EDITOR'S CHOICE

Systematic review of studies comparing combined treatment with paracetamol and ibuprofen, with either drug alone

Edward Purssell

Correspondence to
Edward Purssell, Department of Primary and Intermediate Care, King's College London, James Clerk Maxwell Building, 57 Waterloo Road, London SE1 8WA, UK; edward.purssell@kcl.ac.uk

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ABSTRACT

Objective To evaluate the evidence surrounding the use of combinations of paracetamol and ibuprofen in the treatment of fever.

Design Systematic narrative review of randomised controlled trials using the UK Economic and Social Research Council guidance on the conduct of narrative synthesis.

Setting Inpatient, outpatient and home care.

Patients Children with fever.

Main outcome measures The effect of combination treatments of paracetamol and ibuprofen on fever and comfort, and identification of side effects.

Results Seven studies were identified, six of which provided useful data for the evaluation of the effect of treatment on temperature. Overall these studies showed limited benefit from the combined treatment until around 4 h, after which there was a statistically but only marginally clinically significant benefit. Two studies contained data directly relating to comfort; these suggest a marginal benefit from the combined treatment, but the clinical significance of this was limited. There was no evidence of greater side effects or toxicities associated with the combined treatment. However, it is important to note that these studies were small, short term, and not conducted in the normal setting in which these treatments are given.

Conclusions There is little evidence of any benefit or harm from the combined treatment compared with the use of each drug alone. In the absence of such benefit, there is little to recommend the unnecessary use of polypharmaceutical methods to treat a symptom that does not require treatment, when effective monotherapies exist.

What is known on this subject?

- Fever is a common symptom and, while it may be indicative of serious disease, is not dangerous in itself.
- Parents and professionals often treat this symptom with a combination of paracetamol and ibuprofen, despite the lack of official guidance to this effect.

What this study adds

- A systematic review of randomised controlled trials comparing combinations of paracetamol and ibuprofen to each drug alone, combined with expert opinion in the form of official guidelines.
- Only marginal benefit was shown for the combined treatments compared with each drug individually, which taken alongside the risk of overdose and further increasing the fear of fever, suggests that there is little to recommend this practice.

INTRODUCTION

Fever is a common symptom which consistently causes high levels of anxiety in parents and professionals alike, leading to the widespread and often unnecessary use of antipyretic medications.[1 2] Although paracetamol and ibuprofen on their own are effective, safe and relatively inexpensive antipyretic drugs, some clinicians are known to recommend combining the two drugs, despite the lack of recommendations to this effect.[3]

Recent guidelines from the American Academy of Pediatrics have noted the lack of evidence for this practice, but in recognising that this is a common occurrence they suggest that those who advise or prescribe this treatment ensure carers understand the formulation and dosage, and stress that the primary aim of the treatment is to improve the child's comfort rather than to reduce temperature.[4] This narrative systematic review aims to collate and critique the evidence surrounding the practice of combining paracetamol and ibuprofen, using the principles underlying the UK Economic and Social Research Council guidance on the conduct of narrative synthesis[5] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[6]

METHODS

A systematic literature search was carried out in May 2011 to identify studies comparing the efficacy or effectiveness of any dose of a combination of paracetamol and ibuprofen, either together or separately, with either drug alone. Outcome measures were the effect on temperature, comfort and the occurrence of any side effects or toxicities. Medline (1948–May 2011) and Embase (1980–May 2011) were searched using the keywords ibuprofen; paracetamol; acetaminophen and antipyretic. Trade names were not searched. In addition to the database search, hand searching was done of the references from the UK National Institute for Health and Clinical Excellence (NICE) guidelines on the treatment of fever in children under

the age of 5 years[7] and the American Academy of Pediatrics guidelines on fever and antipyretic use in children.[4]

Inclusion criteria were that studies should be randomised controlled trials with data on any of the three outcomes. For practical reasons, literature was restricted to English language; this is acknowledged as a limitation since the author is aware that combination products are in use in some non-English-speaking countries, although not licensed for use in the European Union. Study quality was assessed using the CONSORT statement for the reporting of pragmatic trials to assess the risk of bias.[8] Additionally, expert opinion was established by examining official recommendations from professional or similar organisations.

