

Ibuprofen or paracetamol for children with fever

QUESTION
Should ibuprofen or paracetamol be given in infants and children with fever?

CONTEXT	Fever in children
<p>Fever in children, especially associated with infections, is very common. While only being a sign or symptom of other illness or disease, an elevated body temperature is associated with discomfort, an increased risk of dehydration and seizures. Fever is one of the most commonly-treated paediatric conditions, and it can be treated easily with over-the-counter antipyretic drugs such as ibuprofen and paracetamol.</p> <p>Widespread use of these medications has shown that they are effective and generally well-tolerated in the reduction of paediatric fever. Ibuprofen is better tolerated than other non-steroidal anti-inflammatory drugs, although it has been associated with renal toxicity, allergic reactions and gastrointestinal adverse events. The most serious and well documented adverse event associated with paracetamol use in children is hepatotoxicity.</p>	

INTERVENTION	Ibuprofen or Paracetamol
<p>Serious adverse events (fatal, life threatening or requiring hospitalization) There were no differences between ibuprofen and paracetamol in the occurrence of acute gastrointestinal bleeding, renal failure and anaphylaxis. <i>Low quality evidence.</i></p>	
<p>Serious adverse events not requiring hospitalization There were no differences between ibuprofen and paracetamol in the occurrence of low white blood cell count. <i>Moderate quality evidence.</i></p>	
<p>Adverse events requiring discontinuation of medication There were no differences between ibuprofen and paracetamol in the occurrence of adverse events that required discontinuation of medication. <i>Moderate quality evidence.</i></p>	
<p>Systemic reactions There were no differences between ibuprofen and paracetamol in the occurrence of systemic reactions. <i>High quality evidence.</i></p>	
<p>Reye's syndrome Paracetamol was not associated with Reye's syndrome. <i>Low quality evidence.</i></p>	
<p>Asthma symptoms Ibuprofen compared to paracetamol did not differ in the rates of hospitalisations due to asthma and produced less outpatients visits. <i>Moderate quality evidence.</i> Paracetamol use was associated with an increased risk of asthma symptoms and showed a dose-response relation. <i>Moderate quality evidence</i></p>	

Summary of evidence	
Risks	<p>A systematic review that compared the tolerability and safety between ibuprofen and paracetamol when used as antipyretic and analgesic agents in children up to 18 years of age was found [1]. It included 24 RCTs and 9 observational studies that compared ibuprofen and paracetamol with each other or with placebo. The majority of studies investigated ibuprofen doses between 5 and 10 mg/kg and paracetamol doses between 10 and 15 mg/kg.</p> <p>There were no differences between paracetamol and ibuprofen in the occurrence of acute gastrointestinal bleeding, renal failure and anaphylaxis that were life threatening or required hospitalisation (1 RCT, 84 192 children, OR 1.31, 95% CI 0.87-1.97).</p> <p>One RCT did not show differences between ibuprofen and paracetamol in the occurrence of low white blood cell count (1 RCT, 83 915 children, 8 events, OR 8.57, 95% CI 0.49 to 148.55). All the observed cases were transient and mild.</p> <p>Ibuprofen compared to paracetamol was not different in the occurrence of adverse events that required discontinuation of medication (2 RCT, 483 children, 10 events, RR 0.54, 95% CI 0.17 to 1.71)</p> <p>Ibuprofen compared to paracetamol was not different in the occurrence of systemic reactions (18 RCT, 32 469 patients, 4 403 events, RR 1.03, 95% CI 0.98 to 1.10) including fever, vomiting, diarrhoea, rhinitis, rash, otitis media and pharyngitis.</p> <p>Two case control studies (466 patients) found no epidemiological link between paracetamol use and development of Reye's syndrome. Ibuprofen was not investigated.</p> <p>Ibuprofen compared to paracetamol did not increase the risk of hospitalization due to asthma (1 RCT, 1879 children, RR 0.63, 95% CI 0.25 to 1.6) and was associated with less outpatient visits related to asthma (1 RCT, 1 879 children, RR 0.56, 95% CI 0.34 to 0.95). Paracetamol was associated with a dose-dependent increased risk of asthma symptoms (1 cohort study, 205 487 patients; once a year use: OR 1.61, 95% CI 1.46 to 1.77; once a month use: OR 3.23, 95% CI 2.91 to 3.60). A case-series (3 089 children) found that paracetamol use was a risk factor for wheeze in children (once a year use: OR 1.53, 95% CI 1.04 to 2.00; once a month use: OR 2.41, 95% CI 1.50 to 3.87).</p>
Applicability	<p>Both ibuprofen and paracetamol appear to have a similar tolerability and safety profile, with serious adverse events being rare occurrences.</p> <p>The results of the systematic review showed that ibuprofen was not different to paracetamol in producing adverse events that required discontinuation of treatment, systemic reactions, acute gastro intestinal bleeding, renal failure, anaphylaxis, low white cell count, or asthma.</p>
Comments	<p>Only 24 of the 36 included studies were RCT and of them, only three investigated safety as a primary outcome. So it is possible that the adverse event data collection in the rest of included studies was inadequate. A meta-analysis could only be done for the outcomes "adverse events that require discontinuation of medication" and "systemic reactions". The dosages used in the included studies were of 5-10mg/kg for ibuprofen and of 10-15mg/kg for paracetamol, which are in accordance with recommended over-the-counter doses.</p>

