.6%) on ibuprofen | 2975 (89.0%)Out of which 320 (89.4%) on ibuprofen | Dose (mg/dose): 120Dose (mg/kg/dose): 8.2 ± 1.7 | Not stated | (16) |
| 4 | 0-18 years | Not stated | Case report –based on a service evaluationSample size not stated | BMI >95th percentile | Not stated | Not stated | Dose calculated using AjBW (co-factor 0.4) to adult max. | Not stated | (17) |

 **Table 2** Demographic information and characteristics of children who were obese and non-obese with the use of ibuprofen. BMI: body mass index; AjBW = adjusted body weight

**Table 3** Study measures of ibuprofen efficacy and reported adverse events in obese and non-obese children. G.I. = gastrointestinal

|  |  |  |  |
| --- | --- | --- | --- |
| Paper No. | Ibuprofen Efficacy | Adverse Drug Reactions Reported | Ref |
| **Obese** | **Non-obese** | **G.I. bleeds** | **Rash** | **Angioedema** | **Headache** | **Acute Kidney Injury** | **Bleeding** | **Agranulocytosis** |
| 1 | Adequate pain control:171 (90%)Inadequate pain control:18 (10%) | Adequate pain control:356 (90%)Inadequate pain control:38 (10%) | Not stated | Not stated | Not stated | Not stated | Not stated | Greater rate of post-tonsillectomy bleeding in children taking ibuprofen (4.1%) than those who took paracetamol only (3.6%) | Not stated | (14) |
| 2 | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | (15) |
| 3 | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | (16) |
| 4 | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | Not stated | (17) |