Efficacy and Safety of Single and Repeated Administration of 1 Gram Intravenous Acetaminophen Injection (Paracetamol) for Pain Management after Major Orthopedic Surgery

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**Background:** Intravenous acetaminophen injection (paracetamol) is marketed in Europe for the management of acute pain. A repeated-dose, randomized, double-blind, placebo-controlled, three-parallel group study was performed to evaluate the analgesic efficacy and safety of intravenous acetaminophen as compared with its prodrug (propacetamol) and placebo. Propacetamol has been available in many European countries for more than 20 yr.

**Methods:** After orthopedic surgery, patients reporting moderate to severe pain received either 1 g intravenous acetaminophen, 2 g propacetamol, or placebo at 6-h intervals over 24 h. Patients were allowed “rescue” intravenous patient-controlled analgesia morphine. Pain intensity, pain relief, and morphine use were measured at selected intervals. Safety was monitored through adverse event reporting, clinical examination, and laboratory testing.

**Results:** One hundred fifty-one patients (intravenous acetaminophen: 49; propacetamol: 50; placebo: 52) received at least one dose of study medication. The intravenous acetaminophen and propacetamol groups differed significantly from the placebo group regarding pain relief from 15 min to 6 h (P < 0.05) and median time to morphine rescue (intravenous acetaminophen: 3 h; propacetamol: 2.6 h; placebo: 0.8 h). Intravenous acetaminophen and propacetamol significantly reduced morphine consumption over the 24-h period: The total morphine doses received over 24 h were 38.3 ± 35.1 mg for intravenous acetaminophen, 40.8 ± 30.2 mg for propacetamol, and 57.4 ± 52.3 mg for placebo, corresponding to decreases of −33% (19 mg) and −29% (17 mg) for intravenous acetaminophen and propacetamol, respectively. Drug-related adverse events were reported in 8.2%, 50% (most of them local), and 17.3% of patients treated with intravenous acetaminophen, propacetamol, and placebo, respectively.

**Conclusion:** Intravenous acetaminophen, 1 g, administered over a 24-h period in patients with moderate to severe pain after orthopedic surgery provided rapid and effective analgesia and was well tolerated.

EFFECTIVE pain management is an important component of postsurgical care. Many patients, however, continue to experience inadequate pain relief. Despite improvements in analgesic delivery, including patient-controlled analgesia (PCA) and sustained-release opioids, several recent surveys have found that up to 80% of patients report moderate to severe pain after surgery. The ideal postoperative analgesic treatment should provide rapid and effective pain relief, have a low incidence of adverse effects, and have minimal impact on major organ systems or no significant interaction with other pharmacologic agents.

Opioids remain the agents of choice for severe pain; however, this class of analgesics is associated with dose-dependent adverse effects and negative postoperative outcomes. Nonopioid analgesics are commonly used alone or as adjuncts to opioid-based analgesia to treat moderate to severe pain. Perioperative administration of acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) has been advocated to provide “multimodal” or “balanced” analgesia that decreases opioid dose requirements and may reduce associated adverse events while reducing postsurgical pain intensity.

Acetaminophen has a well-established safety and analgesic profile. It has few contraindications and lacks significant drug interactions. Hepatic toxicity is relatively rare but can occur with acetaminophen overdose. Its possible potentialization by chronic alcoholism remains controversial.

Until recently, there has not been an intravenous acetaminophen solution available because it is poorly soluble in water and not stable in solution. As a result, propacetamol, an intravenous, water-soluble prodrug of acetaminophen with a well-established analgesic efficacy and safety profile, has been widely prescribed in Europe for the management of acute pain for the past 20 yr. It is not available in the United States.

