

ORIGINAL ARTICLE

Ibuprofen versus paracetamol in pediatric fever: objective and subjective findings from a randomized, blinded study

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ABSTRACT

Objective: The main objective of this study was to compare the single-dose efficacy of 15 mg/kg paracetamol (acetaminophen) versus 10 mg/kg ibuprofen in a general practice setting.

Methods: Children from the age of 3 months to 12 years with a fever of non-serious origin were randomized to receive either ibuprofen or paracetamol. The first dose was given double-blind, using a double-dummy technique. Tympanic temperature was measured at baseline and over the following 8 hours. The second and subsequent doses were administered open-label for up to 3 days by parents at home. At the end of the double-blind and the open-label periods, parents were asked to subjectively rate the efficacy of the product and state whether they would treat their child with the product again. The primary endpoint of the study was the area under the temperature reduction curve expressed as an absolute difference

from baseline, from 0 to 6 hours (AUC₀₋₆). Secondary efficacy endpoints included a variety of objective and subjective measures.

Results: No statistically significant differences in the primary endpoint or any of the objective secondary endpoints were observed. Both agents were equally well tolerated. Compared with parents in the paracetamol group, significantly more parents in the ibuprofen group rated the drug as very efficacious, and reported that they would use the drug again in both the double-blind and open-label phases of the study.

Conclusions: Ibuprofen at a dose of 10 mg/kg and paracetamol at a dose of 15 mg/kg have equivalent efficacy and tolerability; parental opinion in favor of ibuprofen could be explained by additional benefits of ibuprofen that were not measured in this trial and helped allay their anxiety over the treatment of their child.

Introduction

Fever in children is typically treated with ibuprofen or paracetamol. Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activity, and is used for the symptomatic treatment of mild-to-moderate pain and fever. Specific ibuprofen formulations for use in children,

such as suppositories and syrups, have been licensed in many countries. Paracetamol is a long-established general-purpose antipyretic and analgesic drug, which is also indicated for the relief of mild-to-moderate pain and reduction of fever. It is available for oral and rectal administration from a variety of manufacturers. Both ibuprofen and paracetamol are also available without prescription as over the counter (OTC) drugs.

The efficacy of ibuprofen and paracetamol in pediatric fever has been compared in numerous studies in patient populations of children aged from 3 months to 12 years, with various acute illnesses¹⁻⁶. Although many of these studies found no difference in antipyretic efficacy between ibuprofen and paracetamol, two meta-analyses found a tendency for higher efficacy of ibuprofen. In a meta-analysis of 10 randomized, blinded, controlled studies, ibuprofen at doses of 5–10 mg/kg versus paracetamol at doses of 10–15 mg/kg was the superior antipyretic⁷. The relative superiority was more pronounced at 4 and 6 hours after treatment – when the authors estimated that approximately 15% more children were likely to have temperature reduction with ibuprofen than with paracetamol. By restricting the analysis to 10 mg/kg of ibuprofen versus 10–15 mg/kg of paracetamol, the effect sizes in favor of ibuprofen were doubled. The two agents were found overall to be equal in terms of safety. The second meta-analysis, which included eight studies, revealed similar results in that ibuprofen was found to be a more effective antipyretic, not only in terms of maximum temperature drop, but also duration of action⁸. Again, the safety profiles of both drugs were similar.

In some countries, notably France and Australia, the OTC dose of paracetamol has been increased from 12 mg/kg to 15 mg/kg with a maximum daily dose of 60 mg/kg. As there are few direct, comparative data between the 10 mg/kg dose of ibuprofen and the 15 mg/kg dose of paracetamol, it is difficult to judge the most appropriate treatment, since most trials have used 10 mg/kg paracetamol. The main objective of this trial was to compare the single-dose efficacy of 15 mg/kg paracetamol versus 10 mg/kg ibuprofen.

Patients and methods

The study was a multicenter, double-blind, double-dummy, parallel group, randomized, single-dose trial, comparing ibuprofen (10 mg/kg) and paracetamol (15 mg/kg). The double-blind phase was then followed by up to 3 days of open-label dosing. The investigators of this trial were general practitioners (GP) and pediatricians in 27 outpatient centers in France.

The study was conducted in accordance with the Declaration of Helsinki (South Africa, 1996), as referenced in EU Directive 2001/20/EC, and complied with The International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines and applicable regulatory requirements. Written, informed consent was obtained from parents/legal guardians at the inclusion visit. Ethics approval was granted by the Committee for the Protection of Subjects in Biomedical Research of the University of Tours.

