Efficacy and Safety of Acetaminophen in the Treatment of Migraine

Results of a Randomized, Double-blind, Placebo-Controlled, Population-Based Study

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Background: Although most persons with migraine treat their headaches with over-the-counter medication, systematic data on the safety and efficacy of widely used treatment, including acetaminophen, are sparse.

Methods: This is a randomized, double-blind, placebo-controlled study comparing oral acetaminophen, 1000 mg (two 500-mg Extra Strength Tylenol tablets), with identical placebo in the treatment of a single acute migraine attack. Eligible subjects met International Headache Society diagnostic criteria for migraine with or without aura. Patients who usually required bed rest with their headaches or who vomited more than 20% of the time were excluded.

Main Outcome Measures: The percentage of subjects who, at 2 hours after dosing, experienced a change in baseline pain intensity from severe or moderate pain to mild or no pain (headache response); and pain intensity difference from baseline at the 2-hour postmedication assessment.

Results: The headache response rate 2 hours after dosing was 57.8% in the acetaminophen group and 38.7% in the placebo group ($P=.002$). Pain-free rates at 2 hours were 22.4% in the acetaminophen group and 11.3% in the placebo group ($P=.01$). The mean pain intensity difference from baseline 2 hours after dosing was 1.08 in the acetaminophen group and 0.73 in the placebo group ($P<.001$). At 2 hours, other migraine headache characteristics, such as functional disability ($P=.002$), photophobia ($P=.02$), and phonophobia ($P=.08$), were significantly improved after treatment with acetaminophen vs placebo.

Conclusions: Acetaminophen was highly effective for treating pain, functional disability, photophobia, and phonophobia in a population-based sample of persons with migraine, excluding the most disabled persons with migraine. The drug also had an excellent safety profile and was well tolerated.

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MIGRAINE headaches affect 5% to 7% of the men and 14% to 19% of the women in western countries.[1-4] Despite the severe pain and activity limitations of migraine, about 90% of those with migraine self-treat their headaches with over-the-counter (OTC) analgesic medications, and about two thirds use OTC drugs to the exclusion of prescription drugs.[5-7] When effective, OTC medications offer several advantages over prescription drugs, including easy access, lower cost, and fewer adverse effects.[8-10]

Despite their advantages and their widespread use, most OTC analgesics are not approved as treatments for migraine. The first OTC agent for migraine in the United States was approved in 1998.[11] Much self-treatment of migraine pain, therefore, represents off-label drug use.[12] As a consequence, the package label, which serves as a primary source of information for the consumer, does not provide information appropriate for migraine treatment. Clinical trials are, therefore, essential for defining the safety and efficacy of OTC medications in persons with migraine.

Previous studies[6] have reported that most persons with migraine who treat their headaches with OTC medication consider acetaminophen their drug of choice. Acetaminophen is a *p*-aminophenol derivative whose analgesic effects probably are centrally mediated[13-15]; it has only weak anti-inflammatory activity.[16] Although it is not approved for marketing in the United States as a treatment for migraine, limited data support its efficacy in treating the pain of migraine.[17-20] In addition, unlike nonsteroidal anti-inflammatory drugs, acetaminophen is not associated with gastrointestinal tract irritation.[19] Given its

SUBJECTS AND METHODS

SUBJECTS

The study was conducted between March 11, 1998, and August 10, 1998, at study centers in Baltimore and Catonsville, Md. Random-digit dialing was used to screen the community near each research center for potentially eligible persons with migraine headache.[21] Demographic profiles and headache features of those with migraine headache were entered into a database. The database was then used to identify potentially eligible individuals who were contacted by telephone; screened for possible eligibility; and, if willing and eligible, invited to make a clinic visit for an in-person medical assessment.[21]

Subjects were considered potentially eligible if they met International Headache Society diagnostic criteria for migraine with or without aura[22]; were at least 18 years old; were in good general health; and reported a migraine attack frequency of at least 1 episode every 2 months, but no more than 6 episodes per month. Headaches had to be of at least moderate pain intensity when left untreated. Subjects who experienced severely incapacitating migraines requiring bed rest or precluding daily activities more than 50% of the time were excluded. Subjects who experienced vomiting with more than 20% of their migraine attacks also were excluded, because of the probability that they would vomit and, therefore, not absorb the study medication. Subjects reporting nausea without vomiting or vomiting less than 20% of the time were not excluded. Written informed consent was obtained from all subjects. The protocol and consent form were approved by an institutional review board for each site.

Subjects likely to be eligible for randomization based on the telephone interview were invited to make a clinic visit. In the clinic, potential subjects received a semistructured headache interview, provided a detailed medical history, and underwent a physical examination and neurologic evaluation by a study physician. Subjects eligible for the study who agreed to participate were then trained to complete the study diary.

STUDY DESIGN—PROTOCOL

The study protocol called for 140 completed subjects per treatment to provide 90% power (2-tailed at an α level of .05) in detecting a 20% difference in the overall response rate between acetaminophen (55%) and placebo (35%).

At visit 1, qualified subjects were randomly assigned according to a computer-generated randomization schedule to receive a blister card of double-blinded study medication containing either two 500-mg tablets of acetaminophen (provided as unbranded Extra Strength Tylenol by McNeil Consumer Healthcare Company, Ft Washington, Pa) or 2 identical-appearing placebo tablets. The subjects left the centers with instructions to take the study medication to treat the headache pain of 1 acute self-recognized migraine attack. Subjects were asked to treat a headache of at least moderate pain intensity that had a symptom profile meeting the definition of migraine and that was consistent with other study eligibility criteria. Subjects were asked not to take rescue medication for 2 hours, if possible. All treatment information was maintained in a blinded form until after the database was locked and all queries were resolved.

Efficacy Measurements

The primary efficacy end point was the percentage of subjects who responded at the 2-hour postmedication assessment, where *response* was defined as a reduction in baseline pain intensity from severe or moderate to mild or none. An additional primary efficacy end point was the pain intensity difference (PID) from baseline measured at 2 hours. At baseline, subjects reported the presence or absence of aura and vomiting; described their headache characteristics, such as location, pain quality, and character; and rated the severity of their pain, functional disability, nausea, photophobia, and phonophobia. They then rated their level of pain intensity; pain relief (PAR); and functional disability, nausea, vomiting, photophobia, phonophobia, and the presence or absence of vomiting at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, and 6.0 hours after dosing. Subjects used 4-point scales

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safety and widespread use, further studies are needed to assess the efficacy of acetaminophen in the treatment of acute migraine headache.

We report the results of a randomized, double-blind, placebo-controlled, 2-center study designed to assess the safety and efficacy of acetaminophen for the treatment of migraine headache pain. The random-digit–dialing method of subject recruitment described herein is an effective means of identifying a representative, community-based sample of persons with migraine.[21] This method is ideally suited for identifying persons with migraine eligible for nonprescription therapy, regardless of their history of seeking or not seeking medical care. For an OTC treatment, community-based samples better reflect the target population than persons with migraine who have consulted physicians, because the latter are more likely to have intense pain and severe disability.[21,22]

RESULTS

SUBJECT POPULATION

Of the 351 subjects enrolled in the study, 176 (50.1%) were randomly assigned to receive acetaminophen and 175 (49.9%) were randomly assigned to receive placebo (**Figure 1**). Ten subjects (2.8%) were lost to follow-up, and 52 (14.8%) did not take the study medication. The remaining 289 subjects (82.3%) who took the study medication were included in the intent-to-treat analysis, with 147 in the acetaminophen group and 142 in the placebo group.

The 2 treatment groups had similar demographic profiles. Specifically, groups did not differ by age, race, or sex. The groups also did not differ in baseline pain intensity, proportion with aura, or the distribution of baseline migraine symptoms (**Table 1**). Ninety-seven per-

to rate pain intensity (0 indicates no pain; 1, mild pain; 2, moderate pain; and 3, severe pain) and functional disability (0 indicates able to work or function normally; 1, working ability mildly impaired; 2, working ability moderately impaired; and 3, working ability severely impaired) and a 5-point scale to rate PAR (0 indicates no relief; 1, a little relief; 2, some relief; 3, a lot of relief; and 4, complete relief). Nausea, photophobia, and phonophobia were rated using a 4-point scale (0 indicates none; 1, mild; 2, moderate; and 3, severe).

Subjects provided an overall impression of the study medication after the 6-hour treatment period or at the time of taking rescue medication. This overall impression was rated from 0 to 4 (0 indicates poor; 1, fair; 2, good; 3, very good; and 4, excellent).

Other efficacy variables were derived from the scores recorded by the subjects. These included time to taking rescue medication, change in migraine symptoms and functional disability, sum of pain intensity differences from baseline (SPID), and total PAR.

Safety Assessments

Adverse events were recorded in the diary by the subjects and elicited at the visit by the investigators. The intensity, duration, and relation to the study drug were recorded.

Statistical Analysis

The following outcome measures were analyzed: the percentage of subjects experiencing a reduction in headache severity from severe or moderate (grade 3 or 2) to mild or none (grade 1 or 0); the percentage of subjects who were pain free; the time to rescue; the rescue rate 6 hours after taking the study drug; the PIDs from baseline and PAR measurements at each measurement time; the differences from baseline in severity of nausea or vomiting at each measurement time; SPID; total PAR; the differences from baseline in severity of photophobia, phonophobia, and functional disability at each measurement time; and the subject's overall impression of the study medication.

For subjects who took rescue medication, the last reported pain intensity and PAR scores were carried forward to the remaining measurement time. Pain intensity and relief ratings that were missing or that were recorded more than 15 minutes early or late for subsequent measurement intervals were estimated by linear interpolation.

An analysis of rescue rates 6 hours after dosing and of the percentage of subjects who experienced a change in severity from grade 3 or 2 to grade 1 or 0 at 2 hours after dosing was performed using a Cochran-Mantel-Haenszel χ^2 test stratified by initial pain intensity.

The differences between treatments in the distribution of time to rescue were tested using a Wilcoxon test available in SAS statistical software, version 6.12 (SAS LIFETEST; SAS Institute Inc, Cary, NC). The actual remedication times were included in the analysis. Subjects who did not take rescue medication during the study were considered censored observations at 6 hours.

Pain intensity differences from baseline and PAR scores at each point, as well as SPID and total PAR scores, were analyzed using analysis of variance models that included a term for treatment and, for PID and SPID, baseline pain and a treatment by baseline pain interaction.

Differences from baseline in severity of nausea, photophobia, phonophobia, and functional disability were analyzed at each measurement time using data reduction and analysis techniques identical to those used for PID.

Baseline characteristics were tabulated for all subjects. One-way analyses of variance were used to test for differences between treatment groups in the mean values of continuous baseline measurements. χ^2 Tests or Fisher exact tests were used to compare the distributions of categorical variables between treatment groups.

The frequency of adverse events and of withdrawals from the study was compared between treatment groups using a Fisher exact test. All hypothesis tests were 2-sided at an α level of .05. The primary analysis was based on the intent-to-treat population that excluded only subjects who never dosed or who provided no efficacy data. Because the per-protocol data set differed by only 10 subjects, the results were qualitatively and quantitatively similar to the intent-to-treat data set and, therefore, are not reported. The analyses were directed by the Statistics Department of the McNeil Consumer Healthcare Company.

cent of the patients in each group reported that their migraine attack was typical. Mild to severe nausea was reported by 48.1% of the subjects.

PAIN INTENSITY AND PAR

Overall, the response rate at the 2-hour postdose assessment was significantly higher ($P=.002$) in the acetaminophen group (57.8%) than in the placebo group (38.7%), a difference of 19.1%. In addition, the percentage of subjects responding—defined as mild or no pain—was higher in the acetaminophen group than in the placebo group for all points from 0.5 to 6.0 hours after dosing (**Figure 2**). Furthermore, for the 40% of subjects reporting severe baseline pain, the 2-hour response rate for the acetaminophen group was 50.9% compared with 27% for the placebo group ($P=.008$). For the 60% of subjects having moderate baseline pain, the response rate was 62% in the acetaminophen group and 48.1% in the placebo group; this difference did not reach statistical significance ($P=.07$).

