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Research Submission

Effects of Acetaminophen and Ibuprofen in Children With Migraine Receiving Preventive Treatment With Magnesium

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Aim.—The purpose of this study was to evaluate both the effects of ibuprofen and/or acetaminophen for the acute treatment of primary migraine in children in or out prophylactic treatment with magnesium.

Methods.—Children ranging from the ages of 5 to 16 years with at least 4 attack/month of primary migraine were eligible for participation the study. A visual analog scale was used to evaluate pain intensity at the moment of admission to the study (start of the study) and every month up to 18 months later (end of the study).

Results.—One hundred sixty children of both sexes aged 5-16 years were enrolled and assigned in 4 groups to receive a treatment with acetaminophen or ibuprofen without or with magnesium. Migraine pain endurance and monthly frequency were similar in the 4 groups. Both acetaminophen and ibuprofen induced a significant decrease in pain intensity ($P < .01$), without a time-dependent correlation, but did not modify its frequency. Magnesium pretreatment induced a significant decrease in pain intensity ($P < .01$) without a time-dependent correlation in both acetaminophen- and ibuprofen-treated children and also significantly reduced ($P < .01$) the pain relief timing during acetaminophen but not during ibuprofen treatment ($P < .01$). In both acetaminophen and ibuprofen groups, magnesium pretreatment significantly reduced the pain frequency ($P < .01$).

Conclusions.—Magnesium increased the efficacy of ibuprofen and acetaminophen with not age-related effects.

Key words: children, migraine, visual analog scale, acetaminophen, ibuprofen, magnesium

Abbreviations: ADR adverse drug reaction, ANOVA analysis of variance, CGRP calcitonin gene-related peptide, CI confidence interval, CYP450 cytochrome P450, MWoA migraine without aura, NSAID non-steroidal anti-inflammatory drug, TTH tension-type headache, VAS visual analog pain scale

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Headaches are common in children with a prevalence of 4-11% among children from 7 to 11 years old and 8-23% from 11 years of age or older,[1] and may cause an important health-related reduction of quality of life (ie, school performances and social activity).[2,3]

Primary headache could be considered one of the most common painful events in childhood, and the most frequent ones can be considered as migraine without aura (MWoA) and tension-type headache (TTH).[4,5]

Conflict of Interest: None.

Migraine can be considered as an episodic-chronic disorder, and the therapeutic approach should cover not only the acute treatment but also prophylactic treatment. Even when the prophylactic treatment of migraine is successful, the patient will, in most cases, still suffer some migraine attacks and need further treatment.[6]

Headache can be assumed to be a complex condition on a pathogenetic and clinical level, resulting from the interaction between biological, psychological, and environmental factors. Therefore, the headache treatment may be both non-pharmacological (ie, sleep hygiene, regular lifestyle behavior, biofeedback, and magnesium administration) and pharmacological (ie, prochloroperazine, non-steroidal anti-inflammatory drugs [NSAIDs], and anti-epileptic drugs).[7,8]

Previously, we documented that in the acute treatment of migraine, typical NSAIDs (eg, nimesulide and ibuprofen) and/or atypical NSAIDs (acetaminophen) are used commonly.[9] Among the typical NSAIDs, ibuprofen is the most common acute medication after the age of 3 years.[10-12]

Ibuprofen, a 2-proprionic derivative acid, is a balanced cyclooxygenase-1/-2 enzymes inhibitor, and it exerts an analgesic, anti-inflammatory, and antipyretic effect through this mechanism.[13-15]

Among the so-called atypical NSAIDs, the acetaminophen is commonly used in children for safety and for the analgesic/antipyretic effect.[16-18]

For the prophylactic treatment of headache, magnesium salt seems to be effective in treating pediatric episodic and chronic TTH, although further well-controlled studies are needed.[19] In general, the importance of magnesium in the pathogenesis of migraine headaches is clearly established by a large number of clinical and experimental studies. However, the precise role of various effects of low magnesium levels in the development of migraines remains to be discovered. In fact, magnesium concentration has an effect on serotonin receptors, nitric oxide synthesis and release, n-methyl-d-aspartate (NMDA) receptors, and a variety of other migraine-related receptors and neurotransmitters.[20]

However, Wang et al in 2003[21] failed to show a superiority of magnesium with respect to placebo in preventing recurrent migraine attacks in children. To date, no other studies were performed in order to evaluate the effect of magnesium on migraine in children treated with NSAIDs.

Therefore, the purpose of the present study was to evaluate the effects of ibuprofen and/or acetaminophen for the acute treatment of migraine in children in or out of prophylactic treatment with magnesium.

