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ABSTRACT

Background: Although acetaminophen is one of the oldest and most widely used of all analgesic drugs, the incremental benefit of the 1000-mg dose compared with the 650-mg dose has been questioned.

Objective: The aim of this study was to assess the relative efficacy of acetaminophen 1000 mg versus acetaminophen 650 mg over a 6-hour period in patients experiencing at least moderate postsurgical dental pain.

Methods: This single-center, randomized, double-blind, placebo-controlled, single-dose study enrolled patients aged 16 to 50 years who experienced at least moderate pain after surgical removal of impacted third molars. Each patient received either acetaminophen 1000 mg (n = 239), acetaminophen 650 mg (n = 241), or placebo (n = 60) when they had at least moderate pain and a score ≥50 on the 100-mm Visual Analog Scale (VAS) postsurgically. Pain intensity and pain relief were measured over 6 hours (VAS 0–100 mm).

Results: All 540 patients (52% female; age range, 16–30 years; 95% white) were included in the efficacy analysis. For the primary efficacy endpoint (weighted sum of the pain intensity difference from baseline [PID] and pain relief [PAR] scores over 6 hours [SPRID6]), acetaminophen 1000 mg demonstrated a 24% improvement compared with acetaminophen 650 mg (529.4 vs 427.3; $P = 0.001$). In addition, acetaminophen 650 mg was significantly superior compared with placebo ($P < 0.001$). The weighted sum of PID over 6 hours (SPID6), the weighted total pain relief over 6 hours (TOTPAR6), and the percentage of patients with >50% of the maximum possible TOTPAR6 score were significantly greater for patients treated with acetaminophen 1000 mg compared with those receiving acetaminophen 650 mg ($P \leq 0.006$) or placebo ($P < 0.001$) and for patients treated with acetaminophen 650 mg compared with placebo ($P < 0.001$). Time to rescue, rescue rates through 4 and 6 hours, and patient global assessment demonstrated similar findings. Patients treated with acetaminophen 1000 mg or 650 mg had a significantly different distribution in times to confirmed perceptible and meaningful pain relief compared with those receiving placebo ($P < 0.001$). Adverse events were reported by 18.5% of patients, with no clinically important difference between active treatment groups and placebo.

Conclusions: Acetaminophen 1000 mg provided clinically meaningful and statistically significantly greater efficacy in treating postsurgical dental pain compared with acetaminophen 650 mg and placebo. The outcomes of this study are limited to the single-dose design of this study. ClinicalTrials.gov identifier: NCT01115673. (*Clin Ther*. 2012;34:2247–2258)

Key words: acetaminophen, postsurgical dental pain, randomized controlled trial.

INTRODUCTION

At recommended doses, acetaminophen is an effective and well-tolerated analgesic that has been available as a nonprescription medication in the United States for more than 50 years. It is a nonopiate, centrally acting analgesic and antipyretic agent. In the United States, the nonprescription acetaminophen label instructs

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adults and children aged ≥12 years to take single doses of 650 mg every 4 to 6 hours or 1000 mg every 6 hours while symptoms last. Consumers are also currently directed not to take more than a total of 3 grams of acetaminophen in a 24-hour period unless directed by a health care professional. When taken at labeled doses, acetaminophen is widely reported as being well tolerated among over-the-counter (OTC) oral analgesics.[1–3] When taken in overdose, acetaminophen can cause hepatotoxicity.[4] Multiple causes of accidental overdose have been identified and include simultaneous or concomitant use of multiple prescription and OTC medications that contain acetaminophen, and use of greater than the recommended dose of acetaminophen.[5]

Acetaminophen is one of the most widely used OTC analgesics in the United States.[6] At a 2009 US Food and Drug Administration Advisory Committee Meeting[7] that focused on accidental overdose of acetaminophen, the incremental benefit of acetaminophen 1000 mg versus 650 mg was questioned. Although there have been many studies that have separately evaluated the effectiveness of acetaminophen 1000 or 650 mg, only one publication from 1974 has evaluated acetaminophen 1000 mg and acetaminophen 650 mg in the same study.[8] This placebo-controlled study by Hopkinson et al evaluated the 2 doses of acetaminophen over 4 hours in 263 postpartum patients experiencing moderately severe to very severe pain due to episiotomy. The results demonstrated that acetaminophen 1000 mg was significantly superior to acetaminophen 650 mg ($P < 0.01$), and both doses were significantly superior to placebo ($P < 0.01$) for the relief of pain and the reduction of pain intensity, evaluated using 5-point and 6-point categorical scales, respectively. The investigator's global evaluation, assessed with a 5-point categorical scale, also demonstrated that acetaminophen 1000 mg was significantly ($P < 0.01$) superior to acetaminophen 650 mg and placebo.

Since the study by Hopkinson et al[8] was conducted, many advances in the evaluation of the analgesic efficacy of drugs have occurred. One major advance is the wide use of the dental impaction pain model to evaluate the analgesic efficacy of drugs.[9,10] This model is a widely recognized acute pain model that has been in use since the late 1970s.[10] It is a validated and standardized model that can be used to establish relative analgesic efficacy, onset of pain relief, and duration of analgesia.[9,11] This model allows the evaluation of analgesic medications in a well-controlled and quantified environment that minimizes the variability and potential confounding factors that are prominent in other analgesic models such as osteoarthritis and low back pain. In addition, different doses of a specific analgesic can be evaluated and differentiated using this model.[10,12] The dental impaction pain model has been used to evaluate a multitude of prescription and OTC drugs, including NSAIDs, opioids, and combination analgesics.[9] Given the paucity of published data directly comparing acetaminophen 1000 mg with 650 mg and the current clinical relevance of this issue, it is important to generate comparative data using up-to-date methods in a more relevant pain model.

The current study compared the efficacy and tolerability of acetaminophen 1000 mg with acetaminophen 650 mg over a 6-hour period in patients experiencing at least moderate postsurgical dental pain. Cogent OTC management of postsurgical and nonsurgical pain requires analgesia that is both fast-acting and effective but also has a good duration of action and is well tolerated.