Propacetamol is rapidly hydrolyzed to acetaminophen in the blood by the enzymatic action of esterases. Hydrolysis of 2 g propacetamol yields 1 g intravenous
acetaminophen.13 In clinical trials conducted in patients with moderate to severe pain after orthopedic and gynecologic surgery, the analgesic efficacy of propacetamol was similar to that of NSAID comparators.14–16

While providing fast and significant pain relief as well as a significant morphine-sparing effect,17–19 it is not associated with the increased incidence of nausea, vomiting, and respiratory depression observed with opioids or the deleterious gastrointestinal, hematologic, and renal effects associated with NSAIDs and cyclooxygenase (COX)-2 inhibitors.20 Lack of inhibition of COX-1 peripherally by paracetamol may explain its favorable safety effect.21 However, propacetamol has some drawbacks: It must be reconstituted into a solution, and rare cases of contact dermatitis have been reported in healthcare professionals handling the drug.22 In addition, propacetamol can be associated with pain at the intravenous injection site or along the vein being infused.

A ready-to-use formulation of intravenous acetaminophen has recently been developed that does not require reconstitution and is not associated with contact dermatitis or pain at the injection site. In the clinical development program, 1 g intravenous acetaminophen has been found to be bioequivalent to 2 g propacetamol.23 Moreover, clinical studies have shown that intravenous acetaminophen offers improved local safety at infusion sites, compared with propacetamol.23

The aim of this study was to evaluate the analgesic efficacy and safety of a single dose and repeated doses of 1 g intravenous acetaminophen in comparison with 2 g propacetamol and placebo in patients experiencing moderate to severe pain after total hip or knee replacement. These procedures were chosen because patients recovering from them consistently experience moderate to severe postoperative pain and require high doses of opioid analgesics.24–26

Materials and Methods

Patients

Patients aged at least 18 yr who were recovering from total hip or knee replacement performed during general or regional anesthesia and had an American Society of Anesthesiologists physical status of I–III were eligible for the study. Other entry criteria included body weight between 50 and 120 kg, ability to use the pain scales and to operate an intravenous PCA device, and reporting baseline pain of moderate to severe intensity on a categorical rating scale.

Exclusion criteria included known allergy or hypersensitivity or contraindication to opioids or acetaminophen, impaired liver function (transaminases > twice upper limit), renal dysfunction (creatinine > 2.0 mg/dl), uncontrolled chronic diseases, known or suspected history of alcohol or drug abuse. Patients who were pregnant or breastfeeding were excluded. Patients were also excluded if they had received NSAIDs within 8 h, any analgesic drug within 12 h, or corticosteroids within 7 days before administration of study medication.

The 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.

Study Design

This was a repeated-dose, randomized, double-blind, placebo-controlled, three–parallel group study comparing intravenous acetaminophen and propacetamol to placebo and was conducted in seven centers in the United States (see appendix). Patients were enrolled from September 1999 to June 2000.

Propacetamol was chosen as a comparator because it is the only injectable, prodrug form of acetaminophen commercially available and because, having been widely prescribed for many years in Europe, its analgesic efficacy and safety profile have been well characterized. The dose of 2 g propacetamol was chosen because it releases 1 g intravenous acetaminophen.

During the screening visit scheduled within 21 days before the administration of study drug, informed consent and medical history were obtained, physical examination and laboratory testing were performed, and training on the use of the intravenous PCA device and pain scales was provided.

Patients received either general, spinal, or epidural anesthesia as judged appropriate by the attending anesthesiologist on the day of surgery. They did not receive epidural or intrathecal opioids or local anesthetics for postoperative pain control. Most patients received general anesthesia, which included premedication with midazolam, isoflurane–desflurane, fentanyl, and morphine for maintenance. In the postanesthesia care unit, when patients first requested analgesics, a PCA pump containing morphine (1 mg/ml) was connected to the intravenous infusion. The PCA device was programmed to deliver 1-mV boluses of morphine on demand, with a lockout time interval of 6 min. If adequate pain relief was not achieved with the intravenous PCA device alone, supplemental “rescue” boluses of 2 mg intravenous morphine were administered as needed.

On the morning of the first postoperative day, after completion of routine nursing activities, the PCA device was temporarily discontinued, and the total amount of morphine administered to the patient was recorded.