The percentage of subjects who were *free of pain*—defined as pain intensity reduced to zero—was significantly higher in the acetaminophen group (22.4%) than in the placebo group (11.3%) 2 hours after dosing ($P=.01$). Similarly, at 6 hours after dosing, pain-free responses were higher in the acetaminophen group (46.3%) than in the placebo group (28.2%) ($P=.001$) (**Figure 3**).

The mean PID and mean PAR scores were significantly higher in the acetaminophen group than in the placebo group at all points from 0.5 to 6.0 hours. At the primary time point, 2 hours, the mean PID score was 1.08 for the acetaminophen group and 0.73 for the placebo group; the mean PAR score was 1.99 for the acetaminophen group and 1.41 for the placebo group. The SPID during the 6-hour postdose interval was 6.82 in the acet-

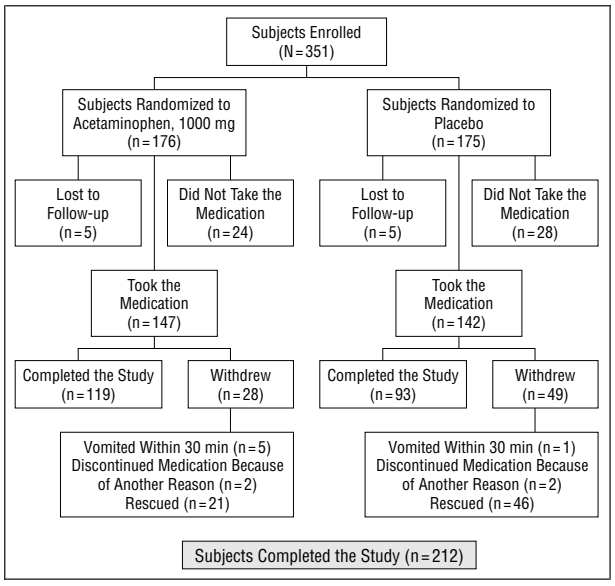

Figure 1. *Distribution of the subjects.*

aminophen group and 4.54 in the placebo group (**Table 2**). The difference between the total PAR scores for each group (12.64 for the acetaminophen group and 8.92 for the placebo group) also was statistically significant (**Table 3**).

RESCUE MEDICATION

The percentage of subjects requiring rescue medication was significantly higher in the placebo group than in the acetaminophen group at each point beyond 1 hour after dosing (**Figure 4**). By the end of the 6-hour postdose interval, the cumulative percentage of subjects who had taken rescue medication was 31.7% in the placebo group and 15% in the acetaminophen group ($P=.001$).

EFFECTS ON OTHER HEADACHE CHARACTERISTICS

The percentage of subjects whose functional disability was reduced to zero was significantly higher in the acetaminophen group (31.4% and 55.7%) than in the placebo group (15.3% and 34.3%) at the 2- and 6-hour ($P=.002$ and $P=.001$) postdose points, respectively (**Figure 5**).

There was no significant difference between the 2 groups at 2 and 6 hours in the percentages of subjects whose severity of nausea was reduced to zero. The percentage of subjects whose severity of photophobia was reduced to zero was significantly higher in the acetaminophen group (32.9% and 58.7%) than in the placebo group (20.5% and 36.4%) at the 2- and 6-hour ($P=.02$ and $P=.001$) postdose points, respectively (**Figure 6**). The percentage of subjects whose severity of phonophobia was reduced to zero was also significantly ($P=.001$) higher in the acetaminophen group (61.2%) than in the placebo group (40.3%) at the 6-hour postdose point; the percentages at the 2-hour postdose assessment were 33.8% and 23.3%, respectively, a difference of borderline significance ($P=.08$) (**Figure 7**).

