Evaluation of ibuprofen versus aspirin and paracetamol on efficacy and comfort in children with fever

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ABSTRACT

Objective: ***We compared efficacy and impact on the comfort of ibuprofen (7.5 mg/kg per dose), aspirin (10 mg/kg/dose) and paracetamol (10 mg/kg per dose) on children with fever aged 6-24 months in an open, randomised study with three parallel groups.***
Methods: ***The main criterion for efficacy was area under the curve (AUC) of percentage temperature reduction. Comfort was assessed on scores depending on general behaviour and degree of relief. General behaviour was assessed on a verbal scale and on a visual analogue scale (VAS) and the degree of relief was assessed in relation to baseline on a verbal scale.***
Results: ***The efficacy of ibuprofen was better than that of aspirin or paracetamol. In spite of more adverse events, the comfort scores were significantly in favour of ibuprofen 6 h after the first dose of treatment.***

*Key words****: ibuprofen, fever, paracetamol, aspirin, child, comfort***

INTRODUCTION

Fever is the most common symptom of disease in children. It is associated with discomfort and convulsions, especially in infants. It needs to be treated by an antipyretic which is rapidly effective and well tolerated. Aspirin and paracetamol (acetaminophen) are the two antipyretic drugs in France for treatment of paediatric fever, in spite of the risk of Reye's syndrom with aspiriin, which is contraindicated in this situation in the United States and in the United Kingdom[1, 7, 9]. Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), is analgesic and antipyretic and is available in 22 countries for paediatric use as an analgesic and antipyretic agent. In France ibuprofen has just been approved for use in paediatric fever. The antipyretic efficacy of ibuprofen has been evaluated in 17 randomised studies conducted in 1 251 children less than 2 years of age[2-4, 6, 8, 10-12]. In children and infants the antipyretic effect of 7.5 $mg \cdot kg^{-1}$ ibuprofen is equivalent degree of tolerability.

Although the analgesic and antipyretic effects of ibuprofen are well established, its impact on quality of life is unknown. Consequently, it seemed important to evaluate not only the efficacy of ibuprofen but also its impact on the patient's comfort in comparison with aspirin and paracetamol.

METHODS

- **Study population**

To be enrolled in the study, children has to be aged 6-24 months, followed on an outpatient basis, and to have a rectal temperature of at least 39°C Children were excluded if they had one of the following criteria: treatment by an antipyretic drug up to 4 h before inclusion; hypersensitivity to NSAID (including aspirin) or paracetamol ; any treatment or condition that might interfere with drug absorption or distribution; or severe hyperthermia with neurological and/or haemodynamic disorders.

- **Methodology and Treatments**

The multicentre, randomised open trial was conducted by 60 paediatricians in private practice in France. The following three antipyretic drugs were compared: ibuprofen syrup 20 $mg \cdot ml^{-1}$ (Junifen syrup), paracetamol syrup 30 $mg \cdot ml^{-1}$ (Efferalgan syrup) or aspirin in sachets containing 150 mg (Catalgine powder).

Ibuprofen was given at a dose of 7.5 $mg \cdot kg^{-1}$, paracetamod and aspirin at a dose of 10 $mg \cdot kg^{-1}$. The first dose of antipyretic was given before 16:00 h to facilitate the follow-up by parents during the first 6 h. No further dose was allowed in the 6 h following the first, but subsequent doses were permitted if necessary. The maximum dose was 30 $mg \cdot kg^{-1} \cdot 24\ h^{-1}$ for ibuprofen and was fixed by the paediatrician for aspirin and paracetamol. Other antipyretic drugs were not allowed throughout the study, but antibiotics were permitted.

Informed written consent of the parent(s) or legal guardian was required. The protocol was approved by the "comité consultatif des personnes" of the University Hospital of Tours.

