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Safety of Multiple-Dose Intravenous Acetaminophen in Adult Inpatients

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Abstract

Background. Intravenous (IV) acetaminophen provides rapid and effective analgesia in the postoperative and inpatient settings. The utility and efficacy of acetaminophen is well established; however, due to chronic excessive dosing of over-the-counter acetaminophen products and prescription opioid combination products resulting in the potential for hepatic toxicity, concerns remain about acetaminophen safety. In order to evaluate the safety of IV acetaminophen 1,000 mg q6h or 650 mg q4h with repeated dosing for 5 days, a randomized, open-label study assessed the safety and tolerability of repeated doses used to treat acute pain or fever in 213 adult inpatients was conducted.

Methods. Subjects were randomized (3:3:1) to receive IV acetaminophen (1,000 mg q6h or 650 mg q4h) or standard-of-care treatment for pain or fever. Safety was assessed according to spontaneous reports of adverse events (AEs) and clinically meaningful changes from baseline laboratory parameters.

Results. Overall, IV acetaminophen was shown to be safe and well tolerated in adult inpatients when given as repeated doses for up to 5 days. Owing to the comorbidities in the study population, the frequency of AEs reported was high. However, the majority of treatment-emergent adverse events (TEAEs) were unrelated to treatment, and only 8% of the study population withdrew because of TEAEs. No major hepatic issues associated with IV acetaminophen warranted concern, and most hepatic events were likely related to underlying medical conditions or recent trauma/surgery.

Conclusions. Consistent with the tolerability and safety results, both treatment groups (1,000 mg q6h and 650 mg q4h) demonstrated statistically significantly better ratings for the Subject Global Evaluations for the level of satisfaction with side effects related to study treatments as compared with the control group. The findings from this trial support the use of IV acetaminophen as a safe therapy in adult patients.

Key Words. Pain Medicine; Acute Pain; Anesthesiology; Chronic Pain

Introduction

Acetaminophen is one of the most commonly used drugs in the United States for treating pain and fever [1]. It exerts its analgesic and antipyretic activity through a variety of central and peripheral mechanisms, including serotonergic, cholinergic, noradrenergic, cannabinoid, nitric acid synthase, and N-methyl-D-aspartate receptor activation [2]. Acetaminophen rarely gives rise to any significant adverse event (AE) and is not associated with the common side effects seen with opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) [3].

Acetaminophen has only been available in the United States in either an oral or rectal formulations. The slow onset of action and variable analgesic activity associated with the oral and rectal routes of delivery make them less desirable in the setting of postoperative or acute care [4–6]. Outside the United States, intravenous (IV) acetaminophen (paracetamol) has been commercialized primarily under the tradename Perfalgan (Bristol-Myers Squibb Company, Plainsboro, NJ) in approximately 80 countries with an estimated 65 million patient exposures. OFIRMEV (acetaminophen for injection; Cadence Pharmaceuticals, Inc.; San Diego, CA) is currently under review for United States Food and Drug Administration (FDA) approval.

In the ex-United States commercial experience, IV acetaminophen has been well tolerated and shares many of the safety aspects of the oral and rectal formulations [7,8]. Clinical and practical advantages associated with the IV route of administration include a faster onset of action and more predictable pharmacokinetics and pharmacodynamic effect across the therapeutic dosing range. Another potential advantage of IV acetaminophen is that it avoids first-pass hepatic exposure and metabolism via portal circulation [9], which may reduce the potential for hepatic injury [10–13]. With therapeutic dosing (up to 4,000 mg daily) [12], acetaminophen is only rarely associated with hepatotoxicity, and has been shown to be safe for use in patients with underlying liver conditions [14,15]. Due to its efficacy and side effect profile, IV acetaminophen has become the most frequently chosen analgesic in inpatient and postoperative settings, especially as part of a multimodal analgesia regimen employed to minimize opioid consumption [16,17].

IV acetaminophen has the potential to fill an important unmet medical need in the United States as a safe and effective parenteral antipyretic and analgesic for adults and pediatric patients. While the IV formulation has been extensively used outside the United States, the published repeated dose exposure data has been short term (≤3 days), and there has been no published data on the 650-mg dose. Therefore, to further define and confirm the favorable safety profile of IV acetaminophen as part of the required regulatory submission package in the United States, it was necessary to evaluate safety issues across a wide range of clinical settings with the IV acetaminophen regimens of 1,000 mg q6h or 650 mg q4h for at least 5 days in a minimum of 50 patients for each. The current report describes the results of a multi-center, randomized repeated dose study designed to assess the safety and tolerability of these IV acetaminophen regimens in hospitalized adults.