Table 1. Demographic and Baseline Migraine Headache Characteristics (Intent-to-Treat Analysis)*

Characteristic	Acetaminophen Group (n = 147)†	Placebo Group (n = 142)	Total (N = 289)	*P*
Sex				
Male	34 (23.1)	24 (16.9)	**58** (20.1)	.19
Female	113 (76.9)	118 (83.1)	**231** (79.9)	
Age, y				
Mean ± SD	37.3 ± 10.4	36.0 ± 9.3	36.6 ± 9.9	.24
Range	18.0-63.0	18.0-60.0	18.0-63.0	
Race				
White	111 (75.5)	99 (69.7)	**210** (72.7)	.50
African American	35 (23.8)	41 (28.9)	**76** (26.3)	
Other	1 (0.7)	2 (1.4)	**3** (1.0)	
Pain intensity				
Moderate	92 (62.6)	79 (55.6)	**171** (59.2)	.23
Severe	55 (37.4)	63 (44.4)	**118** (40.8)	
Aura				
Yes	24 (16.3)	20 (14.1)	**44** (15.2)	.58
No	122 (83.0)	122 (85.9)	**244** (84.4)	
Missing	1 (0.7)	0	**1** (0.3)	
Nausea				
None	77 (52.4)	70 (49.3)	**147** (50.9)	.86
Mild	36 (24.5)	40 (28.2)	**76** (26.3)	
Moderate	30 (20.4)	28 (19.7)	**58** (20.1)	
Severe	2 (1.4)	3 (2.1)	**5** (1.7)	
Missing	2 (1.4)	1 (0.7)	**3** (1.0)	
Sensitivity to noise				
None	7 (4.8)	12 (8.5)	**19** (6.6)	.12
Mild	33 (22.4)	38 (26.8)	**71** (24.6)	
Moderate	83 (56.5)	61 (43.0)	**144** (49.8)	
Severe	23 (15.6)	30 (21.1)	**53** (18.3)	
Missing	1 (0.7)	1 (0.7)	**2** (0.7)	
Sensitivity to light				
None	3 (2.0)	10 (7.0)	**13** (4.5)	.20
Mild	31 (21.1)	26 (18.3)	**57** (19.7)	
Moderate	77 (52.4)	69 (48.6)	**146** (50.5)	
Severe	35 (23.8)	37 (26.1)	**72** (24.9)	
Missing	1 (0.7)	0	**1** (0.3)	
Vomiting				
Yes	3 (2.0)	2 (1.4)	**5** (1.7)	.68
No	143 (97.3)	140 (98.6)	**283** (97.9)	
Missing	1 (0.7)	0	**1** (0.3)	
Ability to work or function‡				
Normal	6 (4.1)	5 (3.5)	**11** (3.8)	.94
Mildly impaired	44 (29.9)	41 (28.9)	**85** (29.4)	
Moderately impaired	75 (51.0)	72 (50.7)	**147** (50.9)	
Severely impaired	21 (14.3)	24 (16.9)	**45** (15.6)	

**Data are given as the number (percentage) of subjects in each group unless otherwise indicated. Percentages may not total 100 because of rounding. All subjects were aged 18 to 64 years.*
†The dose given was 1000 mg.
‡Date are missing for 1 patient in the acetaminophen group.

GLOBAL RATING OF OVERALL IMPRESSION

Subjects' overall impressions of the study medication in the acetaminophen group were superior to those reported in the placebo group. The mean global rating score

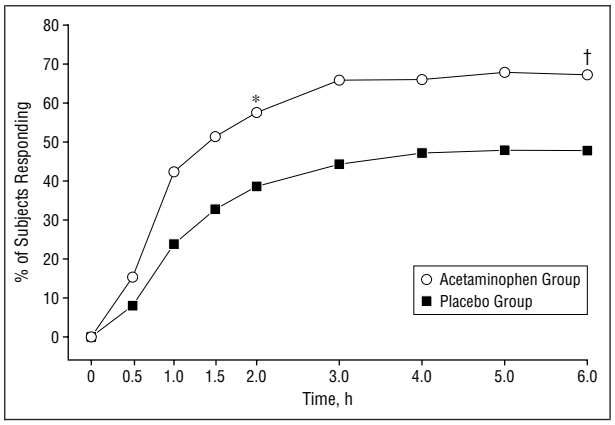

Figure 2. *Headache response rate by time (intent-to-treat analysis).* Headache response *is defined by the transition from moderate to severe pain at baseline to moderate or absent pain. The asterisk indicates* P *=.002; dagger,* P *=.001.*