A study observer closely monitored and recorded the patients’ pain intensity. Patients reporting moderate to severe intensity on a four-point verbal pain intensity categorical scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) were randomly assigned to one of the three treatment groups: 1 g intravenous acetaminophen, 2 g propacetamol, or placebo. The study medications

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were prepared by an unblinded hospital pharmacist who was not involved in the data collection. All of the study medications were administered as a 100-ml solution infused over 15 min at 6-h intervals for the next 24 h. To properly evaluate the local tolerance of the study medication at the infusion site, no other drug was administered through the cannula dedicated to infusion of the study solution.

Efficacy Measurements

Pain intensity was measured immediately before the start of infusion of study medication. The start of the study drug infusion was defined as time 0. Pain intensity at rest was measured at selected intervals (15, 30, and 45 min and 1, 2, 3, 4, 5, 6, 18, 20, and 24 h after the first dose) with a 100-mm visual analog scale (VAS; 0 = no pain to 100 = worst possible pain) and on a four-point verbal scale (0 = none to 3 = severe). Pain relief (primary endpoint) was measured on a five-point verbal scale (0 = none to 4 = complete) at the same selected intervals up to 6 h. Time to rescue medication, quantity of morphine used, and patients’ global evaluations over the 24-h study interval were recorded.

Safety Assessments

Adverse events (AEs) and serious AEs were monitored throughout the study period. Safety was also assessed by infusion site examination, vital signs measurements (systolic and diastolic blood pressure, heart rate, and respiratory rate on the first postoperative day just before the first infusion, 2 h after infusion, and on the morning of day 2), and routine laboratory testing (hematology and biochemistry before and after 48 h after the surgery).

Statistical Analysis

Sample Size. A sample size of 50 patients per group was required to detect a difference of at least one point of pain relief (on the five-point categorical scale) for active treatments versus placebo, with a 90% power and a type I error at 0.0167 (two-sided test adjusted for three comparisons).

All of the analyses were performed in the intent-to-treat population.

Efficacy analyses included 6-h single-dose pain intensity differences on categorical and visual scales (baseline pain minus pain intensity at each time point), summary measures of efficacy (weighted total pain relief, sum of pain intensity difference and pain relief as measured on a categorical scale, weighted summed pain intensity differences from baseline), peak effects, time to remedication (defined as time to request for rescue medication), and PCA morphine use. For the entire 24-h study interval: pain intensity, PCA morphine use, and patients’ global evaluation.

The pain relief and pain intensity scores, global measures of efficacy, and quantity of rescue medication administered were analyzed with an analysis of covariance for overall difference among treatments and the Fisher protected least significant difference for multiple comparison procedure. Time to peak effect and time to first rescue remedication were analyzed using the stratified Gehan-Wilcoxon test with center as the stratum variable applied as the Fisher protected least significant difference procedure and survival distribution using the Kaplan-Meier estimator. The Cochran-Mantel Haenszel test stratified by center and applied as the Fisher protected least significant difference procedure was used for analysis of patients requiring rescue medication and patient global evaluation. Responders were defined as subjects who had a reduction in pain intensity of at least one unit. All efficacy analyses were performed on the intent-to-treat population.

Results

Patients

A total of 156 patients were randomized (intravenous acetaminophen: n = 51; propacetamol: n = 52; placebo: n = 53), and 151 patients (intravenous acetaminophen: n = 49; propacetamol: n = 50; placebo: n = 52) received at least one dose of study medication. All of these 151 patients were included in the intent-to-treat population and analyzed for demographics, efficacy, and safety.

Most of the patients (137 of 151 [90.7%]) received four administrations of the study drug over 24 h. Fourteen patients (9.3%) withdrew from the study after the first study drug administration: 3 (6.1%) from the intravenous acetaminophen group, 6 (12.0%) from the propacetamol group, and 5 (9.6%) from the placebo group. Six of these patients were withdrawn because of consent withdrawal: 2 (4%) in the intravenous acetaminophen group, 2 (4%) in the propacetamol group, and 2 (3.8%) in the placebo group. Four patients were withdrawn because of AEs: 5 (5.9%) in the propacetamol group (local pain at infusion site) and 1 (1.9%) in the placebo group (fever necessitating treatment). Two patients were withdrawn because of lack of compliance: 1 in the intravenous acetaminophen group and 1 in the propacetamol group. Two patients in the placebo group did not meet eligibility criteria but were included in the intent-to-treat population.