PATIENTS AND METHODS

Study Procedures and Design

This was a single-center, randomized, double-blind, single-dose, placebo-controlled study of patients 16 to 50 years old who required surgical removal of impacted third molars but were otherwise healthy. The study complied with International Conference on Harmonisation and Good Clinical Practice guidelines. The study was approved by an institutional review board. All study participants or, where applicable, the parents or legally authorized representative of study participants provided written informed consent. In addition, patients <18 years of age completed the pediatric assent form.

To be eligible for the study, the surgical procedure had to involve the removal of impacted third molars. The mandibular extractions must have been at least 1 full bony impaction or 2 partial bony impactions. Up to 4 third molars could have been removed. Maxillary third molars were removed regardless of impaction level. Within 4 hours of surgery, patients had to experience at least moderate postsurgical pain on a categorical scale of 0 (none), 1 (mild), 2 (moderate), or 3 (severe) and a score ≥50 on the 0- to 100-mm Visual Analog Scale (VAS). The level of postsurgical pain was

commensurate with pain treatable with an OTC analgesic.

Subjects were excluded from the study if they met any of the following conditions: (1) use within the 24 hours preceding surgery of ibuprofen, acetaminophen, any other analgesics, anti-inflammatory products, or any products that could have interfered with the clinical assessments of the study (other than drugs used for anesthesia); (2) gastrointestinal disease that would have interfered with the absorption, distribution, metabolism, and excretion of the study medications; (3) unable to swallow or tolerate the study medication whole; (4) habituation to analgesic drugs (ie, routine use of oral analgesics ≥5 times per week); (5) medical conditions including peptic ulcer disease; clinically important gastrointestinal, renal, or hepatic disease within the past 6 months; clinically significant cardiovascular disease not stable for the past 6 months; uncontrolled hypertension as indicated by systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg; coagulation disorders or hematologic disease; history of seizures; or known, significant, preexisting conditions that would have affected the interpretation of any potential adverse reactions to the study medication; (6) use of warfarin before surgery; (7) acute local infection at the time of surgery that could have confounded the postsurgical evaluation; (8) history of drug allergy to acetaminophen, ibuprofen, or any anesthetic agent (eg, lidocaine with or without epinephrine, benzocaine, and/or nitrous oxide/oxygen) used in the dental procedure; (9) use of monoamine oxidase inhibitors within 14 days before surgery; (10) known alcohol abuse, drug dependency, or history of significant psychiatric illness within the past 12 months; and (11) consumption of methylxanthine-containing products, tobacco or nicotine-containing products, and alcoholic beverages for 12 hours before surgery. Female subjects who were pregnant or breastfeeding were not eligible for enrollment. Additional analgesics or ice packs after the surgical procedure and during the subsequent 6-hour evaluation period were not allowed except as rescue therapy. Surgical anesthesia consisted of a short-acting local anesthetic with or without epinephrine and the optional use of nitrous oxide.

Patients were randomly assigned to receive double-blind study medication (ie, blister cards with a perforated 2-panel label that included a scratch-off section with the treatment assignment) according to a computer-generated randomization schedule prepared by the sponsor in blocks of 9. Neither the patients, investigators, nor personnel directly involved in monitoring the study or reviewing the data knew the treatment assignments until after study completion. Patients received a single dose of either acetaminophen 1000 mg, acetaminophen 650 mg, or placebo in a 4:4:1 allocation ratio and were stratified according to baseline pain rating (moderate or severe). Randomization began with the lowest available randomization number in the stratum (moderate or severe baseline pain) and continued in sequential order within the appropriate stratum according to the randomization schedule. For purposes of blinding, each patient received either two acetaminophen 500-mg caplets and two placebo 325-mg caplets, two acetaminophen 325-mg caplets and two placebo 500-mg caplets, or two placebo 500-mg caplets and two placebo 325-mg caplets based on their randomized treatment. Patients remained on-site for the full 6-hour duration of postdosing assessments even if rescue medication was administered.

On ingestion of the study medication, 2 stopwatches were provided to each patient to record the time of first perceptible pain relief and the time of meaningful pain relief after taking study medications.

Self-reported pain intensity scores were collected at baseline on both the categorical scale and the 100-mm VAS. Pain intensity and pain relief relative to baseline intensity were collected at 15, 30, 45, 60, 75, and 90 minutes and at 2, 3, 4, 5, and 6 hours after dose administration using the 100-mm VAS. At the end of the 6-hour rating (or at the time of rescue medication use, whichever came first), a patient self-reported global assessment of the study medication was collected (0 = poor, 1 = fair, 2 = good, 3 = very good, or 4 = excellent). Patients were encouraged, but not required, to wait at least 90 minutes before taking a rescue analgesic. If rescue therapy was taken before the 6-hour observation, pain intensity scores and global assessment were recorded immediately before such usage and the time the rescue medication use was recorded. Spontaneous adverse events were collected at the site and at the time of a follow-up telephone call conducted between 1 and 3 days after surgery to ask if any adverse events had occurred since the last visit.

Outcome Measures

The primary endpoint was the weighted sum of pain intensity difference from baseline (PID) and pain relief

(PAR) scores over 6 hours (SPRID6). Secondary efficacy measures included the weighted sum of the PID over 6 hours (SPID6); the weighted sum of the PAR scores over 6 hours (TOTPAR6); PID and PAR scores at each assessment time; time to meaningful pain relief; time to confirmed perceptible pain relief; duration of analgesia as estimated by the elapsed time to rescue medication; rescue rates; percentage of patients with >50% of the maximum possible TOTPAR6 score; and patient global assessment.

Adverse Events

An adverse event was defined as any untoward medical occurrence in a patient administered study medication. These events were recorded throughout the course of the study. Normal consequences of dental surgery, such as dry socket, pain, swelling, and bruising at the surgical site, were not recorded as adverse events unless, in the opinion of the investigator, the conditions were aggravated or worsened after administration of the study medication.

Statistical Analysis

A sample size of 240 patients in each acetaminophen group was needed to detect a treatment difference at an α level of 0.05 (2-sided) with 90% power, assuming an effect size of 0.30. With 60 patients in the placebo group, there was ~90% power to detect a treatment difference between each acetaminophen group and placebo, assuming an effect size of 0.50.

