

Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial

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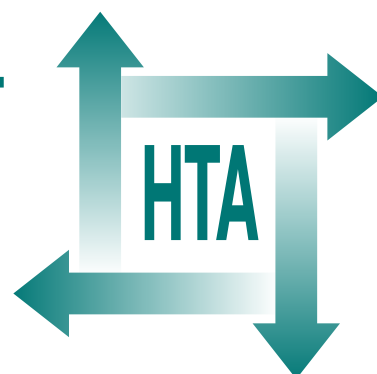
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Executive summary

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Executive summary

Background

Paracetamol and ibuprofen are increasingly used together for fever, despite a lack of evidence regarding their clinical effectiveness or cost-effectiveness.

Objectives

1. To establish the relative clinical effectiveness of both medicines compared with paracetamol and ibuprofen separately for time without fever in young children who can be managed at home.
2. To assess the relative clinical effectiveness of both medicines with paracetamol and ibuprofen separately for the relief of fever-associated discomfort.
3. To use qualitative methods to optimise the overall trial process and explore parents' and clinicians' beliefs about the use, effectiveness and side effects of paracetamol and ibuprofen.
4. To perform an economic evaluation from the perspectives of the NHS and parents comparing the cost and benefits of each treatment.
5. To describe the natural history of fever.

Design

The trial design was a single-centre (multisite), individually randomised, blinded, three-arm trial comparing paracetamol and ibuprofen together with paracetamol or ibuprofen separately.

Setting

There were three recruitment settings, as follows: 'local' where research nurses were recruited from NHS primary care sites; 'remote' where NHS sites notified the study of potentially eligible children; and 'community' where parents contacted the study in response to local media advertisements.

Participants

We recruited children aged between 6 months and 6 years with fever $\geq 37.8^{\circ}\text{C}$ and $\leq 41^{\circ}\text{C}$ due to an illness that could be managed at home.

Children were excluded if they required hospital admission; were clinically dehydrated; had recently participated in another trial; had previously participated in PITCH; had a known trial medicine intolerance, allergy or contraindication; if they had a chronic neurological disease; and/or if their parents could not read or write English.

Interventions

The intervention was the provision of, and advice to give, the medicines for up to 48 hours: paracetamol every 4–6 hours (maximum of four doses in 24 hours) and ibuprofen every 6–8 hours (maximum of three doses in 24 hours). Every parent received two bottles, with at least one containing an active medicine. Parents, research nurses and investigators were blinded to treatment allocation by the use of identically matched placebo medicines. The dose of medicine was determined by the child's weight: paracetamol 15 mg/kg and ibuprofen 10 mg/kg per dose.

Main outcome measures

Primary outcome measures were time without fever in the first 4 hours and fever-associated discomfort at 48 hours, measured using continuous axillary thermometry and a symptom diary respectively. Secondary outcomes were fever clearance (time to first afebrile); time without fever during the first 24 hours; other fever-associated symptoms (appetite, activity and sleep), digital axillary temperature and adverse effects at 24 hours, 48 hours and day 5. Direct costs to the NHS and parents were estimated at 48 hours and day 5; we assumed that parents had bought the study medicines over the counter.

Research findings

For additional time without fever in the first 4 hours, use of both medicines was superior to use of paracetamol alone [adjusted difference 55 minutes, 95% confidence interval (CI) 33 to 77 minutes; $p < 0.001$] and may have been as good as ibuprofen (adjusted difference 16 minutes, 95% CI -6 to 39 minutes; $p = 0.2$). Both medicines together cleared

the fever 23 minutes (95% CI 2–45 minutes; $p = 0.015$) faster than paracetamol alone but no faster than ibuprofen alone (adjusted difference –3 minutes, 95% CI 24–18 minutes; $p = 0.8$). For additional time without fever in the first 24 hours, both medicines were superior to paracetamol (adjusted difference 4.4 hours, 95% CI 2.4–6.3 hours; $p < 0.001$) or ibuprofen (adjusted difference 2.5 hours, 95% CI 0.6–4.5 hours; $p = 0.008$) alone. No reduction in discomfort or other fever-associated symptoms was found, although power was low for these outcomes. An exploratory analysis showed that children with higher discomfort levels had higher mean temperatures. No difference in adverse effects was observed between treatment groups. The recommended maximum number of doses of paracetamol and ibuprofen in 24 hours was exceeded in 8% and 11% of children respectively.

Over the 5-day study period, paracetamol and ibuprofen together was the cheapest option for the NHS due to the lower use of health-care services: £14 [standard deviation (SD) £23] versus £20 (SD £38) for paracetamol and £18 (SD £40) for ibuprofen. Both medicines were also cheapest for parents because the lower use of health care services resulted in personal saving on travel costs and less time off work: £24 (SD £46) versus £26 (SD £63) for paracetamol and £30 (SD £91) for ibuprofen. This more than compensated for the extra cost of medication. However, statistical evidence for these differences was weak due to lack of power.

Overall, a quarter of children were ‘back to normal’ by 48 hours and one-third by day 5. After randomisation, five (3%) children were admitted to hospital, two with pneumonia, two with bronchiolitis and one with a severe, but unidentified ‘viral illness’.

Conclusions

Implications for health care

Doctors, nurses and parents who want to use medicines to treat young children who are unwell with fever should be advised to use ibuprofen first and to consider the relative risks (inadvertently exceeding the maximum recommended dose) and benefits (extra 2.5 hours without fever) of using paracetamol plus ibuprofen over 24 hours. Pragmatically, we speculate that if a child remains unwell after a first dose of ibuprofen, subsequent use of both medicines will be more effective than

either monotherapy. However, if two medicines are used, we recommend that all dose times are carefully recorded to avoid accidentally exceeding the maximum recommended dose. Manufacturers should consider supplying blank charts for this purpose. The economic analysis shows that the use of both medicines should not be discouraged on the basis of cost to either parents or the NHS. Parents and clinicians should be aware that fever is a relatively short-lived symptom, but may have more serious prognostic implications than the other common symptom presentations of childhood.

Recommendations for research (in order of priority)

1. Is a parent education programme that includes information regarding the accurate dosing (by weight) of antipyretics cost effective in improving parents’ ability to care for children in the home?
2. Children’s infections are the single largest contributor to NHS workload. Improving parents’ confidence to care for children in the home, dose medicines accurately and to know when to seek medical help could have major benefits for the NHS.
3. The evidence base for the general components of an effective behavioural change intervention is well established. Previous parent interventions providing written information only regarding the management of common illnesses demonstrated little change in their use of health services. The PITCH study suggested that the ‘dose by weight’ use of combined antipyretic medicines might be cost effective, due to reductions in the use of primary care services when compared with the use of single medicines.

Trial registration

This trial is registered as ISRCTN 26362730.

Publication

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NIHR Health Technology Assessment programme

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The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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