A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Repeat-Dose Study of Two Intravenous Acetaminophen Dosing Regimens for the Treatment of Pain After Abdominal Laparoscopic Surgery

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ABSTRACT

Background: Intravenous acetaminophen has been approved in Europe and elsewhere for the treatment of acute pain and fever, and was recently approved by the US Food and Drug Administration (FDA) for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics, and the reduction of fever.

Objective: The aim of this work was to evaluate the analgesic efficacy and safety of repeated doses of 2 dosing regimens of intravenous acetaminophen compared with placebo over 24 hours in subjects with moderate to severe pain after abdominal laparoscopic surgery.

Methods: This double-blind, placebo-controlled, parallel-group study was conducted at 17 sites in the United States and enrolled adult subjects (aged 18–80 years) who were randomized to 4 groups (IV acetaminophen 1000 mg [100 mL] q6h; IV acetaminophen 650 mg [65 mL] q4h; IV placebo 100 mL q6h; or IV placebo 65 mL q4h), each given as a 15-minute infusion after surgery for 24 hours. An open-label extension was offered to all subjects who remained in the hospital beyond the study period. Two subjects (1 in the placebo 100 mL q6h group and 1 in the IV acetaminophen 1000 mg q6h group) were enrolled in the open-label extension and were eligible to receive unblinded IV acetaminophen 1000 mg. Before randomization, the choice of opioid for patient-controlled analgesia (PCA) rescue was left to the investigator; however, acetaminophen-containing products, NSAIDs, and aspirin were not allowed. The morning after abdominal laparoscopic surgery procedure, subjects' PCA was withheld until pain intensity (PI) was moderate (2) or severe (3) on a categorical scale (range, 0–3) and between 40 and 70 mm, inclusive, on a 100-mm visual analog scale, at which point they were randomized. After the first dose of study medication, intravenous rescue was restricted to morphine or hydromorphone, and oral rescue was restricted to morphine or oxycodone immediate-release tablets. Efficacy analyses were performed using the *modified intent-to-treat* (mITT) population, defined as all randomized subjects who received ≥1 complete dose of study medication before requesting rescue medication, and who had ≥1 completed PI/pain relief (PR) assessment after baseline. The primary efficacy end point was the weighted sum of PI differences over 24 hours (SPID24) using an ANCOVA model. Time to meaningful PR was documented after the first dose of study medication using a double-stopwatch method: at T0, 2 stopwatches were started, and subjects were instructed to stop the first stopwatch when they felt perceptible PR and the second when it became meaningful. Safety was assessed

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via spontaneous adverse event (AE) reporting and laboratory tests.

Results: A total of 349 subjects were screened before elective surgery for eligibility. Of these, 244 subjects were randomized to a study arm (IV acetaminophen 1000 mg [n = 92]; IV acetaminophen 650 mg [n = 42]; IV placebo 100 mL [n = 43]; or IV placebo 65 mL [n = 67]) and included in the ITT population, of whom 81.1% (198/244) were women and 87.3% (213/244) were white; the mean (SD) age was 46.2 (12.51) years (range, 18–78 years), and the mean weight was 174.3 (35.7) lb (range, 103–284 lb). There was an allocation error in the contract research organization's program linking group assignment and kit randomization; therefore, the original randomization procedure was replaced with a modified randomization schedule created by an independent biostatistician under the supervision of the FDA. The mITT population included 241 subjects; of these, 227 completed 24 hours of treatment. Four subjects withdrew before completing treatment because of AEs (1 subject in the placebo group because of fever and 3 in the IV acetaminophen 1000 mg q6h group because of infusion-site pain [n = 1] or infiltration [n = 2]), 8 because of withdrawal of consent, 2 because of early discharge from the hospital, and 2 for other reasons. Only 2 subjects participated in the elective open-label extension. Both intravenous acetaminophen dosing regimens were associated with significantly reduced SPID24 compared with placebo (1000 mg q6h, $P < 0.007$; 650 mg q4h, $P < 0.019$). Among the mITT population, SPID24 (using nonimputed data after first rescue: 1000 mg q6h, $P < 0.001$; 650 mg q4h, $P = 0.020$), sum of PR scores over 24 hours (1000 mg q6h, $P < 0.001$; 650 mg q4h, $P = 0.003$) and 12 hours (1000 mg q6h, $P < 0.001$; 650 mg q4h, $P = 0.001$), and subjects' global evaluations at 24 hours (1000 mg q6h, $P < 0.001$; 650 mg q4h, $P = 0.005$) were statistically significant in favor of both acetaminophen dosing regimens compared with the combined placebo group. Time to meaningful PR (by double stopwatch method) after the first dose was significantly shorter among subjects who received IV acetaminophen 1000 mg compared with subjects in the placebo 100 mL group (median of 24.9 vs 53.9 minutes, respectively). The most common overall AEs (ie, those that occurred in >10% of any group) were constipation, flatulence, nausea, and headache. The frequency of treatment-emergent AEs (TEAEs) across the treatment groups was not statistically significant. Most TEAEs were deemed to be unrelated to study medication. There were 6 subjects with serious TEAEs (1 [0.9%] in the IV acetaminophen 1000 mg group, 3 [7.0%] in the IV acetaminophen 650 mg group, and 2 [1.8%] in the placebo group). There was 1 (2.3%) related hepatic TEAE (transaminase increased) in the placebo group.

Conclusion: Both regimens of intravenous acetaminophen (1000 mg q6h and 650 mg q4h) were associated with statistically significant analgesic efficacy compared with placebo and were well tolerated in these adults after abdominal laparoscopic surgery. ClinicalTrials.gov identifier: NCT00564486. (*Clin Ther.* 2010;32:2348–2369) © 2010 Elsevier HS Journals, Inc.

Key words: abdominal surgery, analgesia, intravenous acetaminophen, laparoscopic surgery, pain.

INTRODUCTION

Pain relief (PR) in the postoperative setting is of particular importance to patients undergoing surgery. Although highly effective in the treatment of acute pain, opioid use is associated with dose-dependent risks including nausea, vomiting, constipation, urinary retention, sedation, and respiratory depression.[1] Evidence suggests that a multimodal approach to postoperative analgesia, including analgesics with different mechanisms of action and regional anesthesia techniques, can reduce opioid consumption, minimize adverse events (AEs), improve PR and patient satisfaction, facilitate earlier recovery, and reduce costs of hospitalization.[2,3]

In the United States, there are a number of nonopioid oral analgesics that, either alone or in combination with opioids, are approved and frequently used for acute pain treatment.[4] Nonopioid analgesics include acetaminophen, aspirin, NSAIDs, and selective cyclooxygenase-2 inhibitors; commonly used opioids include hydrocodone and oxycodone.[5] When oral administration is not feasible, there are only 2 approved intravenous nonopioid analgesics available for use in the United States for inpatient multimodal pain management: ketorolac and ibuprofen, both of which are NSAIDs.[6,7] Unfortunately, intravenous NSAIDs may cause AEs, such as bleeding and renal toxicity, that may limit their use in the perioperative setting.

Intravenous acetaminophen is approved for the short-term treatment of acute pain and fever in >60 countries outside the United States. In countries where

it has been approved, intravenous acetaminophen is considered a valuable component of a multimodal analgesic approach.[8] In the United States, intravenous acetaminophen was approved by the US Food and Drug Administration (FDA) in November 2010 for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics, and the reduction of fever. Its safety profile is supported by >7 years of clinical postmarketing safety experience outside the United States and >60 years of clinical experience with oral and rectal acetaminophen.

Laparoscopic surgery has become an increasingly common way to perform procedures that were previously done with an open incision. The laparoscopic approach is typically associated with reduced length of stay and less severe pain.[9] Because of these characteristics, it was considered an appropriate surgical model for use in the present study of intravenous acetaminophen, which was designed and accepted as 1 of 2 pivotal trials in the new drug application in support of intravenous acetaminophen for an acute pain indication, and in support of an alternative dosing regimen of 650 mg q4h in addition to the 1000 mg q6h regimen approved throughout Europe. The study evaluated the analgesic efficacy and safety of repeated doses of these 2 dosing regimens compared with placebo over 24 hours in subjects with moderate to severe pain after abdominal laparoscopic surgery.

SUBJECTS AND METHODS

Subject Selection and Study Design

This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 17 sites across the United States with subject enrollment from November 2007 (first subject in) to September 2008 (last subject out). The protocol and the informed-consent form were approved by the central institutional review board (Western Institutional Review Board, Olympia, Washington), site-specific institutional review boards operating in compliance with current local regulations and the International Conference on Harmonisation Good Clinical Practice guidelines,[10] or both. This study was conducted in compliance with International Conference on Harmonisation guidelines, the Declaration of Helsinki,[11] and US regulations.[12]

At screening, before surgery or the performance of any study-related procedure, subjects were required to provide informed consent. After signing written informed-consent forms, eligible patients were scheduled for laparoscopic surgery. Eligible patients were those who were scheduled to undergo an abdominal laparoscopic surgical procedure under general anesthesia with the following exceptions: laparoscopic bariatric procedures (including gastric bypass or gastric banding); laparoscopic exploratory procedures in which no visceral dissection was performed; and laparoscopic procedures with minimal visceral dissection (such as laparoscopic sterilization). Other key inclusion criteria included the following: age 18 to 80 years; body mass index >19 and <40 kg/m^2; a negative pregnancy test within 21 days of surgery for women of childbearing potential; an American Society of Anesthesiologists risk class of I, II, or III; ability to read and understand the study procedures and the use of pain scales; and freedom from other physical, mental, or medical conditions that, in the opinion of the investigator, made study participation inadvisable. Key exclusion criteria applied at screening included: use of opioids or tramadol daily for >7 days immediately before study medication administration (to exclude opioid-tolerant subjects); treatment with chaparral, comfrey, germander, jin bu huan, kava, pennyroyal, skullcap, St. John's wort, or valerian within 14 days or monoamine oxidase inhibitors within 7 days before surgery; having a chronic pain condition or any significant medical disease, laboratory abnormality, or condition that, in the investigator's judgment, could compromise the subject's welfare; having known hypersensitivity to the study medication; having known alcohol or drug abuse or dependence; having impaired liver function; or participation in another clinical study within 30 days before surgery. The **appendix** shows all eligibility criteria.