The intention-to-treat analysis included patients who were randomized to receive treatment, took study medication, did not vomit within 60 minutes after dosing, and had a baseline pain score and at least 1 postrandomization assessment. The safety analysis included all patients who were randomized to treatment and took study medication. To control the type I error rate, a closed testing procedure on the primary endpoint was followed. First, acetaminophen 1000 mg was tested versus placebo at the $\alpha = 0.025$ one-tail level. If significant, then acetaminophen 1000 mg versus acetaminophen 650 mg and acetaminophen 650 mg versus placebo were each tested at the $\alpha = 0.025$ one-tail level. Two-sided P values were provided for all comparisons.

For patients who took rescue medication, the last reported pain score or baseline pain score, whichever was worse, was carried forward to the remaining time points; PAR scores after rescue were set to zero.

SPRID6, TOTPAR6, SPID6, PID, PAR, PRID, and patient global evaluation were analyzed with an ANOVA model, with treatment and categorical baseline pain rating in the model. Treatments were compared using the pairwise comparisons of the least squares means from this model.

Treatments were compared for both time to confirmed perceptible pain relief and time to meaningful pain relief using the Wilcoxon test (from the SAS LIFETEST procedure [SAS Institute, Cary, North Carolina]). Patients who did not have relief by 6 hours were censored at 6 hours.

Time to rescue medication use was measured as the elapsed time from when study medication was given until the time rescue therapy was given. Patients who did not use rescue medication during the 6-hour study period were censored at 6 hours. Time to rescue medication use was compared using the log-rank test (from the SAS LIFETEST procedure). The proportion of patients using rescue medication over 4 and 6 hours was compared using a general association from the Cochran-Mantel-Haenszel test stratified according to categorical baseline pain rating.

The maximum possible TOTPAR6 score was 600 (scores of 100-mm VAS over 6 hours); therefore, patients with a TOTPAR6 score >300 would have reached >50% of the maximum possible TOTPAR6 score. Treatments were compared on the proportion of patients with >50% of the maximum possible TOTPAR6 score using a general association from the Cochran-Mantel-Haenszel test stratified according to the categorical baseline pain rating (moderate or severe).

RESULTS

Patient Population

Of 540 patients, there were 239 randomized to receive acetaminophen 1000 mg, 241 to receive acetaminophen 650 mg, and 60 to receive placebo. Figure 1 summarizes the status of all randomized patients according to study group. All 540 patients who were randomized were included in the intention-to-treat efficacy analyses and safety analyses.

Table I provides a summary of demographic and baseline characteristics for the study population. Age and sex were comparable among treatments; the mean age of the patients was 18.4 years, 282 (52.2%) were women, and 515 (95.4%) were white. The mean VAS score for baseline pain severity was 77.6, 78.6, and 78.0 mm in the acetaminophen 1000 mg, acetamino-

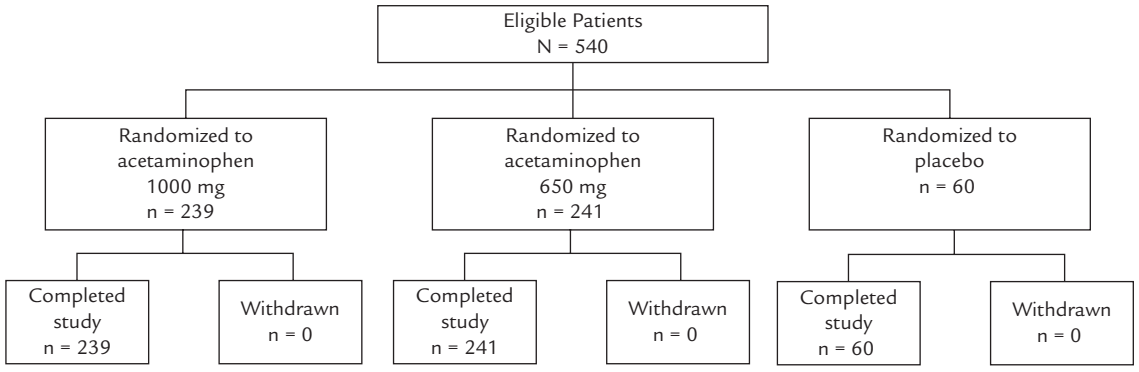

Figure 1. Disposition of patients in this randomized controlled trial.

phen 650 mg, and placebo groups, respectively. There were no clinically important differences among study groups for any of the demographic or baseline characteristics. All patients received a local anesthetic with a vasoconstrictor, and >99% of patients had supplemental nitrous oxide.

Primary Efficacy Endpoint: SPRID6

A 24% improvement in mean SPRID6 was observed for patients treated with acetaminophen 1000 mg (529.4) compared with patients treated with acetaminophen 650 mg (427.3; $P = 0.001$) (Table II). In addition, mean SPRID6 was significantly ($P < 0.001$) greater for patients treated with acetaminophen 1000 or 650 mg compared with patients receiving placebo.

For the PRID scores, the percentage improvement for patients treated with acetaminophen 1000 mg compared with those receiving acetaminophen 650 mg ranged from 13% at 75 minutes to 35% at 6 hours. The results for mean PRID were almost identical for

Table I. Demographic and baseline characteristics of randomized patients.

Characteristic	Acetaminophen 1000 mg (n = 239)	Acetaminophen 650 mg (n = 241)	Placebo (n = 60)
Female sex, n (%)	131 (54.8)	120 (49.8)	31 (51.7)
Age, mean (SD), y	18.5 (2.24)	18.3 (1.96)	18.1 (2.02)
Race, n (%)			
White	227 (95.0)	232 (96.3)	56 (93.3)
Black or African-American	2 (<1.0)	0 (0.0)	0 (0.0)
Asian	2 (<1.0)	3 (1.2)	1 (1.7)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (<1.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	1 (<1.0)	0 (0.0)
Other	8 (3.3)	4 (1.7)	3 (5.0)
Baseline pain severity			
Categorical scale, n (%)			
Moderate	124 (51.9)	124 (51.5)	31 (51.7)
Severe	115 (48.1)	117 (48.5)	29 (48.3)
Visual Analog Scale, mm			
Mean (SD)	77.6 (11.74)	78.6 (12.16)	78.0 (12.95)

Table II. Summary of primary and secondary efficacy endpoints.

