Comparative Study of Ibuprofen Lysine and Acetaminophen in Patients with Postoperative Dental Pain

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ABSTRACT

This single-dose, double-blind, parallel-group, single-site study compared ibuprofen lysine 400 mg with acetaminophen 1000 mg and placebo in 240 patients with moderate-to-severe postoperative dental pain. The relative onset of analgesic response, overall analgesic efficacy, duration of effect, and safety were assessed over a 6-hour postdose period. Analgesic efficacy was assessed by patient self-rating of pain intensity, pain relief, time to meaningful pain relief, need for additional analgesic medication, and patient global evaluation. Both ibuprofen lysine 400 mg and acetaminophen 1000 mg were significantly ($P \leq 0.05$) more effective than placebo. Ibuprofen lysine had a significantly ($P \leq 0.05$) faster onset of action with greater peak and overall analgesic effect than did acetaminophen. All treatments were generally well tolerated.

INTRODUCTION

Ibuprofen lysine is the water-soluble lysine salt of ibuprofen, a propionic acid derivative with anti-inflammatory, analgesic, and antipyretic properties. Ibuprofen lysine was developed to enhance the speed of absorption of ibuprofen and to minimize the time to onset of therapeutic effect. Pharmacokinetic studies[1,2] have demonstrated that ibuprofen lysine is more rapidly absorbed than ibuprofen administered as the free acid.

A film-coated, 200-mg ibuprofen lysine tablet is available without prescription in several European countries. The postoperative dental pain model is often used to assess the relative potency of non-

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prescription analgesics, and provides a reliable and reproducible estimate of analgesic efficacy. Previous studies[3,4] using this model have shown that ibuprofen and acetaminophen are safe and effective. Various measures in these studies have indicated that ibuprofen 400 mg has greater overall analgesic efficacy than acetaminophen 1000 mg, but the studies did not specifically address the time to onset of effect for the two compounds. This placebo-controlled study was conducted to compare the relative onset of analgesic effect, degree of overall analgesic efficacy, duration of analgesia, and safety of single doses of ibuprofen lysine 400 mg and acetaminophen 1000 mg when used to treat patients with moderate-to-severe postoperative dental pain.

PATIENTS AND METHODS

Healthy male and female patients were eligible to participate in the study if they were at least 15 years old, had two or more impacted (at least one partially embedded in bone) third molars surgically removed, and experienced moderate or severe pain associated with the surgical procedure. Patients were excluded from the study if they received any analgesic within 4 hours or a long-acting analgesic within 12 hours of the study medication; received anesthesia other than mepivacaine hydrochloride, fentanyl, or methohexital during the surgery; or were taking any concurrent medication that could confound the evaluation of analgesia or safety. The protocol was approved by an institutional review board before initiation of the study. All patients gave written, informed consent before entering the study. For minors, consent of a parent or legal guardian was obtained.

This double-blind, double-dummy, parallel-group, single-dose study was conducted at a single site. Patients were assigned to one of three treatment groups (ibuprofen lysine 400 mg [two 200-mg tablets], acetaminophen 1000 mg [two 500-mg tablets], or placebo) according to an allocation schedule of random numbers. Each patient who satisfied the admission criteria received a single dose of one of the test medications when the pain was moderate or severe. At the time the study drug was administered, the patient started a stopwatch. Patients were instructed to click off the stopwatch when they experienced meaningful pain relief and to record the elapsed time in a diary that was provided. If the patient did not experience meaningful relief within 2 hours after dosing, use of the stopwatch was discontinued.

Response to treatment was evaluated by patient self-rating of pain intensity (0 = none, 1 = slight, 2 = moderate, 3 = severe) and degree of pain relief (0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete) at 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 5, and 6 hours postdose. At the last evaluation time, the patient provided a global evaluation of the study drug (0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent). Patients were asked not to remedicate, if possible, during the first hour postdose. For patients who did remedicate with a backup analgesic during the 6-hour study period, the time of remedication was noted, as were the efficacy and global evaluations of the study drug. No further efficacy evaluations were done after remedication. The duration, intensity, seriousness, outcome, and relationship to the test drug of any clinical adverse experiences occurring during the 6-hour postdose period were recorded by the study coordinator.

Analgesic efficacy was assessed as follows: time to onset of analgesic effect, duration of analgesic effect, peak analgesic effect, and overall analgesic effect. The pain intensity difference (PID) was calculated by subtracting the pain intensity at each time point from the baseline pain intensity. Time to achieve a change in pain intensity of one category or more (PID ≥ 1) was calculated as a measure of analgesic onset. Additional measures were stopwatch times to meaningful pain relief and direct comparisons of mean PID and pain relief scores at each time point within the first hour postdose. Peak PID and pain relief scores were used to characterize peak analgesic effect. Duration was reflected in the proportion of patients who remedicated and the time to remedication. The weighted sum of the PID scores (SPID) at 6 hours, the weighted sum of the pain relief scores (TOPAR) at 6 hours, and patient global evaluations were used to assess overall analgesic efficacy.

All patients who recorded pain evaluations for at least 60 minutes after taking a study medication were included in the efficacy analysis. Patients who remedicated within the first hour were to be excluded from the efficacy analysis; there were none in this study. A value of 0 was assigned for PID and pain relief at all time points after remedication. All patients who took a study medication were included in the safety analysis.

Statistical Analysis

Overall and pairwise comparisons between treatment groups were made by using analysis of variance (ANOVA) for PID and pain relief at each time point, peak PID, peak pain relief, SPID at 6 hours, TOPAR at 6 hours, and patient's global evaluation. A logistic regression model was used to analyze the proportion of patients with meaningful pain relief within 60 minutes postdose and the proportion who remedicated during the first 6 hours postdose. The time to PID ≥ 1, stopwatch time, and time to remedication were analyzed using a Cox proportional hazards regression model for differences between treatment groups in the time-to-event distributions. The Kaplan-Meier procedure was used to obtain estimates of the time-to-event curves. A two-tailed Fisher's exact test was used for pairwise comparisons of the incidence of adverse experiences. Chi-square tests were used for pairwise comparisons of the distribution of demographic characteristics. ANOVA was used to test baseline comparability of treatment groups for age. Differences were considered statistically significant when $P \leq 0.05$. In the following text, the terms significant or significantly denote $P \leq 0.05$.

RESULTS

Two hundred forty patients were randomly assigned to one of three treatment groups; 99 patients received ibuprofen lysine 400 mg, 101 patients received acetaminophen 1000 mg, and 40 patients received placebo. One of the patients in the ibuprofen lysine group had only one third molar removed and did not record efficacy evaluations; this patient was excluded from the efficacy analysis. Baseline demographic characteristics are presented in Table I. Overall, 65% of the patients were women and 72% were white. Patients ranged in age from 15 to 60 years. There were no significant differences between groups with respect to baseline demographics, number of third molars removed, or baseline pain intensity.

Table I. Patient characteristics.

	Ibuprofen Lysine 400 mg (n = 99)	Acetaminophen 1000 mg (n = 101)	Placebo (n = 40)
Sex (%)			
Male	36 (36)	30 (30)	19 (48)
Female	63 (64)	71 (70)	21 (53)
Age (y)			
Mean ± SD	25.0 ± 6.9	25.3 ± 8.2	24.2 ± 6.2
Range	16–58	15–60	15–48
Race (%)			
White	70 (71)	73 (72)	29 (73)
Black	8 (8)	5 (5)	1 (3)
Hispanic	16 (16)	18 (18)	10 (25)
Other	5 (5)	5 (5)	0 (0)
No. of third molars surgically removed (%)			
1	1 (1)*	0 (0)	0 (0)
2	86 (87)	95 (94)	39 (98)
3	4 (4)	3 (3)	0 (0)
4	8 (8)	3 (3)	1 (3)
Baseline pain intensity (%)			
Moderate	78 (79)	80 (79)	32 (80)
Severe	20 (20)	21 (21)	8 (20)

*This patient did not complete any pain evaluations, including baseline pain, and was excluded from the efficacy analysis.

The mean PID and pain relief values over the 6-hour postdose study period are presented in Figures 1 and 2, respectively. Compared with patients in the acetaminophen and placebo groups, patients treated with ibuprofen lysine had significantly higher mean PID and pain relief scores at 15 minutes through 6 hours postdose. In addition, the mean PID and pain relief scores for the acetaminophen group were significantly higher than those for the placebo group at 30 minutes through 6 hours postdose.

Patients in the ibuprofen lysine group had a significantly shorter time to PID ≥ 1 (onset) than those in the acetaminophen and placebo groups (Table II). The acetaminophen group also had a significantly shorter time to PID ≥ 1 than did the placebo group. The median times to PID ≥ 1 were 25 minutes for ibuprofen lysine, 42 minutes for acetaminophen, and >180 minutes for placebo. The median time to meaningful pain relief, as indicated by the patient clicking off the stopwatch, was significantly shorter with ibuprofen lysine than with acetaminophen or placebo (ibuprofen lysine, 42 minutes; acetaminophen, 59 minutes; placebo, >120 minutes) (Table II). The proportion of patients with meaningful pain relief within 60 minutes was greater in the ibu-

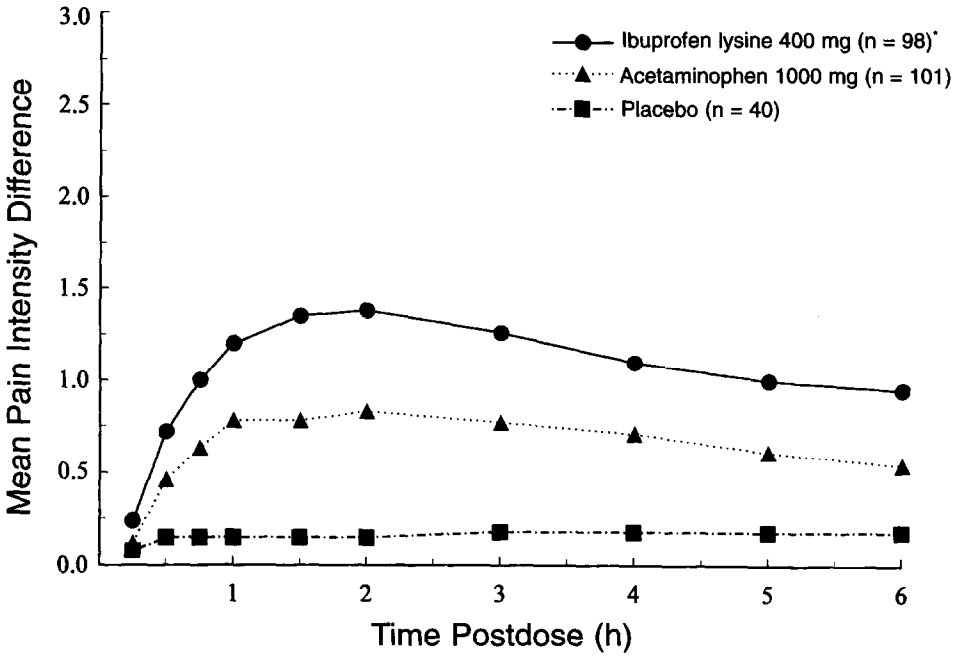

Figure 1. Mean pain intensity difference during 6 hours after a single dose of ibuprofen lysine 400 mg, acetaminophen 1000 mg, or placebo. $P \leq 0.05$, ibuprofen lysine versus acetaminophen at each time point. *One patient did not complete any pain evaluations, including baseline pain, and was excluded from the efficacy analysis.

profen lysine group (71%) than in the acetaminophen group (52%) or the placebo group (12%).

A significantly smaller proportion of patients in the ibuprofen lysine group remedicated during the 6-hour postdose period (26%) compared with the acetaminophen (60%) and placebo (88%) groups. The difference in this measure between the acetaminophen and the placebo groups also was statistically significant. Patients treated with ibuprofen lysine waited a significantly longer time before taking a backup analgesic than those receiving acetaminophen or placebo (Table II). A significant difference between the acetaminophen and placebo groups also was observed in time to remedication.

Measures of peak and overall analgesic effect are summarized in Table II. Peak PID, peak pain relief, SPID at 6 hours, TOPAR at 6 hours, and mean global evaluations were significantly greater in the ibuprofen lysine group than in the acetaminophen group; the scores in the acetaminophen group also were significantly higher than those in the placebo group. Overall, 83% of patients receiving ibuprofen lysine had global evaluations of good to excellent, compared with 51% of patients receiving acetaminophen and 14% of patients receiving placebo.

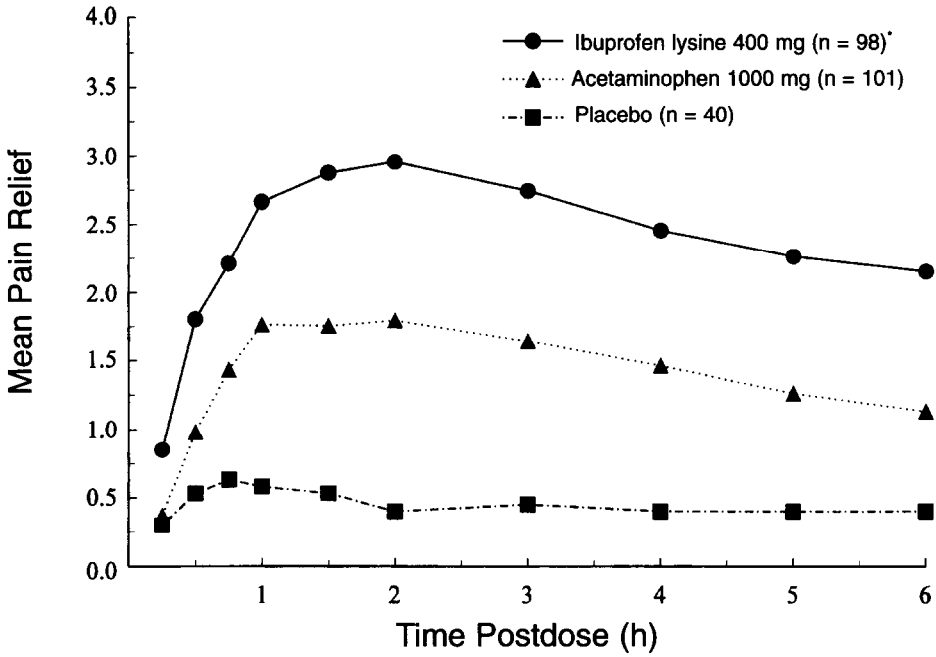

Figure 2. Mean pain relief scores during 6 hours after a single dose of ibuprofen lysine 400 mg, acetaminophen 1000 mg, or placebo. $P \leq 0.05$, ibuprofen lysine versus acetaminophen at each time point. *One patient did not complete any pain evaluations, including baseline pain, and was excluded from the efficacy analysis.

Thirty-three patients (14%) reported having one or more adverse experiences during the 6-hour postdose period: 12 patients (12%) in the ibuprofen lysine group, 17 (17%) in the acetaminophen group, and 4 (10%) in the placebo group. No significant differences were observed between the treatment groups in the proportion of patients with adverse experiences or adverse experiences classified as possibly, probably, or definitely drug related. No serious adverse experiences were reported. Nausea, vomiting, headache, and dizziness were the most frequently reported adverse experiences; these may have been related to the surgical procedure or to the backup analgesic medication.

DISCUSSION AND CONCLUSION

This clinical study was conducted to compare the efficacy and safety of ibuprofen lysine with that of acetaminophen for the treatment of pain resulting from surgical removal of two or more third molars. The postoperative dental pain model is a sensitive, reproducible model for evaluating analgesic efficacy.[5] Two studies[3,4] using this model have indicated that ibuprofen 400 mg has greater overall efficacy than acetaminophen 1000 mg. Our study extends the published literature by demonstrating that ibuprofen lysine, the lysine salt of ibuprofen, has a faster onset of analgesic effect in addition to greater over-

Table II. Summary of analgesic efficacy of ibuprofen lysine 400 mg, acetaminophen 1000 mg, and placebo in patients with moderate-to-severe postoperative dental pain. Unless otherwise noted, all values are given as mean ± SD.