Postsurgical exclusion criteria included the following: any surgery other than the eligible laparoscopic procedures; intraoperative or postoperative complications that, in the view of the investigator, made study participation inadvisable; administration of NSAIDs, steroids, or monoamine oxidase inhibitors on the day of surgery (except for low-dose aspirin for cardioprophylaxis and limited use of topical or inhaled steroids); administration of any neuraxial opioids; use of a local anesthetic agent by injection or continuous infusion by any route (epidural, regional, or percutaneous); or fever (>38.6°C) requiring treatment with antipyretics.

The morning after the laparoscopic procedure, subjects' patient-controlled analgesia was withheld until their pain intensity (PI) reached the level of moderate

(2) or severe (3) on a categorical scale and between 40 and 70 mm, inclusive, on a 100-mm visual analog scale (VAS), at which point they were randomized to 1 of 4 study arms (see "Outcome Measures" for details about the categoric scale and VAS). Each arm consisted of a 15-minute infusion of 1 of the following: IV acetaminophen 1000 mg (100 mL) administered q6h for 4 doses; IV acetaminophen 650 mg (65 mL) administered q4h for 6 doses; IV placebo 100 mL administered q6h for 4 doses; or IV placebo 65 mL administered q4h for 6 doses. An open-label extension was offered to all subjects who remained in the hospital beyond the study period. Two subjects (1 in the placebo 100 mL q6h group and 1 in the IV acetaminophen 1000 mg q6h group) were enrolled in the open-label extension and were eligible to receive unblinded IV acetaminophen 1000 mg. Both subjects were discharged the following day. During the unblinded phase, no efficacy assessments were done.

Materials

For subjects randomized to receive IV acetaminophen 1000 mg* or matching placebo, the entire contents of a 100-mL bottle of blinded study medication was administered by study site personnel or trained facility staff. For subjects randomized to receive 650 mg IV acetaminophen or matching placebo, 35 mL of fluid was removed aseptically from a 100-mL bottle of blinded study medication by the site pharmacist, and the remaining 65 mL was administered by study site personnel or trained facility staff (typically, a nurse). Active drug and placebo solution, bottles, and labels were identical in appearance. Placebo included all the same excipients as the intravenous acetaminophen solution without the acetaminophen.

During the optional open-label extension phase of the study, study medication was labeled as intravenous acetaminophen, and subjects received the same volume and dosing schedule as they received during the blinded portion of the study.

Outcome Measures

Outcome measures were obtained from subjects and recorded by trained study personnel at each site.

*Trademark: Ofirmev™ (Cadence Pharmaceuticals, Inc., San Diego, California).

Pain Intensity

PI was assessed at T0 (start of first study medication infusion), T1, T2, T3, T4, T5, T6, T7, T8, T9, T10, T11, T12, T14, T16, T18, T20, T22, and T24 hours after administration, and immediately before each administration of rescue medication.

Subjects rated PI at rest using a categorical scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe. Subjects also rated PI at rest using a 100-mm VAS labeled *no pain* at its left terminus and *worst pain imaginable* at its right terminus. Subjects placed a perpendicular mark across the VAS line to represent their current perceived PI at rest. The VAS score was the distance in millimeters from the left terminus to the point where the subject's mark crossed the line. For all PI measures, those based on the VAS were of primary interest and those based on the categoric scale were of secondary interest.

Pain Relief

PR was assessed at the same time points as PI.

Subjects rated PR relative to baseline PI using a categorical scale: 0 = none; 1 = a little; 2 = some; 3 = a lot; 4 = complete.

Time to perceptible and meaningful PR was documented after the first dose of study medication using a double stopwatch method: at T0, 2 stopwatches were started; subjects were instructed to stop the first stopwatch at the time that they felt the PR was perceptible, and the second when the PR became meaningful.

Rescue Medication

The time of administration and amount of the first rescue medication were recorded even if they occurred after the first study medication dosing interval. The time/amount of each rescue medication administration was recorded for each dosing interval. Taking into consideration the time lag between administration of the study medication and resulting analgesic effect, subjects were encouraged to wait ≥60 minutes after study medication to request a study-specified rescue medication; however, subjects experiencing intolerable pain could request and receive rescue medication at any time. Before T0, the choice of rescue was left to the investigator; however, acetaminophen-containing products, NSAIDs, and aspirin were prohibited. After randomization and T0, intravenous rescue was restricted to morphine or hydromorphone, and oral rescue was restricted to mor-

phine or oxycodone immediate-release tablets. Consumption of rescue medication was converted to the morphine-equivalent dose for analysis using a prespecified conversion factor.[13] After T24, the choice of rescue was left to investigator discretion, but no acetaminophen-containing products were allowed for 12 hours after the last dose of study medication.

Subjects' Global Evaluations

Subjects rated their overall satisfaction with study treatment and level of satisfaction with AEs related to study treatment at T24 using a categorical scale: 0 = poor; 1 = fair; 2 = good; 3 = excellent.

Efficacy and Safety End Points

The primary efficacy end point was the sum of PI differences (SPID) based on VAS score from 0 to 24 hours (SPID24) of IV acetaminophen 1000 mg versus combined placebo. Key secondary efficacy end points included the SPID24 comparing IV acetaminophen 650 mg with the combined placebo group; for the comparison of each active group with the combined placebo groups, each of the following was assessed as separate end points: subjects' global evaluation at T24; time to first rescue medication administration; total amount of rescue medication consumption over 24 hours; and the AUC using the trapezoidal rule of the curve of change in total PR scores (TOTPAR) from T1 to T24 (TOTPAR24). Other efficacy end points included mean PR scores and mean PI scores for each dosing interval, sum of PI scores over 24 hours, SPID based on VAS score from 0 to 4 hours (SPID4) and TOTPAR from T1 to T4 (TOTPAR4) for the comparison of IV acetaminophen 650 mg and placebo 65 mL, SPID from 0 to 6 hours (SPID6) and TOTPAR from T1 to T6 (TOTPAR6) for the comparison of IV acetaminophen 1000 mg and placebo 100 mL, and SPID24 comparisons among the intravenous acetaminophen groups and their matched placebo groups.

Safety was assessed via the reporting of treatment-emergent AEs (TEAEs) from first dose through a 7-day follow-up period, laboratory assessments, vital signs (ie, blood pressure while semirecumbent, heart rate), and physical examinations. All tests were performed at the sites' affiliated institutional laboratories following their established methods. At screening, blood and urine samples were obtained for complete blood count, coagulation profile, chemistry tests (including liver function tests [LFTs]), and urinalysis. Female subjects of child-bearing potential also underwent either a urine or blood pregnancy test per investigator discretion. After surgery, but before randomization, and at study completion (or, if applicable, at early termination), the same laboratory tests were repeated. Additionally, LFTs were performed just after T24 and daily for subjects participating in the open-label extension study.

Vital signs were assessed at screening, after surgery but before randomization, immediately before and at the conclusion of each study medication infusion, and at study completion/early termination. Body weight and height were recorded at the screening visit. A physical examination was performed at screening, and interim examinations were conducted after surgery (before randomization) and at study completion/early termination. The investigators were solely responsible for making any determination of the relatedness of a TEAE to the blinded study medication.

Statistical Methodology

All statistical analyses were performed using SAS, version 9.1.3 for Windows (SAS Institute Inc., Cary, North Carolina). Efficacy analyses were performed using the *modified intent-to-treat* (mITT) population, defined as all randomized subjects who received ≥1 complete dose of study medication before requesting rescue medication and who had ≥1 completed PI/PR assessment after T0. The safety analysis was carried out using all randomized subjects who received any portion of a dose of study medication.

The primary efficacy end point, SPID24, was analyzed using an ANCOVA model with treatment group, randomization period, and investigational site as the factors and with baseline pain as the covariate. The primary analysis compared the IV acetaminophen 1000 mg group with the combined placebo group using a 2-sided test, with $P < 0.05$ as the threshold of statistical significance. The secondary efficacy end point of SPID24 was analyzed using an ANCOVA model with treatment group and investigational site as the factors and with baseline pain as the covariate, and compared the IV acetaminophen 650 mg group with the combined placebo group using a 2-sided test, with $P < 0.05$ as the threshold of statistical significance. The other secondary end point analyses compared the IV acetaminophen 1000 mg group with the combined placebo group and the IV acetaminophen 650 mg group with the combined placebo group. Continuous variables such as PI, PR, and amount of rescue medication

consumed were analyzed using ANCOVA models with treatment as the fixed effect and baseline PI VAS score (as a continuous variable) as the covariate. Summary statistics at each time point or interval were conducted, along with calculation of the statistical significance of each term in the model and the least squares mean and SE values for the treatment difference. Time to rescue medication consumption was analyzed using a log-rank test. Median times to rescue medication with corresponding 95% CI values were analyzed.

Kaplan-Meier estimates of the percentages of subjects taking rescue medication were calculated at 12 and 24 hours for each treatment group, along with 95% CI values. Subjects' global evaluations at 24 hours were summarized for each treatment group by frequency and percentage for each categorical response. Cochran-Mantel-Haenszel tests using integer scores were used to assess the treatment differences. To account for the effect of the amount of rescue medication use on PI, a nonparametric integrated rank assessment incorporating a pain measurement with the amount of rescue medication was carried out.[14] Subjects' global evaluations at 24 and 48 hours were analyzed with Cochran-Mantel-Haenszel tests.