Methods

Study Overview

By agreement with the FDA, Cadence study CPI-APA-351 was a randomized, open-label, prospective study with a primary objective to assess the safety of IV acetaminophen when used for up to 5 days in adult inpatients for the treatment of acute pain or fever. Secondary objectives included assessment of the efficacy of IV acetaminophen using global satisfaction scores compared with a standard of care control group. This study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and was approved by an institutional review board for each clinical center. All participating patients provided written informed consent. The trial was registered with clinicaltrials.gov (http://www.clinicaltrials.gov) (Identification number: NCT00598559).

Patients and Dosing

Participating patients were at least 18 years of age, with a body weight of at least 41 kg. Subjects had to have IV access and/or require multiday IV treatment (target 5 days) due to a nil per os status or a medical condition that makes oral intake unreliable. Subjects with a known hypersensitivity to acetaminophen or impaired liver function (known active liver disease, clinically significant chronic liver disease or liver enzymes more than three times than normal) were excluded. Females of childbearing age were required to have a negative pregnancy test prior to enrollment.

IV acetaminophen (either 1,000 mg/100 mL or 650 mg/65 mL) was administered as a 15-minute IV infusion. Subjects were randomized (3:3:1) to one of three treatment groups: IV acetaminophen 650 mg q4h or IV acetaminophen 1,000 mg q6h, both administered "around-the-clock," or standard-of-care treatment (control group). Standard-of-care treatment consisted of typical medications that the Investigator deemed appropriate for the treatment of pain or fever in the postoperative or inpatient hospital setting, such as combination oral acetaminophen and hydrocodone, oral or parenteral NSAIDs, and parenteral opioids. Dosing was to occur for all regimens at their respective times around the clock for at least 5 days. Subjects returned to the study site between Days 7–10 for their final study visit. Long-term safety follow-up occurred 30 days after the last IV acetaminophen dose or 30 days after the study completion visit for the control group.

The study design is shown in Figure 1.

Safety

Spontaneous AE reports were collected by study coordinators during daily study visits and were coded according to the Medical Dictionary for Regulatory Activities, Version 10.0. Treatment-emergent AEs were those that started or worsened after the start of study medication or, for the control group, after randomization. Safety was assessed using the following criteria: percentage of subjects with AEs, serious AEs (SAEs), and percentage of subjects withdrawn due to AEs or SAEs. In addition, clinically meaningful changes in baseline laboratory parameters and vital signs were assessed, with specific attention to liver function tests (LFTs). In addition to these safety variables, the safety and efficacy of IV acetaminophen 650 mg q4h

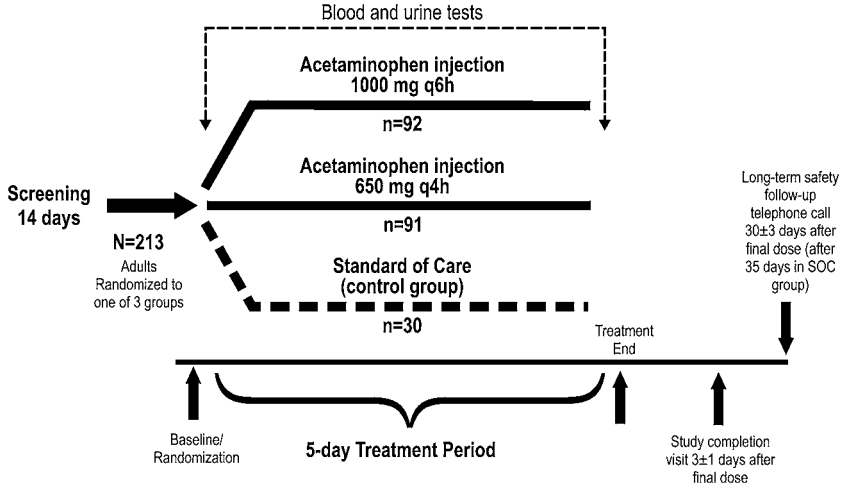

Figure 1 Study design.

versus IV acetaminophen 1,000 mg q6h versus standard of care (control group) over 5 days of treatment were compared.

