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Antipyretic effect of ibuprofen and dipyrone in febrile children

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Abstract

Objective: To evaluate temperature changes in febrile children that received a single oral dose of ibuprofen (10 mg/kg), the dose recommended for high fever, or dipyrone (15 mg/kg), the dose recommended by the manufacturer, at 2, 3, 4, 5, 6, 7 and 8 hours after administration.

Methods: This open-label randomized (1:1) controlled clinical tried enrolled 80 febrile boys and girls aged 6 months to 8 years with baseline axillary temperatures of 38.0 to 40.3 °C. The children were divided into two groups: high fever (> 39.1 °C) and low-grade fever (38.0 to 39.1 °C). The antipyretic effect was analyzed according to discontinuity, safety, response to treatment, tolerability and therapeutic efficacy.

Results: Of the 80 children, 31 remained febrile during the 8 hours (38.8%), but 100% had a temperature decrease in the first 2 hours after the administration of either medication. In the high fever group, the temperature fell in 11 children treated with ibuprofen up to the 5th hour (100.00%) and in the 11 that received dipyrone, up to the third hour (100.00%). The difference in antipyretic efficacy of ibuprofen in the high fever group was statistically significant in the 3rd and 4th hours, and in the low-grade fever group, in the 3rd hour after medication.

Conclusions: A single oral dose of ibuprofen has a greater antipyretic efficacy than dipyrone, particularly when the fever is high. Both drugs were well tolerated and safe in the short term.

J Pediatr (Rio J). 2011;87(1):36-42: Fever, ibuprofen, dipyrone, nonsteroidal anti-inflammatory drugs, children.

Introduction

Fever has always been a reason for frequent visits to pediatric emergency services.[1] It makes parents and caregivers anxious because of the perception that their children are sick or that they may have a febrile seizure.[2] Febrile diseases explain why about 2/3 of the children up to 3 years of age are brought to medical care.[3] Their cases account for 30% of the pediatric visits[4] and 20% of the after-hours phone calls.[5]

Fever is an increase of body temperature controlled by the central nervous system in response to an exogenous or endogenous stimulus.[3] It is a symptom of several diseases, infectious or not, and results from an elevation of the

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thermoregulatory set point, located in the hypothalamus. Normal or subfebrile levels of temperature range from 36.0 to 37.9 °C. When the body temperature reaches 40.5 °C or higher, a large number of cells are damaged. The discomfort of a child with fever has been, for many pediatricians, a sufficient reason to investigate how to alleviate it.[7,8]

The choice of the most effective antipyretic drug has always been controversial. The drugs most often used in pediatrics are ibuprofen, acetaminophen (paracetamol) and dipyrone (metamizole). Several studies have been conducted about the first two, but few compared the antipyretic action of ibuprofen with that of dipyrone, maybe because dipyrone is not commercialized worldwide.[9-11]

Ibuprofen is a propionic acid derivative and a prostaglandin inhibitor prescribed at a dose of 5 mg/kg for low-grade fever and 10 mg/kg for high fever. It is recommended for children 6 months and older, is part of the list of essential drugs issued by the World Health Organization (WHO) and is the anti-inflammatory drug that causes the least gastrointestinal bleeding.[9-12] Dipyrone is a derivative of phenylpyrazole prescribed at a dose of 15 mg/kg (0.6 drop/kg) and recommended for children 3 months and older. The risk of agranulocytosis and aplastic anemia, associated with dipyrone, has been extensively investigated by Schönhöfer et al.[13] but remains unclear. Both drugs act after about 30 minutes, and their peak plasma concentration is reached at 2 hours after oral administration, liver metabolism and renal excretion.[9-11]

This study compared baseline temperatures with the temperatures of febrile children treated with a single oral dose of ibuprofen (10 mg/kg) or dipyrone (15 mg/kg) at 2, 3, 4, 5, 6, 7 and 8 hours after antipyretic medication.

Patients and method

This open-label clinical trial, randomized using previously numbered opaque sealed envelopes, compared the administration of a single dose of ibuprofen or dipyrone in parallel groups of febrile children seen in the Emergency Service of Hospital São Luiz Gonzaga of Santa Casa de São Paulo, in São Paulo, Brazil, from September 2000 to March 2001.

The sample size was calculated for the comparison of mean temperature between the two groups and temperature reduction along time.

Inclusion criteria were: boys and girls, age 6 months to 8 years, weight ≥ 6 and ≤ 22 kg, fever for at least 4 and up to 48 hours, baseline axillary temperature 38.0 to 40.3 °C, and informed consent term signed by parents or guardians. Children were excluded if any analgesic, antipyretic or anti-inflammatory drug had been administered in the previous 6 hours or antibiotics in the 12 hours before the study. Other exclusion criteria were: underlying disease; allergy to the drugs under study; and contraindications for the oral administrations of drugs.