A sample size of 240 subjects was estimated to provide 90% power to detect a difference of 159.8 in SPID24 with an estimated SD of 289.3, and $P < 0.05$ as the threshold of statistical significance on a 2-sided t test. Assuming a dropout rate of ≤15% and a randomization ratio of 2:2:1:1, the target enrollment was ~80 subjects in each of the 2 acetaminophen groups and ~40 subjects in each of the 2 placebo groups. To increase statistical power, the placebo groups were combined for the primary and key secondary analyses, with a planned sensitivity analysis performed to verify that it was appropriate to do so. Additional analyses were performed to compare each active group with its matched placebo group. The study was not powered to perform comparisons between the 2 acetaminophen groups.

For the primary end point, SPID24, the last observation carried forward (LOCF) imputation method was used for missing data before the time of first rescue, and worst observation carried forward (WOCF) imputation was applied in place of actual assessments from the time of first rescue to T24. For the secondary end points, the LOCF imputation method was used for missing data before or after first rescue. For subjects discharged early from the hospital, LOCF was applied after the time of discharge to T24. For subjects who terminated study participation early because of an AE or reasons other than early discharge, the baseline observation carried forward imputation method was applied from the time of early termination to T24.

During the conduct of the study, the biostatistics group within the contract research organization (CRO [Premier Research, Philadelphia, Pennsylvania]) identified an allocation error in the program that linked the group assignment and kit randomization assignment for the interactive voice response system that affected the first 109 subjects, causing subjects to randomize only to the IV acetaminophen 1000 mg q6h and placebo 65 mL q4h groups. An unblinded external biostatistician was retained by the study sponsor (Cadence Pharmaceuticals, Inc., San Diego, California) to implement a corrective randomization method to rebalance group assignments as close to the originally intended randomization plan as possible. The FDA was informed of the error, the intended corrective action, and the plan for sensitivity analyses. During the investigation and subsequent corrective actions, the investigative sites, all CRO employees (except those involved in correcting the error), and all sponsor employees (except 1 individual not involved in the study conduct who was involved with FDA communications) remained blinded throughout the study.

Sensitivity analyses were performed to ensure that it was appropriate to pool the subjects in the 2 placebo groups, as well as to pool the subjects in the 2 enrollment periods to rule out the effect of the different randomization periods and the influence of enrollment timing on the primary efficacy results, SPID24. The sensitivity analyses were conducted using a 1-way ANOVA model with contrast.

RESULTS

Subject Disposition, Demographics, and Clinical Characteristics

A total of 349 subjects were screened before their planned elective laparoscopic surgeries. In all, 106 subjects were determined to be ineligible, including 1 subject who was enrolled in error; therefore, although 243 subjects were deemed eligible postoperatively, 244 subjects were randomized (ITT population) (**Figure 1**). All 244 randomized subjects received ≥1 full dose of study medication and were included in the safety population. One subject randomized to receive IV acetaminophen 1000 mg q6h was actually given 650 mg

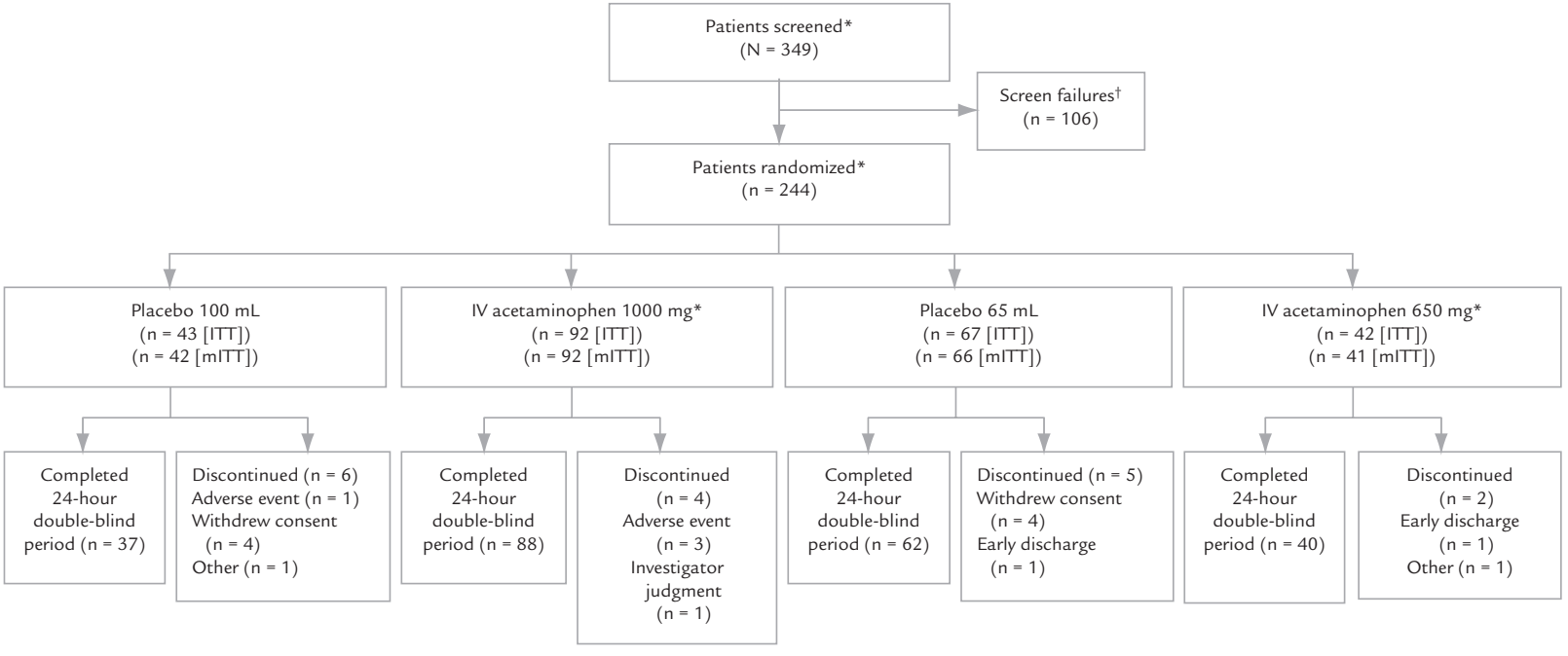

Figure 1. Flow of patients through a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of 2 intravenous acetaminophen dosing regimens for the treatment of pain after abdominal laparoscopic surgery. ITT = intent to treat; mITT = modified ITT (ie, all randomized subjects who received ≥1 complete dose of study medication before requesting rescue medication, including the subject who received IV acetaminophen 650 mg in error). *One subject was randomized to receive IV acetaminophen 1000 mg but was administered IV acetaminophen 650 mg in error. †One subject was randomized and subsequently determined to be ineligible (ie, screening failure). This subject was treated as randomized in the ITT analysis.

q4h in error and received all 6 doses over 24 hours. This subject was categorized as *randomized* (ie, included in the IV acetaminophen 1000 mg mITT population) for purposes of efficacy analyses, but was categorized as *dosed* (ie, included in the IV acetaminophen 650 mg safety population) for AE analyses.

The mITT population included 241 subjects (**Figure 1**), and 227 subjects (93.0% [227/244]) completed the 24-hour double-blind period, including 128 (95.5%) of 134 subjects receiving intravenous acetaminophen and 99 (90.0%) of 110 subjects receiving placebo. Three subjects (1.2%) were excluded from the mITT population (1 each in the IV acetaminophen 650 mg q4h, placebo 100 mL q6h, and placebo 65 mL q4h groups) because they requested rescue before receiving the complete first dose of study medication or because it was not possible to obtain ≥1 PI/PR assessment after T0.

Four subjects (4.3%) in the IV acetaminophen 1000 mg q6h group, 2 (4.7%) in the IV acetaminophen 650 mg q4h group, 6 (14.0%) in the placebo 100 mL q6h group, and 5 (7.5%) in the placebo 65 mL q4h group terminated prematurely from the study. Of the subjects who did not complete the 24-hour study period, 4 did so because of an AE (3 in the IV acetaminophen 1000 mg q6h group: intravenous infiltration [1] or intravenous site pain [2]; and 1 in the placebo 100 mL q6h group: fever), 8 subjects withdrew consent for reasons other than an AE (4 in the placebo 100 mL q6h group and 4 in the placebo 65 mL group), 1 in the IV acetaminophen 1000 mg q6h group was removed because the investigator judged intravenous access to be difficult, 2 were discharged early from the hospital (1 each in the IV acetaminophen 650 mg and placebo 65 mL q4h groups), and 1 because of uncontrollable pain in the IV acetaminophen 650 mg q4h group.

Only 2 subjects (1 from the placebo 100 mL q6h and 1 from the IV acetaminophen 1000 mg q6h groups) continued in the open-label extension and both received IV acetaminophen 1000 mg q6h until discontinuation of intravenous therapy before discharge.

Demographics and baseline characteristics were comparable across groups (**Table I**). Although most participants were categorized as white (87.1% [210/241]), it should be noted that the Hispanic/Latino ethnic group was categorized as white for race, but was listed separately for ethnicity. The distribution of race and ethnicity for subject participants was comparable across the participating sites. There were no clinically relevant differences observed between the placebo and intravenous acetaminophen groups with regard to type of primary abdominal laparoscopic surgery, additional procedures performed, the duration of surgery, or the time from end of surgery to T0 (**Table II**).