METHODS

Study Design.—The study was designed to be a single-blinded, balanced-recruitment, parallel-group, single-center study of outpatient children enrolled at the Pediatric Unit, Pugliese Ciaccio Hospital in Catanzaro, Italy between January 2010 and June 2010.

The study was approved by the Researchers Ethics Committee of the "Pugliese-Ciaccio" Hospital (protocol number 720/2010; EUDRACT NUMBER 2012-005737-36) and was conducted following the Declaration of Helsinki and the Guidelines for Good Clinical Practice criteria.

Population.—Children with MWoA of both sexes aged from 5 to 16 years, with at least 4 attacks per month, were eligible for participation in the study. MWoA was diagnosed according to the criteria for pediatric age of the International Classification of Headache Disorders (International Headache Society 2).[22]

Exclusion criteria consisted of the following: mental retardation (intelligence quotient <70), genetic syndromes (eg, Down syndrome, Prader–Willi syndrome, fragile X syndrome), hypothyroidism, psychiatric disorders (ie, schizophrenia, mood disorders, attention-deficit/hyperactivity disorder [ADHD]), neuromuscular disorders, epilepsy, obesity (body mass index >95 percentiles), liver or renal diseases, gastrointestinal disorders such as peptic or duodenal ulcer, dyspepsia, or heartburn; hypersensitivity to medication studies.

All subjects were recruited in the same urban area, all were Caucasian and of middle socioeconomic status. Informed written consent was obtained from the parents.

Experimental Protocol.—In a balanced recruitment study, eligible outpatients with primary acute migraine were assigned to receive at pain onset: acetaminophen (15 mg/kg) or ibuprofen (10 mg/kg).

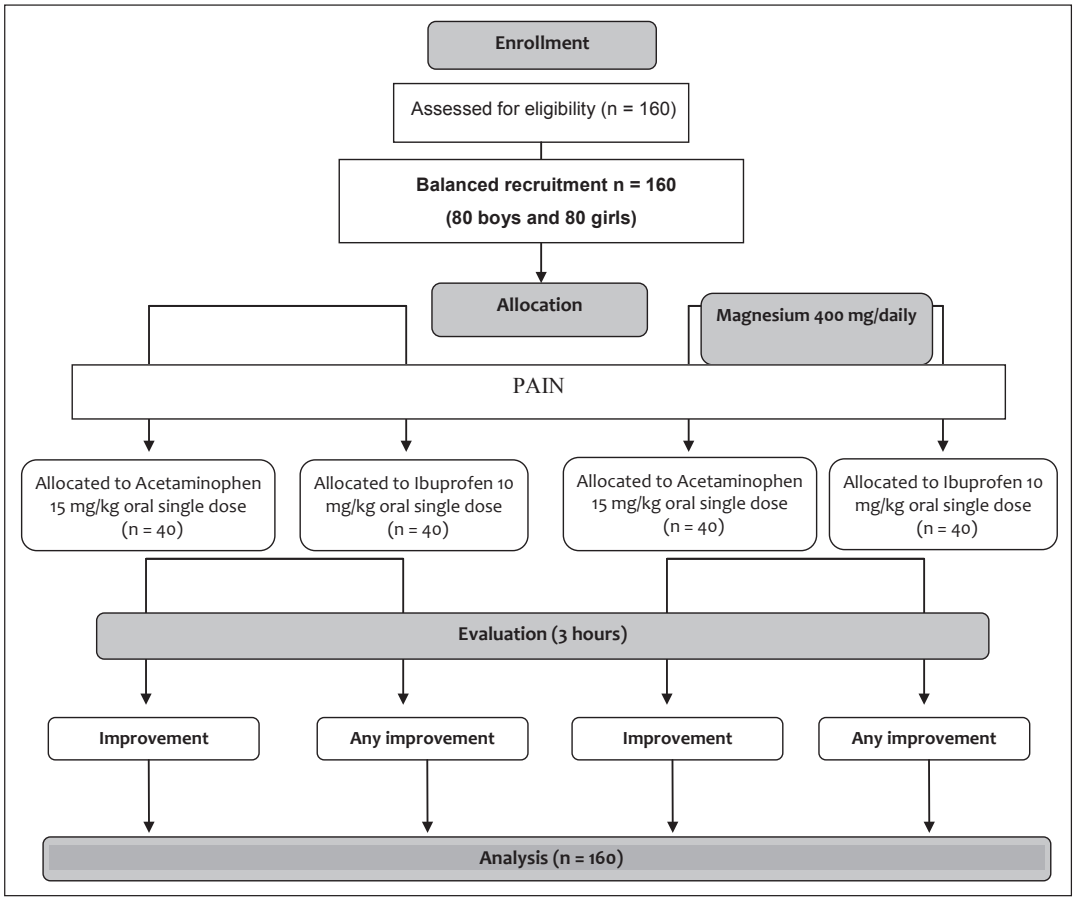

Fig 1.—Schematic representation of experimental groups.