Eligible patients were included in the study when the temperature reached ≥ 38.0 °C in the second of two consecutive readings at a 15 minute interval. The second reading was the value used as the baseline temperature in the study if the variation between readings was ≤ 0.3 °C; if the variation was > 0.3 °C, the temperature was measured a third time. The third reading was the value used as the baseline temperature when the variation was ≤ 0.3 °C. Patients were divided into two groups according to temperature: low-grade fever – temperature between 38.0 and 39.1 °C; and high fever – temperature between > 39.1 and 40.3 °C.

After two hours, in case the temperature increased after an initial decrease, the observation was discontinued and another antipyretic drug (acetaminophen) was administered. In patients with a diagnosis of bacterial infection, treatment with the appropriate antibiotic was initiated. Clinical history and physical examination data were recorded using a standardized clinical evaluation form. Inclusion was completed after baseline temperature was measured according to the chronological order of recruitment, and the author was blinded to the sequence of envelopes. Patients were randomized at a 1:1 ratio for the subgroup ibuprofen or dipyrone according to fever intensity.

Measurements were made using a Becton Dickinson® clinical digital thermometer with accuracy and quality approved by the Brazilian Metrology Institute (INMET), and this standard was validated for measurements at 10, 20, 30, 45 minutes and every hour after that up to 8 hours after drug administration. In this study, measurements after peak drug effect, as described in the literature, were made 2 hours after administration. Each medication vial and each thermometer were used for only one patient.

A nurse previously trained to follow the study protocol was exclusively assigned to measure temperatures under the supervision of the author during all hospitalization time (8 hours).

Data about weight, height and age were analyzed using the body mass index (BMI) according to graphs and tables for both sexes. Data about children older than 2 years were evaluated and compared using BMI tables and graphs for sex and age according to the standardization prepared by Must et al.[14] and by the Center for Disease Control and Prevention (CDC).[15] Data for children aged 6 months to 2 years were evaluated using the weight-for-height chart for children 0-36 months.[16]

Discontinuity, safety, response to treatment according to quantitative criteria, tolerability and therapeutic efficacy were evaluated to analyze antipyretic effects.

Discontinuation was chosen when, after 2 hours, there was therapeutic failure, that is, the temperature was the

same or greater than baseline temperature; or when the temperature went up to 38.0 °C or higher after having reached lower thresholds; or, still, when the variation between two readings was greater than 0.3 °C.

Response to treatment was evaluated every hour and classified as: excellent – temperature fell to ≤ 37.2 °C, that is, the child was no longer febrile; satisfactory – oscillations of ≤ 0.3 °C and temperature of 37.2 to 37.9 °C, which indicated that child was not febrile; and not satisfactory: when there was a temperature elevation or the temperature remained ≥ 38.0 °C, that is, the child was febrile.

Tolerability was assessed by means of reports of caregivers about any event that affected the patient during observation.

Therapeutic efficacy was analyzed by means of duration of antipyretic action and comparison of temperatures along time in response to drug administration in each group.

The study and the informed consent term were approved by the Ethics in Research Committee (IRB-equivalent) of Santa Casa de Misericórdia de São Paulo and by the Brazilian National Research Committee (CONEP).

The chi-square, the Student's *t*, the Mann-Whitney tests and analysis of variance (ANOVA) for repeated measures were used for statistical analyses. The level of significance was set at 5%.

Results

In this study, 81 children met inclusion criteria. One child had vomits immediately after the administration of dipyrone and was excluded from the study. Of the 80 children, 41 received ibuprofen (51.2%) and 39, dipyrone (48.8%). According to baseline temperature, 22 were randomized to the high fever group (27.5%) and treated with dipyrone (n = 11) or ibuprofen (n = 11), and 58, to the low-grade fever group (72.5%) and treated with dipyrone (n = 28) or ibuprofen (n = 30). Mean age was 27 months, and standard deviation was 20 months. There were 45 boys (56.2%), 47 (58.7%) children were white, and 33 were Afro-descendents (41.3%). The analysis of nutritional status revealed that 64 children were well nourished (80.0%) and 16 were undernourished (20%). There were no statistically significant differences in patient distribution according to age, sex, ethnicity, nutritional status or diagnosis in the four study groups.