Efficacy

IV Acetaminophen 1000 mg

With regard to the primary outcome measure, SPID24 using WOCF imputation after rescue medication, the pain improvement results were statistically significant in favor of the acetaminophen IV 1000 mg q6h group compared with the combined placebo group (−194.1 and −45.2 mm, respectively; $P < 0.007$) (**Figure 2**A). With PI data included after first rescue medication administration (no imputation) to calculate the SPID24 end point, the results were also statistically significant in favor of IV acetaminophen 1000 mg q6h compared with the combined placebo group (−529 and −364 mm, respectively; $P < 0.001$) (**Figure 2**B). TOTPAR24 results were statistically significant in favor of IV acetaminophen 1000 mg compared with the combined placebo group, as were both SPID6 and TOTPAR6 (51.1 vs 41.8, $P < 0.001$; −101.4 vs −54.7 mm, $P < 0.001$; and 10.1 vs 7.9, $P = 0.001$, respectively) (**Figures 3–5**). Time to meaningful PR after the first dose was significantly shorter in subjects who received IV acetaminophen 1000 mg compared with subjects in the placebo 100-mL group, with median values of 24.9 versus 53.9 minutes, respectively ($P < 0.003$) (**Table III**). Subjects' global evaluation of satisfaction with study treatment was observed to be statistically significant in favor of IV acetaminophen 1000 mg over the combined placebo group (excellent, 37 [40.2%] vs 25 [23.1%]; good, 43 [46.7%] vs 51 [47.2%]; fair, 7 [7.6%] vs 21 [19.4%]; poor, 3 [3.3%] vs 11 [10.2%]; all comparisons, $P < 0.001$) (**Figure 6**). Mean scores for PI based on the VAS are shown in **Figure 7**A.

IV Acetaminophen 650 mg

Although single-dose effects at 650 mg were less than those observed for 1000 mg, statistically significant differences in favor of IV acetaminophen 650 mg compared with the combined placebo group were observed in most repeated dose end points. For example, overall SPID24 using WOCF imputation after first rescue and SPID24 using actual PI data after first rescue medication administration were significantly better with IV acetaminophen 650 mg than the combined

Table I. Summary of subject demographics and baseline characteristics in the modified intent-to-treat population (ie, all randomized subjects who received ≥1 complete dose of study medication before requesting rescue medication) in a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of 2 intravenous acetaminophen (APAP) dosing regimens for the treatment of pain after abdominal laparoscopic surgery.*

Characteristic	IV APAP 1000 mg q6h (n = 92)	Placebo 100 mL q6h (n = 42)	IV APAP 650 mg q4h (n = 41)	Placebo 65 mL q4h (n = 66)
Age, y				
Mean (SD)	45.3 (12.26)	46.0 (11.70)	47.3 (13.04)	46.5 (13.08)
Range	19–73	18–72	21–71	21–78
Sex, no. (%)				
Female	74 (80.4)	36 (85.7)	32 (78.0)	53 (80.3)
Male	18 (19.6)	6 (14.3)	9 (22.0)	13 (19.7)
Race, no. (%)				
White	76 (82.6)	36 (85.7)	38 (92.7)	60 (90.9)
Black	15 (16.3)	5 (11.9)	1 (2.4)	3 (4.5)
Asian	1 (1.1)	0	1 (2.4)	2 (3.0)
Other	0	1 (2.4)	1 (2.4)	1 (1.5)
Ethnicity, no. (%)				
Hispanic/Latino	15 (16.3)	9 (21.4)	12 (29.3)	12 (18.2)
Height, in				
Mean (SD)	65.5 (3.73)	65.2 (3.52)	64.9 (3.93)	65.7 (3.54)
Range	59–75	59–72	60–75	59–76
Weight, lb				
Mean (SD)	172.48 (36.95)	176.45 (38.80)	170.48 (35.03)	177.57 (32.33)
Range	103–256	110–284	120–254	115–252
Heart rate, mean (SD), beats per minute	76.1 (12.14)	77.6 (11.99)	73.6 (12.64)	75.0 (13.06)
Blood pressure, mm Hg				
Systolic, mean (SD)	119.3 (16.93)	119.2 (18.85)	114.4 (18.64)	119.7 (17.56)
Diastolic, mean (SD)	69.5 (11.66)	67.8 (11.57)	66.9 (14.29)	69.2 (10.38)
Pain intensity†				
VAS, mean (SD)	51.9 (12.6)	57.5 (12.1)	57.4 (14.9)	49.2 (16.3)
Categoric scale, no. (%)				
Mild	16 (17.4)	4 (9.5)	4 (9.8)	16 (24.2)
Moderate	72 (78.3)	36 (85.7)	33 (80.5)	48 (72.7)
Severe	4 (4.3)	2 (4.8)	4 (9.8)	2 (3.0)

VAS = visual analog scale.

* All parameters except pain intensity (PI) assessments represent values obtained at screening before surgery. PI values represent values obtained after surgery but before start of study medication.

† Subjects rated PI at rest using a 100-mm VAS (ranging from *no pain* to *worst pain imaginable*) by placing a perpendicular mark across the VAS line to represent their current perceived pain; the VAS score was the distance in millimeters from the left terminus to the point where the subject's mark crossed the line. Subjects also rated PI at rest using a categorical scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

Table II. Summary of surgical procedures in the modified intent-to-treat population (ie, all randomized subjects who received ≥1 complete dose of study medication before requesting rescue medication) in a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of 2 intravenous acetaminophen (APAP) dosing regimens for the treatment of pain after abdominal laparoscopic surgery.

Characteristic	IV APAP 1000 mg q6h (n = 92)	Placebo 100 mL q6h (n = 42)	IV APAP 650 mg q4h (n = 41)	Placebo 65 mL q4h (n = 66)
Procedure type, no. (%)				
Cholecystectomy	12 (13.0)	6 (14.3)	8 (19.5)	9 (13.6)
Hysterectomy	44 (47.8)	19 (45.2)	19 (46.3)	29 (43.9)
Unilateral salpingectomy	1 (1.1)	0	0	1 (1.5)
Bilateral salpingectomy	0	0	0	2 (3.0)
Unilateral salpingo-oophorectomy	5 (5.4)	3 (7.1)	4 (9.8)	3 (4.5)
Bilateral salpingo-oophorectomy	15 (16.3)	2 (4.8)	3 (7.3)	11 (16.7)
Hernia repair	6 (6.5)	3 (7.1)	3 (7.3)	9 (13.6)
Colonic resection	5 (5.4)	4 (9.5)	4 (9.8)	2 (3.0)
Rectocele repair	1 (1.1)	0	0	0
Colectomy	2 (2.2)	2 (4.8)	2 (4.9)	2 (3.0)
Sigmoidectomy	1 (1.1)	0	0	0
Colostomy	1 (1.1)	0	1 (2.4)	0
Colon resection	0	2 (4.8)	1 (2.4)	0
Cystoscopy	7 (7.6)	2 (4.8)	0	3 (4.5)
Prostatectomy	9 (9.8)	4 (9.5)	3 (7.3)	4 (6.1)
Robotic	7 (7.6)	3 (7.1)	3 (7.3)	3 (4.5)
Myomectomy	3 (3.3)	1 (2.4)	0	1 (1.5)
Lysis of adhesions	1 (1.1)	0	0	0
Monarc sling	2 (2.2)	0	0	1 (1.5)
Other	23 (25.0)	6 (14.3)	8 (19.5)	13 (19.7)
Perineorrhapy	1 (1.1)	0	0	0
Bladder suspension	0	1 (2.4)	0	0
Adrenalectomy	0	0	0	1 (1.5)
Nephrectomy	0	0	0	2 (3.0)
Pyeloplasty	1 (1.1)	0	0	0
Heller myotomy with fundoplication	0	0	0	1 (1.5)
McCall culdoplasty	1 (1.1)	0	0	0
Transobturator	1 (1.1)	0	0	0
Liver biopsy	0	0	1 (2.4)	0
Portacath removal	0	0	0	1 (1.5)
Vaginal sling	0	1 (2.4)	0	0
Dilation and curettage	5 (5.4)	0	1 (2.4)	0
Cystourethroscopy	0	0	1 (2.4)	1 (1.5)
Fulguration of endometriosis	1 (1.1)	0	0	1 (1.5)
Laparoscopic rectopexy	0	0	1 (2.4)	0
Perforated bladder	1 (1.1)	0	0	0
Endometriosis	2 (2.2)	2 (4.8)	0	2 (3.0)
Cystectomy	3 (3.3)	2 (4.8)	0	1 (1.5)
Duration of surgery, mean (SD), h	2.55 (1.37)	2.52 (1.23)	2.18 (1.01)	2.34 (1.16)
Time from surgery to T0, mean (SD), h*	19.03 (3.17)	19.50 (3.34)	18.97 (3.17)	19.55 (2.76)

* Time from surgery end to the time of first intravenous infusion of study medication.