Moreover, in order to evaluate the prophylaxis effect of magnesium in another set of experiments, eligible children were assigned to receive a daily magnesium supplement (400 mg/daily) and then 1 single dose of acetaminophen (15 mg/kg) or ibuprofen (10 mg/kg) at the time of pain (Fig. 1). In this study, in agreement with the Declaration of Helsinki (1991), we did not use a placebo group.

In each group, children were assigned in accordance to age and gender in order to obtain similar groups of treatment.

In order to assess the intensity of pain, before and up to 3 hours after the administration of both drugs used in the present protocol, a non-standardized *ad hoc* scale and a visual analog scale (VAS) were used.

Specifically, for the predose assessments, the pain intensity was measured on an arbitrarily established categorical scale in response to the question, "What is your pain level at this time?" with response choices from 0 to 3, where 0 = none, 1 = mild, 2 = moderate, and 3 = severe. In addition, VAS was used to assess pain severity before, during, and after the treatment. Patients were asked to draw a single vertical line on the 100-mm VAS, where 0 = no pain (score 0) and 100 mm = worst pain (score 10). This scale had been previously used to measure pain in pediatric populations.[23,24]

The safety on medication studies was assessed in terms of frequency and nature of adverse drug reactions (ADRs). In order to evaluate the association between ADRs and drug treatment, the Naranjo Adverse Probability Scale was applied.[25]

Number, duration, severity of pain attacks, analgesic intake, and the occurrence of ADRs were recorded in a daily diary card 1 month prior to the trial and subsequently during the entire period of study. For each patient, follow-up sessions were

planned every month after enrollment and continued for 18 months (until the end of the study).

End Points.—The primary end point was when pain-relief took place and pain intensity differences from baseline (0 hour) to 3 hours after drug treatment. This measurement was defined as the area under curve (AUC) for the sum of the 2 measurements (pain relief and pain intensity difference) at each time point from 0 to 3 hours.

The secondary end point included the effects that drug treatment had on migraine exacerbation and ADR developments. Physicians who were blinded to the treatment assessed the overall clinical response during the study. Moreover, in order to evaluate the role of genetic cytochrome P450 (CYP450) polymorphisms in drugs safety, toxicity, and efficacy at the time of the enrollment, a blood sample was taken.

Sample Size.—The primary outcome for power calculation was pain intensity measured with a 100-mm VAS. Prior data indicated a difference of 10 mm in the VAS measurements observed before drug intake and then 3 hours later.[26] The difference in the response of matched pairs distributed with standard deviation of 4 could be considered clinically significant.

To detect a clinically relevant difference between each group, 38 subjects assigned to each group was necessary (power >85%, alpha 0.05, delta 2).

Pharmacogenetic Evaluation.—Blood testing has been performed in order to analyze the main allelic variants of the CYP450 isoforms CYP2E1, CYP1A2, CYP3A4, CYP2D6, CYP2C9, and CYP2C19 genes. According to previous work, they were identified and analyzed through real-time polymerase chain reaction by TaqMan kits purchased from Applied Biosystems (Monza, Italy).[27-29]

Statistical Analysis.—The analysis of variance (ANOVA) test was used to analyze differences in efficacy measures between NSAIDs for both primary and secondary end points. The paired *t*-test was used to analyze any change in efficacy measurements within the same group. Comparisons in pain levels among the groups were assessed with ANOVA and Student–Newman–Keuls test. Finally, Pearson's test was used to evaluate time-dependent effects of each drug on a VAS scale.

The threshold of statistical significance was set at $P < .05$. The SPSS software (SPSS, Inc., Chicago, IL, USA) and G*Power (Institut fur Experimentelle Psychologie, Heinrich Heine Universitat, Dusseldorf, Germany) were used for the statistical analyses.

RESULTS

Patients.—Starting population was composed of 210 children aged 5-16 years (98 males, mean age 11.02 ± 2.2 years, and 112 females mean age 11.5 ± 2.5 years) consecutively referred to the Pediatric Unit of "Pugliese-Ciaccio" Hospital of Catanzaro for MWoA. After securing a detailed clinical history and completing a neurological examination, the study sample consisted of 160 children aged 5-16 years, composed by 80 girls (mean age 12.15 ± 2.66) and 80 boys (mean age 10.64 ± 2.29) (Table 1).