Male and female patients from the age of 3 months to 12 years inclusive were eligible to participate in the study. Only participants requiring treatment on an outpatient basis were recruited. The other main inclusion criterion was a tympanic temperature – at least 38.5°C, with an upper boundary of 40.5°C – associated with various pathologies such as sore throat, influenza, respiratory tract infection, ear infection or immunization.

Exclusion criteria included hypersensitivity to any of the study drug constituents or fructose; a history of any condition that interfered with the absorption, distribution, metabolism or excretion of the study drugs; a history of asthma, angioedema, urticaria, bronchospasm or rhinitis related to treatment with NSAIDs, aspirin or paracetamol; a history of peptic or duodenal ulcers or gastrointestinal bleed; severe hyperthermia with neurologic and/or hemodynamic disorders; patients with severe hepatic failure, severe renal failure, severe heart failure, bilateral acute otitis media, systemic lupus erythematosus, confirmed or suspected infection with varicella. Patients, who had received treatment with an antipyretic drug up to 6 hours before inclusion, or treatment with antibiotic therapy in the 12 hours before the start of the trial, were also excluded.

Patients were recruited into this study as they presented at the center with fever. This constituted the first of the two visits required for the study. Tympanic thermometry was used for this study, as this was deemed an accurate, noninvasive measure of temperature and was recommended by the Ethics Committee as being particularly suitable for use in babies and young children.

The first tympanic temperature was taken by the investigator, who instructed the parent in the correct methodology. At this stage, a dynamic computerized interactive voice response system (IVRS) was used to allocate patients to a treatment arm (only a treatment pack number was provided to the investigator). The IVRS was also used to calculate the volumes of each study medication to be administered to that patient. The dose volume was based on the child's weight.

The first dose of study medication was administered on-site by the parent, under the supervision of the investigator, using supplied oral dosing syringes. To maintain blinding of the study drugs, a double-dummy technique was used – each child received one dose of active drug and one dose of matched placebo of the other treatment. The initial double-dummy dose involved the child receiving either a 10 mg/kg oral suspension of ibuprofen plus a paracetamol placebo, or a 15 mg/kg oral suspension of paracetamol plus an ibuprofen placebo. The parent measured the child's tympanic

temperature 30 minutes after dose administration under the supervision of the investigator, to ensure the procedure was performed correctly. The temperature reading and actual time of the reading were recorded in a diary card (as were all subsequent readings).

The parent and child left the center after the 30-minute measurement. The child's temperature was measured again at 2, 3, 4, 5, 6 and 8 hours after dose administration or until a second dose was required. If, after 6 hours (4 with the permission of the investigator) of the administration of the first dose, the child's temperature was still $\geq 38.5^{\circ}\text{C}$, parents opened the carton given to them at the center in order to administer the second dose. Children who were given ibuprofen on a random, double-blind basis, received ibuprofen in the open-label phase, while those who received paracetamol, continued with paracetamol.

The carton contained three bottles of active study medication, oral dosing syringes, a timer to facilitate compliance with the required timing of temperature measurements and a card with dosing details (name of the active study medication, re-dose instructions and the maximum number of doses allowed in 24 hours). The investigator instructed the parent not to give their child a second dose of medication unless the child's temperature was $\geq 38.5^{\circ}\text{C}$ and at least 6 hours had passed since the initial dose. However, if the child was not responding to the treatment or was displaying symptoms of distress, parents were instructed to call the investigator, who could make the decision to allow a second dose to be given earlier. The minimum interval that was allowed between doses was 4 hours, but the maximum daily dosages (three doses of ibuprofen; four doses of paracetamol) were not exceeded. These timings and doses were selected to be consistent with the current terms of the French licenses for ibuprofen and paracetamol pediatric suspensions. With subsequent dosing, temperature readings were taken before each dose of study medication.

Parents were asked to respond to the global assessment questions in the diary card before administering the second dose, while still in the double-blind phase of the study. This allowed for objective judgment of treatment efficacy. The first question referred to the parents' overall opinion of the treatment with four levels of qualitative answers: (1) very efficacious; (2) efficacious; (3) slightly efficacious; and (4) not efficacious. The second question was 'if your child develops a fever again in the future, would you give him/her the same treatment?' There were two levels of answer; yes or no. Parents were also allowed to make comments.