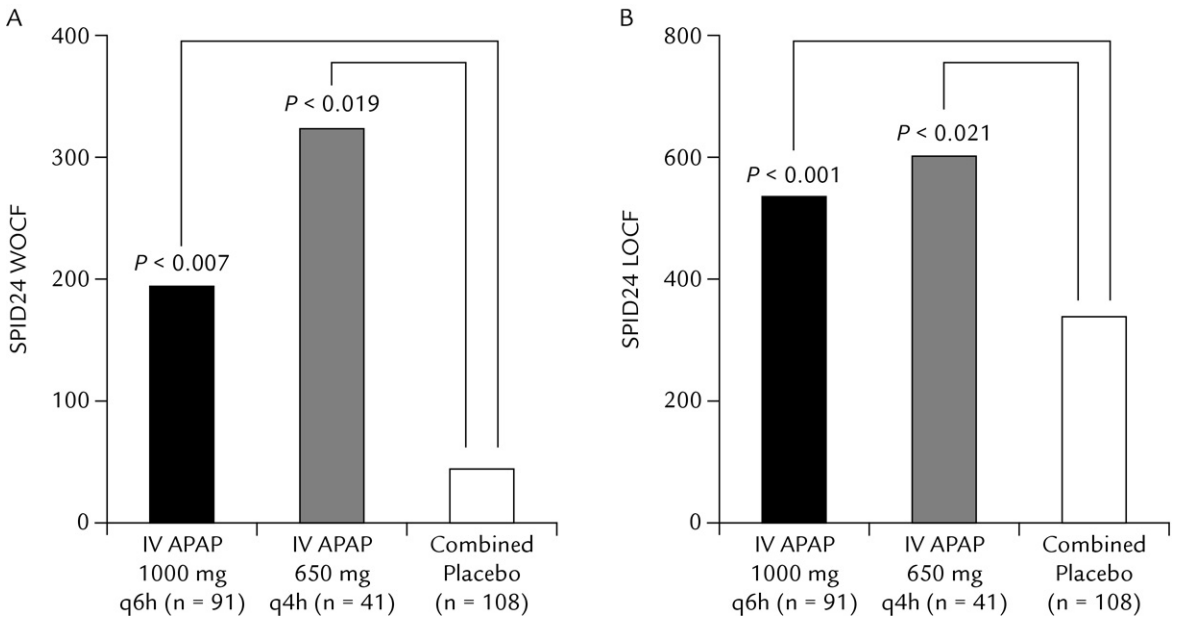

Figure 2. Weighted sum of pain intensity differences over 24 hours (SPID24) in the modified intent-to-treat population (ie, all randomized subjects who received ≥1 complete dose of study medication before requesting rescue medication) in a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of 2 intravenous acetaminophen (APAP) dosing regimens for the treatment of pain after abdominal laparoscopic surgery. SPID24 values represent reductions from baseline. (A) Worst observation carried forward (WOCF) analysis. (B) Last observation carried forward (LOCF) analysis.

placebo group (−597 vs −364 mm, respectively [$P < 0.019$] and −65.4 vs −35.4 mm, respectively [$P < 0.021$]) (Figure 2). TOTPAR24 (51.8 vs 41.8, respectively [$P < 0.003$]) and subjects' global evaluation of satisfaction with study treatment (excellent, 22 [53.7%] vs 25 [23.1%]; good, 12 [29.3%] vs 51 [47.2%]; fair, 3 [7.3%] vs 21 [19.4%]; poor, 2 [4.9%] vs 11 [10.2%]; $P < 0.002$) were also statistically significant in favor of IV acetaminophen 650 mg compared with the combined placebo group (51.8 vs. 41.8, respectively; $P < 0.001$) (Figure 3 and Figure 6).

Observed single-dose effects with IV acetaminophen 650 mg appeared less than those observed with IV acetaminophen 1000 mg; however, the study was not powered for comparisons between the active-treatment groups; therefore, statistical analyses were not performed for active-group comparisons. The median time to meaningful PR was 29.1 minutes with the acetaminophen 650 mg group, compared with 24.9 minutes with the 1000 mg group, but the value was not significantly different from placebo (Table III). SPID4 was statistically significantly in favor of IV acetaminophen 650 mg compared with placebo 65 mL (−65.4 vs −35.4 mm, respectively; $P < 0.001$) (Figure 4). However, TOTPAR4 was not significantly different between the IV acetaminophen 650-mg and matched placebo groups (5.6 and 4.9, respectively) (Figure 5). Mean scores for PI based on the VAS are shown in Figure 7B.

Rescue Medication

The IV acetaminophen 1000 and 650 mg groups had median times to first rescue that were numerically, but not significantly, longer than those observed for the combined placebo group (10.4 and 16.4 hours, respectively, vs 9.3 hours). A numerically (but not significantly) larger percentage of subjects in the matched placebo groups required rescue medication from T0 to T24 compared with the intravenous acetaminophen groups: IV acetaminophen 1000 mg versus placebo 100 mL, 56.5% versus 64.3%; IV acetaminophen 650 mg versus placebo 65 mL, 48.8% versus 54.5%. There were no statistically significant differences observed between the active-treatment groups and the combined

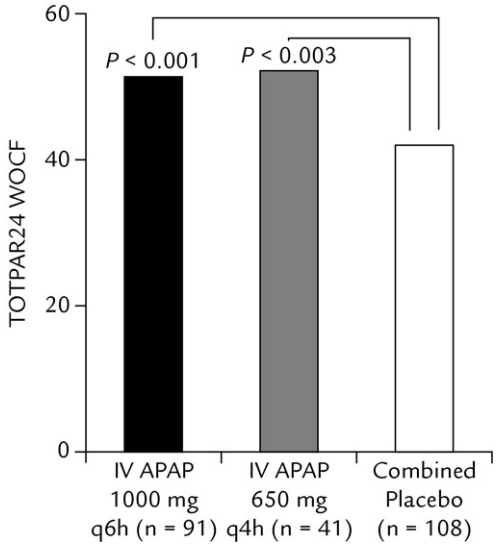

Figure 3. Worst observation carried forward (WOCF) analysis of the AUC using the trapezoidal rule of the curve of the total PR scores from T1 to T24 (TOTPAR24) in the modified intent-to-treat population (ie, all randomized subjects who received ≥1 complete dose of study medication before requesting rescue medication) in a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of 2 intravenous acetaminophen (APAP) dosing regimens for the treatment of pain after abdominal laparoscopic surgery.

placebo group, or between the individual placebo groups for the amount of rescue-medication consumption. The combined placebo group used a mean (SD) of 17.4 (11.3) mg from T0 to T12 and 18.5 (16.9) mg from T12 to T24; the placebo 100 mL q6h group used 16.1 (13.4) and 19.0 (21.9) mg, respectively; the placebo 65 mL q4h group used 18.2 (9.9) and 18.2 (13.5) mg the IV acetaminophen 1000 mg q6h group used 18.3 (14.2) and 19.4 (11.1) mg; and the IV acetaminophen 650 mg q4h group used 18.9 (11.8) and 16.0 (8.2) mg.

Safety Profile

The overall frequency of TEAEs across the treatment groups was not significantly different (**Table IV**). Most TEAEs (eg, constipation, flatulence, nausea, vomiting, fever, incision pain, headache) were those typically observed in the postoperative setting; except for incision-site pain (n = 5 [5.5% vs 0%]) and dyspnea (n = 3 [7.0% vs 0%]), which were observed with significantly greater frequency in the intravenous acetaminophen groups compared with the placebo groups ($P = 0.018$ and $P = 0.021$, respectively), none of other TEAE comparisons between the intravenous acetaminophen groups and the combined placebo group reached statistical significance ($P < 0.05$) based on the Fisher exact test. It should be noted that none of the incision-site pain or dyspnea events were deemed to be related to intravenous acetaminophen.

Of the common TEAEs (ie, those occurring at a frequency of ≥5% in any group), only vomiting, infusion-site pain, injection-site pain, and dyspnea appeared to oc-

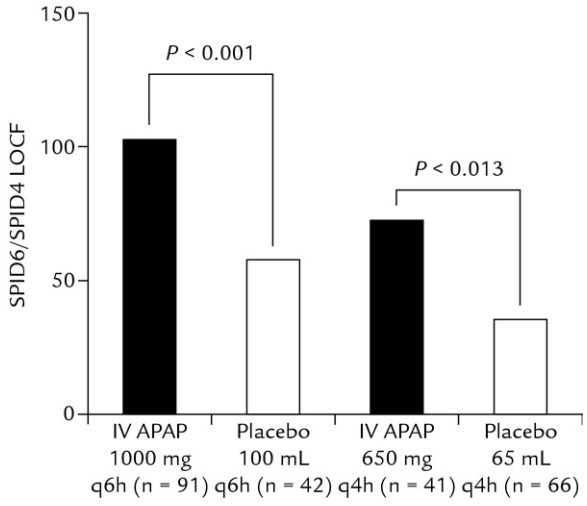

Figure 4. Last observation carried forward (LOCF) analysis of the ratio of sum of pain intensity differences (SPID), based on 100-mm visual analog scale, from time of study drug administration to 6 hours after (SPID6), to SPID from time of administration to 4 hours (SPID4), in the modified intent-to-treat population (ie, all randomized subjects who received ≥1 complete dose of study medication before requesting rescue medication) in a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of 2 intravenous acetaminophen (APAP) dosing regimens for the treatment of pain after abdominal laparoscopic surgery. SPID values represent reductions from baseline.

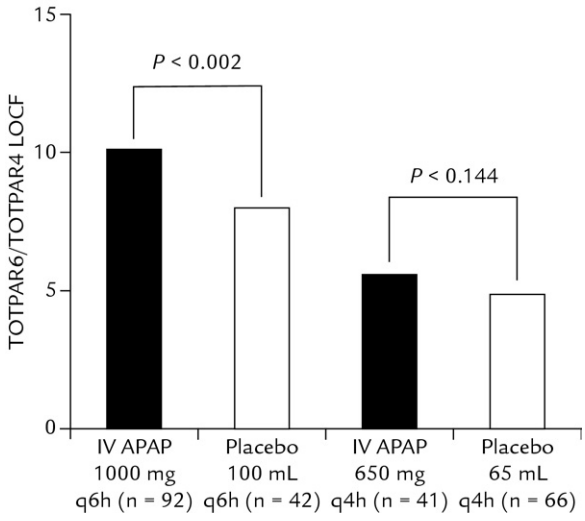

Figure 5. Last observation carried forward (LOCF) analysis of the ratio of the trapezoidal rule of the curve of change in pain-relief scores (TOTPAR), from time of study drug administration to 6 hours after (TOTPAR6), to TOTPAR from time of administration to 4 hours (TOTPAR4), in the modified intent-to-treat population (ie, all randomized subjects who received ≥1 complete dose of study medication before requesting rescue medication) in a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of 2 intravenous acetaminophen (APAP) dosing regimens for the treatment of pain after abdominal laparoscopic surgery.

cur more frequently in the intravenous acetaminophen groups compared with the combined placebo group, but these differences were not statistically significant (**Table V**). Back pain appeared to occur more frequently in the placebo group than the acetaminophen groups, but the difference was not statistically significant (**Table V**). Among the 13 subjects with vomiting, none of the events were deemed to have been related to study medication. Among the 32 subjects with nausea, only 2 events each in the IV acetaminophen 1000 mg q6h and placebo groups were considered to have been at least possibly related to study medication. Among the 11 subjects receiving intravenous acetaminophen and 1 receiving placebo who experienced infusion- or injection-site pain, 3 events in the acetaminophen groups and 1 in the placebo group were deemed possibly related to study medication; this difference was not statistically significant.