Efficacy

Efficacy was measured with daily and overall Subject Global Evaluations, which consisted of two questions that asked the subject to rate the following on a 4-point categorical scale: 1) their level of satisfaction with study treatments; and 2) their level of satisfaction with treatment-related side effects.

Statistical Methods

All safety analyses were performed on the safety population, defined as all subjects who received a portion of a dose of IV acetaminophen and all subjects in the control group. All efficacy analyses were performed on the modified intent-to-treat (mITT) population, which was defined as all subjects randomized to the IV acetaminophen groups who received at least one complete dose of IV acetaminophen and all subjects assigned to the control group. Note that the sample size was not based on a formal power calculation. The sample size was intended to be sufficient to provide the required additional open-label prospective safety data on the use of IV acetaminophen treatment in repeated dose/multiday clinical use in adults.

Additional analyses included displays of the number of subjects reporting at least one AE (incidence table), total number of episodes of each AE by body system and by severity, total number of episodes of each AE by body system, and by attribution. LFT abnormalities were graded using the Common Terminology Criteria for Adverse Events. For each clinical laboratory parameter, descriptive statistics (n, mean, standard deviation [SD], median, and range) were tabulated for baseline and final values. Change from baseline was tabulated for those subjects who had both baseline and final LFT values. LFTs were also evaluated using values that were normalized to the upper limit of normal range (ULN) for the standard set of laboratory ranges. A shift table was prepared to present the shift in baseline LFTs that were clinically relevantly high or low at baseline and/or final measurement. Descriptive statistics (n, mean, SD, median, and range) were tabulated for changes in vital signs from baseline to final measurement.

Comparisons of efficacy endpoints between the following pairs of treatment groups were investigated using 2-sided tests at the 5% level of significance: IV acetaminophen 1,000 mg versus standard-of-care treatment, IV acetaminophen 650 mg versus standard of care, and IV acetaminophen 1,000 mg versus IV acetaminophen 650 mg. A one-way analysis of variance (ANOVA) model with treatment group as the factor was used to test the treatment difference between these pairs. All groups were included in this analysis model, and CONTRAST statement was used to define the comparisons. The *P* values from the ANOVA model were presented along with the summary statistics.

Results

Safety

A total of 213 adult study subjects were enrolled in the trial; 92 subjects were administered IV acetaminophen 1,000 mg q6h, 91 subjects received IV acetaminophen 650 mg q4h, and 30 subjects were assigned to the control group. The vast majority of subjects were postoperative after major surgery. The most common surgeries in each group were total hip or knee arthroplasty or revision, colectomies with or without other ancillary procedures, other orthopedic procedures (e.g., open-reduction internal fixation fracture repair), open abdominal or pelvic procedures (including cholecystectomy, gastrectomy, pancreatectomy, prostatectomy, nephrectomy, and exploratory laparotomies), major thoracic and cardiac procedures (including thoracotomy, esophagectomy, coronary artery bypass grafting, valve replacement, and abdominal aortic aneurysm repair), and spine surgeries. The few subjects with nonsurgical indications included diverticulitis (2),

Table 1 Summary of Subject Disposition and IV Acetaminophen Exposure

Subject Disposition and IV Acetaminophen Exposure Parameters	Adult Subjects		
	IV 1,000 mg q6h N = 92 n (%)	IV 650 mg q4h N = 91 n (%)	Control N = 30 n (%)
Randomized population	92 (100.0)	91 (100.0)	30 (100.0)
mITT population*	92 (100.0)	91 (100.0)	30 (100.0)
Indication			
Pain	91 (98.9)	90 (98.9)	30 (100.0)
Fever	1 (1.1)	1 (1.1)	0 (0.0)
Completed 5 days of treatment	65 (70.7)	63 (69.2)	27 (90.0)
Did not complete 5 days of treatment	27 (29.3)	28 (30.8)	3 (10.0)
Reasons for not completing 5 days of treatment			
AE	11 (12.0)	7 (7.7)	0 (0.0)
Withdrew consent	2 (2.2)	2 (2.2)	0 (0.0)
Noncompliance	1 (1.1)	0 (0.0)	0 (0.0)
Early discharge from hospital	9 (9.8)	12 (13.2)	3 (10.0)
Other	4 (4.3)	7 (7.7)	0 (0.0)
Completed last study visit	83 (90.2)	77 (84.6)	28 (93.3)
Did not complete last study visit	9 (9.8)	14 (15.4)	2 (6.7)
Reasons for not completing			
AE	0 (0.0)	1 (1.1)	0 (0.0)
Withdrew consent	5 (5.4)	6 (6.6)	0 (0.0)
Noncompliance	0 (0.0)	1 (1.1)	0 (0.0)
LTFU	1 (1.1)	0 (0.0)	0 (0.0)
Other	3 (3.3)	6 (6.6)	2 (6.7)
Time on study medication (days) mean (SD)	4.2 (1.06)	4.1 (1.21)	n/a
Total number of study medication doses mean (SD)	17.5 (4.19)	25.4 (7.07)	n/a

