Solubilized Ibuprofen: Evaluation of Onset, Relief, and Safety of a Novel Formulation in the Treatment of Episodic Tension-type Headache

Barry Packman, MD; Elias Packman, ScD; Geraldine Doyle, PhD; Stephen Cooper, DMD, PhD; Elizabeth Ashraf, PhD; Karen Koronkiewicz, MBA; Shyamalie Jayawardena, PhD

Objective.—To evaluate the relative efficacy of a new solubilized formulation of ibuprofen compared with acetaminophen caplets.

Methods.—This double-blind, randomized, parallel group study evaluated 154 subjects taking a single dose of solubilized ibuprofen, 400 mg; acetaminophen, 1000 mg; or placebo for the relief of episodic tension-type headache. Time to relief was measured using a stopwatch, and overall efficacy was measured using traditional categorical pain and relief scales.

Results.—Ibuprofen capsules (liquigel), 400 mg, were significantly faster than both acetaminophen, 1000 mg, and placebo for all time-to-relief measures. Ibuprofen liquigel had a median time to first perceptible pain relief of 39 minutes compared with 47 minutes for acetaminophen and 113 minutes for placebo. For median time to meaningful relief, ibuprofen liquigel had a time of 39 minutes compared with 53 minutes for acetaminophen and more than 180 minutes for placebo ($P \leq .02$ for both measures). In addition, ibuprofen liquigels demonstrated significantly superior overall analgesic efficacy compared with acetaminophen, 1000 mg, for the relief of episodic tension-type headache. Both active treatments had a side effect profile similar to placebo.

Conclusions.—Although several other studies have demonstrated the overall analgesic superiority of ibuprofen to acetaminophen, this study demonstrated that the liquigel formulation also provides a clinically relevant advantage for time to analgesic effects.

Key words: ibuprofen, headache, tension-type headache, onset, headache relief, time to headache relief

Abbreviations: OTC over-the-counter, SPRID2(3) sum of pain relief and pain intensity scores for 2(3) hours, PRID2(3) pain relief intensity difference at 2(3) hours

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Almost all of the general population will encounter and self-treat a headache during their lifetime.[1] The most common variety of headache, characterized as "tension-type," is usually treated with over-the-counter (OTC) analgesics. The ideal analgesic to treat tension-type headaches should work quickly, provide complete pain relief, and be devoid of adverse effects.

The development and optimization of drug delivery systems sometimes lead to drugs that are more quickly absorbed or act faster, or both. One such novel formulation, capsules (liquigels) filled with solubilized ibuprofen, has been shown to have a kinetic profile similar to an ibuprofen suspension. Both the suspension and liquigel formulations reach higher peak plasma levels (C_{max}) in a shorter time (T_{max}) than a solid tablet. Higher plasma levels of ibuprofen have been shown to be correlated with a faster and higher peak analgesic response.[2] Cooper et al demonstrated

From the Institute for Applied Pharmaceutical Research, Philadelphia, Pa (Drs. Packman and Packman); and the Clinical Research Department, Whitehall-Robins Healthcare, Madison, NJ (Drs. Doyle, Cooper, Ashraf, and Jayawardena and Ms. Koronkiewicz).

Address all correspondence to Dr. Elizabeth Ashraf, Whitehall Robins Healthcare, 5 Giralda Farms, Madison, NJ 07940.

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that, compared with solid formulations, the solubilized form of ibuprofen attained higher drug levels in traumatized tissue, and this was correlated with both faster and greater analgesic effects.[3] These data suggested that the pharmacokinetic profile of solubilized ibuprofen would have a clinically faster time to an analgesic effect than the currently available solid oral dosage forms.

Many studies have consistently demonstrated that various nonprescription ibuprofen formulations provide overall analgesic superiority to acetaminophen, 1000 mg, in the treatment of episodic tension-type headache as well as other painful conditions,[4-10] however, no study has clearly demonstrated a significant enhancement of time to relief. Given the pharmacokinetic enhancement in time to C_{max} with solubilized ibuprofen, the primary purpose of this clinical trial was to determine whether this pharmacokinetic difference translated into a clinical advantage over acetaminophen with respect to the speed of achieving meaningful relief—an important factor to consumers.