	Ibuprofen Lysine 400 mg (n = 98)*	Acetaminophen 1000 mg (n = 101)	Placebo (n = 40)
Median time to PID ≥ 1† (min)	25‡§	42‡	>180
Median stopwatch time to meaningful relief† (min)	42‡§	59‡	>120
Proportion with meaningful relief within 60 min	71%	52%	12%
Proportion remedicated	26%‡§	60%†	88%
Median time to remedication† (min)	>360‡§	251†	84
Peak PID	1.54 ± 0.75‡§	1.09 ± 0.92‡	0.32 ± 0.57
Peak pain relief	3.20 ± 1.00‡§	2.38 ± 1.41‡	0.95 ± 1.11
SPID 6 h	6.46 ± 3.72‡§	3.95 ± 4.47‡	0.98 ± 2.37
TOPAR 6 h	14.39 ± 6.46‡§	8.39 ± 7.92‡	2.62 ± 5.09
Global evaluation‖	2.60 ± 1.13‡§	1.57 ± 1.35‡	0.45 ± 0.81
Excellent	18%	8%	0%
Very good	48%	23%	2%
Good	17%	20%	12%
Fair	8%	18%	12%
Poor	8%	32%	72%

PID = pain intensity difference; SPID = weighted sum of the pain intensity difference scores; TOPAR = weighted sum of the pain relief scores.

*One patient did not complete any pain evaluations, including baseline pain, and was excluded from the efficacy analysis.

†Statistical analysis performed on the distribution of time-to-event data.

‡$P \leq 0.05$, compared with placebo.

§$P \leq 0.05$, compared with acetaminophen.

‖Percentages do not total 100% due to rounding.

all efficacy when compared with acetaminophen in the treatment of patients with postoperative dental pain.

Multiple measures showed that the difference in onset of analgesia between ibuprofen lysine 400 mg and acetaminophen 1000 mg was both statistically and clinically significant. Time to onset of analgesia as measured by PID ≥ 1 was significantly shorter with ibuprofen lysine than with acetaminophen. The stopwatch time to meaningful pain relief was also significantly shorter with ibuprofen lysine than with acetaminophen. For both measures, the difference in median times, favoring ibuprofen lysine, was 17 minutes. Compared with the acetaminophen group, the proportion of patients with meaningful relief within 60 minutes was 19 percentage points greater in the ibuprofen lysine group (71% vs 52%). The significant difference in time to meaningful relief, as defined by the patient, confirms by independent measure the statistically significant differ-

ences shown in mean PID and pain relief scores at 15 minutes.

The advantage of ibuprofen lysine in onset of analgesia has been noted in other postoperative dental pain studies. Cooper et al[6] reported that ibuprofen lysine 400 mg has a faster onset of effect than ibuprofen 400 mg. In that pharmacokinetics/pharmacodynamics study, the mean time to maximum concentration in the ibuprofen lysine group was appreciably shorter than that of the ibuprofen group. Nelson et al[7] concluded that ibuprofen lysine 200 mg has a faster onset of effect than aspirin 500 mg.

Our study also demonstrated differences in traditional measures of peak and overall analgesic effect. Mean peak PID and pain relief scores were significantly greater with ibuprofen lysine than with acetaminophen. The overall analgesic effect as measured by aggregating PID and pain relief scores (SPID and TOPAR, respectively) at 6 hours postdose was significantly greater with ibuprofen lysine than with acetaminophen. The two measures of duration—proportion of patients who remedicated and time to remedication—indicated that patients in the acetaminophen group remedicated significantly sooner than those in the ibuprofen lysine group.

Single doses of ibuprofen lysine, acetaminophen, and placebo appeared to be equally well tolerated. The adverse experience profile for ibuprofen lysine 400 mg observed in this study is consistent with that reported for ibuprofen 400 mg.[8]

The postoperative dental pain model is a standard model for comparing the efficacy profiles of nonprescription analgesics. In this study, ibuprofen lysine and acetaminophen were both effective analgesics in the treatment of patients with moderate-to-severe postsurgical pain, but ibuprofen lysine had a faster onset and greater peak and overall analgesic effect than did acetaminophen. The magnitude of the differences in analgesic onset by several measures, in conjunction with a large and statistically significant difference in mean global scores in favor of ibuprofen lysine 400 mg over acetaminophen 1000 mg, demonstrates that the difference in efficacy between these treatments is clinically meaningful.

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