* All subjects randomized to the IV acetaminophen groups who received at least one dose of IV acetaminophen and all subjects assigned to the control group.
IV = intravenous; mITT = modified intent-to-treat; AE = adverse event; LTFU = lost to follow-up; SD = standard deviation.
Note: The percentages were calculated based on the total number of randomized subjects.

infections (3; such as pneumonia, sepsis, and cellulitis), small bowel obstruction (1), decubitus ulcers (1), postfracture or trauma pain (2), and snake bite (1). The groups were similar with respect to treatment indications.

Table 1 provides a summary of subject disposition and exposure to IV acetaminophen throughout the study. Only one subject in each IV acetaminophen group received study medication for the indication of fever alone (several in each group were being treated for a combination of pain and fever). No subject received a partial dose of IV acetaminophen; therefore, the safety population and mITT population were identical. The majority of subjects in all three groups completed 5 days on study with early termination due mostly to an AE or early discharge from the hospital. The mean number of days of IV acetaminophen 1,000 mg q6h and 650 mg q4h exposure was 4.2 and 4.1 days, respectively. The percentage of subjects withdrawing prior to 5 days as a result of a treatment-emergent AE (TEAE) is consistent with the study's open-label design, and the majority of these TEAEs were deemed unrelated to IV acetaminophen.

Table 2 presents a summary of the commonly (≥5%) reported TEAEs regardless of relatedness. Table 3 presents a summary of overall TEAEs, and as can be seen, most TEAEs were assessed by the investigators to be mild or moderate in severity. There were no clinically relevant differences between treatment groups in the frequency of serious or overall TEAEs. Table 4 presents the incidence of all related TEAEs considered by the investigators to be certainly, possibly, or probably related to IV acetaminophen. The majority of TEAEs were considered unrelated to IV acetaminophen. In addition, there were no clinically relevant differences between the three treatment groups regarding laboratory assessments, vital signs, or physical examinations

The population enrolled in this study consisted of subjects who were medically compromised or complicated, typically postsurgical who demonstrated baseline (prior to IV acetaminophen administration) alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBL) values that were commonly greater than the ULN (Table 5). Nonetheless, no severe hepatic TEAEs were

Table 2 Summary of Most Common (≥5% in any Treatment Group) Reported Treatment Emergent Adverse Events (Subjects [%])

	Adult Subjects n/N (%)			*P* value*	
MedDRA System Organ Class/Preferred Term	q6h Group (N = 92)	q4h Group (N = 91)	Control Group (N = 30)	q6h vs Control	q4h vs Control
Blood and Lymphatic system disorders					
Anemia	11 (12.0)	10 (11.0)	6 (20.0)	0.361	0.222
Leukocytosis	3 (3.3)	0 (0.0)	2 (6.7)	0.596	0.060
Cardiac disorders					
Tachycardia	5 (5.4)	3 (3.3)	1 (3.3)	1.000	1.000
Gastrointestinal disorders					
Constipation	18 (19.6)	21 (23.1)	5 (16.7)	1.000	0.610
Diarrhea	5 (5.4)	4 (4.4)	1 (3.3)	1.000	1.000
Nausea	23 (25.0)	34 (37.4)	8 (26.7)	1.000	0.377
Vomiting	6 (6.5)	10 (11.0)	1 (3.3)	1.000	0.289
General disorders and administration site conditions					
Edema peripheral	7 (7.6)	7 (7.7)	2 (6.7)	1.000	1.000
Pyrexia	4 (4.3)	3 (3.3)	2 (6.7)	0.635	0.597
Metabolism and nutrition disorders					
Hyperglycemia	5 (5.4)	2 (2.2)	0 (0.0)	0.332	1.000
Hypocalcaemia	10 (10.9)	4 (4.4)	2 (6.7)	0.728	0.637
Hypomagnesaemia	5 (5.4)	2 (2.2)	2 (6.7)	1.000	0.256
Nervous system disorders					
Headache	7 (7.6)	5 (5.5)	4 (13.3)	0.461	0.223
Psychiatric disorders					
Anxiety	4 (4.3)	2 (2.2)	3 (10.0)	0.361	0.097
Insomnia	13 (14.1)	17 (18.7)	5 (16.7)	0.769	1.000
Skin and subcutaneous tissue disorders					
Pruritus	11 (12.0)	13 (14.3)	2 (6.7)	0.517	0.353
Vascular disorders					
Hypertension	6 (6.5)	5 (5.5)	0 (0.0)	0.334	0.331
Hypotension	7 (7.6)	9 (9.9)	2 (6.7)	1.000	0.730
Phlebitis	0 (0.0)	1 (1.1)	2 (6.7)	0.059	0.152