The treatment groups were comparable with respect to demographics, anesthetic and surgical procedure, and
baseline pain intensity. The overwhelming majority of patients had symptoms of severe debilitating or painful osteoarthritis. Patients were aged 22–87 yr, had American Society of Anesthesiologists physical status of predominantly II (68.2%) or III (25.8%), and were experiencing moderate to severe pain (99%) after total hip (57%) or knee replacement (43%) (standard cemented arthroplasties) performed during general (64.2%), regional (21.8%), or combined general and regional anesthesia (13.9%). Before study drug administration, the mean baseline pain intensity on the 100-mm VAS was 58/110 mm (table 1).

### Efficacy Measures

**Pain Intensity and Pain Relief Scores and Global Measures of Efficacy.**

**Six-hour Evaluation Period (Single Dose).** The primary efficacy criterion was pain relief. For both active groups, intravenous acetaminophen and propacetamol, pain relief scores were significantly higher than those of the placebo group from 15 min to 6 h ($P < 0.05$; fig. 1).

Maximal pain relief scores were similar in the two active groups (2.0 ± 1.4) and significantly higher than that observed in the placebo group (0.9 ± 1.1). The median time to peak effect for pain relief was 30 min in both active groups.

Pain intensity differences (verbal scores and VAS) from baseline were significantly higher for both active groups in comparison with the placebo group at each assessment interval from 15 min (intravenous acetaminophen) and 30 min (propacetamol) up to 6 h ($P < 0.05$; fig. 2).

Summary measures of efficacy over 6 h were equivalent in the intravenous acetaminophen and propacetamol groups and superior to that reported in the placebo group ($P < 0.05$; table 2).

In general, the response was lower for all treatment groups for the knee than for the hip surgery subjects. However, the magnitude of the active treatments effect (active vs. placebo) was statistically significant and similar for the hip and knee patients.

**Median Time to First Rescue Medication.** Time to first rescue medication was significantly ($P < 0.001$) longer for both active groups than for placebo but was not significantly different between the two active groups. The median (95% confidence interval) times to first rescue medication were 3 (1.4–4.0) h for intravenous acetaminophen, 2.6 (1.6–4.0) h for propacetamol, and 0.8 (0.6–1.1) h for placebo (fig. 3). The analyses of median time to rescue medication performed among responders (defined as subjects who had a reduction in pain intensity of at least one unit) showed that the median times for first rescue medication were 4.0 (3.3–4.3) h for intravenous acetaminophen, 3.8 (2.5–5.2) h for propacetamol, and 1.6 (1.0–2.6) h for placebo (table 3).

**Pain Intensity over 24-h Evaluation Period (Repeated Dose).** Throughout the 24-h evaluation period, the mean VAS pain intensity scores were significantly reduced in both active groups as compared with the placebo group (−8 and −10 mm for intravenous acetaminophen and propacetamol, respectively; $P < 0.01$).

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### Table 1. Baseline Patient Demographics (ITT Population)