The enrolled children were assigned in 4 groups of 40 subjects (20 boys and 20 girls): acetaminophen 15 mg/kg, acetaminophen 15 mg/kg and magnesium 400 mg/daily, ibuprofen 10 mg/kg, and ibuprofen 10 mg/kg and magnesium 400 mg/daily.

The mean age of the enrolled children was 11.39 ± 2.48 years (range 5-16) (Table 1); 117 of these (73.25%), 57 boys (71.25%) and 60 girls (75%), had a family history of headache (Table 1), and this feature was found to be significantly more common among the magnesium groups rather than in the other groups ($P < .01$) (Table 1).

Several children presented a long clinical history of MWoA with a mean time of 29 months ± 4.8 and a range of 1-120 months (Table 1). The time of migraine distress did not result in any significant different between boys (mean 29.36 ± 3.7 months) and girls (mean 27.35 ± 4.8 months) (data not shown).

Migraine pain endurance and monthly frequency (days/month of headache) were similar in both acetaminophen and magnesium, and ibuprofen and magnesium groups, with a range of 30-360 minutes and 4-30 days, respectively (Table 1).

Efficacy and Safety.—In 34 children belonging to the acetaminophen-group (88.46%), the pain relief evaluated with the VAS scale did not show differences among the 2 sexes (Fig. 2). Using ANOVA and Student–Newman–Keuls tests, we documented that these effects were significant ($P < .01$) beginning at

Table 1.—Characteristics of the Children (n = 160) at the Time of the Enrollment: Acetaminophen (ACT) 15 mg/kg, Acetaminophen (ACT; 15 mg/kg) and Magnesium (Mg; 400 mg/daily), Ibuprofen 10 mg/kg, and Ibuprofen 10 mg/kg and Magnesium (Mg; 400 mg/daily)

Mean	ACT N = 40	Ibuprofen N = 40	ACT + Mg N = 40	Ibuprofen + Mg N = 40
Age (years)	10.97 ± 2.53	12.37 ± 2.47	10.38 ± 2.46	11.85 ± 2.44
Parents with migraine	26 (65%)	28 (70%)	29 (72.5%)	32 (80%)
Duration of migraine disease (months)	18.05 ± 18.02	34.15 ± 25.11	25.22 ± 18.61	40.25 ± 24.15
Duration of pain attacks (minutes)	112.5 ± 58,18	106.75 ± 40.77	131.8 ± 102.73	120 ± 54.04
VAS	6.95 ± 2.91	6.55 ± 2.85	7.57 ± 2.55	7.35 ± 2.93
Pain levels (%)	Mild 25 Moderate 17.5 Severe 57.5	Mild 30 Moderate 17.5 Severe 52.5	Mild 15 Moderate 10 Severe 75	Mild 20 Moderate 5 Severe 75
Days/month of migraine	8.0 ± 5.6	6.3 ± 3.82	13.2 ± 9.33	9.15 ± 6.45

The data represent the mean and standard deviation.
VAS = visual analog scale.

the first month and lasting during the follow-ups at 3 and 18 months (Fig. 2).

Ibuprofen induced a significant ($P < .01$) decrease of pain intensity evaluated through the VAS scale among 38 of the enrolled children (95%) with no gender differences (Fig. 2; Table 2).

However, Pearson's test did not show any time-dependent correlation between the effects of either acetaminophen or ibuprofen as far as pain intensity was concerned within different periods (Table 2).

The decrease of acute pain was significantly faster with ibuprofen (mean 31.95 ± 1.7 minutes) than with acetaminophen (mean 48.5 ± 5.16 minutes) ($P = .004$; 95% confidence interval [CI] –27.54 to –5.54; $t = –3.045$).