RESULTS

Seven studies were retrieved and screened, all of which met the inclusion criteria and were therefore included in the review. Details of these are shown in table 1.[9–15] The CONSORT scores ranged from 17 to 22 out of 22, and all studies were included in at least one part of the analysis. Although one study contained no extractable numerical temperature data, it did include useful laboratory values, and the findings are included in the analysis of safety only. This paper also had the lowest CONSORT score.[9] Six of the studies contained useful data about temperature response to combination treatment, albeit in different and non-directly combinable forms; two studies contained data on comfort; and three had sufficient follow-up time to detect side effects and toxicities. Details of how significant temperatures were defined in the studies are shown in table 2. Data were extracted onto a standard template by one reviewer on two separate occasions.

TREATMENTS

There were a variety of dosages and timings making direct comparison difficult. Experimental groups in the studies used a variety of combinations, including a single combined dose of both drugs[14]; a single dose of each drug but which were separated by 3[12 15] or 4 h[13]; or multiple combined[9] or alternating doses.[10 11] Doses of paracetamol and ibuprofen also varied from 12.5 to 15 mg/kg and 5 to 10 mg/kg respectively; no dosage adjustments were made for the combination treatments. There were similar differences in dosing intervals, with paracetamol being given 4–6 hourly and ibuprofen 6–8 hourly. Within these studies there are therefore a multitude of different treatment approaches, and although they fall into two main categories, namely combined or alternating doses, there are insufficient data to treat them as separate treatments.

EFFECT ON TEMPERATURE

The primary outcome measure of all studies was the effect of the treatment on temperature. Again they fell into two broad categories: those that looked primarily at the short-term effects, that is under 8 h; and those that took a longer view. Details of the outcomes are shown in table 3. No studies reporting temperature decline as a primary outcome showed a difference between combined and individual treatments within the first 3 h, however by 4 h a consistent difference did occur. In one study comparing a combined treatment and paracetamol the difference was 0.6°C at 4 h (p=0.05) and 0.8°C at 5 h (p=0.003), but this had fallen to 0.1°C by 6 h[12]. The other study reporting these data found that both a single combined dose, and a single alternating dose were superior to ibuprofen alone at 4, 5 and 6 h. At 4 h the difference between both

Table 1 Study characteristics

Study	Interventions	Temperature	Age	Follow-up time
Lal *et al*[9]*	G1: paracetamol 10 mg/kg 8 hourly, n=33 G3: paracetamol 10 mg/kg and ibuprofen 10 mg/kg 8 hourly, n=18	>38.5°C axilla	Mean (95% CI) 2.85 years (1.75 to 3.95) and 3.02 (2.34 to 3.7)	5 days
Erlewyn-Lajeunesse *et al*[14]	G1: paracetamol 15 mg/kg single dose, n=37 G2: ibuprofen 5 mg/kg single dose, n=35 G3: paracetamol 15 mg/kg and ibuprofen 5 mg/kg single dose, n=36	≥38°C tympanic	6 months–10 years	2 h
Nabulsi *et al*[13]	G2: ibuprofen 10 mg/kg, followed by placebo at 4 h, n=33 G3: ibuprofen 10 mg/kg, followed by paracetamol 15 mg/kg at 4 h, n=36	≥38.8°C rectal	6 months–14 years	8 h
Sarrell *et al*[11†]	G1: paracetamol 12.5 mg/kg 6 hourly, n=154 G2: ibuprofen 5 mg/kg 8 hourly, n=155 G3: paracetamol 12.5 mg/kg alternately with ibuprofen 5 mg/kg 4 hourly, n=155	≥38.4°C rectal	6 months–3 years	10 days
Hay *et al*[10]	G1: paracetamol 15 mg/kg 4–6 hourly, n=52 G2: ibuprofen 10 mg/kg 6–8 hourly, n=52 G3: paracetamol 15 mg/kg 4–6 hourly and ibuprofen 10 mg/kg 6–8 hourly, n=52	37.8–41°C axilla	6 months–6 years	5 days
Kramer *et al*[12]	G1: paracetamol 15 mg/kg followed by placebo at 3 h and paracetamol 15 mg/kg at 4 h, n=19 G3: paracetamol 15 mg/kg followed by ibuprofen 10 mg/kg at 3 h and placebo at 4 h, n=19	>38°C oral (rectal <2 years)	6 months–6 years	24 h
Paul *et al*[15]	G1: ibuprofen 10 mg/kg followed by paracetamol 15 mg/kg at 3 h, n=20 G2: ibuprofen 10 mg/kg G3: ibuprofen 10 mg/kg and paracetamol 15 mg/kg	>38°C temporal artery	6 months–6 years	6 h