- **Evaluation**

The study included two visits, one vefore treatment and one 5 days after inclusion. A telephone interview was conducted 14 days after inclusion to assess possible delayed adverse effects. Rectal temperature was measured with a mercury thermometer before the first administration of the study medication (H0) and then 1 (H1), 4 (H4) end 6 (H6) h after the first dose. Four types of criteria were used to assess the treatment: clinical effects, child's and parents' comfort and global assessment.

- *Clinical effects*

The main criterion for assessment of antipyretic activity was the area under the curve of percentage reduction of temperature with time. Accessory criteria were the percentage of children with a rectal temperature ≤ 38°C at H6, and the mean reduction in temperature at H4 and H6. Safety was evaluated by the number of adverse effects recorded throughout the study and by thelephone interview at day 14.

- *Child's comfort*

The impact of treatement on the child's comfort was evaluated at H4 and H6 using:

1. The child's reaction to pain measured by the sum of two items of the "CHEOPS" multidimensional behaviour scale[5]: the child's crying (0 not crying; 1 fretting; 2 crying or whimpering; 3 crying with sobs or screams), and the expression on the child's face: (0 smiling, frankly happy expression; 1 peaceful, neutral expression; 2 grimacing, frankly unhappy expression),

2. The general behaviour of the child on a four-level rating scale (0 as good as before the illness; 1 slightly abnormal; 2 fairly abnormal; 3 very abnormal), and on a 100-mm horizontal visual analogue scale [graduatec from (0) as good as before to (100) very abnormal]. The general behavioural change was the difference between H0 and the 2 h (H4 and H6) of evaluation post-treatment for the general behaviour rating scale and the general behaviour visual analogue scale.

3. The avaluation of the child's relief on a five-level rating scale (3 completely relieved; 2 fairly received; 1 little relieved; 0 not at all relieved; - 1 aggravated).

To obtain a 6-h measurement of the child's general behaviour change and of the relief after treatment, the time-related waighted sums of the change in general behaviour rating scale, of the change in the general behaviour visual analogue scale and of relief measured every hour were calculated. The weights used were inversely proportional to time to emphasize early action of the drug. The weighting was 1 at H1, ½ at H2 and 1/6 at H6. these sums represent unidimensional evaluation criteria of the child's comfort. Finally we studied a global score including the child's

general behaviour and relief, i.e. the weighted sum of primary scores (general behaviour rating scale, general behaviour visual analogue scale, relief).

- *Parent's comfort*

The impact on parent's comfort was measured by their level of anxiety (not at all, slightly, fairly or very anxious) and by the quality of their sleep (slept very well, fairly well, fairly poorly, did not sleep at all) for the night before the first administration and then every morning up to the second visit (day 5). To evaluate the effects of illness on their professional life every day up to the second visit (day 5), the parents stated whether they were able to report for work and whether or not they had to seek extra help to mind the child.

Parents' global assessment of the treatment was evaluated by the answer to the following question "If your child develops a fever again in the future would you agree to give him or her the same treatment ?".

- **Statistical methods**

The sample size (100 patients per group) was calculated on the basis of a difference of 50% of the area under the curve (AUC) of the reduction in temperature with time, an alpha risk of 5% and a beta risk of 10% [16]. At baseline, the characteristics of the three treatment groups were compared using a one-way variance analysis for the quantitative parameters, and the χ^2 test for the qualitative parameters. The different criteria of efficacy were analysed using a one-way analysis variance. If there was a significant treatment effect, a Newman-Keuls test was used to compare the groups two by two. The effects of the illness on the parents were compared using the χ^2 test. If this test showed any overall significant difference between the three groups, the groups were then analysed two by two using another χ^2 test. Pearson's correlation coefficient, calculated to control the global score of the child's comfort, was well correlated with the principal criterion of efficacy (AUC).