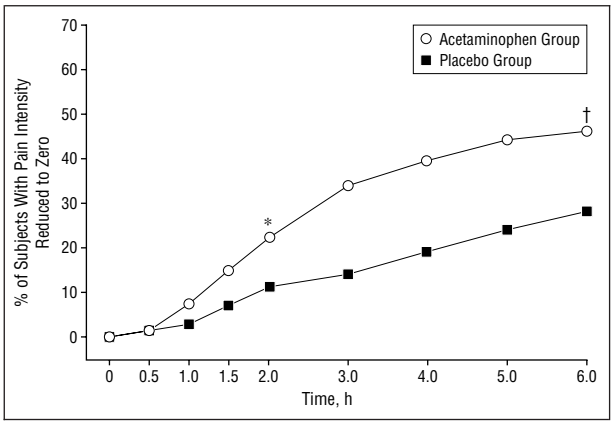

Figure 3. *Percentage of subjects with pain intensity reduced to zero by time (intent-to-treat analysis). The asterisk indicates* P *=.01; dagger,* P *=.001.*

Table 2. Unadjusted Pain Intensity Differences From Baseline by Time and SPID (ITT Analysis)*

	Assessment Time Points, h								
Treatment	**0.5**	**1.0**	**1.5**	**2.0**	**3.0**	**4.0**	**5.0**	**6.0**	**SPID**
Acetaminophen	0.32 (0.57) [146]	0.72 (0.85) [146]	0.93 (0.91) [146]	1.08 (0.98) [145]	1.27 (1.05) [136]	1.31 (1.12) [131]	1.36 (1.16) [128]	1.35 (1.21) [125]	6.82 (5.57) [147]
Placebo	0.17 (0.48) [142]	0.40 (0.74) [141]	0.61 (0.86) [139]	0.73 (0.93) [136]	0.81 (1.03) [125]	0.88 (1.13) [116]	0.93 (1.21) [104]	0.97 (1.25) [97]	4.54 (5.48) [142]
P	.005	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001

**Data are given as the mean (SD) unless otherwise indicated. Values in brackets are the number of subjects. SPID indicates sum of pain intensity differences from baseline; ITT, intent to treat.*

Table 3. Unadjusted Pain Relief Scores by Time and TOTPAR Score (ITT Analysis)*

	Assessment Time Points, h								
Treatment	**0.5**	**1.0**	**1.5**	**2.0**	**3.0**	**4.0**	**5.0**	**6.0**	**TOTPAR Score**
Acetaminophen	0.71 (0.99) [146]	1.33 (1.24) [146]	1.73 (1.43) [146]	1.99 (1.49) [145]	2.28 (1.52) [136]	2.41 (1.55) [131]	2.52 (1.58) [128]	2.55 (1.58) [125]	12.64 (7.95) [147]
Placebo	0.41 (0.75) [142]	0.89 (1.10) [141]	1.20 (1.17) [139]	1.41 (1.32) [136]	1.58 (1.41) [125]	1.73 (1.49) [116]	1.78 (1.58) [104]	1.87 (1.62) [97]	8.92 (7.41) [142]
P	.003	.002	<.001	<.001	<.001	<.001	<.001	<.001	<.001

**Data are given as the mean (SD) unless otherwise indicated. Values in brackets are the number of subjects. TOTPAR indicates total pain relief; ITT, intent to treat.*

was 1.68 in the acetaminophen group and 1.01 in the placebo group, a statistically significant difference (*P*=.001). In addition, 51.7% of the subjects in the acetaminophen group rated the medication as good to excellent, while only 28.2% of those in the placebo group gave these ratings.

SAFETY RESULTS

No serious adverse events were reported in this study. There was no statistically significant difference between the 2 groups for adverse events reported; 1 or more adverse events were reported by 47 of the subjects in the acetaminophen group and by 52 of the subjects in the placebo group. Digestive complaints accounted for most of the adverse events, with nausea being the most common. These complaints may also have been manifestations of the migraine and not related to the study medication. The differences between the 2 groups, however, were not statistically significant. Twenty-seven subjects (18.4%) in the acetaminophen group reported nausea vs 29 (20.4%) in the placebo group (*P*=.77), and 6 subjects (4.1%) in the acetaminophen group reported vomiting vs 3 (2.1%) in the placebo group (*P*=.50). Adverse events reported by more than 1% of the subjects are summarized in **Table 4**.