This study evaluated the safety and efficacy of a single dose of ibuprofen liquigel, 400 mg, compared with acetaminophen, 1000 mg, and placebo for the relief of pain due to episodic tension-type headache, the most common type of headache usually treated with OTC analgesics.[11]

METHODS

Subjects.—This was a single-dose, double-blind, randomized, placebo-controlled, parallel group study conducted among inpatients at a single site. Males and females (older than 12 years) who had a history of episodic tension-type headache, as defined by the International Headache Society diagnostic criteria, were enrolled.[12] Typical headaches were at least moderately severe and generally responded to an OTC analgesic. Onset of these headaches had to be before the age of 50 years. Potential subjects were excluded if they were habituated to analgesics, had a history of recurrent migraine (ie, on average, more than one migraine per month over past 6 months), menstrual

Table 1.—Demographic Profile and Headache History

Variable	Total (N = 154)	Placebo (n = 32)	Ibuprofen (n = 60)	Acetaminophen (n = 62)
Ratio of males to females	37:117	8:24	14:46	15:47
Age, y (mean ± SD)	39.6 ± 11.8	38.3 ± 12.4	38.5 ± 10.4	41.2 ± 12.6
Mean headache history, y (range)	10 (0.5-35)	9 (0.5-30)	10 (0.5-35)	11 (1-30)
Mean headache frequency per month* (range)	6.2 (4-15)†	5.5 (4-12)	6.5 (4-12)	6.2 (4-15)
Mean headache frequency per month by severity:				
Mild	0.7	0.6	0.8	0.7
Moderately severe	4.3	4.0	4.5	4.2
Severe	1.2	0.9	1.2	1.3
Duration of headache untreated, %				
>2-4 h	84	81	82	89
>4 h	16	19	18	11
Duration of headache treated, %				
≤1 h	23	31	18	23
>1-2 h	76	69	80	76
>2-4 h	1	0	2	1
Characteristics of currrent headache				
Visual problems prior to headache		No	No	No
Headache pain on one side only		No	No	No
Nausea/vomiting		No	No	No
Photophobia and phonophobia		No	No	No
Worsening of pain on physical activity		No	No	No

*Estimated by subjects at entry.
†Only one subject reported 15 headaches per month.

headaches, allergic hypersensitivity or other contraindications to aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or acetaminophen. All subjects provided written, informed consent.

Potential subjects were required to report to the study center within 1 hour of the onset of a moderately severe headache. Upon arrival at the site, subjects had to rate their headache pain as at least "moderately severe" on a four-point Categorical Pain Rating Scale that was confirmed by a score of at least 66 mm on a 100-mm visual analog pain scale. Qualifying subjects were stratified by sex and then randomized according to a computer-generated code to receive either ibuprofen, 400 mg (2×200-mg liquigels); acetaminophen, 1000 mg (2×500-mg caplets); or placebo.

Following dosing, the time of first perceptible and meaningful relief was recorded using two stopwatches (A and B) whose faces were covered and started at the time of dosing. Stopwatch A was used to record time to "first perceptible relief" and, if needed, stopwatch B was stopped to record time to "meaningful relief." Subjects were to depress stopwatch A when they obtained any headache relief. The subjects were then asked if this relief was meaningful. If the pain relief was not considered meaningful, the subject was then given stopwatch B and instructed to depress the watch when meaningful relief was obtained. Pain intensity and relief were also measured using traditional categorical four-and five-point scales, respectively, at 2 and 3 hours postdosing and at the time of rescue medication (if required). The area under the curve measurement of the sum of pain relief and pain intensity difference scores for 3 hours (SPRID3) was calculated. Pain relief intensity difference (PRID) values at 2 and 3 hours were also calculated. Adverse effects, observed by the study coordinator or reported by the subject, were recorded by the study coordinator when they occurred.

Subjects remained at the study facility for the 3-hour postdosing evaluation and were allowed to perform only nonstrenuous activities.

Formulation.—The liquigel formulation used in this clinical trial is a unique dosage form developed to enhance drug absorption. The process involves encapsulating solubilized ibuprofen in a soft gelatin shell, which is formed by spreading a molten gelatin mass into two lubricated ribbons that shape the liquigel. Ibuprofen is then injected through a wedge in the gelatin mold.