Final diagnoses were: 48 cases of upper airway infection (60.0%), 40 as a result of influenza, 5 of otitis media, and 3 of laryngitis; 27 (33.7%) cases equally distributed into 9 of gastroenterocolitis, 9 of pulmonary disease, and 9 of tonsillitis; and 5 cases of other diseases (6.3%).

Response to treatment, analyzed for all participants and according to drug, was excellent in 48.8, 61.0, 57.4, 63.0, 55.6, 64.3, and 67.7% of the cases at 2, 3, 4, 5, 6, 7 and 8 hours. The difference was statistically significant for ibuprofen in the high fever group at 3 (p = 0.014) and 4 hours (p = 0.047) after administration. In the low-grade fever group, response to treatment was at the borderline of significance for ibuprofen 3 hours after administration (p = 0.106). Figure 1 shows that there was a statistically significant difference between the two drugs in the high fever group (p = 0.019), as well as in the low-grade fever group (p = 0.022) (Figure 2). The temperature went down along time in both groups (p = 0.001). Figures 1 and 2 show that, when antipyretic action initiated, there was a fall in the temperature in the two groups at 10 minutes, although more marked in the high fever group.

Table 1 shows that 100% of the children in the high fever group who received ibuprofen remained in the study up to the 5th hour, and 100% of the children in the dipyrone group, up to the 3rd hour. After the 5th hour, there was discontinuity in both groups, greater in the dipyrone group. In the high fever group, discontinuity was seen after the 3rd hour, but was more marked after the 6th hour. All the study criteria were met by 31 children (38.8%). Table 1 also shows the mean and standard deviation values for all the temperatures measured. There was a statistically significant difference in antipyretic effect of ibuprofen, which was better in the high fever group at 3 and 4 hours (p = 0.007 and p = 0.025). In the low-grade fever group, the antipyretic effect was statistically significant at 3 hours (p = 0.004). In the low-grade fever group, antipyretic effect reached borderline statistical significance at 2 hours (p = 0.067).

Discontinuity due to therapeutic failure was seen in 14 patients (17.5%) and due to temperature elevation in 29 (36.2%). Consent was withdrawn by 6 parents after 6 hours because their children were no longer febrile (7.5%).

Discontinuity was seen in all disease groups and losses were similar when compared with each other: 25/48 upper airway infections (52%); 5/9 acute gastroenterocolitis (55.6%); 5/9 pulmonary diseases (55.6%), except in cases of tonsillitis (7/9), in which discontinuity reached 77.7% in both groups and with both drugs without statistically significant differences.

There were five adverse events (6.3%). Two were severe and required hospitalization, but were not associated with the study drugs and were caused by the underlying disease at presentation (Table 2).

The drugs were well tolerated during all the observation time.

Discussion

Numerous studies in the literature have compared acetaminophen with ibuprofen or dipyrone with acetaminophen, but few have investigated ibuprofen and dipyrone.

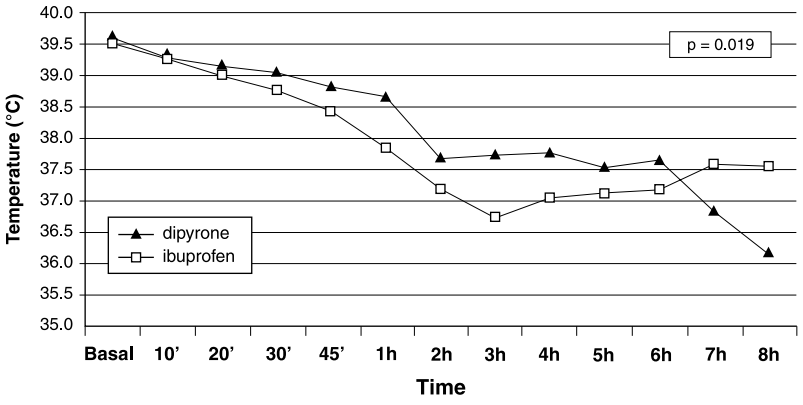

Figure 1 - Therapeutic efficacy along time in the high fever group treated with a single dose of ibuprofen or dipyrone