RESULTS

- **Entry profile**

Three hundred and fifty-one children were included in the study, 117 in each of the 3 treatment groups. Eight children – one in the ibuprofen, two in the paracetamol and five in the aspirin group – were included by mistake (five because of temperature < 39 °C and three because they were less than 6 months old or more than 24 months old), but were taken into account in the Intention To Treat analysis (ITT). Thirty-five patients (12 in the ibuprofen, 10 in the paracetamol and 13 in the aspirin group) did not follow the protocol because they also received other antipyretic or an NSAID on day 1 (no details of the time being indicated) and were included in the ITT analysis. Three children (one in each treatment group) did not take the study medication because their rectal temperature was below 39 °C at entry, and were not taken into account. Therefore, the analysis of efficacy and tolerability involved 348 children with 116 in each treatment group. Ninety-five percent of the children (n = 332) were withdrawn from treatment before the second visit (day 5) for similar reasons (Table 1) in the three groups. At inclusion the three groups were comparable for age, sex ratio, weight, height, method of minding and general behavious. The mean rectal temperature was 39.4 (0.4) °C in the ibuprofen group, and 39.3 (0.4) °C in the paracetamol and aspirin groups.

Table 1 Reasons for treatment withdrawal [*n* = number of patients (treatment could have been withdrawn for more than one reason)]

	Ibuprofen (*n* = 116)	Paracetamol (*n* = 116)	Aspirin (*n* = 116)	
Apyrexia	108	109	102	
Adverse effects	7	0	2	
Refused treatment	1	0	1	*P* = 0.43
Lack of efficacy	6	7	3	
Intercurrent event	4	1	1	
Not specified	0	1	1	

- **Clinical efficacy**

The AUC between H0 and H6 was significantly different (P = 0.0007) between the three groups (Fig. 1). The AUC was significantly greater with ibuprofen than with paracetamol (P < 0.05) or aspirin (P < 0.05), but not different between paracetamol and aspirin. The mean reduction in temperature (Table 2) was significantly different between the three groups at HA (P = 0.003) and H6 (P = 0.019). This reduction (P < 0.05) was greater in the ibuprofen froup than in the acetaminophen and aspirin groups, but not different between paracetamom and aspirin.

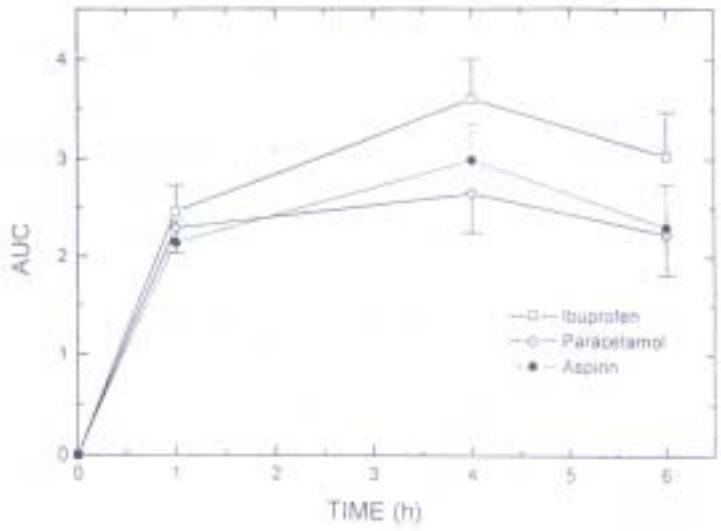

Fig. 1 Area under the curve (AUC) of percentage reduction in temperature

Table 2 Mean reduction in temperature (°C) 1, 4 and 6 h after treatment (*n* = number of patients)

Time (h) after treatment	Ibuprofen *n*	Ibuprofen Mean (SD)	Paracetamol *n*	Paracetamol Mean (SD)	Aspirin *n*	Aspirin Mean (SD)	*P*
1	114	−0.97 (0.58)	114	−0.90 (0.56)	114	0.84 (0.49)	NS
4	112	−1.42 (0.85)	110	−1.04 (0.85)	113	−1.18 (0.79)	0.003
6	108	−1.19 (0.94)	108	−0.88 (0.85)	109	−0.91 (0.93)	0.019

The percentage of children with a rectal temperature < 38 °C at H4 (Table 3) was lower in the paracetamol treatment group than in the other two groups (P = 0.008).