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>1 g Intravenous Acetaminophen</th>
<th>2 g Propacetamol</th>
<th>Placebo</th>
<th>Overall</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>49</td>
<td>50</td>
<td>52</td>
<td>151</td>
<td>0.656</td>
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<td>Age, yr</td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
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<td>59.5</td>
<td>59.2</td>
<td>60.1</td>
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<tr>
<td>SD</td>
<td>16.9</td>
<td>14.2</td>
<td>13.4</td>
<td>14.8</td>
<td>0.05</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>28 (57.1)</td>
<td>27 (54)</td>
<td>22 (42.3)</td>
<td>77 (51)</td>
<td>0.288</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>21 (42.9)</td>
<td>23 (46)</td>
<td>30 (57.7)</td>
<td>74 (49)</td>
<td>0.05</td>
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<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>85.7</td>
<td>85.7</td>
<td>81</td>
<td>84.1</td>
<td>0.0246</td>
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<tr>
<td>SD</td>
<td>13.0</td>
<td>18.8</td>
<td>17.3</td>
<td>16.6</td>
<td>0.05</td>
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<tr>
<td>Height, cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
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<td>171.6</td>
<td>168.7</td>
<td>170.7</td>
<td>0.317</td>
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<tr>
<td>SD</td>
<td>10.7</td>
<td>12.8</td>
<td>10.6</td>
<td>11.4</td>
<td>0.05</td>
</tr>
<tr>
<td>ASA physical status classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, n (%)</td>
<td>3 (6.1)</td>
<td>3 (6.0)</td>
<td>3 (5.8)</td>
<td>9 (6.0)</td>
<td>0.792</td>
</tr>
<tr>
<td>II, n (%)</td>
<td>34 (69.4)</td>
<td>32 (64.0)</td>
<td>37 (71.2)</td>
<td>103 (68.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>III, n (%)</td>
<td>12 (24.5)</td>
<td>15 (30.0)</td>
<td>12 (23.1)</td>
<td>39 (25.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>PAI (VAS), mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>62.0</td>
<td>55.7</td>
<td>56.4</td>
<td>58.0</td>
<td>0.156</td>
</tr>
<tr>
<td>SD</td>
<td>19.1</td>
<td>17.6</td>
<td>16.9</td>
<td>18.0</td>
<td>0.05</td>
</tr>
</tbody>
</table>

ASA = American Society of Anesthesiologists; ITT = intent-to-treat; PAI = pain intensity measure on visual analog scale; VAS = visual analog scale.
Morphine Consumption. Morphine consumption over the 6 h after the first dose was significantly \( (P < 0.01) \) lower for both active groups \((9.7 \pm 10\) and \(9.3 \pm 8.9\) mg for intravenous acetaminophen and propacetamol, respectively) than for the placebo group \((17.8 \pm 16.7\) mg). This reduction was maintained over 24 h (repeated doses), with total doses of \(38.3 \pm 35.1, 40.8 \pm 30.2,\) and \(57.4 \pm 52.3\) mg for intravenous acetaminophen, propacetamol, and placebo, respectively. Reduction of PCA morphine in the intravenous acetaminophen group was \(8\) mg \((-46\%)\) after the first dose and \(19\) mg \((-33\%)\) over 24 h (repeated doses). Reduction of PCA morphine in the propacetamol group was \(9\) mg \((-48\%)\) after the first dose and \(17\) mg \((-29\%)\) over 24 h (repeated doses).

**Patient Global Evaluation.** The patients’ global evaluations of satisfaction with study treatment after the initial dose and at 24 h (repeated doses) were significantly \((P < 0.01)\) higher for both active treatment groups than for the placebo group. The proportions of subjects with fair to excellent satisfaction with the study treatment at 24 h were 79.6, 83.7, and 65.4% for intravenous acetaminophen, propacetamol, and placebo, respectively.

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**Fig. 1.** Mean pain relief scores, single dose (intent-to-treat population). Comparisons versus placebo: \(\ast P < 0.05; \ast\ast P < 0.001.\) Comparisons between active groups: not significant at each evaluation time. IV = intravenous.

**Fig. 2.** Mean pain intensity differences categorical scale, single dose (intent-to-treat population). Comparisons versus placebo: \(\ast P < 0.05; \ast\ast P < 0.001.\) Comparisons between active groups: not significant at each evaluation time. IV = intravenous.
Adverse Events

There was no significant difference between treatment groups regarding the number of patients experiencing AEs. Ninety-seven patients (64.2%) experienced at least one AE after the first administration of the study medication: 32 (65.3%) in the intravenous acetaminophen group, 33 (66%) in the propacetamol group, and 32 (61.5%) in the placebo group (table 4). Constipation, nausea, injection site pain, anemia, pruritus, and vomiting were the most frequently reported AEs (table 4).