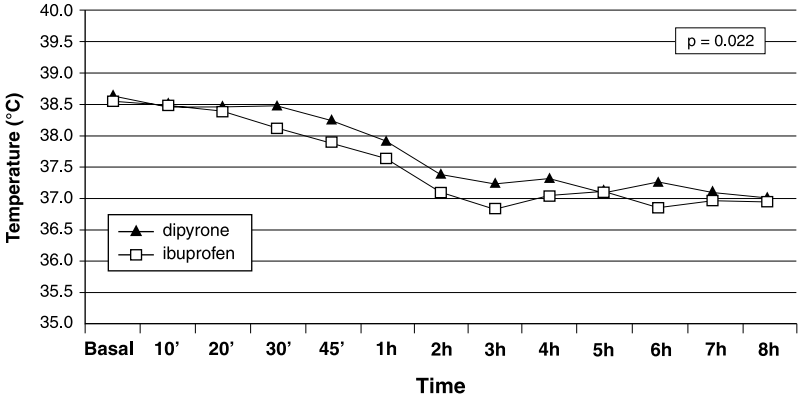

Figure 2 - Therapeutic efficacy along time in the low-grade fever group treated with a single dose of ibuprofen or dipyrone

The studies conducted by Wong et al.,[9] who measured tympanic temperatures for 6 hours, and Prado et al.,[11] who measured rectal temperatures for 2 hours, are the only available in the literature that compare the antipyretic efficacy and tolerability of ibuprofen and oral dipyrone. Yilmaz et al.[10] compared the efficacy of IM dipyrone (10 mg/kg) with oral ibuprofen (10 mg/kg) and oral nimesulide using axillary measurements for 2 hours. Therefore, no study in the literature compared the two drugs using the same dose, study duration, mode of administration and measurement as in our study.

The ibuprofen dose used in our study was 10 mg/kg, as recommended in the literature[8,10,17,18] and in a meta-analysis conducted by Perrot et al.[19] to fight fever. For dipyrone, we chose to administer 15 mg/kg, the dose recommended by the manufacturer and used in other studies.[9,11,20-22] Several caregivers and pediatricians use dipyrone at a dose of one drop/kg, which corresponds to 25 mg/kg, which

Table 1 - Comparison of therapeutic efficacy (p) and mean temperatures of febrile children that received a single dose of ibuprofen or dipyrone along time

	Time (hours)							
Group/drug	**Baseline**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
High*								
Dipyrone								
N	11	11	11	9	7	6	3	2
Mean	39.6	37.7	37.7	37.8	37.5	37.7	36.8	36.2
SD	0.4	0.8	0.8	0.7	0.7	1.1	1.4	1.1
Ibuprofen								
N	11	11	11	11	11	8	6	4
mean	39.5	37.2	36.7	37	37.1	37.2	37.6	37.6
SD	0.3	0.6	0.4	0.6	0.8	0.7	0.9	1
p	0.562	0.217	0.007	0.025	0.246	0.414	‡	‡
Low†								
Dipyrone								
N	28	28	26	26	21	19	15	12
mean	38.7	37.4	37.3	37.3	37.1	37.3	37.1	37
SD	0.3	0.6	0.5	0.8	0.7	0.8	0.7	0.7
Ibuprofen								
N	30	30	29	29	26	21	18	13
mean	38.6	37.1	36.9	37.1	37.1	36.9	37	37
SD	0.2	0.6	0.5	0.7	0.8	0.7	0.9	0.6
p	0.213	0.067	0.004	0.175	0.093	0.093	0.644	0.814

SD = standard deviation.
* Mann-Whitney test.
† Student *t* test.
‡ Statistical tests were not performed due to low frequencies (9 and 6 patients).

Table 2 - Distribution of febrile children according to occurrence of adverse events

Fever	Drug	Adverse event	Cause	Sever	Recovery
High	Ibuprofen	Fever persistence at 24 h	Not probable	No	Yes
High	Dipyrone	Hospitalization*	Not probable	Yes	Yes
High	Dipyrone	Hypothermia after 8 h	Probable	No	Yes
Low	Ibuprofen	Bronchitis	Unclear	No	Yes
Low	Dipyrone	Hospitalization†	Not probable	Yes	Yes

* Tonsillitis associated with poor general condition.
† Acute gastroenterocolitis.

may explain the perception that dipyrone has a greater antipyretic efficacy than other drugs.[21]

Wong et al.[9] compared the antipyretic efficacy of ibuprofen at 5 mg/kg in low-grade fever and 10 mg/kg in high fever, of dipyrone at 15 mg/kg, and of a third drug, acetaminophen, at 12 mg/kg. They defined efficacy as we did, that is, as a decrease of 1.5 °C in temperature and not as absence of fever. This reduction was more marked between 2 and 3 hours in 78% of the ibuprofen cases and in 82% of the dipyrone group, a difference that was not statistically significant. After that time, temperature went up again, but at a statistically significant lower intensity in the dipyrone group. The elevation threshold for exclusion in the study conducted by Wong et al.[9] was 0.5 °C, greater than the difference used in our study (0.3 °C); and the discontinuity and withdrawal rates were 23% for both drugs, much lower than the rate found in our study, although our criteria were different.

