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CLINICAL TRIALS

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Assessment of the efficacy and safety of paracetamol, ibuprofen and nimesulide in children with upper respiratory tract infections

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Abstract *Objective*: The aim of this study was to assess and compare the efficacy and tolerability of paracetamol, ibuprofen and nimesulide in children with upper respiratory tract infections (URTIs).
Methods: Ninety children with acute URTIs and fever were enrolled to the study. The patients were allocated to three groups. The first group was treated with paracetamol 10 mg/kg thrice daily; the second group with ibuprofen 10 mg/kg thrice daily; and the third group received nimesulide 2.5 mg/kg twice daily for 5 days.
Results: The anti-pyretic activity of nimesulide was greater and more rapid than either paracetamol or ibuprofen. The number of patients with normal temperature was significantly greater in the first 2 days for the nimesulide group. The improvement in cough for the paracetamol group was better than the others.
Conclusion: The results of this study demonstrated that the anti-pyretic effectiveness of nimesulide is better than paracetamol and ibuprofen in febrile children with URTIs. However, new studies in larger paediatric populations are required to explore the anti-inflammatory effect of nimesulide.

Key words Childhood · Fever

Introduction

Fever is the most common presenting symptom in the paediatric unit and is generally considered to be a complex manifestation of the inflammatory response. Although fever enhances the immunological response, it also causes increased metabolic demands and the risk of possible complications, such as febrile convulsion and hyperpyrexia, in children [1, 2]. Furthermore, for the management of children with fever, the risk of complications, the child's discomfort and the concern of the parents should be taken into account. However, the use of anti-pyretic drugs in the febrile child may carry some risks; such as intoxication and Reye's syndrome [1–3]. Besides, usage is usually outside the hospital and treatment most often occurs without medical control. The medical treatment of paediatric fever requires a safe, effective and well-tolerated anti-pyretic with rapid onset of action.

Paracetamol is a widely used agent for treatment of fever in childhood, but can cause hepatic failure and renal toxicity [1–3]. Ibuprofen, a phenylalkanoic acid derivative, has been shown clinically to have significant analgesic, anti-pyretic and anti-inflammatory properties. It is increasingly being used to treat fevers [3–10]. However, ibuprofen has potential toxicity [3, 7]. Nimesulide is a recently developed non-steroidal anti-inflammatory drug. Some studies in children have shown it to have anti-pyretic, anti-inflammatory and analgesic activities and to be well tolerated [11–15].

In paediatric patients, one of the areas in which anti-pyretics are frequently used is upper respiratory tract infections (URTIs). Fever is a frequently presenting symptom of the URTIs. Symptomatic therapy with anti-pyretics is an important part of treatment in these patients. The aim of this study was to assess and compare the efficacy and tolerability of paracetamol, ibuprofen and nimesulide in febrile paediatric patients with URTIs.

Materials, methods and subjects studied

This study was designed as a randomised, open-labelled, parallel clinical study. Ninety children aged 2–14 years with acute URTIs and fever who were admitted to the Ankara University Hospital Out-Patient Department of Paediatrics were enrolled in this study. Before inclusion in the study, written informed consent was obtained from the parent of every child.

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Patients had to be suffering from a febrile URTI characterised by the presence of the following signs: fever (axillary temperature greater than 38 °C); pharyngeal hyperaemia and pain; cough; nasal obstruction; rhinorrhoea; adenopathy; anorexia and impaired state of general health. Exclusion criteria were: the presence of a major infection, e.g. septicaemia, pneumonia, meningitis, requiring intravenous antibacterial treatment; the presence of haematological, cardiac, renal and gastrointestinal diseases; allergy or hypersensitivity to paracetamol, ibuprofen or nimesulide; or other drug treatment during the 7 days before entry to the study.

Laboratory tests were performed at baseline of treatment. On each of these occasions, blood samples were drawn to determine haemoglobin, red and white blood cell count, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) levels, and liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT)], urinalysis and throat swab cultures were performed. Afterwards, patients were randomly allocated to treatment with paracetamol, ibuprofen or nimesulide. The first group ($n = 30$) was treated with paracetamol (suspension) 10 mg/kg p.o. thrice daily; the second group ($n = 30$) was treated with ibuprofen (suspension) 10 mg/kg p.o. thrice daily; and the third group ($n = 30$) received nimesulide (suspension) 2.5 mg/kg p.o. twice daily. Anti-pyretic therapy was given for 5 days. Antibacterial therapy was given in 49 patients with streptococcal pharyngitis, acute otitis media or acute sinusitis. Throat swab cultures were performed for the diagnosis of streptococcal pharyngitis in 21 patients. The diagnosis of otitis media was based on visualisation of the tympanic membrane by otoscopic examination in 27 patients. In one patient, acute sinusitis was diagnosed by radiological examination. When antibiotic therapy was indicated, amoxicillin, azitromycin or penicillin V was given for 10 days. All of the patients were evaluated by physical examination and laboratory tests such as; haemoglobin, red and white blood cell count, CRP level, ESR and liver function tests on the 5th day of treatment. The patients who received antibiotic therapy were re-evaluated by physical examination, and throat swab culture was performed in children with streptococcal pharyngitis on the 12th day of the study.

