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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 ($AUC_{0-6}$). 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 illnesses[1-6]. 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 antipyretic[7]. 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 action[8]. 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 ≥ 38.5°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 ≥ 38.5°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 $[AUC]_{0-6}$ °C.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°C; (5) time to reach a temperature of ≤ 38°C; and (6) time to maximal temperature reduction and time to reach apyrexia (≤ 37.4°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 $\alpha$ 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