In the study conducted by Prado et al.,[11] measurements were made up to 2 hours to evaluate if 15 mg/kg IM dipyrone had a better antipyretic response than 15 mg/kg oral dipyrone and 10 mg/kg oral ibuprofen based on the popular, and even medical, belief that IM administration has a better antipyretic response. The authors found that mean decrease was similar: 1.2, 1.1 and 1.0 °C for oral ibuprofen, oral dipyrone and IM dipyrone. In our study, mean decreases were 2.3 and 1.9 °C in the high fever group, and 1.5 and 1.3 °C in the low-grade fever group for ibuprofen and dipyrone. Yilmaz et al.[10] found that IM dipyrone was more efficacious than oral ibuprofen, but suggested that oral administration should be used for children.

Although our study started 2 hours after the administration of the drug, temperatures were measured at 10, 20, 30 and 45 minutes and at 1 hour to monitor the febrile child closely and to act if necessary.

Physicians know that the antipyretic peak of the drugs under study is at about 2 hours after oral administration. This fact confirms the pharmacokinetics of the drugs under analysis and would not add any information to previous studies. An antipyretic drug is expected to act for 6 to 8 hours to be efficacious.

The discontinuity rates in this study should be primarily assigned to the criteria adopted. A temperature elevation might have compromised the well being of the children included in the study.[23]

This study showed that, in the initial phase of a disease, it is not always possible to fight fever for 8 hours, as already demonstrated by other authors.[9,17]

In 25 of the cases (31.3%), the appropriate antibiotic was initiated because it would have been unethical to withhold adequate treatment for 8 hours.

Due to the scarcity of studies in the literature, we compared our findings with studies that reported on isolated conclusions about the drugs under investigation here, and not comparisons with other drugs. Walson et al.[17] evaluated ibuprofen at 5 and 10 mg/kg for high fever (oral temperature between 39.2 and 40 °C) and low-grade fever (38.3 to 39.1 °C) and acetaminophen (10 mg/kg). Eight hours after ibuprofen administration at 10 mg/kg, 54.1% of the children had a temperature lower than baseline in the high fever group, and 38% in the low-grade fever group. Our results were 36.4 and 43.3% for high and low-grade fever. The study conducted by De Chiara[21] with acetaminophen (13 mg/kg) and dipyrone (15 mg/kg) for febrile children found that 32.5% of the children still had a temperature 1.5 °C lower than baseline in the 6th hour. In our dipyrone group, a decrease was found in 54.5 and 67.9% of the cases of children with high fever and low-grade fever at 6 hours. A study with ibuprofen conducted by Martinón Sánchez et al.[24] revealed that the antipyretic effect size was greater in high fever in the 3rd and 4th hours after oral administration in the ibuprofen group, similar results to those reported by Walson et al.[17] and Nahata et al.,[18] who found a temperature decrease 2 hours after administration and a maximum decrease in the 4th hour. These authors found that, although the temperature might rise after 4 hours, it did not go back to baseline values.

The analysis of therapeutic response was based on a quantitative criterion and evaluated statistically, which makes its results more accurate. The evaluation made by Autret et al.[25] included subjective data, such as level of discomfort felt by the child according to crying and facial expressions interpreted by a guardian; and the one made by Lomar & Ferraz[20] used the investigator's opinion. An excellent and statistically significant response was found in the ibuprofen group with high fever in the 3rd and 4th study hours.

In agreement with other studies, tolerability was excellent for the two drugs.[9,19,20,26]

Therapeutic efficacy in the low-grade fever group was similar to that reported by Walson et al.,[17] and the ibuprofen results were statistically better after 3 hours and up to the 5th hour.

The groups did not differ in age, sex, ethnicity, nutritional status or diagnosis, and these variables do not seem to affect results, according to Brown et al.[27]

We could not keep 49/80 children (61.2%) without fever for 8 hours. Therefore, we suggest that, when there are symptoms or fever phobia, the alternate use of antipyretic drugs should perhaps be considered. Alternate use is supported by Mayoral et al.[28] and by the results of the meta-analysis conducted by Sarrel et al.,[29] who recommended that, in the initial phase of the diseases that often affect children seen in emergency departments, antipyretic drugs should be administered every 4 hours, a procedure that has no adverse effects but that should be performed under medical supervision to avoid overdoses.[6,30]

This study analyzed the antipyretic effect of ibuprofen and dipyrone in febrile children and found that a single oral dose of ibuprofen has a better antipyretic effect than a single oral dose of dipyrone, particularly in cases of high fever. Both drugs were well tolerated and safe in the short term.

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