The therapeutic efficacy of the test drugs was evaluated by observation of body temperature and symptoms of URTIs. Axillary temperature (°C) was measured using a mercury thermometer before administration of the first dose of anti-pyretic and, subsequently, at hourly intervals for 4 hours on day 1 by a nurse in the hospital. Afterwards, it was recorded at least twice daily, in the morning and in the evening for 5 days by the parents at home. In addition, intensity of symptoms, tolerance to drugs and side effects were assessed daily by use of a 4-point rating scale (0 absent, 1 slight, 2 moderate, 3 severe) by the parents.

Statistical analysis

Statistical analysis was done by a statistics computer programme (SPSS for windows, Release 5.0.1), using the following methods; analysis of variance and Chi-square tests for the demographic data of patients; repeated-measurements ANOVA to compare between groups, baseline value versus repeated measures of temperature on first day; Chi-square test to compare the number of the patients showing normal body temperature and the alteration of symptoms density over the time of treatment between groups; analysis of variance for laboratory data. Results were considered significantly different at the level of $P < 0.05$.

Results

All the recruited children completed the study. The three groups were not significantly different ($P > 0.05$) with respect to age, gender, baseline body temperature, diagnosis and antibiotic therapy (Table 1). All of the three drugs had an anti-pyretic effect in the patients. However, after administration of the first dose, the anti-pyretic activity of nimesulide was greater and more rapid than paracetamol and ibuprofen (Fig. 1). The differences became statistically significant in the second hour ($P < 0.05$). The mean of the differences in body temperature between baseline and in the 4th hours after the first dose of anti-pyretics was 1.29 ± 0.71 °C in the paracetamol group, 1.86 ± 0.74 °C in the ibuprofen group and 2.19 ± 0.61 °C in the nimesulide group. They were significantly higher in the nimesulide and ibuprofen groups than in paracetamol-treated patients ($P < 0.001$).

The mean body temperatures of patients in treatment groups over the following 5 days are shown in Fig. 2.

Table 1 Patient characteristics. Where applicable, SD are given in parentheses

	Paracetamol ($n = 30$)	Ibuprofen ($n = 30$)	Nimesulide ($n = 30$)
Gender (male/female)	15/15	20/10	17/13
Age (years)	5.6 (2.9)	4.7 (2.5)	5.7 (3.7)
Baseline temperature (°C)	38.63 (0.42)	38.71 (0.43)	38.79 (0.55)
Diagnosis (no. of patients)			
Viral URTIs	13	13	15
Streptococcal pharyngitis	9	9	3
Acute otitis media	8	8	11
Acute sinusitis	–	–	1
Antibiotic receiving rate (%)	57	57	50

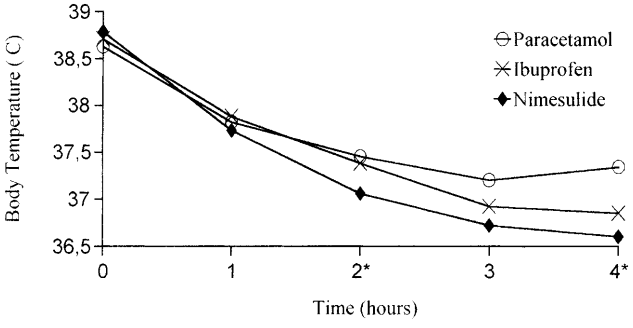

Fig. 1 Body temperature measurements during the first 4 h after the initial dose. *Statistical significance $P < 0.05$ at the second hour for nimesulide versus other drugs, $P < 0.001$ at the fourth hour for nimesulide and ibuprofen versus paracetamol

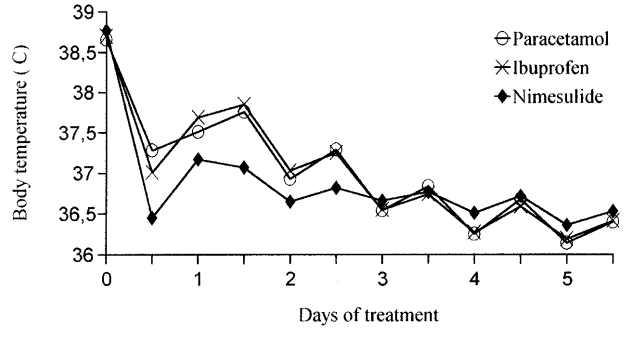

Fig. 2 Mean body temperatures of patients in treatment groups

Table 2 Intensity of the symptoms of the patients on entry and at the 5th day of the treatment

	Paracetamol (n = 30)	Ibuprofen (n = 30)	Nimesulide (n = 30)
Cough			
On entry	28	24	26
Decreased	25	17	14
Unchanged/increased	3	7	12
Rhinorrhoea			
On entry	20	22	24
Decreased	16	19	16
Unchanged/increased	4	3	8
Anorexia			
On entry	25	25	29
Decreased	17	10	14
Unchanged/increased	8	15	15

The percentage of patients showing normal body temperature was significantly greater ($P < 0.05$) on the first day for the nimesulide (57%) and paracetamol groups (43%) than the ibuprofen group (23%). These values for nimesulide, paracetamol and ibuprofen were 97%, 80% and 53%, respectively, on the second day of the treatment. This statistical difference was significant for the nimesulide group ($P < 0.001$). Furthermore the data of the patients not taking any antimicrobial therapy have been statistically analysed in all groups. Thirteen patients in the paracetamol group, 13 patients in the ibuprofen group and 15 patients in the nimesulide group did not take the antibiotics. The body temperature of the patients in the nimesulide group was significantly lower than those in the ibuprofen group ($P < 0.05$) on the first and second days. There was no statistically significant difference between nimesulide and paracetamol groups.