Costs	<p>A Health Technology Assessment was found [2]. It was based on a RCT that compared paracetamol and ibuprofen together with paracetamol or ibuprofen separately for treating children aged between 6 months and 6 years with fever due to an illness that could be managed at home.</p> <p>The costs for the NHS due to use of health care services were of £18 (SD £40) for ibuprofen and £20 (SD £38) for paracetamol. The costs for parents, due to travel costs and time off work were of £30 (SD £91) for ibuprofen and £26 (SD £63) for paracetamol. The combination of both drugs was the cheapest option both for NHS and parents (£14 (SD £23) and £24 (SD £46)). However, statistical evidence for these differences was weak due to lack of power.</p>
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1. Southey ER, Soares-Weiser K, Kleijnen J. Systematic review and meta-analysis of the clinical safety and tolerability of ibuprofen compared with paracetamol in paediatric pain and fever. *Curr Med Res Opin.* 2009;25:2207-22.

2. Hay AD, Redmond NM, Costelloe C, Montgomery AA, Fletcher M, Hollinghurst S et al. Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomized controlled trial. *Health Technol Assess* 2009; 13(27).

TABLE GRADE evaluation of clinical outcomes.									
Number of studies (N)	Outcome	Comparison	Evidence type	Quality	Consistency	Direct evidence	Precision	GRADE	Comments
1 RCT (84192 children)	Acute GI bleeding, renal failure and anaphylaxis	Ibuprofen Paracetamol	4	0	0	0	-2	Low	Only one RCT. Wide confidence interval. Unknown number of events.
1 (8 events)	Low white blood cell count	Ibuprofen Paracetamol	4	0	0	0	-1	Moderate	Only one RCT. Very low number of events.
2 (5 events)	Discontinuation of medication due to adverse events	Ibuprofen Paracetamol	4	0	0	0	-1	Moderate	Very low number of events
18 (4403 events)	Systemic reactions	Ibuprofen Paracetamol	4	0	0	0	0	High	
2 (466 patients)	Reye's syndrome	Paracetamol	1	-	-	-1	-	Low	Low quality evidence, due to case controls studies.
1 (1879 patients)	Hospitalization and outpatient visits concerning asthma	Ibuprofen Paracetamol	4	0	0	0	-1	Moderate	Only one RCT. Unknown number of events.
1 (205 487)	Asthma symptoms	Paracetamol	2	-	-	-1	-	Moderate	Cohort study. Large effect size(+1). Dose-response relation(+1).

Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion