Efficacy and Safety of Acetaminophen, Aspirin, and Caffeine in Alleviating Migraine Headache Pain

Three Double-blind, Randomized, Placebo-Controlled Trials

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Objective: To assess the effectiveness of the nonprescription combination of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain.

Design: Three double-blind, randomized, parallel-group, single-dose, placebo-controlled studies.

Setting: Private practice, referral centers, and general community.

Patients: Migraineurs with moderate or severe headache pain who met International Headache Society diagnostic criteria for migraine with aura or without aura. The most severely disabled segment of migraineurs, including those whose attacks usually required bed rest, or who vomited 20% or more of the time, were excluded. Of the 1357 enrolled patients, 1250 took study medication and 1220 were included in the efficacy-evaluable data set.

Intervention: Two tablets of the nonprescription combination of acetaminophen, aspirin, and caffeine orally as a single-dose treatment of 1 eligible acute migraine attack.

Main Outcome Measures: Pain intensity difference from baseline; percentage of patients with pain reduced to mild or none.

Results: Significantly greater reductions in migraine headache pain intensity 1 to 6 hours after dose were seen in patients taking the acetaminophen, aspirin, and caffeine combination than in those taking placebo in each of the 3 studies. Pain intensity was reduced to mild or none 2 hours after dose in 59.3% of the 602 drug-treated patients compared with 32.8% of the 618 placebo-treated patients (P<.001; 95% confidence interval [CI], 55%-63% for drug, 29%-37% for placebo); at 6 hours after dose, 79% vs 52%, respectively, had pain reduced to mild or none (P<.001; 95% CI, 73%-82% vs 48%-56%). In addition, by 6 hours after dose, 50.8% of the drug-treated patients were pain free compared with 23.5% of the placebo-treated patients (P<.001; 95% CI, 47%-55% for drug, 20%-27% for placebo). Other migraine headache characteristics, such as nausea, photophobia, phonophobia, and functional disability, were significantly improved 2 to 6 hours after treatment with the acetaminophen, aspirin, and caffeine combination compared with placebo (P≤.01).

Conclusions: The nonprescription combination of acetaminophen, aspirin, and caffeine was highly effective for the treatment of migraine headache pain as well as for alleviating the nausea, photophobia, phonophobia, and functional disability associated with migraine attacks. This drug combination also has an excellent safety profile and is well tolerated.

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PATIENTS AND METHODS

PATIENTS

Three studies, conducted between August 17, 1995, and June 22, 1996, used a uniform double-blind, randomized, parallel-group, placebo-controlled design, and differed only in the methods of patient recruitment. Study 1, a single-center trial, used random-digit dialing exclusively to identify potentially eligible subjects.19 Study 2 and study 3 were multicenter trials that relied on both conventional (77%) (eg, private practice patients, referrals, local advertising) and random-digit dialing (23%) methods for recruiting.

Inclusion and exclusion criteria for the 3 studies were identical. Patients met International Headache Society diagnostic criteria for migraine without aura or migraine with aura,15 were at least 18 years old, were in good general health, and had experienced migraine headaches at least once every 2 months but no more than 6 times monthly. Headaches were of at least moderate pain intensity when left untreated. Patients who were usually incapacitated (ie, required bed rest for their attacks) were excluded. Patients who experienced vomiting 20% or more of the time were also excluded because of the probability that they would vomit and not absorb study medication. Nausea, however, was not an exclusion. Written informed consent was obtained from all patients. The protocol and consent form were approved by an institutional review board for each clinic.

To ensure that all subjects actually suffered from migraine, each provided a complete medical history, including a semistructured diagnostic headache interview, and underwent a physical examination and neurologic evaluation by a study clinician. Patients were trained to complete the study diary.

STUDY DESIGN—PROTOCOL

At visit 1, qualified patients were randomly assigned (1:1 ratio) according to a computer-generated randomization schedule, to receive a bottle of double-blind study medication containing either 2 tablets of unbranded Excedrin Extra-Strength (acetaminophen, 250 mg; aspirin, 250 mg; and caffeine, 65 mg per tablet; Bristol-Myers Squibb Co, New York, NY) or 2 identical-appearing placebo tablets to treat the headache pain of 1 acute self-recognized migraine attack. If the headache symptom profile met the definition of migraine, if the headache pain was of at least moderate intensity, and if the attack was otherwise eligible, the patient was instructed to take study medication. Patients 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 measurements were pain intensity difference from baseline and the percentage of patients with pain reduced to mild or none 2 hours after the dose. At baseline, patients rated their pain intensity, functional disability, nausea, vomiting, photophobia, and phonophobia. They also rated these symptoms, together with pain relief, at 0.5, 1, 2, 3, 4, and 6 hours after the dose. Patients rated pain intensity by means of a 4-point scale (0, no pain; 1, mild pain; 2, moderate pain; and 3, severe pain). They rated pain relief from 0 to 4 (0, no relief; 1, a little relief; 2, some relief; 3, good relief; 4, complete relief).

PATIENT POPULATION

Of the 1357 patients randomized in the 3 studies, 92.1% took study medication (Figure 1). Baseline or postdose evaluations were missing for 2 patients treated with acetaminophen, aspirin, and caffeine and 1 placebo-treated patient; consequently, these patients were excluded from all efficacy evaluations, leaving a total of 1247 patients in the ITT group. The ITT and efficacy-evaluable data sets differed by only 27 patients (1247 ITT, 1220 efficacy-evaluable). The 27 patients not included in the efficacy-evaluable analyses were 14 who treated a headache that did not meet protocol criteria for migraine, 9 who did not complete their evaluations at 2 hours after dose, and 4 who did not take the entire dose of study medication.

The 2 treatment groups had similar demographic profiles and migraine headache histories (Table 1) in each of the studies. Without treatment, usual migraine headache pain was moderate in 27.6%, severe in 69.8%, and incapacitating in less than 1%; 39.1% had reported

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They rated functional disability from 0 to 4 (0, none; 1, usual activities require a little additional effort; 2, require some additional effort; 3, require a great deal of additional effort; and 4, inability to perform usual activities). Nausea, photophobia, and phonophobia were rated separately by means of a 0 to 3 scale (0, none; 1, mild; 2, moderate; and 3, severe intensity) for each symptom.

Patients provided a global evaluation of analgesic efficacy at the end of the 6-hour treatment period or when they took rescue medication. The investigators provided similar evaluations. Global evaluations were rated from 1 to 5 (1, poor; 2, fair; 3, good; 4, very good; and 5, excellent).

Other efficacy variables were derived from the scores recorded by patients. These included pain intensity difference; percentage of patients with pain intensity reduced to mild or none; percentage of patients considered pain free; and percentage of patients who required rescue medication during the 6-hour evaluation period.

Safety Assessments

Adverse experiences were recorded in the diary by the patients and elicited at visit 2 by the investigators. The intensity, duration, and relation to the study drug were recorded. Clinical laboratory data were not systematically collected.

Statistical Analysis

For each study, a sample size of 200 patients per arm provided at least 85% power to detect a clinically meaningful difference of at least 15% in the proportion of patients with pain reduced to mild or none (two-sided, \( \alpha = .05 \)).

Treatment group comparability was assessed by means of analysis of variance for quantitative variables (eg, age and sex) and \( \chi^2 \) tests for categorical variables (eg, sex). The 2 treatment groups were compared, in each study, with respect to demographics and baseline characteristics.

Data missing for any scheduled evaluation period in otherwise evaluable patients (eg, patient fell asleep) were interpolated. For example, if the 0.5-hour observation was missing, it was replaced by the average of the baseline and the 1-hour observation value. For patients requiring rescue medication, post–rescue medication severity scores for pain intensity, functional ability, and nausea were assigned either the baseline or the last recorded value, whichever was the most severe. Post–rescue medication pain relief scores were assigned “no relief.”

The primary efficacy analysis was based on the efficacy-evaluable patient population. The data were also analyzed on an intent-to-treat (ITT) basis. Each study was analyzed separately. The results of the independent studies were tested for poolability.

Comparisons between the 2 treatment groups were made at each time point by means of an analysis of covariance model for changes from baseline severity in pain intensity, functional ability, and severity of nausea, photophobia, and phonophobia. An analysis of variance model was used to compare the treatments with respect to pain relief and patient’s global evaluation at 6 hours after dose and the investigator’s global evaluation at visit 2. The Cochran-Mantel-Haenszel test, stratified by baseline pain intensity, was used to analyze the percentage of patients with pain intensity reduced to mild or none, percentage of patients with pain intensity reduced to none, and percentage of patients who remedicated. Statistical significance was declared if \( P \) was less than or equal to .05.

### Eligible Patients (N=1357)

- Randomized to Take Active Medication (n=677)
  - Took Active Medication (n=618)
    - Did Not Take (n=59)
      - No HA (n=32)
        - Other (n=27)
    - Did Not Take (n=48)
      - No HA (n=28)
        - Other (n=20)
  - Intent-to-Treat Analysis (n=616)
    - Excluded: No Baseline Evaluation (n=1)
    - No Postbaseline Evaluations (n=1)
    - Evaluable for per Protocol Efficacy Analysis (n=602)
      - Excluded (n=14):
        - HA Not Migraine (n=8)
        - No 2-h Evaluation (n=3)
        - Did Not Take Entire Dose (n=3)
  - Evaluable for per Protocol Efficacy Analysis (n=618)

- Randomized to Take Placebo (n=680)
  - Took Placebo (n=632)
    - Did Not Take (n=48)
      - No HA (n=28)
        - Other (n=20)
    - Intent-to-Treat Analysis (n=631)
      - Excluded: No Baseline Evaluation (n=1)
  - Evaluable for per Protocol Efficacy Analysis (n=618)

- Other (n=27)
  - Did Not Take (n=59)
    - No HA (n=32)
      - Other (n=27)
  - Other (n=20)

### Pain Intensity and Pain Relief

In each of the 3 studies, patients taking the drug combination had significantly higher mean pain intensity difference scores than patients taking placebo at all time points from 1 hour to 6 hours after dose (\( P < .001 \)). In the pooled analysis and in study 1 and study 3, patients who received active treatment also had significantly higher mean pain intensity difference scores than did placebo-treated patients beginning at the 0.5-hour time point (\( P \leq .02 \)) (data not shown).
A larger proportion of drug-treated patients than placebo-treated patients experienced a reduction in headache pain intensity to mild or none starting 1 hour after dose and continuing to the 6-hour time point in all 3 studies \((P = .002)\). In the pooled analysis, differences were statistically significant at 0.5 hour after dose \((P = .01)\) and at all subsequent time points \((P < .001)\) (Figure 2, left). Pooled data showed that at 2 hours after dose, 59.3\% of the 602 drug-treated patients had mild or no headache pain compared with 32.8\% of the 618 placebo-treated patients \((P < .001; 95\% \text{ CI}, 55\%-63\% \text{ for drug}, 29\%-37\% \text{ for placebo})\) (Table 3). By 6 hours, 50.8\% of the patients receiving active treatment and 23.5\% of the patients receiving placebo were free of pain \((P < .001; 95\% \text{ CI}, 47\%-55\% \text{ for drug}, 20\%-27\% \text{ for placebo})\) (Table 4).

Mean pain relief scores for the drug combination were significantly higher in the individual studies and in the pooled analysis at all time points from 0.5 hour to 6 hours after dose \((P < .001)\) except for study 2 at 0.5 hour (data not shown). Analysis of these primary efficacy measurements with the use of the ITT population produced essentially identical results.