End Point	APAP 1000 mg (n = 239)	APAP 650 mg (n = 241)	Placebo (n = 60)	*P* APAP 1000 or 650 mg vs Placebo	*P* APAP 1000 vs 650 mg
Primary efficacy endpoint					
SPRID6, least squares mean (SE)*	529.4 (22.31)	427.3 (22.21)	60.0 (44.51)	<0.001	0.001
Secondary efficacy endpoints					
SPID6, least squares mean (SE)*	222.5 (10.49)	174.3 (10.44)	−4.2 (20.93)	<0.001	0.001
TOTPAR6, least squares mean (SE)*	306.9 (12.02)	253.0 (11.96)	64.3 (23.98)	<0.001	0.002
Percentage of patients with >50% of maximum possible TOTPAR6 score†	56.9	44.4	6.7	<0.001	0.006
Median time to rescue, min‡	>360	>360	99.5	<0.001	<0.001
Rescue rate through 4 h, %†	20.1	32.4	80.0	<0.001	0.002
Rescue rate through 6 h, %†	29.3	45.6	80.0	<0.001	<0.001
Median time to confirmed perceptible pain relief, min‡	22.2	22.2	>360	<0.001	0.934
Median time to meaningful pain relief, min‡	53.7	56.1	>360	<0.001	0.260
Patient global assessment, least squares mean (SE)*	2.28 (0.073)	1.95 (0.073)	0.60 (0.146)	<0.001	0.001

APAP = acetaminophen; SPRID6 = weighted sum of the pain intensity difference from baseline and pain relief scores over 6 hours; SPID6 = weighted sum of the pain intensity difference from baseline over 6 hours; TOTPAR6 = weighted sum of the pain relief scores over 6 hours.

**P* values were based on pairwise comparison of the least squares means from an ANOVA model with treatment and baseline categorical pain rating as factors.

†*P* values were based on the Cochran-Mantel-Haenszel test of general association stratified by categorical baseline pain (moderate or severe).

‡*P* values were based on the log-rank test (time to rescue) or Wilcoxon test (time to confirmed perceptible or meaningful pain relief) from PROC LIFETEST comparing survival curves.

acetaminophen 1000 mg and acetaminophen 650 mg for the first 45 minutes, at which time the treatments began to separate (**Figure 2A**). Acetaminophen 1000 mg was statistically superior ($P \leq 0.043$) to acetaminophen 650 mg from 75 minutes through 6 hours.

Figure 2B presents SPRID6 values for all patients and for patients stratified according to baseline pain rating. Acetaminophen 1000 mg and 650 mg were effective at both levels of baseline pain, with 20% and 28% improvement of acetaminophen 1000 mg over acetaminophen 650 mg for moderate and severe baseline pain, respectively.

Secondary Efficacy Endpoints

Statistically significant ($P \leq 0.006$) differences in favor of acetaminophen 1000 mg compared with acetaminophen 650 mg were observed for 7 of the 9 secondary endpoints (SPID6, TOTPAR6, percentage

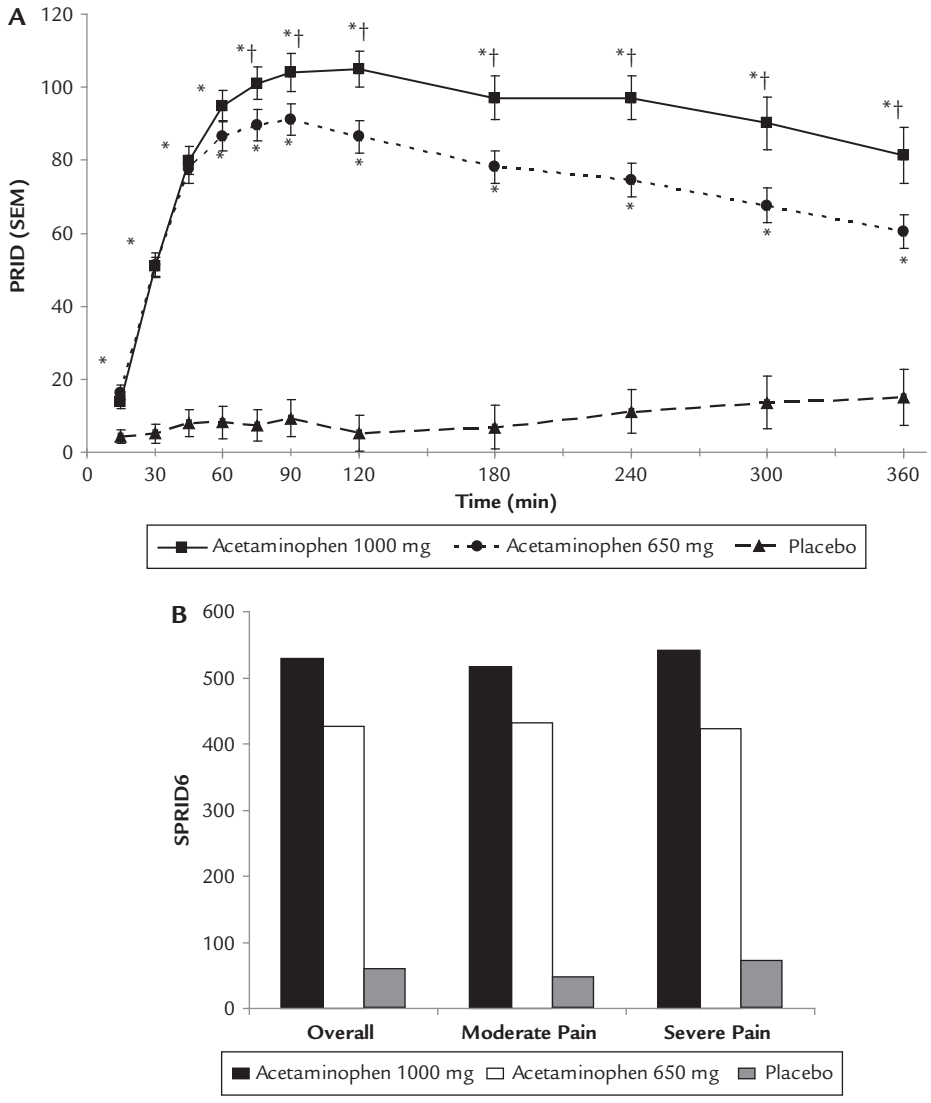

Figure 2. (A) Mean pain relief plus pain intensity difference (PRID [SEM]) at each time point. *$P < 0.05$ vs placebo; †$P < 0.05$ vs acetaminophen 650 mg. *P* values are based on pairwise comparison of the least squares means from an ANOVA model with treatment and baseline categorical pain rating as factors. (B) Mean pain relief plus pain intensity difference from baseline scores over 6 hours (SPRID6) overall and according to baseline pain.

of patients with >50% of the maximum possible TOTPAR6 score, distribution of time to rescue, rescue rates through 4 and 6 hours, and patient global assessment) (Table II). Statistically significant ($P < 0.001$) differences in favor of acetaminophen 1000 mg and acetaminophen 650 mg compared with placebo were observed for all 9 secondary endpoints.