Adverse events were considered related to the trial medication in 38 patients (25.2%), with the highest number observed in the propacetamol group (25 patients [50%]) and significantly less in the intravenous acetaminophen (4 [8.2%]) and placebo groups (9 [17.3%]) ($P < 0.05$). The proportion of subjects reporting local administration site AEs was significantly ($P < 0.001$) lower for intravenous acetaminophen (1 of 49 [2%]) than for propacetamol (21 of 50 [38%]) and not different from that of placebo (1 of 52 [2%]) (table 5). There was no significant difference between the intravenous acetaminophen and placebo groups (table 5). In the propacetamol group, all of the local AEs were considered related to the study drug. Nearly half of them led to reductions in infusion dose rate, interruption of the infusion, or even discontinuation of therapy.

Eight patients (5.3%) experienced 11 treatment-emergent serious AEs that were not considered related to the study drug.

Intravenous acetaminophen and propacetamol infusions were not associated with clinically significant alterations in vital signs. Regarding blood chemistry test results, hemoglobin, hematocrit, and leukocyte and platelets counts, the incidence of treatment-emergent clinically significant values was low. There were no serious hepatic events related to treatment with intravenous acetaminophen.

Discussion

This study demonstrates that 1 g intravenous acetaminophen is a safe and effective intravenous, nonopioid analgesic for the treatment of postoperative pain in patients recovering from lower extremity joint replacement surgery. Intravenous acetaminophen was similar to propacetamol and consistently superior to placebo for the main efficacy criterion of pain relief, as well as for
pain intensity changes from 15 min to 6 h after the first dose and throughout the 24-h evaluation period after repeated dose administration. In addition, intravenous acetaminophen had significantly improved local tolerability.

Acetaminophen (paracetamol) is a widely prescribed analgesic devoid of clinically significant antiinflammatory effects. Intravenous administration of acetaminophen either as intravenous acetaminophen or propacetamol avoids variabilities associated with gastric absorption and first-pass hepatic metabolism, resulting in higher plasma concentrations and greater analgesic efficacy than orally administered drug.28

Major orthopedic surgery is extremely painful, and monotherapy with acetaminophen would not be expected to provide complete relief on the day surgery was performed. Therefore, in the current investigation, acetaminophen infusions were started the day after surgery to allow patients to stabilize in the acute postoperative setting and to reduce confounding factors for drug assessment, e.g., the possible synergistic analgesic effect of the anesthetic on the study drug in the postoperative period. This also allowed the evaluation of the monotherapeutic efficacy of intravenous acetaminophen in reducing pain intensity. Onset and duration of analgesic effect for intravenous acetaminophen and propacetamol seemed comparable to data previously reported for propacetamol.16 Although double-stopwatch assessments of perceptible and meaningful effect were not performed, the assessment used (a minimum of 10 mm decrease in VAS pain intensity) provided a reasonable

### Table 3. Median Time to Rescue Medication

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>1 g Intravenous Acetaminophen (n = 49)</th>
<th>2 g Propacetamol (n = 50)</th>
<th>Placebo (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>32 (65.3)</td>
<td>33 (66.0)</td>
<td>32 (61.5)</td>
</tr>
<tr>
<td>No. of patients with ≥1 AE</td>
<td>32 (65.3)</td>
<td>33 (66.0)</td>
<td>32 (61.5)</td>
</tr>
<tr>
<td>No. of patients with ≥1 AE</td>
<td>4 (8.2)</td>
<td>25 (50.0)</td>
<td>9 (17.3)</td>
</tr>
<tr>
<td>Gastrointestinal system disorders*</td>
<td>21 (42.9)</td>
<td>16 (32.0)</td>
<td>16 (30.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (20.4)</td>
<td>8 (16.0)</td>
<td>12 (23.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (26.5)</td>
<td>9 (18.0)</td>
<td>7 (13.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (12.2)</td>
<td>3 (6.0)</td>
<td>7 (5.8)</td>
</tr>
<tr>
<td>Abdomen enlarged</td>
<td>3 (6.1)</td>
<td>0</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Other gastrointestinal disorder</td>
<td>3 (6.1)</td>
<td>0</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Application site disorders</td>
<td>2 (4.1)†</td>
<td>21 (42)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>2 (4.1)†</td>
<td>19 (38.0)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0</td>
<td>3 (6.0)</td>
<td>0</td>
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<tr>
<td>Body-as-a-whole general disorders</td>
<td>4 (8.2)</td>
<td>3 (6.0)</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>Fever</td>
<td>1 (2.0)</td>
<td>1 (2.0)</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Erythrocyte disorders</td>
<td>4 (8.2)</td>
<td>5 (10.0)</td>
<td>7 (13.5)</td>
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<tr>
<td>Anemia</td>
<td>4 (8.2)</td>
<td>5 (10.0)</td>
<td>7 (13.5)</td>
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<td>Skin and appendage disorders</td>
<td>5 (10.2)</td>
<td>4 (8.0)</td>
<td>5 (9.6)</td>
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<td>Pruritus</td>
<td>5 (10.2)</td>
<td>4 (8.0)</td>
<td>5 (9.6)</td>
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<td>Respiratory system disorders</td>
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<td>3 (5.8)</td>
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<tr>
<td>Coughing</td>
<td>3 (6.1)</td>
<td>0</td>
<td>1 (1.9)</td>
</tr>
</tbody>
</table>