Statistical Methods.—A sample size of 57 subjects per active treatment group was estimated to provide 80% power (at a 5% level of significance) to detect a

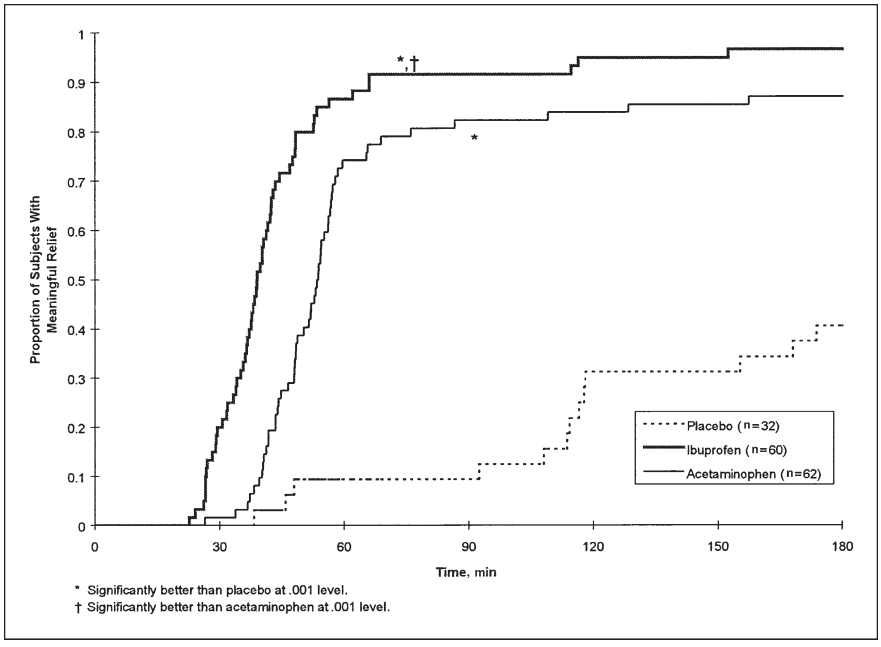

Fig 1.—Proportion of subjects attaining meaningful relief over time.

70% higher instantaneous event rate for the time to first perceptible relief (ie, a hazard ratio of 1.7) for ibuprofen liquigel, 400 mg, compared with acetaminophen caplet, 1000 mg.

The comparability of the treatment groups was assessed by analysis of variance with treatment and sex effects for quantitative variables (eg, age) and by the Cochran-Mantel-Haenszel (CMH) test stratified by sex for categorical variables (eg, race). The three treatment groups were compared with respect to demographic and baseline pain characteristics.

Pairwise efficacy comparisons were declared significant only when the corresponding overall treatment effect was also significant. Efficacy variables included time to meaningful relief, time to first perceptible relief, PRID2 and 3, and overall efficacy measured as SPRID3. The cumulative proportion of subjects with first perceptible relief and meaningful relief were analyzed using the CMH test. Distribution of time to relief was estimated using Kaplan-Meier estimates, and the median time and 95% confidence limit were derived by the method of Simon and Lee.[13] Covariate effects were assessed via the Cox proportional hazards model. Analysis of variance was used to compare differences among treatment groups for SPRID3 and hourly PRID2 and 3 values.

RESULTS

Patient Population.—All 154 subjects randomized to treatment completed the study and were evaluable. The three treatment groups had similar demographic profiles including headache frequency and severity (Table 1).

Time to Relief.—Ibuprofen had a significantly earlier median time to relief than acetaminophen and placebo for first perceptible relief (39 minutes versus 47 minutes [acetaminophen], and 113 minutes [placebo]) and meaningful relief (39 minutes versus 53 minutes [acetaminophen] and >180 minutes [placebo]; $P \leqslant .02$; Table 2). In the ibuprofen group, 85% of subjects reported that their first perceptible relief was also meaningful compared with 67% of those who received acetaminophen. The estimated probability of attaining each of the direct stopwatch measures of relief over time are depicted in Figure 1 (meaningful relief) and Figure 2 (first perceptible relief). Both ibuprofen and acetaminophen were significantly faster than placebo for both first perceptible and meaningful relief. A significantly higher proportion of subjects, 20% in the ibuprofen treatment group compared with only 2% of acetaminophen-treated subjects, achieved first perceptible relief as well as meaningful relief by 30 minutes after dosing ($P \leqslant .009$). No subject in the placebo