* *P* values are based on Fisher's exact test.
MedDRA = Medical Dictionary for Regulatory Activities.

reported. The frequency and extent of quantitative LFT elevations were higher for ALT and AST in the control group (26.7 and 26.7%, respectively) compared with either IV acetaminophen group (q6h group: 15.2 and 12.0%, respectively; and q4h group: 13.2 and 15.4%, respectively) and were comparable for gamma glutamyltansferase, TBL and alkaline phosphatase (Table 5A). Despite the frequency of LFT elevations in the control group, no hepatic TEAEs were reported. Note that the data presented in Table 5A represents those patients who had quantitative LFT values that were either within normal limits at baseline and became high (>ULN) as recorded at the final measurement (e.g., at early termination or last study visit), or had quantitative LFT values that were >ULN at baseline and increased further by at least 20% as recorded at the final measurement. Additionally, Table 5B demonstrates that patients receiving IV acetaminophen who had elevated ALT or AST values at baseline were more likely to have values that were within normal range by the final assessment (q6h group 16.3%, q4h group 11.0%, and control group 6.6%).

There were few subjects with quantitative ALT values that exceeded 3 × ULN during the study: two (2.2%) in the q6h group, three (3.3%) in the q4h group, and one (3.3%) in the control group. In each case, the increase was most likely related to an underlying medical condition (postcoronary bypass with low output cardiomyopathy and oliguria) or recent trauma/surgery (muscular trauma). Seven deaths were reported during the study's follow-up period; there were six in the 1,000 mg q6h group and one in the 650 mg q4h group. However, all deaths occurred several days after completion of IV acetaminophen treatments, and were deemed by the investigators to be related to postsurgical complications or existing medical conditions or trauma and not to IV acetaminophen.

Table 3 Summary of Overall TEAEs

TEAE Overall Summary	Adult Subjects n/N (%) q6h Group N = 92	q4h Group N = 91	Control Group N = 30
Subjects (%) ith any TEAE	77 (83.7)	86 (94.5)	26 (86.7)
Subjects (%) with a severe TEAE	9 (9.8)	9 (9.9)	0 (0.0)
Subjects (%) with a related TEAE	11 (12.0)	9 (9.9)	0 (0.0)
Subjects (%) with a severe, related TEAE	0 (0.0)	0 (0.0)	0 (0.0)
Subjects (%) with a hepatic TEAE	8 (8.7)	7 (7.7)	0 (0.0)
Subjects (%) with a serious TEAE	14 (15.2)	11 (12.1)	3 (10.0)
Subjects (%) who discontinued the study due to a TEAE	12 (13.0)	6 (6.6)	0 (0.0)

TEAE = treatment-emergent adverse event.

Efficacy

As shown in Figure 2, both of the IV acetaminophen treatment groups (1,000 mg q6h and 650 mg q4h) produced statistically higher satisfaction scores on the Subject Global Evaluations for study treatments at Day 5 (Day 4 look-back) and End of Day 5 (Day 5 look-back), compared with the control group. There were no statistically significant differences between the active treatment groups with respect to Subject Global Evaluations during the study; however, the study was not powered to obtain such a result.