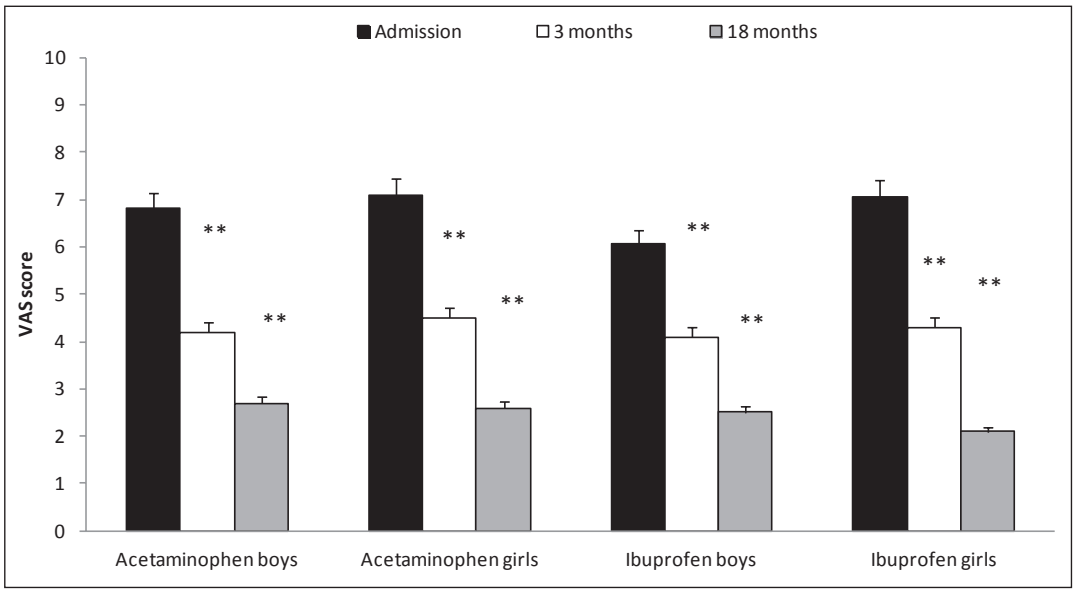

Fig 2.—Visual analog scale (VAS) score evaluated in both boys (N = 20 for each group) and girls (N = 20 for each group) enrolled in this study and treated with acetaminophen or ibuprofen. VAS score was recorded at the time of admission, and 3 and 18 months later. Values are expressed as mean ± standard error of the mean for each group of treatment. Statistical analysis was performed through analysis of variance test. **$P < .01$.

Table 2.—Statistical Correlation (Pearson's Test) Between Drug Treatment in Different Periods (Admission, 3 Months, 18 Months) and Pain Intensity Evaluated Through VAS

		Admission	3 months	18 months
Admission	Pearson's test	1	0.823	–0.191
	P		.177	.809
3 months	Pearson's test	0.823	1	–0.019
	P	.177		.981
18 months	Pearson's test	–0.191	–0.019	1
	P	.809	.981	

VAS = visual analog scale.

Nevertheless, both acetaminophen and ibuprofen were unable to significantly reduce headache frequency in the whole sample (Fig. 3).

Magnesium treatment in both acetaminophen and ibuprofen groups significantly reduced pain intensity ($P < .01$) (Table 3) (Fig. 4) because Pearson's test failed to document a time-dependent correlation (Table 4). On the other hand, magnesium treatment did not significantly strengthen the effects of acetaminophen or ibuprofen regarding pain intensity but reduced significantly ($P = .022$; 95% CI 1.99-24.17; $t = 2.388$) pain-relief timing for acetaminophen (from 48.5 ± 5.16 minutes for acetaminophen group to 35.42 ± 1.84 minutes for acetaminophen + magnesium group), even if it did not significantly modify the pain relief timing for ibuprofen (from 31.95 ± 1.7 minutes ibuprofen-group to 31 ± 2.24 minutes for ibuprofen + magnesium) ($P = 0.737$; 95% CI –4.74 to 6.64; $t = 0.338$). These effects were not age-related (Fig. 5).

All administered medications were well tolerated, and compliance appeared to be satisfactory in all treatment groups.

Genetic Evaluation.—All patients were not carriers for any CYP2E1, CYP1A2, CYP3A4, CYP2D6, CYP2C9, and CYP2C19 detrimental allele. They also did not carry extra copies of a functional allele