Of the 4 subjects with severe TEAEs, 2 receiving IV acetaminophen 650 mg had 4 severe TEAEs (impaired gastric emptying, nausea, vomiting, and hypertension) and 2 in the combined placebo group had 3 severe TEAEs (abdominal pain, flatulence, and back pain). None of these events were deemed to be related to study medication.

Among the 18 subjects with TEAEs that were possibly, likely, or certainly related to study medication, 7 subjects in the IV acetaminophen 1000 mg group reported 8 TEAEs: infusion-site pain (3), nausea (2), abdominal tenderness (1), constipation (1), and headache (1); 1 subject in the IV acetaminophen 650 mg group reported 1 TEAE of palpitations; and 10 subjects in the combined placebo group reported 14 TEAEs: constipation (3), nausea (2), headache (2), upper abdominal pain (1), dry mouth (1), chest pain (1), infusion-site pain (1), increased transaminase (1), migraine (1), and rash (1).

There were 6 subjects with serious TEAEs that were all deemed unrelated or not likely related to study medication. One subject in the IV acetaminophen 1000 mg group completed the 24 hours of treatment after laparoscopic hysterectomy and was discharged home, but returned 3 days later with vomiting and was readmitted, treated conservatively, and discharged home. The event was characterized as moderate and not likely related to study medication.

Three subjects in the IV acetaminophen 650 mg group had serious TEAEs. One subject, who had undergone laparoscopic hysterectomy, developed gastroparesis (severe and determined to be unrelated to study medication) 4 days after completing her course of study medication. A workup including an abdominal computed tomography scan and esophagogastroduodenoscopy was performed after readmission, and the investigators determined that the subject's gastroparesis was related to her type 1 diabetes; it resolved uneventfully. Another subject developed postoperative ileus during the day of study medication after laparoscopic incisional hernia repair. He received all 6 doses of study medication uneventfully and was discharged. The next day he developed severe abdominal pain and was readmitted. The subject was diagnosed with a small bowel adhesion, underwent adhesiolysis, and was discharged a week later. Both the ileus and bowel adhesion were deemed to be moderate in severity and

Table III. Time to meaningful pain relief in the modified intent-to-treat population (ie, all randomized subjects who received ≥1 complete dose of study medication before requesting rescue medication) in a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of 2 intravenous acetaminophen (APAP) dosing regimens for the treatment of pain after abdominal laparoscopic surgery.

	Median (95% CI)			Median (95% CI)		
Time to Meaningful Relief	IV APAP 1000 mg q6h (n = 92)	Placebo 100 mL q6h (n = 42)	*P*	IV APAP 650 mg q4h (n = 41)	Placebo 65 mL q4h (n = 66)	*P*
T0–T6	24.9 (17.5–34.7)	53.9 (14.7–301.1)	<0.003			
T0–T4				29.1 (13.4–57.3)	32.1 (22.5–71.2)	<0.219

APAP = acetaminophen.
T0 = start of first study medication infusion; T6 = 6 hours after start of first study medication infusion; T4 = 4 hours after start of first study medication infusion.

unrelated to study medication. The remaining subject (who had undergone laparoscopic sigmoid colectomy) developed postoperative ileus (moderate and not likely related to study medication) 18 days after completing her uneventful course of study medication. She was readmitted and treated conservatively over 2 days, recovered uneventfully, and was discharged home.

Two subjects in the combined placebo group had serious TEAEs. One subject (who had undergone laparoscopic adrenalectomy) developed an exacerbation of chronic obstructive pulmonary disease (moderate and unrelated to study medication) 6 days after uneventfully completing his study medication. He was admitted to the hospital with a 1-day history of dyspnea, fever, and cough productive of yellow sputum. A chest x-ray, bilateral leg Doppler scans, and chest computed tomography scan were negative. He was treated with a combination of antibiotics and pulmonary inhalers and responded well. Another subject (who had undergone laparoscopic cholecystectomy) developed an intra-abdominal abscess (mild and unrelated to study medication) at the surgical site a week after uneventfully completing a course of placebo. This subject was admitted for intravenous antibiotics and was discharged in good condition with continued oral antibiotics after 2 days.

There were no clinically significant changes in vital signs or physical examinations during the study. Other than the shift in LFT values, there were no clinically significant changes in clinical laboratory tests during the study. Clinically significant (>3× upper limit of normal range [ULNR]) changes in LFT values did not appear to follow any trends or patterns across the treatment groups (**Table VI**). Two subjects in the combined placebo group and 2 in the intravenous acetaminophen group had alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values >3× ULNR. Both placebo subjects had values that were above ULNR at baseline before the first study medication dose: ALT 72 IU and AST 60 IU, and ALT 168 IU and AST 179 IU, with maximum values of ALT 222 and 158 IU, and AST of 229 and 179 IU, respectively. Similarly, the IV acetaminophen 1000 mg subjects had elevated values at baseline before T0: ALT 49 IU and AST 77 IU, and ALT 119 IU and AST 102 IU, with maximum ALT values of 301 and 210 IU, and AST values of 95 and 167 IU, respectively.

Based on shifts in quantitative ALT and AST values, the likelihood of values that started above the ULNR at the postoperative LFT assessment and returned to within the normal range while receiving intravenous acetaminophen were comparable to those that started in the normal range for this assessment and became elevated during treatment. For ALT, 4.4% (4/91) of IV acetaminophen 1000 mg q6h, 4.7% (2/43) of IV acetaminophen 650 mg q4h, and 2.7% (3/110) of placebo subjects started above ULNR after surgery and normalized during treatment, whereas 5.5% (5/91), 2.3% (1/43), and 3.6% (4/110), respectively, started in the normal range and increased above ULNR during treatment. Similar findings were observed for AST. As previously described, there were 2 clinically significant (>3×

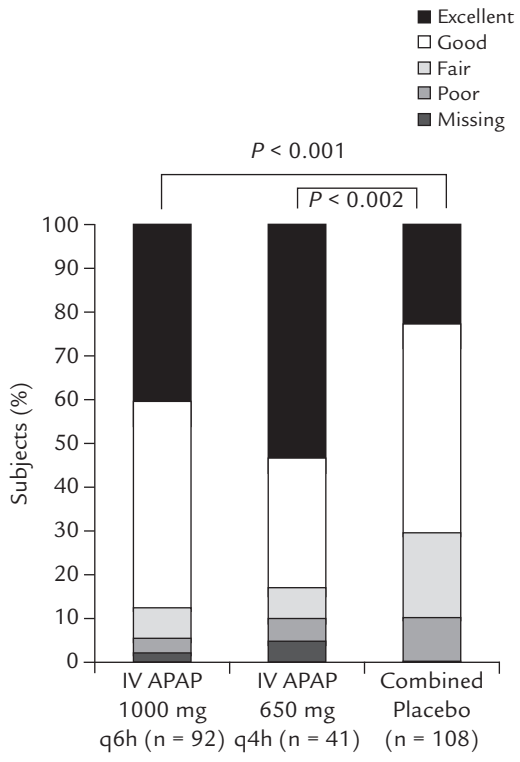

Figure 6. Subjects' global evaluation of pain relief at 24 hours after administration in the modified intent-to-treat population (ie, all randomized subjects who received ≥1 complete dose of study medication before requesting rescue medication) in a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of 2 intravenous acetaminophen (APAP) dosing regimens for the treatment of pain after abdominal laparoscopic surgery.

ULNR) shift results for ALT and AST in each of the combined active and placebo groups (**Table VI**). Two subjects in the intravenous acetaminophen groups and 2 in the placebo groups had either ALT or AST values that were >3× ULNR during the time from the postoperative assessment to the day-7 study completion visit. In each case, the values for ALT or AST were above normal postoperatively, increased during treatment, and normalized thereafter.

DISCUSSION

The data from this study suggest that IV acetaminophen 1000 mg q6h and 650 mg q4h were both efficacious, compared with placebo, for the treatment of moderate to severe postoperative pain after abdominal laparoscopic surgery procedures. Intravenous acetaminophen was well tolerated with a safety profile that did not differ significantly from that of placebo. The main efficacy outcome measure, sum of PI differences (based on VAS score) from 0 to 24 hours, significantly favored both dosing regimens of intravenous acetaminophen compared with placebo. During the first treatment period (6 hours for IV acetaminophen 1000 mg and 4 hours for IV acetaminophen 650 mg), both dosing regimens were statistically significant in favor of intravenous acetaminophen versus placebo for the sum of PR scores and sum of PI differences.

Most TEAEs reported in the present study were typical of those seen after surgery (eg, constipation, flatulence, nausea, vomiting, fever, incision pain, headache). Nearly every TEAE was assessed by the investigator to be mild or moderate in severity, and none of the severe or serious events were considered to have been related to study medication.