Parents were instructed to make an appointment for a follow-up visit once the febrile episode was over. They were asked to bring the completed diary card and

medication pack with them. At this visit, at the end of the open-label phase, parents were also asked the same two global assessment questions.

At baseline, demographic data and the medical history of the child were obtained. A standard physical examination was conducted and vital signs and temperature were measured. At the second visit, a standard physical examination was conducted once again, diary completeness was assessed, and parents' global assessment of treatment was recorded. Adverse events (description, severity and relationship to study medication) were also recorded.

The primary endpoint of the study was the area under the temperature reduction curve expressed as an absolute difference from baseline, from 0 to 6 hours (area under the curve $[\text{AUC}]_{0-6}^{\circ}\text{C}\cdot\text{min}$). How far the temperature can fall clearly depends on what it is at baseline, and it is also known that the rate of fall is faster in younger subjects; consequently, subgroup analyses were performed according to age and baseline temperature^{5,9}.

The secondary endpoints were as follows: (1) parental global assessments of treatment at the end of the double-blind period and end of the open-label period; (2) the area under the temperature reduction curve from 0 to 4 hours (AUC_{0-4}) and from 0 to 8 hours (AUC_{0-8}); (3) individual temperature readings at each time point from 30 minutes to 8 hours; (4) time to recurrence of a temperature $> 38.5^{\circ}\text{C}$; (5) time to reach a temperature of $\leq 38^{\circ}\text{C}$; and (6) time to maximal temperature reduction and time to reach apyrexia ($\leq 37.4^{\circ}\text{C}$).

As there was no estimate of variability for the AUC data, the sample size was based on the detectable difference between the two treatments at 4 hours from historical data. Assuming a variability of 0.9°C in temperature reduction, a minimum of 140 subjects per group were required in order to demonstrate a difference of 0.35°C for temperature reduction between the two treatments with 90% power. As a safeguard, it was decided to recruit 150 subjects per group in order to maintain a high power to detect a difference of 0.35°C between the two treatments for the area under the temperature reduction curve from 0 to 6 hours (AUC_{0-6}).

The null hypothesis of the study was that there is no difference in the antipyretic efficacy between the two agents as measured by the AUC_{0-6} .

The primary endpoint was analyzed by an analysis of covariance (ANCOVA), which included baseline temperature and age as covariates and a factor for treatment group. Comparisons between the treatments were assessed at a two-sided α of 0.05. A 95% confidence interval (CI) for the difference between the two treatments was calculated from the fitted model.

For variables measured on continuous scales, differences between treatment groups were estimated

using the same ANCOVA model as used for the primary endpoint. Differences between the treatment groups for the time-to-event parameters were assessed using a Cox regression analysis, with baseline temperature and age included in each of the models as covariates. For variables measured on ordinal or binary scales, differences between the two treatments were assessed using logistic regression, which included baseline temperature and age as covariates.

Results

A total of 304 patients were enrolled. One was prescribed ibuprofen by the investigator, not randomized using the IVRS, and two had no post-baseline assessments, therefore the intent-to-treat (ITT) population consisted of 301 patients. The per-protocol (PP) population contained 288 patients – six patients contravened the study protocol by receiving the second dose within 6 hours and seven patients were receiving prohibited concomitant medication. There were no differences between the results in the PP analysis and the ITT analysis and only the latter results are presented here. Baseline characteristics were similar in the two groups and no clinically relevant differences were identified (Table 1). The mean age was 3.78 years (range 0.4–11 years) and mean weight was 17.56 kg (range 6.2–84.1 kg).

Results indicated that there were no statistically significant differences in the primary endpoint or in any of the objective secondary endpoints.

The treatment group difference for the primary endpoint was not statistically significant (Figure 1). The mean $AUC_{(0-6)}$ was $-7.77 \pm 3.54^\circ\text{C}\cdot\text{min}$ in the ibuprofen group and $-7.66 \pm 3.76^\circ\text{C}\cdot\text{min}$ in the paracetamol group ($p = 0.82$). Subgroup analyses were performed according to age and baseline temperature. For the analysis according to age, the patient population