**RESCUE MEDICATION**

In the pooled analysis, the proportion of patients who required rescue medication was significantly greater in the placebo group than in the acetaminophen-aspirin-caffeine group from 3 to 6 hours after dose \((P < .001)\). For example, by hour 6, only 12.5\% of the 602 drug-treated patients needed to remedicate, compared with 27.2\% of the 618 placebo-treated patients \((P < .001; 95\% \text{ CI}, 10\%-15\% \text{ for drug}, 24\%-31\% \text{ for placebo})\) (data not shown).

### Table 1. Demographics and Migraine Headache History of Efficacy-Evaluable Patients

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
<th>Pooled</th>
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<td>Placebo (n=191)</td>
<td>APAP-ASA-CAF (n=206)</td>
<td>Placebo (n=221)</td>
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<tr>
<td>Sex, %</td>
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<td></td>
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<tr>
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<td>25</td>
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<td>81</td>
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<tr>
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<tr>
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<tr>
<td>Without aura</td>
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<td>85</td>
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<td>With aura</td>
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<td>&lt;1</td>
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<tr>
<td>Always</td>
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<tr>
<td>Frequently</td>
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<td>46</td>
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<tr>
<td>Rarely</td>
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<td>20</td>
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<td>Both</td>
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<td>12</td>
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</table>

* APAP-ASA-CAF indicates acetaminophen, aspirin, and caffeine.
† Percentages may not add to 100 because of rounding.
‡ Statistical analysis did not include patients with missing data.
GLOBAL EVALUATIONS

Global evaluations of headache pain relief by patients and investigators were significantly higher for the drug combination than for placebo \((P<.001)\). Investigators’ global evaluations were good to excellent in 51% of patients in the drug group, compared with 19.7% in the placebo group \((P<.001; 95\% \text{ CI, } 47\%-55\% \text{ vs } 17\%-23\%)\). Results were similar for patients’ global evaluations (data not shown).

EFFECTS ON OTHER HEADACHE CHARACTERISTICS

The percentage of patients with restoration of function (ability to perform activities with little or no additional effort) was significantly higher in the drug-treated group than in the placebo-treated group in the pooled analysis \((P<.001)\) and in each study separately \((P<.006)\) (data not shown) from 1 hour after dose to the 6-hour time point and at 0.5 hour after dose in study 1 \((P=.04)\) (Figure 3).

Although patients who vomited 20% or more of the time were excluded, 60% had nausea at baseline. The percentage of patients without nausea was significantly greater in the drug-treated group than in the placebo-treated group from 1 to 6 hours after dose in study 3 \((P<.05)\), from 3 to 6 hours after dose in study 1 \((P<.03)\), and from 4 to 6 hours after dose in study 2 \((P<.02)\) (data not shown). In the pooled analysis, the proportion of patients without nausea was significantly greater in the drug-treated group than in the placebo-treated group from 2 to 6 hours after dose \((P<.01)\) (Figure 4).

The pooled analysis also showed that the percentage of patients without photophobia or phonophobia was significantly greater in the drug-treated group than in the placebo-treated group from 1 hour after dose through the 6-hour time point \((P<.001)\) (Figure 4).

SAFETY RESULTS

No serious adverse experiences were reported in any of the studies, and the incidence of adverse effects considered severe was low (2%) and similar in the 2 treatment groups across the 3 studies (1.9% of the 618 patients in the drug-treated group; 1.7% of the 632 patients in the placebo-treated group). One placebo-treated patient experienced vomiting and chills that resulted in discontinuation from study 2. Adverse experiences with an incidence greater than 1% were few and expected. Those with a higher incidence than that seen in placebo-treated patients were nausea (4.9%...
Interestingly, significantly more placebo-treated patients experienced vomiting than those receiving active treatment: 1.6% of the placebo-treated patients vs 0.2% of the drug-treated patients (P = .01). No adverse effects different than those previously associated with single doses of aspirin, acetaminophen, or caffeine were seen in these studies. Pooled adverse experience data, including adverse experiences that occurred in more than 1% of patients, are summarized in Table 5.