*This study also included a nimesulide arm not analysed here.
†Half of each group were initially loaded with paracetamol and ibuprofen; because there was no difference these were analysed together.

combined treatments and ibuprofen was 0.6°C (p=0.002), at 5 and 6 h the difference was 1.1°C and 1.3°C for the single dose, and 1.2°C and 1.6°C for the alternate dose respectively (p<0.001).[15]

An alternative view of effectiveness is to study the number who were afebrile at different time points. The percentage achieving this was similar at 6 h, but at 7 and 8 h more children were afebrile in the combined than the ibuprofen group, the difference being 40.9% at 7 h and 45.1% at 8 h (p<0.001), although the maximum temperature decline was similar at 2.2°C and 2.1°C in the combined and ibuprofen groups respectively.[13] One study did suggest a faster rate of fall in the combined group compared with individual drugs, with the percentages having a temperature >37.2°C being 36% for paracetamol, 15% for ibuprofen and 9% for the combined treatments at 2 h, the equivalent figures for 4 h being 29%, 15% and 2% respectively.[10]

There were two studies that looked at longer-term outcomes, albeit in different forms. One found that those in the combined group had more time without fever in the first 24 h than both those receiving paracetamol or ibuprofen alone, however this was only statistically significant compared with paracetamol, the difference being 277.1 min (p<0.001), while that for ibuprofen was 162.2 min (p=0.2).[10] Maximum recorded daily temperatures also differed among treatments, while there was no difference between paracetamol and ibuprofen: on days 1–3 the combined treatment led to a lower maximum temperature of 0.91°C, 0.96°C and 0.8°C compared with paracetamol alone, and 0.96°C, 0.88°C and 1.11°C compared with ibuprofen (all p<0.001).[11]

Table 2 Definitions of significant temperature

Study	Definitions
Erlewyn-Lajeunesse *et al*[14]	Difference of 1°C at 1 h clinically significant
Nabulsi *et al*[13]	Normal temperature 36.5–37.9°C
Sarrell *et al*[11]	Afebrile if <37.8°C
Hay *et al*[10]	Time without fever <37.2°C
Kramer *et al*[12]	Fever if >38°C
Paul *et al*[15]	38°C standard temperature threshold used by schools and day-care for exclusion

EFFECT ON DISCOMFORT AND SIDE EFFECTS

Two studies looked at discomfort, one asking parents about discomfort at 24 h, 48 h and at 5 days,[10] the other asking parents to assess their child using the non-communicating children's pain checklist.[11] In the first of these there was no significant difference between treatments, at 24 h: 44% of the paracetamol children were without discomfort compared with 69% in the ibuprofen and 56% in the combined groups. For 48 h this was 65%, 71% and 69%; and at 5 days 88%, 61% and 76% respectively. In the latter study paracetamol was superior