There were no related hepatic TEAEs reported in either intravenous acetaminophen group. The frequency of LFT elevations seen in the intravenous acetaminophen groups was similar to what was observed in the combined placebo group and, when evaluating the quantitative shift in ALT/AST values from baseline to study completion, values starting above the normal range normalized during treatment with intravenous acetaminophen about as frequently as values starting in the normal range increased from normal to beyond ULN. Only 2 subjects receiving intravenous acetaminophen and 2 receiving placebo had more than 3-fold elevations in ALT or AST, and each of these subjects had above normal values at the postoperative baseline assessment. Across numerous placebo-controlled trials, the frequency of ALT or AST elevations observed with intravenous acetaminophen was numerically lower than but not significantly different from that seen with placebo.[15] Additionally, first-pass modeling suggests that intravenous acetaminophen avoids first-pass hepatic exposure seen with oral acetaminophen, reducing hepatic exposure by ~50% at equivalent doses.[16]

Hepatic enzyme elevations are often observed following laparoscopic surgery, compared with the same open procedure. Factors such as liver manipulation, pressure effects from the pneumoperitoneum, anesthetic drugs, and underlying pathology may contribute.[17] For example, Guven and Oral[18] reported that compared with open

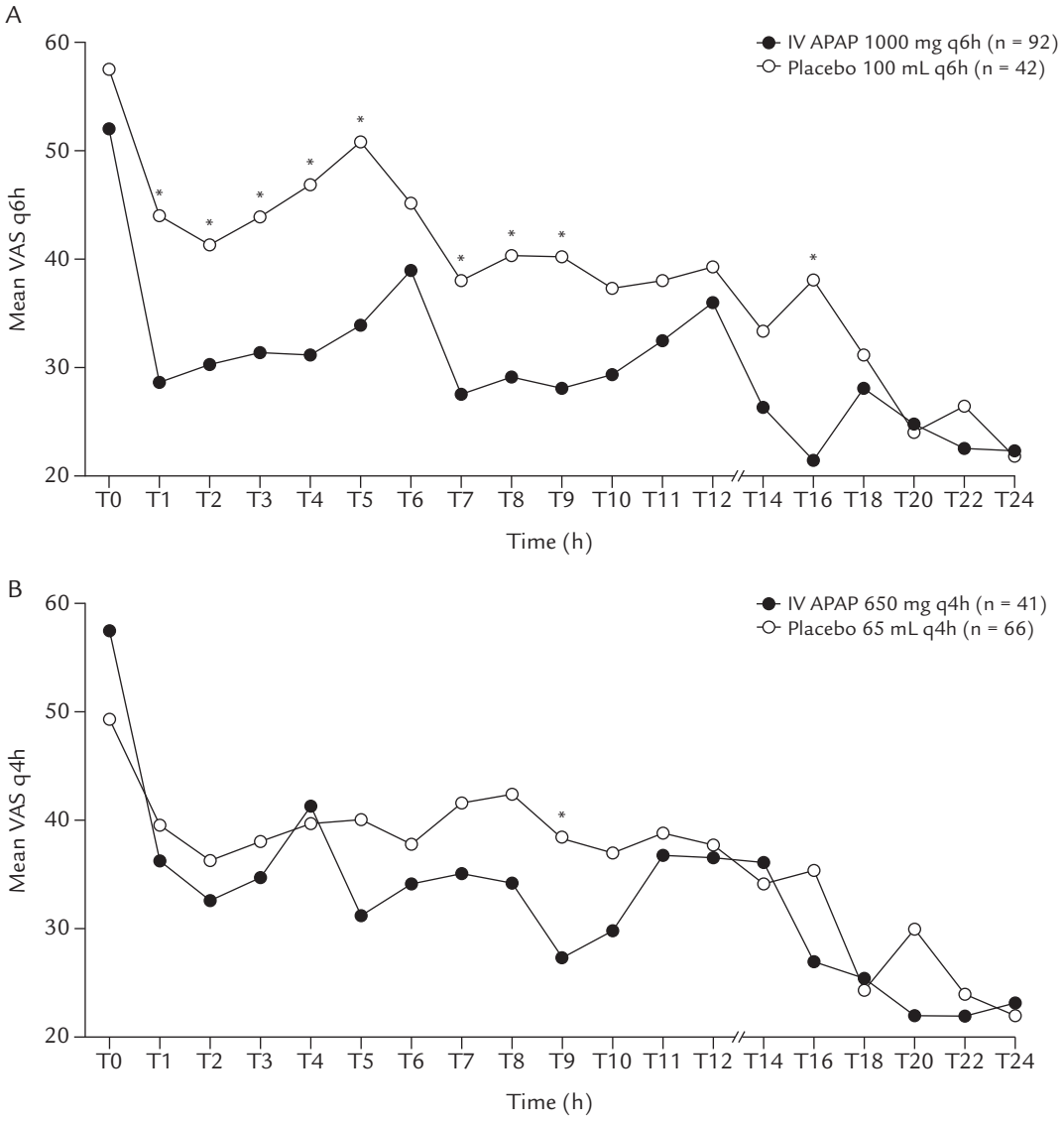

Figure 7. Mean scores for pain intensity, based on 100-mm visual analog scale (VAS), at each assessment time up to 24 hours in the modified intent-to-treat population (ie, all randomized subjects who received ≥1 complete dose of study medication before requesting rescue medication) in a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of 2 intravenous acetaminophen (APAP) dosing regimens for the treatment of pain after abdominal laparoscopic surgery. (A) Intravenous APAP 1000 mg q6h versus placebo. (B) Intravenous APAP 650 mg q4h versus placebo. $*P < 0.05$.

cholecystectomy, a laparoscopic approach was associated with mean ALT/AST elevations at 24 hours postoperatively that were ~3-fold higher than presurgical baseline values, with normalization over the next few days. In Guven and Oral, of 267 patients who underwent laparoscopic cholecystectomy between January 2003 and December 2005, 86 (32.2%) of the patients who had no complications during their procedure were evaluated for LFT elevations. Twenty-six patients who underwent an open procedure during the same interval were used as a control group. LFTs were assessed before and 24 hours after the surgery. Mean preoperative and postoperative ALT and AST values for the laparoscopic group were 21.6 and 22.8 IU, respectively, compared with 60.3 and

Table IV. Summary of treatment-emergent adverse events (TEAEs) in the safety population (ie, all subjects who received ≥1 dose of study medication) in a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of 2 intravenous acetaminophen (APAP) dosing regimens for the treatment of pain after abdominal laparoscopic surgery.* *TEAEs* were defined as AEs that began after T0 (start of first study medication infusion) or, if ongoing before T0, worsened after T0. All values (other than *P* values) are shown as number (%) of subjects.

Event	Combined Placebo (n = 110)	IV APAP 1000 mg q6h (n = 91)	*P*, IV APAP 1000 mg q6h vs Combined Placebo	IV APAP 650 mg q4h (n = 43)	*P*, IV APAP 650 mg q4h vs Combined Placebo
Any TEAE	68 (61.8)	65 (71.4)	0.178	28 (65.1)	0.853
Severe	2 (1.8)	0	0.502	2 (4.7)	0.314
Related TEAEs	10 (9.1)	7 (7.7)	0.803	1 (2.3)	0.183
Severe	0	0	–	0	–
Hepatic TEAE†	1 (0.9)	4 (4.4)	0.178	1 (2.3)	0.484
Serious	2 (1.8)	1 (1.1)	1.000	3 (7.0)	0.135
Discontinued because of TEAE	1 (0.9)	3 (3.3)	0.330	0	1.000

Related = certainly, possibly, or probably related to study medication (included TEAEs with unreported relationship to study regimen).

* The safety population included 1 subject who was randomized to receive IV APAP 1000 mg but was administered IV APAP 650 mg in error.

† All reported hepatic TEAEs were mild or moderate in severity. Only 1 hepatic TEAE (increased transaminase) in the placebo group was deemed to be treatment related. There were no hepatic AEs reported concomitantly with perturbations in liver function tests captured as hepatic TEAEs.

61.7 IU representing a 2.8- and 2.7-fold elevation, whereas the open cholecystectomy control group had ALT and AST values of 40.7 and 32.7 IU, ($P < 0.001$).

In a prospective study conducted from January to October 2002, Hasukic et al[19] evaluated 146 consecutive patients eligible for cholecystectomy and randomized 100 consecutive patients with American Society of Anesthesiology patient classification status of I or II who had normal LFTs preoperatively (50 underwent a laparoscopic cholecystectomy and 50 underwent an open procedure) to compare preoperative LFTs to values taken 24 and 48 hours postoperatively. The groups were similar in age, sex, weight, and height. The number of patients who had postoperative ALT and AST values ≥2× their preoperative values in the laparoscopic group were 26 (52%) and 23 (46%) versus 5 (10%) and 6 (12%), respectively, for the open procedure ($P < 0.001$ for each comparison).

The safety profile of intravenous acetaminophen may offer potential advantages over that of NSAIDs, because short-term therapeutic use of acetaminophen has not been associated with AEs such as bleeding, renal toxicity, or gastrointestinal toxicity.[20,21] In this study, as with other analyses,[9] the safety profile of intravenous acetaminophen was not significantly different from that of placebo. Intravenous acetaminophen may offer patients and physicians advantages in the perioperative setting, especially if renal function or gastrointestinal and postsurgical bleeding are issues that require careful monitoring.

The results from this study are consistent with those of previously published studies in which intravenous acetaminophen was reported to be more effective than placebo and comparable to several nonopioid and opioid analgesics in the treatment of postoperative acute pain in a wide range of surgical settings, ranging from tonsillectomy and endoscopic sinus surgery to spine and cardiac surgery.[22–34] This wide range of surgical settings offers an opportunity to study the efficacy of intravenous acetaminophen in treating acute pain

Table V. Treatment-emergent adverse events (TEAEs) occurring at a frequency ≥5% in any group in the safety population (ie, all subjects who received ≥1 dose of study medication) in a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of 2 intravenous acetaminophen (APAP) dosing regimens for the treatment of pain after abdominal laparoscopic surgery.* *TEAEs* were defined as AEs that began after T0 (start of first study medication infusion) or, if ongoing before T0, worsened after T0. All values (other than *P* values) are shown as number (%) of subjects.