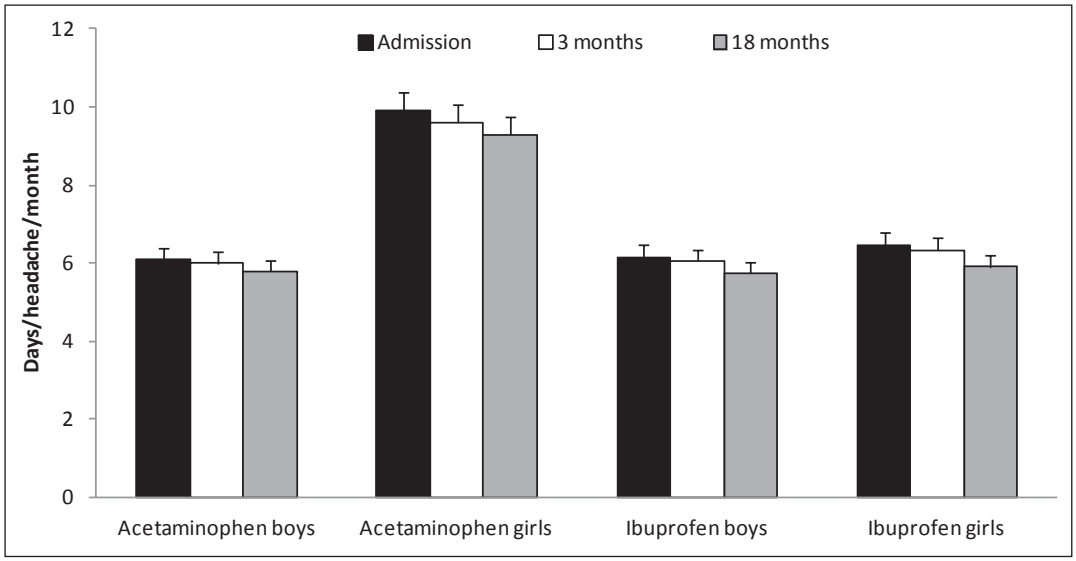

Fig 3.—Headache frequency expressed as days/headache/month evaluated in both boys (N = 20 for each group) and girls (N = 20 for each group) enrolled in this study and treated with acetaminophen or ibuprofen. Headache frequency was evaluated at the time of admission and 3 and 18 months later. Values are expressed as mean ± standard error of the mean for each group of treatment. Statistical analysis was performed through analysis of variance test.

Table 3.—Statistical Evaluation of VAS Score in All Groups of Treatment

	Acetaminophen + magnesium boys N = 20			Acetaminophen + magnesium girls N = 20		
Time	*P*	95% CI	*t*	*P*	95% CI	*t*
Admission vs 3 months	.002	0.87-3.63	3.308	.002	0.87-3.63	3.308
3 months vs 18 months	.000	2.32-4.48	6.389	.000	2.32-4.48	6.389
	Ibuprofen + magnesium boys N = 20			Ibuprofen + magnesium girls N = 20		
Time	*P*	95% CI	*t*	*P*	95% CI	*t*
Admission vs 3 months	.003	0.60-2.72	3.168	.003	0.69-3.01	3.238
3 months vs 18 months	.000	2.44-4.16	7.776	.000	2.64-4.16	9.08

CI = confidence interval; VAS = visual analog scale.

CYP2E1, CYP1A2, CYP3A4, CYP2D6, CYP2C9, and CYP2C19.

Therefore, the individuals enrolled in the study were not genetically classifiable as ultrarapid or poor metabolizers for these enzymes.

DISCUSSION

The pathogenetic mechanisms of migraine remain incompletely understood, and although numerous drugs for the acute and prophylactic treatment of migraine are available for adults, specific