The 3 large, double-blind, randomized, parallel-group, placebo-controlled clinical trials reported herein each show that the nonprescription combination of acetaminophen, as-
pirin, and caffeine is effective in treating the pain of migraine headache. Treatment differences for the prospectively defined outcomes measures were highly significant in favor of the drug combination in both the population-based study (study 1) and in the studies that used primarily conventional recruiting methods (studies 2 and 3). Significant differences favoring the drug treatment were found in each of the 3 studies from 1 to 6 hours after dose. Significant differences between drug and placebo were observed as early as 0.5 hour after dose for pain intensity difference from baseline and for pain reduced to mild or none in 2 studies and in the pooled analysis. Patients in the drug groups also experienced significant improvements in ability to perform usual activities at 1 hour after dose and all time points thereafter.

In this study program, recruitment methods, including random-digit dialing and local advertising, were used to identify a broad range of the migraine population, independent of physician consulting status. Because we wanted to target migraine sufferers for whom a nonprescription medication might be appropriate, we excluded subjects who experience vomiting with more than 20% of their attacks and those whose attacks usually require bed rest.

In addition to pain and disability, migraine occurs as part of a symptom complex that often includes nausea, photophobia, and phonophobia. Migraine-specific prescription agents have demonstrated significant benefits in treating this symptom complex. The present studies show that the combination of acetaminophen, aspirin, and caffeine also produces statistically significant improvement in nausea, photophobia, and phonophobia. Improvement in these associated symptoms in the pooled analysis became statistically significant at 30 minutes. In these studies, pain relief preceded relief of associated symptoms. Perhaps relief of associated symptoms is a consequence of the relief of pain.

Migraine was a significant health problem for the patients in these studies. Although we excluded the most disabled patients, at baseline, 66.6% of the patients rated their headache pain as moderate and 33.4% of the patients rated it as severe. Nearly 82.9% of the patients reported that they had significant functional impairment: 47.3% required some additional effort to perform their usual activities; 30.2% required a great deal of additional effort; and 5.3% reported that they were incapacitated (unable to perform their usual activities). Thus, the benefits of the drug combination were demonstrated in patients with moderate to severe pain and significant impairment of function. However, since the most severely disabled segment of migraineurs were not studied in these trials, the present results cannot be generalized to such patients.

Figure 3. Percentage of pooled efficacy-evaluable patients requiring some or a great deal of additional effort to perform usual activities or unable to perform usual activities after treatment with acetaminophen, aspirin, and caffeine (APAP-ASA-CAF) or placebo. Asterisk indicates P < .001 vs placebo.

Figure 4. Percentage of pooled efficacy-evaluable patients with migraine symptoms (ie, nausea, photophobia, phonophobia) after treatment with acetaminophen, aspirin, and caffeine (APAP-ASA-CAF) or placebo. Asterisk indicates P < .001 vs placebo; dagger, P < .01 vs placebo; double dagger, P < .05 vs placebo.
As might be expected with an approved nonprescription drug, no clinically significant safety concerns were identified. No serious adverse experiences were reported in any of the studies. Those that were reported were similar in type and severity to those previously associated with single doses of aspirin, acetaminophen, or caffeine.15,17,23,24

These results have important implications for clinical practice and for headache health care policy. Most approved prescription drugs for migraine are expensive, and many have therapy-limiting side effects and contraindications.18,23,26 These studies demonstrate that acetaminophen-aspirin-caffeine, a nonprescription combination analgesic with a favorable safety profile, can effectively treat the pain, disability, and associated symptoms of migraine. This combination is likely to represent a safe and cost-effective treatment alternative for patients with migraine.

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REFERENCES