System Organ Class Preferred Term	Combined Placebo (n = 110)	IV APAP 1000 mg q6h (n = 91)	*P,* IV APAP 1000 mg q6h vs Combined Placebo	IV APAP 650 mg q4h (n = 43)	*P,* IV APAP 650 mg q4h vs Combined Placebo
Gastrointestinal disorders					
Constipation	18 (16.4)	16 (17.6)	0.852	5 (11.6)	0.616
Diarrhea	6 (5.5)	3 (3.3)	0.516	0	0.186
Flatulence	10 (9.1)	14 (15.4)	0.194	4 (9.3)	1.000
Nausea	12 (10.9)	16 (17.6)	0.220	4 (9.3)	1.000
Vomiting	2 (1.8)	7 (7.7)	0.082	4 (9.3)	0.053
General disorders and administrative-site conditions					
Infusion-site pain	1 (0.9)	5 (5.5)	0.093	1 (2.3)	0.484
Pyrexia	7 (6.4)	2 (2.2)	0.188	0	0.192
Injury, poisoning, and procedural complications					
Incision-site pain	0	5 (5.5)	0.018	0	–
Musculoskeletal and connective tissue disorders					
Back pain	7 (6.4)	1 (1.1)	0.075	2 (4.7)	1.000
Nervous system disorders					
Headache	12 (10.9)	12 (13.2)	0.666	4 (9.3)	1.000
Psychiatric disorders					
Insomnia	5 (4.5)	2 (2.2)	0.460	3 (7.0)	0.687
Respiratory, thoracic, and mediastinal disorders					
Dyspnea	0	0	–	3 (7.0)	0.021

APAP = acetaminophen.
* The safety population included 1 subject who was randomized to receive IV APAP 1000 mg but was administered IV APAP 650 mg in error.

across a variety of surgical models and PIs from mild to severe.

For clinical trial oversight, an important lesson learned in this study is the necessity of ensuring that the CRO has performed adequate checks of all links in the randomization chain before enrolling the first patient, to avoid the type of allocation error that occurred in this study. Fortunately, once the error was identified, a rapid correction was instituted and the study was deemed adequate to support the intravenous acetaminophen new drug application submitted to the FDA.

This study had several limitations. First, it was designed to evaluate moderate pain by limiting enrollment to those with VAS scores ≤70 mm and starting the study

Table VI. Clinically important shifts in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) from postoperative baseline values to study completion in the safety population (ie, all subjects who received ≥1 dose of study medication) in a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of 2 intravenous acetaminophen (APAP) dosing regimens for the treatment of pain after abdominal laparoscopic surgery.* All values are shown as number (%) of subjects.

Parameter	IV APAP 1000 mg q6h (n = 91)	IV APAP 650 mg q4h (n = 43)	Combined Placebo Group (n = 110)
ALT			
≥3× ULNR	1 (1.1)	0	1 (0.9)
≥5× ULNR	1 (1.1)	0	0
AST			
≥3× ULNR	1 (1.1)	0	0
≥5× ULNR	0	0	1 (0.9)

APAP = acetaminophen; ULNR = upper limit of normal range.
* The safety population included 1 subject who was randomized to receive IV APAP 1000 mg but was administered IV APAP 650 mg in error.

on postoperative day 1, thereby reducing assay sensitivity. Allowing randomization of subjects with severe pain (VAS >70 mm) might have provided greater assay sensitivity. However, even in previously conducted studies enrolling subjects with higher VAS scores, statistically significant efficacy in favor of intravenous acetaminophen was reported compared with placebo.[30]

The allocation error that occurred after subject 109 (of 244 enrolled) was problematic because it caused a different allocation to groups before and after identifying the problem than was originally intended in the 2:2:1:1 randomization. The sensitivity analyses did not indicate that the primary end-point results from the different randomization periods would have been altered. Nonetheless, the patient populations enrolled before and after the randomization correction could have been different in subtle ways not detected by the sensitivity analyses.

Patients with uncomplicated laparoscopic surgeries are typically discharged from the hospital by 1 day after the procedure. Because, in this study, the intent was to assess subjects for 24 hours starting with the morning of postoperative day 1, many subjects had to agree to remain as inpatients to participate in the study. In uncomplicated cases, subjects may not have had sufficient pain in the latter half of the study to detect a difference between active and placebo groups. The fact that in the present study, 43.5% of subjects in the IV acetaminophen 1000 mg group (compared with 36.7% of subjects in the matched placebo group) and 51.2% of subjects in the IV acetaminophen 650 mg group (compared with 45.5% in the matched placebo group) did not require rescue during the 24-hour treatment period supports this hypothesis.

There were also study design issues that may have contributed to the lack of statistical significance for time to rescue and rescue medication consumption. Because patients were enrolled during the late morning of postoperative day 1, T14 would coincide with the typical bedtime for most subjects. It is possible that bedtime analgesic doses were requested to ensure uninterrupted sleep before discharge the next morning, rather than rescue medication in response to increased pain. Rescue data for the period from T12 to T14 was not captured separately; however, a review of the first 12-hour rescue results did not suggest a noticeable difference between the groups.

Finally, this study was designed to evaluate the efficacy of a single agent, intravenous acetaminophen. The literature has lacked studies evaluating multimodal combinations of various parenteral analgesics or nonpharmacologic modalities to demonstrate a benefit of multimodal approaches in the immediate postoperative setting, in which patients may be prohibited from

taking anything by mouth. Additionally, head-to-head studies of intravenous acetaminophen versus other intravenous analgesics (nonopioid and opioid) are needed.

CONCLUSIONS

In this study, 2 dosing regimens of intravenous acetaminophen (1000 mg q6h and 650 mg q4h) were associated with analgesic efficacy that was statistically significant compared with placebo in adults with pain on the day after abdominal laparoscopic surgery procedures. Both regimens were well tolerated, with a safety profile that did not differ significantly from that of placebo.

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Appendix. Eligibility criteria for a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of 2 intravenous acetaminophen dosing regimens for the treatment of pain after abdominal laparoscopic surgery.

Inclusion Criteria

To be eligible for entry to the study, a subject was required to meet all of the following criteria before surgery:

1. Subject provided signed, written informed consent before participation in the study.
2. Subject was scheduled to undergo abdominal laparoscopic surgery under general anesthesia. (Excluded abdominal laparoscopic surgeries were bariatric procedures including gastric bypass or gastric banding, exploratory procedures in which no visceral dissection was performed, and procedures with minimal visceral dissection, such as laparoscopic sterilization.)
3. If subject was a female of childbearing potential, had a negative pregnancy test within 21 days before surgery.
4. Subject was aged ≥18 and ≤80 years.
5. Subject had a body mass index >19 and <40 kg/m^2.
6. Subject had an American Society of Anesthesiologists patient classification status of I, II, or III.
7. Subject had the ability to read and understand the study procedures and the use of the pain scales, and had the ability to communicate meaningfully with the investigator and staff.
8. Subject was free of other physical, mental, or medical conditions which, in the opinion of the investigator, made study participation inadvisable.

Exclusion Criteria

A subject was not eligible for study entry if any of the following criteria was met during the screening period:

1. Subject used opioids or tramadol daily for >7 days before study medication administration. (Subjects who, in the investigator's opinion, had or were developing opioid tolerance were also excluded.)
2. Subject had been treated with chaparral, comfrey, germander, jin bu huan, kava, pennyroyal, skullcap, St. John's wort, or valerian within 14 days before surgery.
3. Subject had a chronic pain condition or any significant medical disease, laboratory abnormality, or condition that, in the investigator's judgment, could have compromised the subject's welfare, ability to communicate with the study staff, complete study activities, or otherwise contraindicated study participation.
4. Subject had known hypersensitivity to opioids, acetaminophen, or the inactive ingredients (ie, excipients) of the study medication.
5. Subject had known or suspected history of alcohol or drug abuse or dependence within the previous 2 years.
6. Subject had impaired liver function (eg, aspartate aminotransferase/alanine aminotransferase/bilirubin ≥3× upper limit of normal range, active hepatic disease, evidence of clinically significant liver disease, or other condition such as alcoholism, cirrhosis, or hepatitis) that suggested the potential for an increased susceptibility to hepatic toxicity with study medication exposure.
7. Subject had been treated with monoamine oxidase inhibitors within 7 days before surgery.
8. Subject had participated in another clinical study for an investigational or marketed product within 30 days before surgery.

Postoperative Eligibility Exclusion Criteria

A subject was not eligible for entry if any of the following criteria was met after abdominal laparoscopic surgery:

1. Subject had any surgery other than the planned laparoscopic surgery or had intraoperative or postoperative complications that, in the view of the investigator, made study participation inadvisable.
2. Subject had taken NSAIDs, steroids, or monoamine oxidase inhibitors on the day after surgery. (The use of low-dose aspirin [eg, 81 mg/d] for cardioprophylaxis and the limited use of topical or inhaled steroids were acceptable.)
3. Subject had any neuraxial (spinal or epidural) opioid injected perioperatively.
4. Subject had a local anesthetic agent injection (including into the surgical wound at closure) or continuous infusion by any route.
5. Subject had an epidural, regional, or percutaneous intrawound catheter with continuous local anesthetic infusion used for postoperative analgesic management.
6. Subject had a fever (ie, temperature >38.6°C or >101.5°F) requiring treatment with antipyretics.