There also was no statistically significant difference (*P*=.38) between the 2 groups for adverse events considered related to the study drug; 1 or more of these events were reported by 43 (29.3%) of the subjects in the acetaminophen group and by 49 (34.5%) of the subjects in the placebo group.

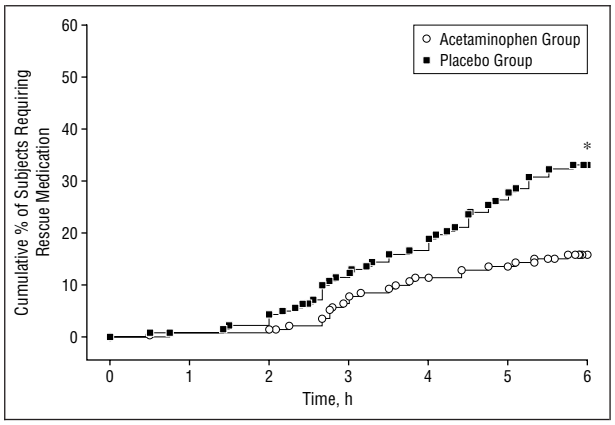

Figure 4. *Kaplan-Meier estimate of the cumulative percentage of subjects requiring rescue medication (intent-to-treat analysis). The asterisk indicates* P *=.001 for the percentage of subjects requiring rescue medication by the end of the 6-hour postdose interval.*

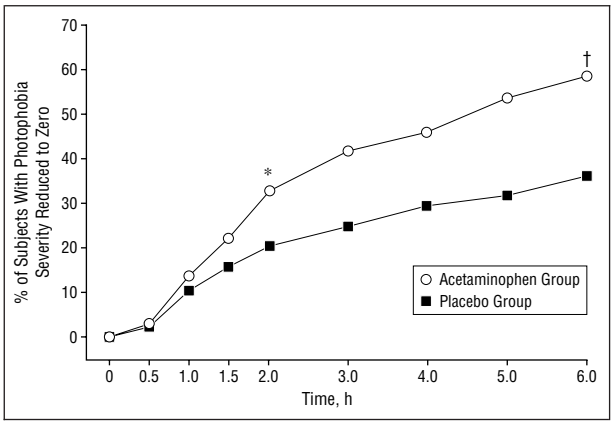

Figure 6. *Percentage of subjects with photophobia severity reduced to zero by time (intent-to-treat analysis). The asterisk indicates* P *=.02; dagger,* P *=.001.*

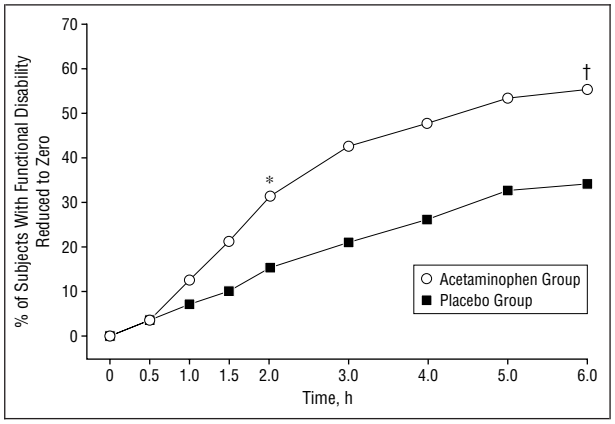

Figure 5. *Percentage of subjects with functional disability reduced to zero by time (intent-to-treat analysis). The asterisk indicates* P *=.002; dagger,* P *=.001.*