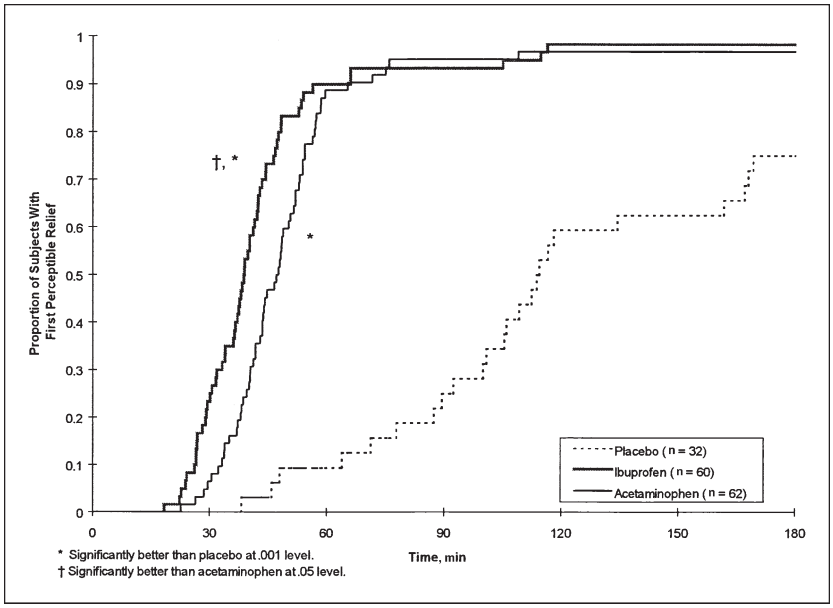

Fig 2.—Proportion of subjects achieving first perceptible relief over 6 hours.

group experienced meaningful relief within 30 minutes. Furthermore, by the third hour after dosing, 75% of ibuprofen-treated subjects reported complete pain relief compared with only 32% of those who received acetaminophen and 13% of those who received placebo ($P \leq .001$, Figure 3). The fact that only 3% of the placebo group experienced complete pain relief by 2 hours, and 13% reported complete relief by the third hour, demonstrates the robust assay sensitivity of this model.

Consistent with the stopwatch data, ibuprofen was significantly better than acetaminophen ($P < .001$), and both active drugs were significantly better than placebo ($P < .001$), for the individual time points PRID2 and 3 and summed SPRID3.

No subject in this study reported adverse effects.

COMMENTS

The acute pain of tension-type headache requires a safe self-treatment that provides fast and complete relief. While many previous studies have shown that a single dose of ibuprofen, 400 mg, provides superior overall analgesic efficacy compared with acetaminophen, 1000 mg,[4-7] this study was the first to demonstrate that the new solubilized ibuprofen formulation can be further differentiated from the acetaminophen 1000-mg caplet by providing a faster time to relief.

In this trial, 85% of the subjects receiving ibuprofen liquigel, 400 mg, reported that their first perceptible relief was also meaningful relief compared with 67% of those who received acetaminophen. The median time of first perceptible and meaningful relief for solubilized ibuprofen was 39 minutes; this was significantly faster than acetaminophen, 1000 mg, which had a median time to first perceptible relief of 47 minutes and a median time to meaningful relief of 53 minutes.

Measuring the time to relief involves a complex interplay of variables including type and severity of pain, time of drug intervention, and choice of measuring instrument. Although several measures are widely used to estimate time to analgesic effect, assessing the time to meaningful relief with a stopwatch was considered the most clinically relevant end point.[14-18] This measure relies on the subject's own interpretation of both meaningful relief and when it occurs. In acute pain, where the highest level of pain is usually experienced during the first 2 hours of the episode, a faster time to meaningful relief is a highly desirable attribute for an analgesic. Although all of the measures of time to relief have value, and all of those