≤ 3 years of age consisted of 167 children (82 in the ibuprofen group and 85 in the paracetamol group). The analysis demonstrated that although there was a trend in favor of ibuprofen in children ≤ 3 years, the difference was not statistically significant ($-7.34 \pm 3.43^\circ\text{C}\cdot\text{min}$ in the ibuprofen group versus $-7.02 \pm 3.67^\circ\text{C}\cdot\text{min}$ in the paracetamol group; $p = 0.741$). For the analysis according to baseline temperature, the patient population with a body temperature $> 39^\circ\text{C}$ at baseline consisted of 81 children (39 in the ibuprofen group and 42 in the paracetamol group). The analysis also revealed that there was a trend in favor of ibuprofen in children with body temperature $> 39^\circ\text{C}$ at baseline; however, the difference was not statistically significant ($-9.06 \pm 3.21^\circ\text{C}\cdot\text{min}$ in the ibuprofen group versus $-8.58 \pm 3.21^\circ\text{C}\cdot\text{min}$ in the paracetamol group; $p = 0.498$).

Parents found in favor of ibuprofen on both items of the questionnaire. At the end of the assessments after the first dose (end of double-blind phase), 59.2% of parents in the ibuprofen group and 37.2% in the paracetamol group graded the treatment as being very efficacious ($p < 0.001$) in the logistic regression model fitted to these data (Figure 2). More parents in the ibuprofen group reported they would use the treatment again than in the paracetamol group (96.5% versus 88.8%, $p = 0.018$) in the logistic regression model fitted to these data (Figure 3).

Table 1. Demographics and baseline data of patients in the study groups (ITT population)

	Ibuprofen (n = 151)	Paracetamol (n = 150)
Mean age \pm SD, years	3.84 \pm 2.78	3.71 \pm 2.71
Male, %	48.3	52.0
Caucasian, %	87.4	88.0
Mean weight \pm SD, kg	17.54 \pm 7.96	17.58 \pm 8.97
Mean temperature \pm SD, $^\circ\text{C}$	38.91 \pm 0.36	38.91 \pm 0.37

ITT = intent-to-treat; SD = standard deviation

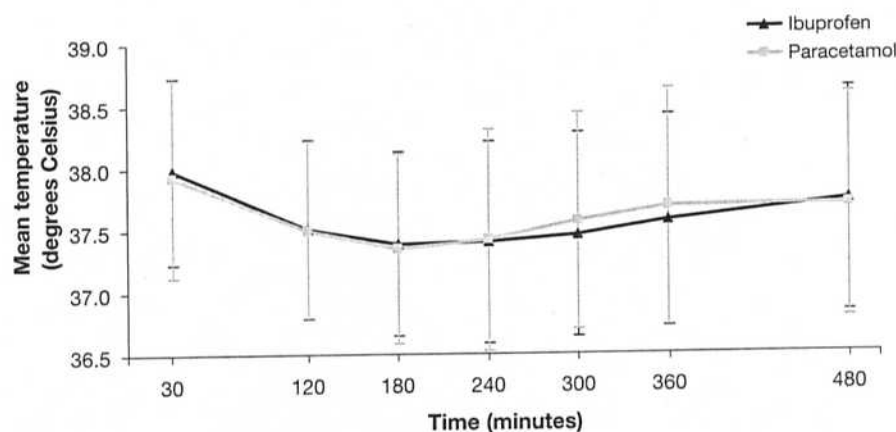


Figure 1. Mean temperature at different time points in children treated with ibuprofen or paracetamol (intent-to-treat [ITT] population)