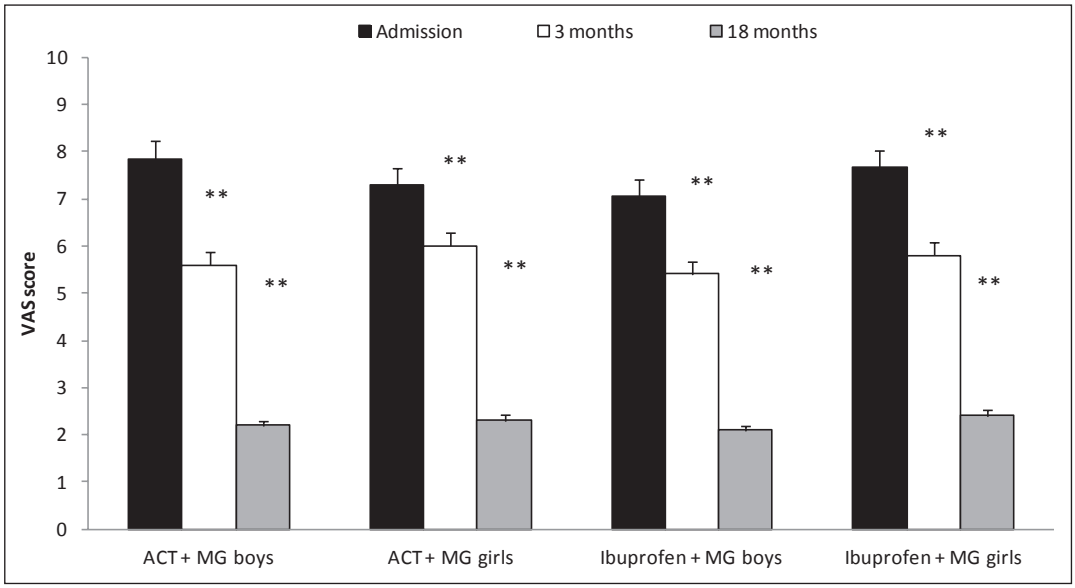

Fig 4.—Visual analog scale (VAS) score evaluated in both boys (N = 20 for each group) and girls (N = 20 for each group) enrolled in this study and treated with acetaminophen (ACT) + magnesium (MG) or ibuprofen + MG. VAS score was recorded at the time of admission, and 3 and 18 months later. Values are expressed as mean ± standard error of the mean for each group of treatment. Statistical analysis was performed through analysis of variance test. **$P < .01$.

Table 4.—Statistical Correlation (Pearson's Test) Between Drug Treatment in More Than 1 Period of Time (Admission, 3 Months, 18 Months) and Pain Intensity Evaluated Through VAS

		Admission	3 months	18 months
Admission	Pearson's test	1	0.190	0.446
	P		.405	.277
3 months	Pearson's test	0.190	1	0.800
	P	.405		.100
18 months	Pearson's test	0.446	0.800	1
	P	.277	.100	

VAS = visual analog scale.

agents for childhood are lacking so that alternative treatments are commonly given.[30]

In this light, data on efficacy and safety of drugs in children are limited, and drugs suitable for adults must not be used routinely in young patients.[31]

Headache is a common complaint among children and adolescents, and it represents the third leading cause of emergency room referrals.[32-34]

The most common type of acute headache in children is MWoA with a prevalence of 3% in younger school-age children and of about 20% in adolescents.[30]

MWoA is often accompanied by severe disabilities such as low quality of emotional functioning, school absenteeism, and impairment in academic performance.[35] In fact, children with migraine present a school absenteeism rate that is double in comparison with patients without MWoA.[9,36]

Usually, drug treatment should be limited in order to avoid medication overuse and should be taken shortly after onset of migraine in order to optimize its effects even though there is inadequate scientific evidence that can support this statement.[37]

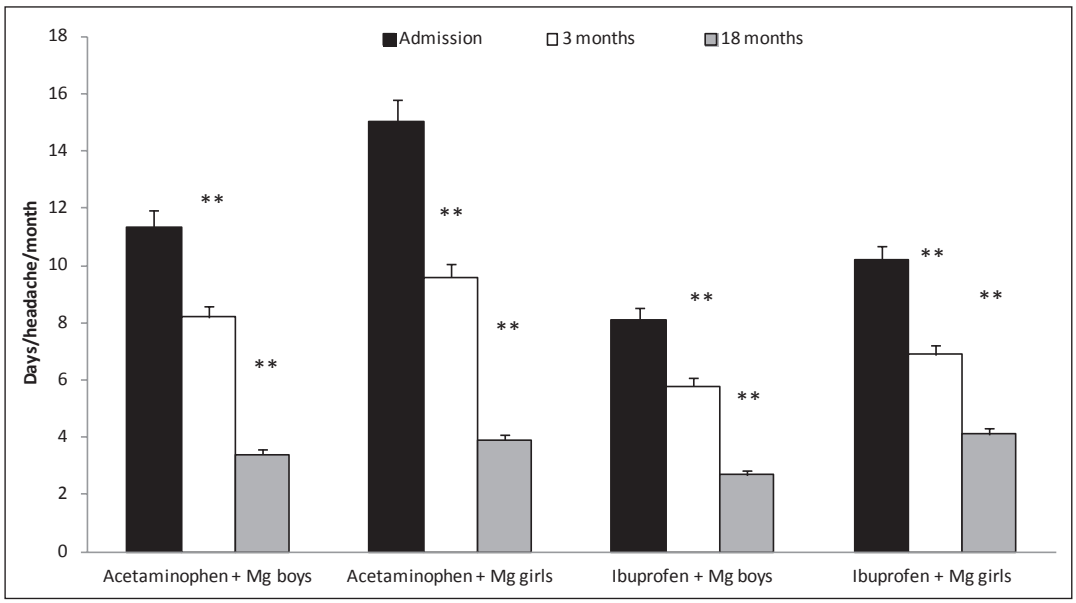

Fig 5.—Headache frequency expressed as days/headache/month evaluated in both boys (N = 20 for each group) and girls (N = 20 for each group) enrolled in this study and treated with acetaminophen + magnesium (Mg) or ibuprofen + Mg. Headache frequency was evaluated at the time of admission, and 3 and 18 months later. Values are expressed as mean ± standard error of the mean for each group of treatment. Statistical analysis was performed through analysis of variance test. **$P < .01$.