Discussion

In healthy outpatients, long-term acetaminophen therapeutic use (dosing ≤ 4 g/day) has been demonstrated to be safe. However, the safety data for therapeutic exposure in medically compromised inpatients has been lacking. In both the published literature and the clinical development package submitted in support of the IV acetaminophen New Drug Application, the safety of IV acetaminophen was studied in a placebo-controlled design for periods of up to 72 hours with a demonstrated safety profile similar to that of placebo; however, no data has been generated evaluating longer periods of exposure (e.g., up to 5 days) in hospitalized adults. Additionally, in the ex-United States experience, there has been no data generated on the 650 mg q4h dose regimen. Therefore, by agreement with the FDA, it was deemed necessary to provide long-term safety data including at least 50 patients with 5 days of repeated dose exposure to each of the proposed dosing regimens (1,000 mg q6h and 650 mg q4h) in the types of patients in which the product would likely be used in a postmarketing context.

Presumably, a concern with the use of IV acetaminophen in medically compromised inpatients is that of possible hepatotoxicity. Largely because of the uncontrolled outpatient usage of acetaminophen-containing products (over-the-counter or prescription combination products), acetaminophen dosing well beyond the daily recommended dose of 4 g has become the primary culprit in drug-related acute liver failure. While hospitalized patients may be more at risk than outpatients, the controlled inpatient environment should substantially reduce the potential for exceeding the daily maximum dose.

Table 4 Incidence of All TEAEs Considered to be Related* to IV Acetaminophen (Subjects [%])

MedDRA System Organ Class/Preferred Terms	IV Acetaminophen Groups n/N (%) q6h Group N = 92	q4h Group N = 91
Gastrointestinal disorders		
Constipation	1 (1.1)	0 (0.0)
Nausea	0 (0.0)	1 (1.1)
Vomiting	1 (1.1)	2 (2.2)
General disorders and administration-site conditions		
Infusion-Site Pain	1 (1.1)	0 (0.0)
Investigations		
AST increased	0 (0.0)	1 (1.1)
Blood alkaline phosphatase increased	0 (0.0)	1 (1.1)
GGT increased	2 (2.2)	2 (2.2)
Hepatic enzyme increased	1 (1.1)	1 (1.1)
Liver function test abnormal	1 (1.1)	1 (1.1)
Transaminases increased	2 (2.2)	1 (1.1)
Hepatotoxicity		
Platelet count increased		
Nervous system disorders		
Headache	2 (2.2)	0 (0.0)
Skin and subcutaneous tissue disorders		
Pruritis	1 (1.1)	1 (1.1)
Vascular disorders		
Hot flush	0 (0.0)	1 (1.1)
Phlebitis	0 (0.0)	1 (1.1)

* Considered by the Investigators to be certainly, possibly, or probably related to IV acetaminophen.
TEAEs left blank were not reported.
AST = aspartate ainotransferase; GGT = gamma glutamyltransferase; TEAEA = Treatment-Emergent Adverse Events; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities.

Table 5 Changes in Quantitative Liver Function Test Values (Modified Intent-to-Treat Population)

A: Elevation During the Study

LFT Parameters	IV 1 g q6h N = 92 n (%)	IV 650 mg q4h N = 91 n (%)	Control N = 30 n (%)
ALT	14 (15.2)	12 (13.2)	8 (26.7)
AST	11 (12.0)	14 (15.4)	8 (26.7)
ALP	15 (16.3)	12(13.2)	5 (16.7)
GGT	33 (35.9)	34 (37.4)	12 (40.0)
TBL	1 (1.1)	0 (0.0)	0 (0.0)

Note: Patients included in this table had quantitative LFT values that were either within normal limits at baseline and increased to >ULN as recorded at the final measurement (e.g., at early termination or last study visit) or had quantitative LFT values that were high (>ULN) at baseline and increased further by at least 20% as recorded at the final measurement.

B: Normalization During the Study

LFT Parameters	IV 1 g q6h N = 92 n (%)	IV 650 mg q4h N = 91 n (%)	Control N = 30 n (%)
ALT	6 (6.6)	4 (4.4)	1 (3.3)
AST	9 (9.8)	6 (6.6)	1 (3.3)
ALP	0 (0.0)	2 (2.2)	0 (0.0)
GGT	1 (1.2)	1 (1.1)	0 (0.0)
TBL	5 (5.5)	2 (2.2)	0 (0.0)

Note: Patients included in this table had quantitative LFT values that were high (>ULN) at baseline, but normalized by the final measurement.
ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; GGT = gamma glutamyltransferase; LFT = liver function test; TBL = total bilirubin; ULN = upper limit of normal range.