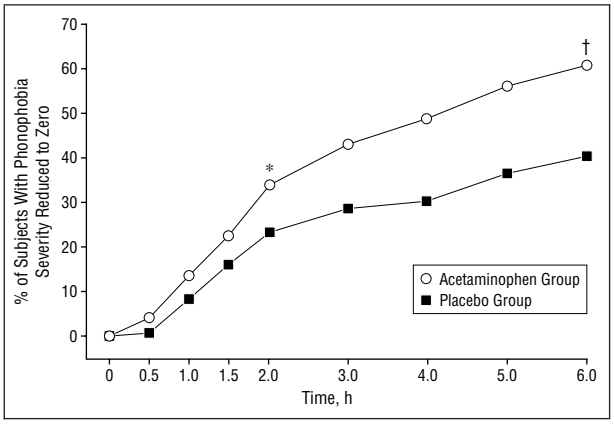

Figure 7. *Percentage of subjects with phonophobia severity reduced to zero by time (intent-to-treat analysis). The asterisk indicates* P *=.08; dagger,* P *=.001.*

COMMENT

This large, population-based, clinical trial indicates that the nonprescription drug acetaminophen is effective in relieving the pain of migraine headache. These results also indicate that acetaminophen can help alleviate the phonophobia, photophobia, and functional disability that frequently occurs with migraine attacks. Statistically significant intergroup differences favoring acetaminophen over placebo were observed for both of the primary outcome measures—the percentage of subjects who responded (moderate or severe pain becomes mild or absent) at the 2-hour postmedication assessment and the PID at 2 hours. These effects remain robust even for persons with severe migraine pain, whose response rate was nearly 25 percentage points better than that in the placebo group at 2 hours after taking the study medication. These results are generally consistent with other reports[17-20] of the effectiveness of acetaminophen in the treatment of migraine. Placebo response rates in this study were generally comparable with those reported in other studies[8] of similar design evaluating OTC migraine medications.

The random-digit–dialing method used in this study facilitated the selection of a broad cross section of the population with migraine. To ensure the enrollment of persons with migraine for whom nonprescription medication would be appropriate, subjects were excluded if more than 20% of their headaches were accompanied by vomiting or if their headaches were usually incapacitating. Even after these exclusions, more than 40% of the subjects in both groups reported severe pain at baseline. Since persons with migraine that is usually incapacitating were excluded from the study, these results are generalizable to a large segment

Table 4. Incidence of Adverse Events Within Body System Occurring in 1% or More of Subjects*

Body System	Acetaminophen Group (n = 147)†	Placebo Group (n = 142)	*P*
Any adverse event	47 (32.0)	52 (36.6)	.46
Cardiovascular system	0	3 (2.1)	.12
Digestive system	31 (21.1)	31 (21.8)	.89
Nervous system	5 (3.4)	3 (2.1)	.72
Special senses	25 (17.0)	33 (23.2)	.19

**Data are given as the number (percentage) of subjects in each group unless otherwise indicated.*
†The dose given was 1000 mg.

of the population with migraine, particularly those likely to use OTC medications.

Acetaminophen effectively relieved the functional limitation that occurred in the less-disabled segment of persons with migraine. As the goals of acute migraine therapy include relief of pain and restoration of the ability to function, this is an important benefit. In addition, the photophobia and phonophobia commonly associated with migraine were significantly reduced in the acetaminophen treatment group. The effect on nausea did not reach statistical significance.

Generally, at recommended doses of up to 4 g/d in adults, there are no serious adverse effects associated with acetaminophen.[11] In this study, the rates of adverse events reported were no different from those reported in the placebo group. The somewhat elevated rates of nausea and vomiting reflect the character and nature of associated symptoms in patients with migraine. The safety profile of acetaminophen is well established. This study in patients with migraine headache raised no additional safety concerns. Adverse event reporting was equivalent for acetaminophen and placebo, and no serious adverse events were reported.

These results have important implications for the clinical treatment and the self-management of migraine headaches. The economic burden of migraine is substantial. It costs employers $13 billion per year in the United States because of absenteeism and reduced effectiveness at work.[23] Many prescription medications for migraine are expensive and have potential adverse effects that limit their use by certain individuals.[9,10] This study demonstrates that acetaminophen, a nonprescription analgesic with an excellent safety profile, can effectively treat the pain, disability, and associated symptoms of migraine in a population sample of persons with migraine, excluding individuals who usually require bed rest. Acetaminophen, therefore, represents a safe and cost-effective treatment option for many people with migraine and is available to those who do not seek medical care.[24]

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