In our study, children received acetaminophen or ibuprofen with or without magnesium supplementation. However, it is necessary to emphasize that in agreement with the Declaration of Helsinki, no placebo group had been formed.

Other reports in a pediatric population show that the acute use of paracetamol (15 mg/kg per dose) and ibuprofen (7.5-10 mg/kg per dose) seems to be effective and well tolerated;[38,39] indeed, over 16 years of age, ibuprofen (200 or 400 mg) is indeed effective for relief of pain intensity.[40,41]

In this paper, we have shown that because ibuprofen is able to induce a rapid decrease in baseline migraine pain intensity compared with acetaminophen, both drugs may be useful to reduce pain intensity, but not the frequency.

Alternatively, the pharmacogenetic evaluation excluded the presence of genetic polymorphisms; therefore, we hypothesize that these effects can be related to ibuprofen's mechanisms of action. In fact, it has been well described that migraine attacks involve activation of trigeminovascular afferents and the release of calcitonin gene-related peptide (CGRP), and other inflammatory substances and neuropeptides (ie, neurokinin A and substance P) that are both released from primary sensory nerve terminals that innervate the dural vessels and localized within the nerves of the trigeminal system and play a central role in the pathophysiology of migraine leading to significant vasodilatation and increased dural blood flow.[42,43]

Thus, the effects on migraine of anti-inflammatory drugs (ie, ibuprofen) could be better than those of analgesic drugs (ie, acetaminophen).

It has been reported that if not terminated, peripheral trigeminal nerve activity tends to provoke central (trigeminal nucleus caudalis) neuronal sensitization. Recruitment of the latter during the process of migraine renders the condition more refractory to management.

In our paper, the clinical effectiveness of both acetaminophen and ibuprofen had increased with the administration of magnesium.

Conversely, magnesium is considered as a non-pharmacological agent, with a good efficacy in migraine prophylaxis mainly in some conditions such as episodic TTH.[19] The recommended dose is 400 mg daily.[44] Herein, the treatment with magnesium (400 mg/daily) induced a significant improvement of headache for both the primary and secondary end points.

We also document that magnesium reduced significantly ($P < .01$) pain-relief timing after acetaminophen administration.

We were not, however, able to document the specific synergism between magnesium and acetaminophen; however, several mechanisms could be postulated to explain these effects.

In fact, magnesium is able to:

- reduce the catecholamine release and then prevent central sensitization caused by peripheral nociceptive stimulation;[45]
- blocks the entrance of ions such as calcium through the bounding to the NMDA receptor.[46]

In contrast, we reported that magnesium did not increase the effect of ibuprofen, and it could be related to the pharmacological properties of ibuprofen in migraine. In fact, recently, Summ et al[47] reported that ibuprofen is able to bypass the blood brain barrier, and in the central nervous system, it is able to inhibit the neurogenic vasodilation and the related release of CGRP that play a central role in the development of migraine.

Finally, the clinical efficacy of acetaminophen or ibuprofen with and without magnesium was not related to the pain intensity, nor was it time-dependent.

Previously, we recorded that NSAIDs treatment is able to induced the development of side effects such as skin reactions and gastrointestinal toxicity.[48-50]

In this paper, we did not record any ADR during the acetaminophen treatment – as well as in ibuprofen-group – in association with magnesium probably because of the high safety of both drugs or perhaps related to the short period of treatment and absence of polytherapy.

On the other hand, we have to take into account some limitations of the current study such as the short time of pharmacological treatment, the absence of chronic migraine, the typology of study (single-blind),

and the absence of randomization. We must, however, stress the difficulty of performing clinical trials on the efficacy of drug treatment with respect to the gold standard in children in agreement with the Declaration of Helsinki and with the necessity of the local Ethical Committee.

Finally, we would emphasize that this paper represents the first study evaluating the preventive effects of magnesium in children with migraine receiving a symptomatic treatment with acetaminophen and ibuprofen. Therefore, because this is an open-label study, it could represent an initial treatment for children with migraine that is usually undertreated or mistreated. In conclusion, our data shows that magnesium is able to increase the efficacy, but not the toxicity, of both acetaminophen and ibuprofen.

STATEMENT OF AUTHORSHIP

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