Table 3 Summary of outcome measures

Study	Temperature	Side effects	Comfort
Lal *et al*[9]	Insufficient data	Slightly raised SGPT, SGOT, urea and creatinine in mixed group. No clinical significance	No data
Erlewyn-Lajeunesse *et al*[14]	**Mean fall over 1 h °C (t)** No clinically or statistically significant difference P 0.95, I 0.92, PI 1.22	No data	No data
Nabulsi *et al*[13]	**% Afebrile at 6–8 h (r)** greater in mixed group 6 h: I 57.6, PI 83.3, p=0.018 7 h: I 45.2, PI 86.1, p<0.001 8 h: I 35.5, PI 80.6, p<0.001 **Max temperature decline** no difference	No serious adverse reactions. No sign of GI, hepatic, renal toxicity	No data
Sarrell *et al*[11]	**Mean max temperature on days 1–3 °C (r)** lowest in mixed group, highest in paracetamol 1 day: P 40.6, I 40.6, PI 39.6 p<0.001 2 day: P 39.7, I 39.7, PI 38.8 p<0.001 3 day: P 39.3, I 39.6, PI 38.5 p<0.001	No differences in renal and liver values and no abnormalities at 14 days	NCCPC score and repeat dosages on days 1–3 lower in mixed group, highest in paracetamol group
Hay *et al*[10]	**Minutes without feverfirst 4 h (a):** greatest in mixed group, shortest in paracetamol group P 116.2, I 156, PI 171.1 **Pairwise comparison**mixed vs paracetamol p<0.001, ibuprofen vs paracetamol p=0.001 **First 24 h:** same pattern P 940.3, PI 1055.2, PI 1217.4	Diarrhoea, vomiting, rash, cough, cold to touch, admitted to hospital no differences and none considered to be related to study	No discomfort at 48 h, pairwise comparisons no difference
Kramer *et al*[12]	**Mean temperature at 3–6 h °C (o/r)**no difference at 3 or 6 h, at 4 and 5 h lower in mixed group 4 h: P 38, PI 37.4, p=0.05 5 h: P 37.9, PI 37.1, p=0.003	No side effects prevented administration and did not differ between groups	Repeat dosages needed at 3 and 4 h no difference
Paul *et al*[15]	**Mean temperature at 1–6 h °C (ta)** no difference at 1–3 h, at 4–6 h lower in mixed (PI) and alternating (IP) than ibuprofen (note order of groups) 4 h: IP 36.9, I 37.5, PI 36.9, p=0.002 5 h: IP 36.8, I 38, PI 36.9, p<0.001 6 h: IP 36.9, I 38.5, PI 37.2, p<0.001	Did not evaluate effect of multiple doses or adverse events that could occur from this	No data

a, axilla; I, ibuprofen; GI, gastrointestinal; NCCPC, non-communicating children's pain checklist; o, oral; P, paracetamol; PI/IP paracetamol and ibuprofen; r, rectal; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; t, tympanic; ta, temporal artery.

on the first day (d0), but the combined treatment was superior on subsequent days. This statistically significant difference is, however, difficult to assess from a clinical perspective. There were few reports of side effects, none of which could be directly attributed to the drugs, and there was no difference between them. However, none of the studies were of sufficient sample size or length to exclude toxicity, and most relied on passive reporting, reducing the sensitivity of the studies to identify toxicity as opposed to side effects.

EXPERT OPINION

Four official guidelines were searched for evidence of expert opinion about the use of antipyretics in general, and opinion about the use of combinations specifically.[4 7 16 17] The benefit of this is that it allows the integration of different interpretations of the evidence to be included in the review, although some of these are somewhat dated, and do not include the most recent studies. NICE guidelines state that antipyretics in general should be considered in children who are distressed or unwell, but not with the sole aim of reducing temperature, and not as a combination or alternately as a routine, although these guidelines are currently being updated. The American Academy of Pediatrics recommendations, which are the most recent, being published in 2011, are similar, stating that the primary goal should be that of promoting comfort, and that there is insufficient evidence to support or refute routine use of combination treatment. The Italian Paediatric Society recommendations state that antipyretics should only be used when fever is associated with discomfort, and that combined or alternating use of ibuprofen and paracetamol is not recommended. In the *Integrated management of childhood illness manual*, which is aimed at developing countries, the World Health Organisation recommends a single dose of paracetamol for what they describe as high fever, which they define as being over 38.5°C. A search of the European Medicines Agency, Medicines and Healthcare Products Regulatory Authority, and the Federal Drug Administration databases did not reveal any regulatory or safety data on combined or alternating treatments.