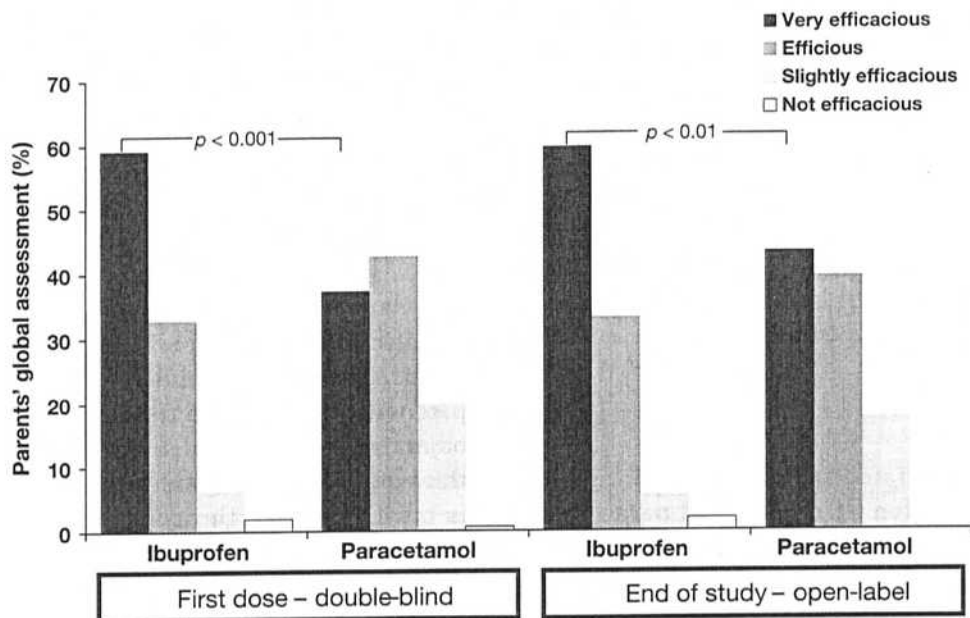


Figure 2. Parents' global assessment of treatment – efficacy rating – during the double-blind and open-label phases of the study

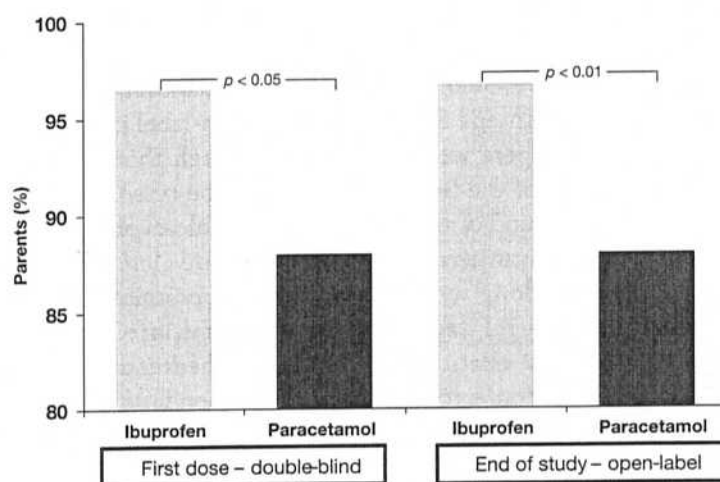


Figure 3. Proportion of parents who responded that they would use the treatment again during the double-blind and open-label phases of the study

When the parent(s) returned to the clinic after the 3 days (end of open-label phase), they were asked the same two questions again. The statistically significant differences in favor of ibuprofen were maintained, with 59.6% of parents judging the treatment to be very efficacious in the ibuprofen group compared with 43.3% of parents in the paracetamol group ($p = 0.002$). A significantly greater percentage of parents reported that they would use the treatment again in the ibuprofen group than in the paracetamol group; (96.7% versus 87.9%, $p = 0.008$).

The safety population consisted of 303 patients; 152 received ibuprofen and 151 received paracetamol. Overall, the safety profiles of the two drugs were similar and no clinically relevant differences between the two arms were noted.

A total of 17 (11.2%) patients in the ibuprofen group and 16 (10.6%) in the paracetamol group reported adverse events. Of the 21 adverse events reported in each group, nine in the ibuprofen and eight in the paracetamol groups occurred in patients who were receiving concomitant antibiotics. The most commonly reported adverse events were infections (3.3% in the ibuprofen group and 4.6% in the paracetamol group), gastrointestinal disorders (2.6% in both groups) and respiratory disorders (2.6% in both groups).

All adverse events reported were either mild or moderate in severity. One serious adverse event was reported in a patient after having taken seven doses of randomized treatment (paracetamol) on the first day. The child was suffering from persistence of wavering fever and onset of cough – an X-ray revealed

pneumopathy. The child recovered 4 days later but withdrew from the trial. The event was recorded as having no relationship to study drug. Three adverse events (7.1%) were graded as having an unlikely relationship to study medication and the remaining 38 (90.5%) events had no relationship to study medication. Only one adverse event was graded as being possibly related to the study medication (a case of vomiting in the ibuprofen group).

Discussion

This study demonstrated the equivalent antipyretic efficacy of ibuprofen 10 mg/kg and paracetamol 15 mg/kg. Although a number of previous studies and meta-analyses have shown ibuprofen to be superior to paracetamol, they had included a paracetamol dose of 10–15 mg/kg. Another finding of this study was that, in contrast to the objective measures, the subjective ones revealed statistically significant differences in favor of ibuprofen.