Table 3 Number (%) of children with a rectal temperature equal to or below (38 °C) (*n* number of patients)

Time (h) after treatment	Ibuprofen *n* (%)	Paracetamol *n* (%)	Aspirin *n* (%)	*P*
1	33 (29)	25 (22)	23 (20)	NS
4	69 (62)	45 (41)	59 (52)	0.008
6	43 (49)	40 (37)	37 (34)	NS

- **Tolerance**

Of the 348 patients included, 14 patients experienced 18 adverse effects. The percentage of patients reporting at least one adverse effect was higher (P < 0.05) in the ibuprofen than in the other two groups. In the ibuprofen group, 9 patients reported 13 advserse effects, 1 of which was experienced twice. In the paracetamol group, one child had one adverse effect and in the aspirin group four patients had four adverse effects. The number and nature of these adverse effects are shown in Table 4. There was less disgust or refusal reported for paracetamol (n = 4) than with ibuprofen (n = 11) or aspirin (n = 17) (P < 0.05).

Table 4 Number (%) of children with adverse effects (*n* number of adverse effects)

Nature	Ibuprofen *n* (%)	Paracetamol *n* (%)	Aspirin *n* (%)	
Gastrointestinal	6 (46%)			
Vomiting	2			
Diarrhoea	4			
Skin	3 (23%)	1	3	*P* = 0.024
Rash	3		3	
Perianal erythema		1		
Epistaxis			1	
Others	4 (31%)			
Hypoglycaemia	1			
Agitation	3			
Total	13	1	4	

- **Child's comfort**

At H4, there was no significant difference between the three groups for all the criteria, except for the general behavioural visual analogue scale change (Table 5). This score was better with ibuprofen than with paracetamol ($P < 0.05$), but not different between the ibuprofen and aspirin groups.

Table 5 Child's comfort scores 4 and 6 h after the first dose of treatment (n number of patients, *GBC-S* general behavioural rating scale change, *GBC-VAS* general behavioural visual analogue scale change, *GBC-S-WS* time-related weighted sums of GBC-S, *GBS-VAS-WS* time-related weighted sums of GBC-VAS, *R-WS* time-related weighted sums of relief, *GB* general behaviour)

	Ibuprofen		Paracetamol		Aspirin		
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*P*
Score at H4							
GBC-S	116	0.8 (1)	113	0.6 (0.9)	113	0.8 (0.9)	NS
GBC-VAS	114	27.8 (29.5)	108	18.3 (26.5)**	110	20.8 (26)	0.03
CHEOPS	114	2.2 (0.9)	112	2.5 (1)	112	2.4 (1)	NS
GBC-S-WS	115	1.4 (1.6)	109	1 (1.4)	113	1.2 (1.5)	NS
GBC-VAS-WS	113	41.8 (48.5)	104	31.4 (39.4)	109	30.8 (39.1)	NS
R-WS	115	3.8 (1.4)	110	3.4 (1.3)	111	3.5 (1.4)	NS
GS	107	4.9(3.7)	102	3.9 (3.8)	103	4.2 (4.1)	NS
Score at H6							
GBC-S	114	0.8 (1)	112	0.5 (1)	112	0.5 (0.9)	NS
GBC-VAS	112	26.7 (30.6)	107	15.9 (31.1)**	110	14.9 (26.9)*	0.005
CHEOPS	111	2.3 (0.9)	113	2.5 (1)	111	2.6 (1.1)*	0.04
GBC-S-WS	113	1.7 (1.9)	104	1.2 (1.7)	111	1.4 (1.6)	NS
GBC-VAS-WS	110	51.8 (56.9)	100	36.5 (48.1)	107	36.9 (46.3)	0.043
R-WS	112	4.6 (1.6)	106	4 (1.5)**	109	4.2 (1.6)	0.03
GS	105	4.6 (3.8)	102	2.9 (4.6)	103	3.1 (4.3)*	0.007

*Ibuprofen > aspirin, **Ibuprofen > paracetamol

At H6, the child's reaction to pain (sum of two items of "CHEOPS") was different ($P = 0.04$) between the three treatments and significantly better in the ibuprofen group than in the aspirin group.