The improvement in symptom intensity of the patients during the 5 days of treatment is summarised in Table 2. No significant differences were detected in improvement in rhinorrhoea and anorexia symptoms between the treatment groups. The improvement in cough for the patients treated with paracetamol was better than for those patients in the other groups. This difference was statistically significant in the paracetamol group relative to the nimesulide and ibuprofen groups ($P < 0.05$). Differences between groups in the change in ESR and CRP levels were not statistically significant. All of the patients were healthy when physically examined on the 12th day of the study.

Paracetamol, ibuprofen and nimesulide were remarkably well tolerated and there were no drug-related side effects recorded, including haematological abnormality and hepatotoxicity.

Discussion and conclusions

Anti-pyretic therapy can be an important part of the process of evaluating fever in children and can also make children more comfortable during episodes of fever. An anti-pyretic agent that is widely and frequently used in children must be safe, effective and well tolerated. A double blinded and controlled study design is the most preferred for evaluation of the efficacy and safety of the drugs. However, this study was not blinded and there was no control group. The drugs used in this study were provided from the market. The blinded packing of the drugs was not possible. Moreover, the dose intervals of nimesulide and other drugs were different (two times and three times daily) and each one of these drugs have different colours. Therefore, this study was designed as a non-blinded study. The children with URTI had fever, pain and general discomfort. Anti-pyretic drugs were given also for general discomfort and pain, not only for fever. For this reason, all of the children with fever enrolled in this study were treated with one of the study drugs and no control group was allocated to placebo.

Nimesulide has been administered to adults orally or rectally for the treatment of severe inflammatory and painful diseases; in particular, it has been used successfully to treat fever and URTIs [11, 16]. Anti-pyretic activity of nimesulide has been evaluated in a number of trials since 1983. Recently, some authors reported that nimesulide is a safe and effective anti-pyretic agent for children with fever [11–15, 17]. In a multicenter, placebo-controlled trial involving children receiving simultaneous antibiotic medication, nimesulide exhibited anti-pyretic activity of 36-h duration [11]. In Rodriguez's study, the anti-pyretic activity of nimesulide and naproxen have been assessed in children with respiratory infection [13]. After 3 days of therapy, fever resolved in most of those receiving nimesulide, whereas naproxen had little effect. In other studies of the effectiveness of nimesulide relative to paracetamol, nimesulide was shown to be more potent than paracetamol in reducing the temperature of children [12, 15, 17]. The results of this study indicated that nimesulide provides a better anti-pyretic effect than paracetamol and ibuprofen; this includes both faster and greater temperature decrement, mainly on the first and second days of treatment. Our findings were similar to the results of previous studies.

The anti-inflammatory effect of nimesulide in children with URTIs was shown in recent studies [13–15, 17]. Furthermore, an anti-tussive effect has been reported in patients treated either with nimesulide by itself or combined with antibiotic therapy [14, 16]. However, in this study, a statistically significant difference in anti-inflammatory effects of the drugs was not found and cough was not significantly eased in the nimesulide-treated group relative to the paracetamol and ibuprofen groups.

Recent studies confirm the conclusion that ibuprofen is more potent than paracetamol in children in terms of maximum decrease in fever achieved 3–4 h after administration [2–5, 8–10]. But ibuprofen-induced reductions in temperature were observed and determined to be dose related [3, 6, 7]. The recommended dose of ibuprofen is 10 mg/kg in children with high fever for maximum defervescence [3, 10]. In this study, ibuprofen (10 mg/kg) was more effective than paracetamol for

reducing fever. The effectiveness of ibuprofen is greater than paracetamol; however, its potential toxicity, which includes an anti-platelet effect, potential hypersensitivity and gastrointestinal irritation, should be considered.

Recently, the potential side effects of nimesulide, such as hepatic and renal toxicity, have been mentioned [18, 19]. Acute hepatic failure and renal impairment in adult patients were reported. These authors suggested that this should be considered if nimesulide is to be given on a long-term basis to elderly patients. However, in our patient population, no relevant side effects were noted over the 10-day study period in any patients.

In conclusion, the results of this study demonstrated that the anti-pyretic effectiveness of nimesulide is better than that of paracetamol or ibuprofen in febrile children with URTIs. Nimesulide may become a valid alternative to other widely used anti-pyretic drugs. However, new studies with different doses of nimesulide are required to explore the anti-inflammatory effect, and potential toxicities in paediatric populations.

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