A 28% improvement in mean SPID6 was observed for patients treated with acetaminophen 1000 mg (222.5) compared with patients treated with acetaminophen 650 mg (174.3; $P = 0.001$). In addition, mean SPID6 was significantly ($P < 0.001$) greater for patients treated with acetaminophen 1000 mg or 650 mg compared with patients receiving placebo. The percent improvement in PID for patients treated with acetaminophen 1000 mg compared with acetaminophen 650 mg ranged from 15% at 75 minutes to 40% at 6 hours. Acetaminophen 1000 mg was statistically supe-

rior ($P \leq 0.041$) to acetaminophen 650 mg from 75 minutes through 6 hours (see **Supplemental Figure 1** in the online version at http://dx.doi.org/10.1016/j.clinthera.2012.11.003).

Likewise, a 21% improvement in mean TOTPAR6 was observed with acetaminophen 1000 mg (306.9) compared with acetaminophen 650 mg (253.0; $P = 0.002$). In addition, mean TOTPAR6 was significantly ($P < 0.001$) greater with acetaminophen 1000 or 650 mg compared with placebo. The percent improvement in PAR for patients treated with acetaminophen 1000 mg compared with those receiving acetaminophen 650 mg ranged from 12% at 75 minutes to 31% at 6 hours. Acetaminophen 1000 mg was statistically superior ($P \leq 0.050$) to acetaminophen 650 mg from 75 minutes through 6 hours. Significantly ($P \leq 0.050$) greater PID, PAR, and PRID scores were observed with acetaminophen 1000 mg and 650 mg compared with placebo beginning at 15 minutes and continuing through 6 hours (see **Supplemental Figure 2** in the online version at http://dx.doi.org/10.1016/j.clinthera.2012.11.003).

The prespecified responder definition was patients who obtained >50% of the maximum possible TOTPAR6 score (ie, >300 of a maximum possible score of 600). A significantly greater percentage of patients treated with acetaminophen 1000 mg (56.9%) were responders compared with patients receiving acetaminophen 650 mg (44.4%; $P = 0.006$) or placebo (6.7%; $P < 0.001$). **Figure 3** presents the distribution of the percentage of patients for varying definitions of a "responder" based on the percentage of maximum possible TOTPAR6. Compared with acetaminophen 650 mg, more patients treated with acetaminophen 1000 mg were responders over a wide range of responder definitions based on TOTPAR6.

The percentage of patients using rescue medication was 20.1%, 32.4%, and 80.0% through 4 hours and 29.3%, 45.6%, and 80.0% through 6 hours for patients receiving acetaminophen 1000 mg, acetaminophen 650 mg, and placebo, respectively. Significant differences in favor of acetaminophen 1000 mg were observed compared with acetaminophen 650 mg ($P \leq 0.002$) or placebo ($P < 0.001$). **Figure 4** presents the cumulative percentage of patients using rescue medication within each group.

No significant difference was observed between acetaminophen 1000 mg and acetaminophen 650 mg in the distribution of time to confirmed perceptible pain relief (median was 22.2 minutes with both doses) or the time to meaningful pain relief (median was 53.7 minutes with acetaminophen 1000 mg and 56.1 minutes with acetaminophen 650 mg) (**Table II**). By 75 minutes, 90% of acetaminophen 1000 mg–treated patients had obtained confirmed perceptible pain relief compared with 82% of acetaminophen 650 mg–treated patients and 37% of patients receiving placebo (see **Supplemental Figure 3** in the online version at http://dx.doi.org/10.1016/j.clinthera.2012.11.003). By 180 minutes, 77% of acetaminophen 1000 mg–treated patients had obtained meaningful pain relief compared with 67% of acetaminophen 650 mg–treated patients and 20% of placebo-treated patients (see **Supplemental Figure 4** in the online version at http://dx.doi.org/10.1016/j.clinthera.2012.11.003).

The mean for patient global evaluation was significantly greater for acetaminophen 1000 mg (2.28) compared with acetaminophen 650 mg (1.95; $P = 0.001$) or placebo (0.60; $P < 0.001$). The percentage of patients who rated their overall impression of study medication as "very good" or "excellent" was 49%, 34%, and 3% for patients receiving acetaminophen 1000 mg, acetaminophen 650 mg, and placebo, respectively (**Figure 5**).

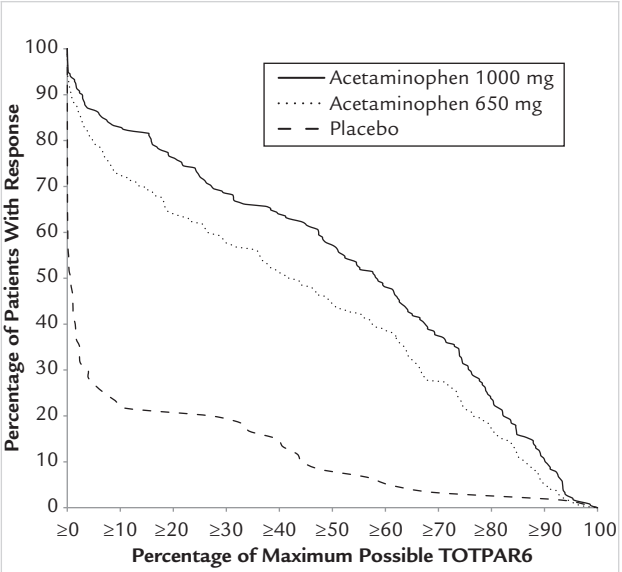

Figure 3. Distribution of responder rates based on percentage of maximum possible weighted sum of the pain relief scores over 6 hours (TOTPAR6).

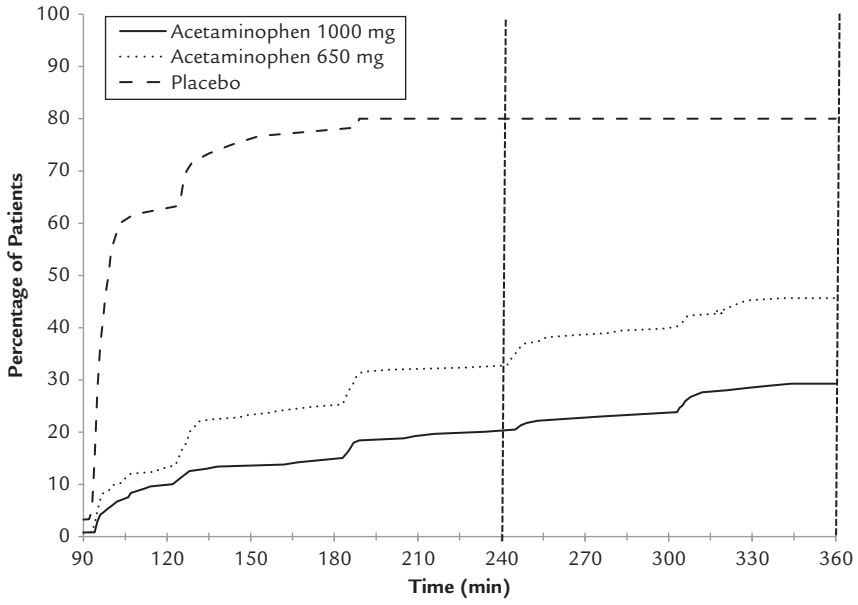

Figure 4. Kaplan-Meier estimates of the cumulative percentage of patients using rescue medication. Dashed vertical lines represent the percentage of patients who used rescue medication through 4 and 6 hours.

Calculation of the effect size for acetaminophen 1000 mg versus acetaminophen 650 mg in the current study yielded effect sizes of 0.30, 0.29, and 0.30 for SPRID6, TOTPAR6, and SPID6, respectively. Effect sizes for acetaminophen 1000 mg versus placebo were 1.36, 1.31, and 1.40 for SPRID6, TOTPAR6, and SPID6, respectively, whereas the effect sizes for these same 3 measures were 1.06, 1.02, and 1.10 for acetaminophen 650 mg versus placebo.

Safety Profile

Adverse events were reported by 18.8%, 17.4%, and 21.7% of patients receiving acetaminophen 1000 mg, acetaminophen 650 mg, and placebo, respectively (see the **Supplemental Table** in the online version at http://dx.doi.org/10.1016/j.clinthera.2012.11.003). There were no clinically important differences among treatment groups. No serious adverse events were reported, and no patients discontinued the study due to an adverse event (**Table III**). Adverse events that were reported by ≥5% of patients in 1 or more study groups included nausea, vomiting, and dizziness.

DISCUSSION

Given the widespread use of acetaminophen as an OTC analgesic and the paucity of any efficacy data comparing the 1000-mg and 650-mg doses in a representative model for an OTC pain condition, the current study has great clinical relevance.

This large, randomized, double-blind, placebo-controlled study in patients with postsurgical dental pain demonstrated that acetaminophen 1000 mg provides clinically meaningful and statistically significantly greater efficacy compared with acetaminophen 650 mg. In addition, both acetaminophen 1000 mg and 650 mg were significantly superior to placebo. Acetaminophen 1000 mg was 24% more effective than acetaminophen 650 mg for the primary efficacy endpoint, SPRID6. Significant differences in favor of acetaminophen 1000 mg compared with acetaminophen 650 mg were also observed for 7 of the 9 secondary endpoints.

Significant differences in favor of acetaminophen 1000 mg and acetaminophen 650 mg compared with placebo were observed for all 9 secondary endpoints. Significantly greater PID, PAR, and PRID scores were observed with acetaminophen 1000 mg compared with acetaminophen 650 mg beginning at 75 minutes after drug administration and continuing through 6 hours.

When the efficacy endpoints were categorized according to analgesic onset, total effect, and duration, clinical improvements were observed with acetamino-

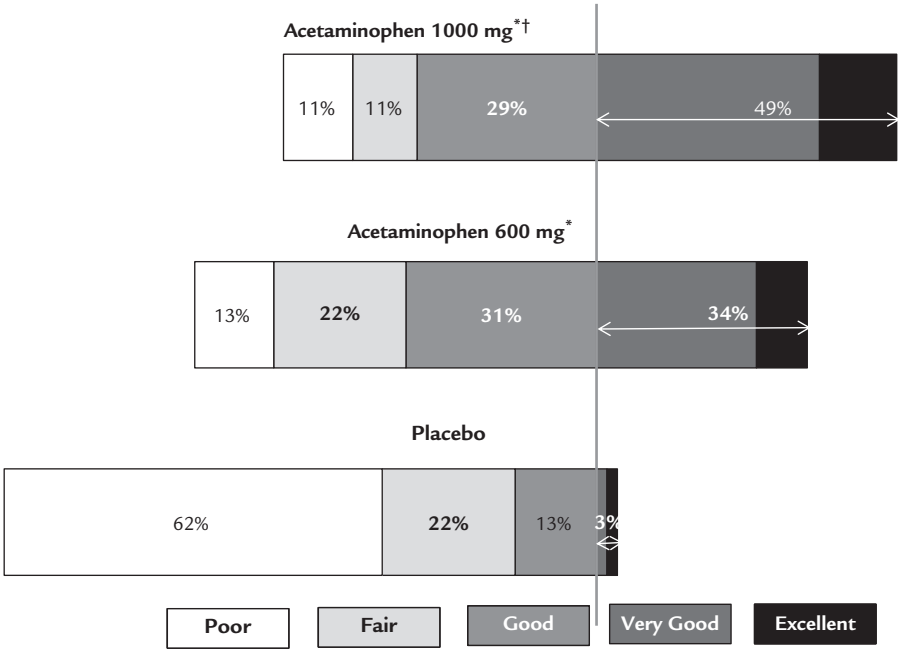

Figure 5. Percentage of patients with a global assessment of poor, fair, good, very good, or excellent. *$P < 0.001$ vs placebo; †$P = 0.001$ vs acetaminophen 650 mg. *P* values are based on pairwise comparison of least squares mean from ANOVA model with treatment and baseline categorical pain ratings as factors.

phen 1000 mg compared with acetaminophen 650 mg for endpoints that assessed analgesic total effect and duration. Endpoints that assessed onset, such as time to confirmed perceptible pain relief and time to meaningful pain relief, were similar for the acetaminophen 650-mg and 1000-mg doses. This finding was consistent with the results observed for the early PRID time points in which both acetaminophen doses were similar through 60 minutes. Endpoints that assessed total effect of analgesia (SPRID6, SPID6, and TOT-

Table III. Summary of adverse events. Values are given as number (%).

Evaluation	Acetaminophen 1000 mg (n = 239)	Acetaminophen 650 mg (n = 241)	Placebo (n = 60)
Any adverse event	45 (18.8)	42 (17.4)	13 (21.7)
Treatment-related* adverse event	2 (0.8)	3 (1.2)	0 (0.0)
Serious adverse event	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawals from treatment due to adverse events	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events reported in ≥5% of patients in ≥1 treatment group			
Nausea	29 (12.1)	26 (10.8)	9 (15.0)
Vomiting	11 (4.6)	11 (4.6)	4 (6.7)
Dizziness	10 (4.2)	8 (3.3)	4 (6.7)

*Events with a relation to study medication marked as possible, probable, or very likely related.

PAR6) showed increased response in scores of 21% to 28% for the 1000-mg dose compared with the 650-mg dose. When assessing duration using the rate of rescue medication use, 16% more patients treated with the 1000-mg dose completed the entire 6-hour study period without using rescue medication compared with the 650-mg dose.

Given that this was a single-dose study, the safety profile was not a primary focus. As expected, there were no clinically important differences in the reports of adverse events among the treatment groups. No serious adverse events were reported. The most frequently reported events were nausea, vomiting, and dizziness, which are common sequelae after surgery and use of anesthetics and anesthesia.

It has been reported that efficacy results from studies using the postsurgical dental impaction pain model can be generalized to other pain states. Urquhart[11] reported that the dental pain impaction model provided valuable information on the treatment of acute pain in general, because the pathophysiology of the dental pain model has shared elements with other pain states, including acute trauma and postsurgical pain. In addition, Norholt[10] reported that the dental pain impaction model was a valid predictor of efficacy for treating other conditions of acute pain. In a review by Cooper and Desjardins,[9] results of pain relief for the same products across multiple pain states (dental vs general postsurgical pain, dental vs obstetrics-gynecological surgical pain, and dental vs bunionectomy pain) yielded similar results for analgesics across these models. Similarly, Barden et al[13] conducted a meta-analysis of studies that evaluated pain and analgesic response after third molar extraction and other postsurgical pain and concluded that it was appropriate to extrapolate analgesic efficacy from one pain state to another.

One limitation of the current study is that the results are focused on the evaluation of a single dose of medication for treating an acute episode of postsurgical dental pain. Although a single-dose study is useful for establishing relative analgesic efficacy, onset of pain relief, and duration of analgesia,[9,11] this design was not intended to demonstrate the tolerability of multiple doses of acetaminophen. The tolerability of multiple doses of acetaminophen has been evaluated in other studies.[14–16]

The problems associated with acetaminophen overdose are a serious public health concern, especially because symptoms of liver injury may not be recognized by patients until significant injury has occurred. Although reducing the maximum single dose of acetaminophen 1000 mg is an option, the results of this study in patients with postsurgical dental pain suggest that there would be an associated reduction in analgesic efficacy. For those individuals who have contraindications, cannot tolerate the use of NSAIDs, or do not respond to NSAIDs, acetaminophen is often the OTC drug of choice. When used chronically at recommended doses, acetaminophen is well tolerated with no evidence of liver injury. Alternative options, such as educating consumers on the dangers of overdose, could aid in reducing or preventing accidental overdose.

CONCLUSIONS

In addition to being well tolerated, the optimal OTC analgesic should have a fast onset, sustained duration of action, and good overall efficacy over the indicated dosing period. In this study of patients with postsurgical dental pain, both acetaminophen 1000 mg and 650 mg provided a significantly more rapid and efficacious analgesia compared with placebo from the 15-minute observation through the final 6-hour observation. Importantly, the 1000-mg dose provided a significantly greater analgesic response than the 650-mg dose from 75 minutes through 6 hours.

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All authors contributed to the preparation and interpretation of the data and the writing, review, and approval of the manuscript.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

SUPPLEMENTAL MATERIAL

A supplemental appendix accompanying this article can be found in the online version at doi: http://dx.doi.org/10.1016/j.clinthera.2012.11.003.