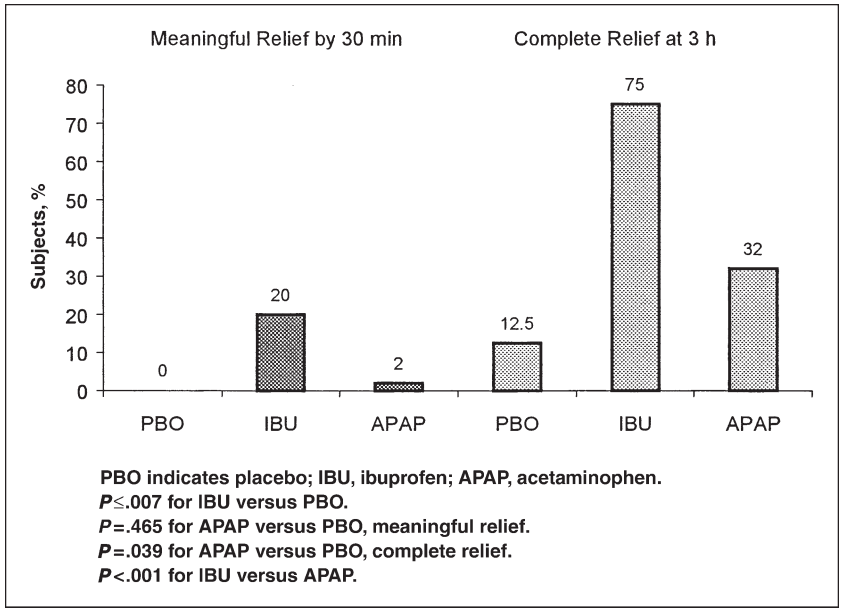

Fig 3.—Percentage of subjects obtaining meaningful relief by 30 minutes and complete relief by 3 hours.

Table 2.—Time to Relief and Overall Efficacy Parameters

Variable	Placebo (n = 32)	Ibuprofen (n = 60)	Acetaminophen (n = 62)	*P*
Median time to FPR, min	113	39	47	≤.02* <.001†‡
Median time to MR, min	>180	39	53	<.001†‡*
Complete relief at 3 h, %	13	75	32	<.001†‡*
2-h PRID, mean	1.8	4.7	3.8	<.001†‡*
3-h PRID, mean	2.2	5.7	4.5	<.001†‡*
3-h SPRID, mean	5.8	15.2	12.2	<.001†‡*

FPR indicates first perceptible relief; MR, meaningful relief; PRID, pain relief combined with pain intensity difference; and SPRID, sum of pain relief scores combined with pain intensity difference scores over 3-hour evaluation period.
* Ibuprofen versus acetaminophen.
†Ibuprofen versus placebo.
‡Acetaminophen versus placebo.

used in this study reached statistical significance, the median time to achieve meaningful relief has gained recognition as a reliable and recognized estimate of onset among analgesiologists.[14-18]

In support of the stopwatch method, other measures can also be used to assess the time to relief. The 2-hour efficacy assessment derived from the pain relief and pain intensity scales (2-hour PRID score) also demonstrated superiority of ibuprofen liquigel compared with acetaminophen ($P<.001$), and both active treatments were significantly better than placebo ($P<.001$). This measure confirms that any advantages in time to relief seen with stopwatch measures are consistent, sustained, and clinically meaningful.

This trial also confirmed the results of several previous studies demonstrating the overall superiority in its efficacy of ibuprofen compared with acetaminophen in various types of pain amenable to self-treatment.[4-7]

None of the subjects in this study reported an adverse experience, which is not atypical of short-term, OTC dosing regimens. Epidemiological data as well as pooled data from other single- and multiple-dose studies using OTC doses of ibuprofen and acetaminophen indicate that the overall frequency of side effects with ibuprofen is low.[19-21] For self-limited acute pain conditions such as tension headache, there are no data showing that the side-effect profile of OTC ibuprofen differs from that of placebo when taken as directed.[22] Supporting this finding is a recently completed trial in 1200 volunteers that specifically evaluated the gastrointestinal safety and tolerance of ibuprofen versus placebo following a maximum OTC dosing of 1200 mg for 10 consecutive days.[23] In this study, the side-effect profile, including gastrointestinal events and frequency of positive occult blood in stools, was indistinguishable from placebo.

We conclude from this study that 400-mg solubilized ibuprofen liquigels have a significantly earlier time to relief than 1000-mg acetaminophen caplets in relieving episodic tension-type headache. Ibuprofen also provided significantly better overall efficacy than acetaminophen. To our knowledge, this study is the first to discriminate the time to effect of these two nonprescription analgesics.

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