The inpatients enrolled in this study represented a medically compromised or at risk population with the vast majority of patients having undergone major surgery. Nonetheless, there were no clinically relevant differences between the treatment groups in the frequency of overall TEAEs. Over 50% of subjects in the control group were treated with concomitant oral acetaminophen (usually in combination with hydrocodone), which could have contributed to the liver enzyme elevations observed in this group. Despite these elevations, no hepatic TEAEs were reported in this group, while in both IV acetaminophen groups, patients were reported to have experienced hepatic TEAEs. The fact that the frequency of quantitative elevations for ALT and AST was numerically higher in and the extent of elevations similar to the control group compared with both active treatment groups suggests that a reporting bias was likely present due to the open-label design. With respect to quantitative LFT values, there were few that exceeded 3 × ULN during the study and in most of these cases the extent of the change appeared to be due to the underlying medical condition.

This study has several limitations. The protocol was designed to be open-label, so all participants and healthcare professionals knew that IV acetaminophen or standard of care treatments were being given. This may have lead to some bias in the reporting of TEAEs, especially in the control group who received no active study medication. Additionally, as the control group received whatever medication was deemed appropriate by their treating physician, which could have resulted in inadequate treatments leading to higher satisfaction scores for the IV acetaminophen groups. The vast majority of the subjects were entered into the study after major surgery which could have been the etiology for not only most of the reported TEAEs, but also the LFT perturbations. Finally, the amount of acetaminophen, either alone or as a combination medication, was not limited in the control group and could have been the etiology of the increased LFTs noted in this group. While the open-label design has these obvious limitations, it can still provide the type of safety information that is likely to be generated in "real life" practice.

Overall, IV acetaminophen dosed at 1,000 mg q6h or 650 mg q4h was well tolerated when given in repeated doses for up to 5 days in the adult inpatient population studied. There were no clinically relevant differences between the treatment groups in the frequency of serious or overall TEAEs. The majority of TEAEs was deemed by the investigators to be unrelated to IV acetaminophen and nearly all cases were mild or moderate in severity.

While a secondary objective, the efficacy of IV acetaminophen was also demonstrated in the study. Both IV

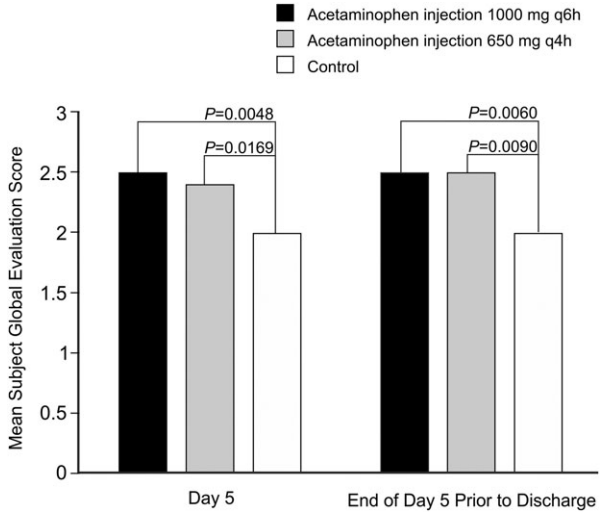

Figure 2 Level of satisfaction with side effects related to study treatments in adult patients.

acetaminophen treatment groups (1,000 mg q6h and 650 mg q4h) produced statistically better satisfaction ratings for the Subject Global Evaluation scale compared with the control group. While satisfaction ratings are often difficult to interpret in the absence of other efficacy outcome measures, these positive results could be interpreted as providing at least indirect evidence of an IV acetaminophen treatment effect and additional confirmation of its tolerability. The results are supported by more than 40 randomized, controlled trials demonstrating efficacy in a variety of acute pain (operative and nonoperative) settings [18,19].

The results of this study are consistent with IV acetaminophen's long clinical record of safety and tolerability. With rapid and effective analgesic activity and a favorable safety profile, IV acetaminophen is poised to be a first-line analgesic for the management and treatment of inpatient adult pain and fever when IV treatment is clinically indicated or when a fast onset of efficacy is desired.

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