A number of hypotheses can be formulated to explain these findings. First, it may have been a chance finding combined with non-adjustment for multiple secondary comparisons. In total, there were four subjective assessments; two at the end of the first dosing period (double-blind) and two at the end of the open-label treatment period. All four were positively in favor of ibuprofen. This observation, along with the maintenance of the difference over several days, argues against the finding being due to chance. Furthermore, a *post hoc* analysis using the Bonferroni correction method demonstrated that the parental efficacy ratings were still statistically significantly different. Another explanation may be that fewer doses were required with ibuprofen (three times a day), compared with paracetamol (four times a day) during the open-label phase; however, this does not explain the difference observed in the first part of the study. The tolerability profiles of the two agents were also similar; therefore, parental preference for ibuprofen cannot be attributed to any superior tolerability.

Another possible explanation is that ibuprofen is more effective than paracetamol in addressing additional symptoms that were not evaluated in this study, particularly for reducing pain and myalgia often associated with fever in common childhood conditions such as otitis media and upper respiratory tract viral infections. However, in a recent double-blind study of children aged 6–17 years old with pain from a musculoskeletal injury, ibuprofen 10 mg/kg was shown to have a significantly greater analgesic effect than paracetamol 15 mg/kg¹⁰. The absence of measures of other symptoms was

related to the heterogeneity of diseases causing fever (e.g., sore throat, influenza, respiratory tract infection, ear infection). Consequently, it is difficult to provide a common measurement scale or tool.

As parental perception of treatment efficacy was not specifically directed at a reduction in temperature, but was global ('What is your general judgment on the treatment?'), and as it is reasonable to assume that patients in this trial were experiencing one or more additional symptoms, ibuprofen may well have provided superior benefits to paracetamol. Although parental perception of treatment efficacy is not an objective criterion, given the double-blind design, the significant difference between treatment groups is most probably the consequence of the overall better resolution of all the symptoms of the disease that caused the fever, rather than a bias in favor of a particular product.

Interestingly, the answers to both global assessment questions asked after the double-blind and open-label phases of the study were similar in the ibuprofen group. However, with regard to the second question (asking whether they would use the medication again), more parents reported that they would use paracetamol again after the open-label phase than after the double-blind phase, although this difference was not statistically significant. The reason for this difference is unknown, but one possible explanation is parental perception of the product.

In pediatric practice, the first goal is to treat children effectively and safely, and second to keep parents confident in the treatment they are giving to their child. New recommendations in France for the treatment of fever in children note that fever is only a symptom, and it is more important to address the overall comfort of the child. Fever is associated with great discomfort, especially in young children who may not be able to understand and rationalize the source of their discomfort. As there is little evidence that fever (not hyperthermia) is harmful, therapy is usually aimed at promoting comfort rather than reducing temperature¹¹. Many parents believe that fever is a disease rather than a symptom or sign of illness, which gives rise to undue anxiety¹². Parental anxiety influences their judgment, their understanding of the condition, compliance with their child's treatment and subsequent recovery¹³. Consequently, parental anxiety about their child's illness and treatment must be an integral part of a comprehensive strategy in the treatment of children. By providing additional benefits, ibuprofen may have fulfilled these goals. Indeed, in one randomized, comparative trial between ibuprofen (7.5 mg/kg) and paracetamol (10 mg/kg), ibuprofen not only showed a tendency towards antipyretic superiority, but was also associated with superior comfort

scores compared with paracetamol¹. Comfort was assessed on scores depending on general behavior (assessed on verbal and visual analog scales) and degree of relief (assessed in relation to baseline on a verbal scale).

Conclusions

Ibuprofen at a dose of 10 mg/kg and paracetamol at a dose of 15 mg/kg have equivalent efficacy and tolerability in children with fever. However, in both the double-blind and open-label phases of the study, more parents in the ibuprofen group compared with parents in the paracetamol group, rated the drug as very efficacious and reported that they would use the drug again. Parental opinion in favor of ibuprofen could be explained by additional benefits of ibuprofen that were not measured in this trial. By providing these additional benefits, ibuprofen may have allayed the anxiety of parents, thus enhancing their perception of treatment efficacy. These additional benefits of ibuprofen warrant further evaluation.

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Gibb is an employee of Reckitt Benckiser Healthcare International Ltd.

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