The three groups did not differ on the general behavioural rating scale change nor on the sum of these previous parameters. On the other hand, the groups differed on the general behavioural visual analogue scale change were different between the three groups ($P = 0.05$) and ibuprofen gave better results ($P < 0.05$) than aspirin but not paracetamol. The time-related weighted sums of relief were different between the three treatments ($P = 0.03$), and better with ibuprofen than paracetamol ($P < 0.05$). the global score was different between the three groups ($P = 0.07$) and better in the ibuprofen group than in the two others.

The correlation coefficients between the AUC and the comfort criteria varied between 0.35 and 0.52 in absolute terms. At H6 the results ($r = 0.48$) were similar to those obtained at H4 ($r = 0.52$).

- **Parents' comfort**

For D0 to D5 parents'anxiety was not different between the three groups. At D2, the percentage of parents who "had a good sleep" was significantly different between the treatments ($P = 0.03$= and higher in the ibuprofen group (62%) than in the aspirin (48%) and paracetamol (46%) groups. At D4, there was also an overall difference between the three groups, and the percentage of parents who "had a good sleep" was significantly greater in the ibuprofen group (92%) than in the aspirin group (81%) but no greater than in the paracetamol group (90%). The percentage of parents taking time off work was not different between the three groups, for D0 and following days; neither was the percentage of parents who had to seek extra help to take care of their child.

- **Parents' global judgement**

The patient's global assessment of the treatment was not different between the three drugs; 90%, 92% and 95% of the parents in the aspirin, ibuprofen and paracetamol groups, respectively, would accept using the same drug for their child in a future febrile episode.

DISCUSSION

Unlike previous published studies, which included children with fever higher than 38 °C, our study showed that ibuprofen was more effective than aspirin or paracetamol in fever higher than 39 °C[2, 5, 8, 11, 12]. Unfortunately, ibuprofen was less tolerated than paracetamol or aspirin. Nevertheless, ibuprofen gave better comfort for children than paracetamol or aspirin at H6 for five of the seven parameters studied. At H4, there was a tendency for better results with ibuprofen than with aspirin or paracetamol. These results were most likely due to lack of power rather than to lack of sensitivity, because the sample size was calculated in order to demonstrate antipyretic efficacy more than to compare the child's comfort. To prove better results with ibuprofen on the child's comfort, the number of patients had to be calculated using a single criterion taking into account the measurement of all the primary behaviours. We therefore considered that the global score met this requirements: it integrated all the primary behaviour scales, and was well correlated with the clinical criterion of efficacy (AUC) (at H4 r = 0.52; at H6 r = 0.48).

A febrile episode in children can disturb the parents'professional life. Howevern in our study many children were cared for at home by one parent and therefore we found no difference between the three groups in the percentage of parents who had to seek extra help.

At D2 more than one-third of parents had difficulties in sleeping (38% in the ibuprofen, 54% in the paracetamol, 52% in aspirin groups). It was surprising that parents in the ibuprofen group slept better than in the two other groups, even through ibuprofen had more adverse effects. It was difficult to assume that parents'sleep was linked to ibuprofen efficacy, because we did not know what happened to the child's temperature over 6 h. If they continued to be feverish, it was due to the underlying cause of the fever rather than to inefficacy of the antipyretic drug.

In conclusion, ibuprofen at a dose of 7.5 $mg \cdot kg^{-1}$ is more effective in terms of fever reduction over than 6 h than paracetamol at a dose of 10 $mg \cdot kg^{-1}$ or aspirin at a dose of 10 $mg \cdot kg^{-1}$. In spite of more numerous adverse effects, this study clearly showed that ibuprofen leads to better comfort for the child compared to the other treatments.

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