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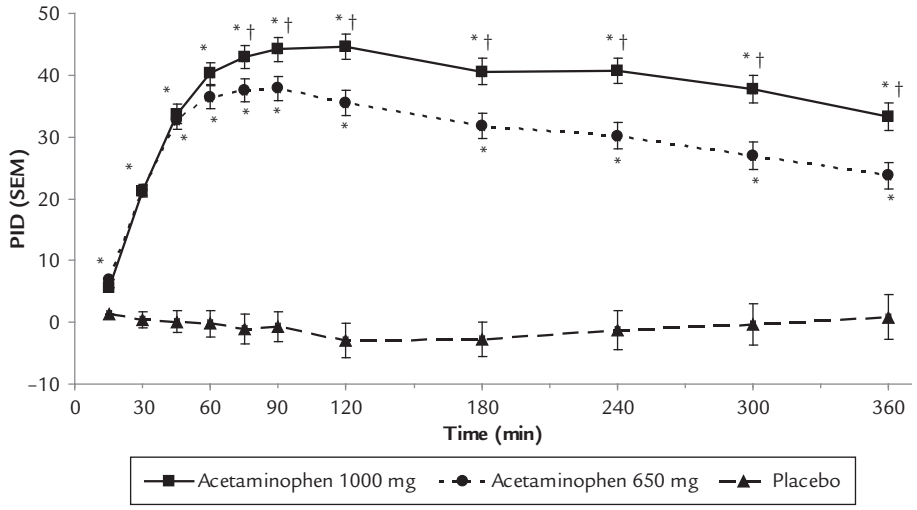
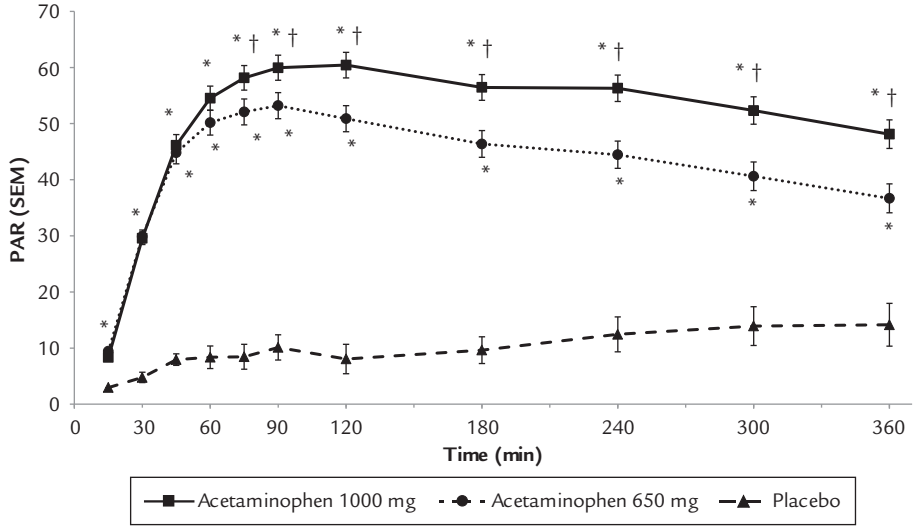
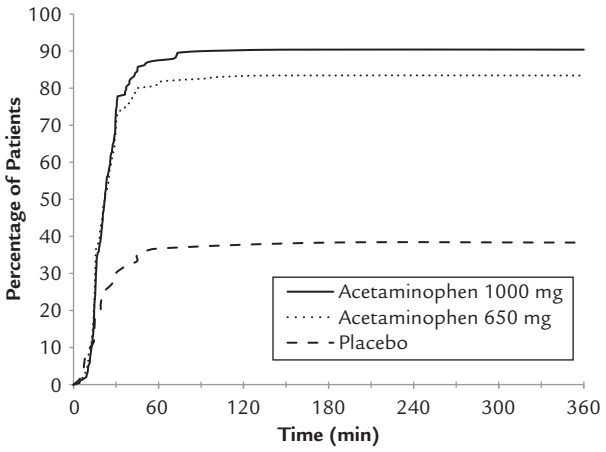


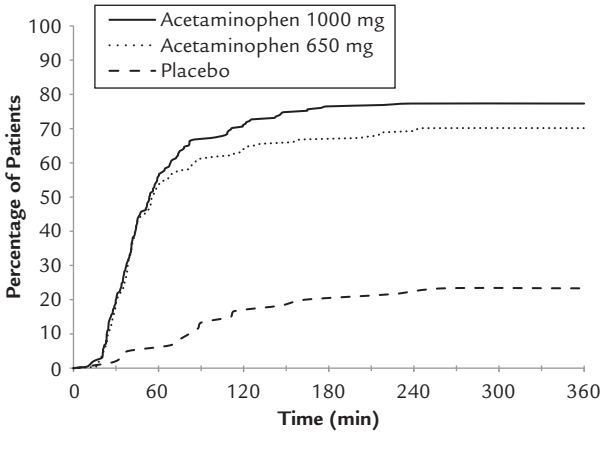
Supplemental Figure 1. Mean pain intensity difference from baseline (PID [SEM]) at each time point. *$P < 0.05$ vs placebo; †$P < 0.05$ vs acetaminophen 650 mg. *P* values are based on pairwise comparison of the least squares means from an ANOVA model with treatment and baseline categorical pain rating as factors.



Supplemental Figure 2. Mean pain relief (PAR [SEM]) at each time point. *$P < 0.05$ vs placebo; †$P \leq 0.05$ vs acetaminophen 650 mg. *P* values are based on pairwise comparison of the least squares means from an ANOVA model with treatment and baseline categorical pain rating as factors.



Supplemental Figure 3. Kaplan-Meier estimates of the time to confirmed perceptible pain relief showing the cumulative percentage of patients with confirmed perceptible pain relief.



Supplemental Figure 4. Kaplan-Meier estimates of the time to meaningful pain relief showing the cumulative percentage of patients with meaningful pain relief.

Supplemental Table. Summary of all adverse events.

Evaluation	Acetaminophen 1000 mg (n = 239)	Acetaminophen 650 mg (n = 241)	Placebo (n = 60)
Any adverse event, n (%)	45 (18.8)	42 (17.4)	13 (21.7)
Nausea	29 (12.1)	26 (10.8)	9 (15.0)
Vomiting	11 (4.6)	11 (4.6)	4 (6.7)
Abdominal discomfort	1 (<1.0)	–	–
Hypoesthesia oral	1 (<1.0)	–	–
Dizziness	10 (4.2)	8 (3.3)	4 (6.7)
Headache	6 (2.5)	8 (3.3)	2 (3.3)
Syncope	1 (<1.0)	1 (<1.0)	–
Tremor	1 (<1.0)	1 (<1.0)	–
Loss of consciousness	1 (<1.0)	–	–
Presyncope	1 (<1.0)	–	–
Feeling hot	3 (1.3)	5 (2.1)	–
Feeling cold	1 (<1.0)	1 (<1.0)	–
Chills	–	1 (<1.0)	–
Hyperhidrosis	1 (<1.0)	3 (1.2)	2 (3.3)
Dyspnea	1 (<1.0)	–	–
Epistaxis	1 (<1.0)	–	–
Tachypnea	–	1 (<1.0)	–
Pallor	–	2 (<1.0)	–
Ear pain	1 (<1.0)	–	–
Vision blurred	–	1 (<1.0)	–
Drug hypersensitivity	1 (<1.0)	–	–
Operative hemorrhage	–	1 (<1.0)	–
Myalgia	–	1 (<1.0)	–
Emotional disorder	1 (<1.0)	–	–