DISCUSSION

Many parents have unfounded fears of fever,[1] fears that are shared by some healthcare professionals.[18] Consequently the use of antipyretic drugs is popular, and although both paracetamol and ibuprofen are associated with possible toxicities such as hepatotoxicity[19], and gastric and antiplatelet effects respectively,[20] they are generally both safe and effective drugs.[21] Combining the two drugs for high fever, or fever that does not respond to one drug alone, is not officially recommended, but may be a common practice.[3] There are a number of concerns about this, in particular possible renal toxicity caused by the additive and possibly synergistic effects of drug metabolites in dehydrated children,[22] misdosing, and its effect on increasing parental concern about fever.[23 24] Although some studies did seek to identify side effects, there are few data regarding toxicity, and based on these studies no conclusion can be reached regarding the safety of any treatments. Furthermore, these studies contain no data on children under the age of 6 months.

This review aimed to analyse the major concern of parents, that is fever[1]; the recommendation of official bodies that treatment be aimed at improving comfort[4 7 17]; and the overall concern about possible toxicities and side effects. Because of the methodological heterogeneity it is not possible to statistically integrate the studies; instead they are considered under three headings: the direction of effects; the size of these effects; and the robustness and generalisability of the findings.[5]

Most studies showed some additional reduction in temperature associated with combined or alternating treatment, although this rarely reached clinically or statistically significant levels. Furthermore it is not clear what constitutes the best measure of antipyretic activity. Mean fall in temperature is easy to measure, but it is far from clear that this is of most benefit to the child and family; and the proportion who are afebrile at a given time point or the total time spent without fever might be more relevant.

There were no significant reports of toxicities and side effects in any treatment group, however studies were generally short term, often did not look at this outcome or lacked the power to identify these. Additionally it is often impossible to identify which are the result of the treatment, and which the disease. The limited data also mean that it is difficult to come to any conclusion about comfort because few studies looked at this outcome and those that did used different methods for doing so; indeed it is not clear what constitutes comfort.

The robustness and generalisability of these studies is limited by a number of factors: they are all small studies that lacked power and were too short term, particularly to identify toxicities and side effects; they were often carried out in healthcare facilities which differs from the setting in which antipyretics are often given, thus they study efficacy rather than effectiveness[25]; they used different interventions and methods of recording temperature; many children who might be given antipyretics were excluded from the studies, particularly those at higher risk from toxicities such as those suffering dehydration or comorbidity.

Although there are two distinct approaches within the studies, namely alternating or combining the drugs, there are insufficient data to say that one is superior to the other or to either drug alone in any respect. Because of the heterogeneity of the studies, it is difficult to assess the effect of publication bias, although both positive and negative effects are reported. With these limitations, based on these data there is little evidence to suggest that combining drugs provides much benefit over each drug alone, either in antipyretic efficacy or the promotion of comfort, however there is no evidence of harm either. Despite this, the lack of therapeutic indication for either alternating or combined treatments makes such use of these drugs unwise, even in the absence of data suggesting harm.

CONCLUSION

From this evidence it appears that there is little benefit from combining paracetamol and ibuprofen, and although there was no evidence of increased toxicity, the studies may have been too small, too short term and excluded children who are most at risk of such toxicities. While it is tempting to conclude that further research should be undertaken, based on the small size and short duration of most existing studies, this is not really necessary. These studies have shown that there is limited benefit from combination treatment; however, this benefit was not immediate. This, alongside the lack of indications for combination therapy, and the ethical and practical difficulties of conducting such research, suggests that resources could be better targeted elsewhere.

This analysis supports the recommendations which suggest that this practice should not be encouraged. In particular, clinicians and parents should note the lack of evidence of increased

effectiveness either in terms of temperature or comfort; the relative lack of safety data; the effective nature of each drug individually; and the effect that routine co-administration of these drugs might have on increasing parental and professional fever phobia. The emphasis for intervention should therefore be on education of professionals and parents to understand fever; in particular that it is a symptom, and to use resources such as the NICE 'traffic light' system[7] to treat the underlying condition appropriately.

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