* Per US Food and Drug Administration communication, time to rescue should be relevant to subset of subjects who responded to treatment. Subjects whose pain intensity reduction was at least 1 unit (on a four-point verbal score) were included in the analysis. CI = confidence interval; ITT = intent-to-treat.

### Table 4. Adverse Events Greater Than 5% in Any Treatment Group (Safety Population)

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>1 g Intravenous Acetaminophen (n = 49)</th>
<th>2 g Propacetamol (n = 50)</th>
<th>Placebo (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>32 (65.3)</td>
<td>33 (66.0)</td>
<td>32 (61.5)</td>
</tr>
<tr>
<td>No. of patients with ≥1 AE</td>
<td>32 (65.3)</td>
<td>33 (66.0)</td>
<td>32 (61.5)</td>
</tr>
<tr>
<td>No. of patients with ≥1 AE</td>
<td>4 (8.2)</td>
<td>25 (50.0)</td>
<td>9 (17.3)</td>
</tr>
<tr>
<td>Gastrointestinal system disorders*</td>
<td>21 (42.9)</td>
<td>16 (32.0)</td>
<td>16 (30.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (20.4)</td>
<td>8 (16.0)</td>
<td>12 (23.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (26.5)</td>
<td>9 (18.0)</td>
<td>7 (13.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (12.2)</td>
<td>3 (6.0)</td>
<td>7 (5.8)</td>
</tr>
<tr>
<td>Abdomen enlarged</td>
<td>3 (6.1)</td>
<td>0</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Other gastrointestinal disorder</td>
<td>3 (6.1)</td>
<td>0</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Application site disorders</td>
<td>2 (4.1)†</td>
<td>21 (42)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>2 (4.1)†</td>
<td>19 (38.0)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0</td>
<td>3 (6.0)</td>
<td>0</td>
</tr>
<tr>
<td>Body-as-a-whole general disorders</td>
<td>4 (8.2)</td>
<td>3 (6.0)</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>Fever</td>
<td>1 (2.0)</td>
<td>1 (2.0)</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Erythrocyte disorders</td>
<td>4 (8.2)</td>
<td>5 (10.0)</td>
<td>7 (13.5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (8.2)</td>
<td>5 (10.0)</td>
<td>7 (13.5)</td>
</tr>
<tr>
<td>Skin and appendage disorders</td>
<td>5 (10.2)</td>
<td>4 (8.0)</td>
<td>5 (9.6)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5 (10.2)</td>
<td>4 (8.0)</td>
<td>5 (9.6)</td>
</tr>
<tr>
<td>Respiratory system disorders</td>
<td>4 (8.2)</td>
<td>0</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Coughing</td>
<td>3 (6.1)</td>
<td>0</td>
<td>1 (1.9)</td>
</tr>
</tbody>
</table>

* Number of patients with at least one adverse event (AE) by body system or preferred term, percentages refer to total number of patients. † For one patient (number 144), two local AEs (injection site pain and extravasation occurred at the opposite intravenous site relative to the study drug infusion site (opposite arm). AE = adverse event.
Advocates of multimodal analgesia suggest that coadministration of nonopioid analgesics reduces opioid consumption and pain intensity and may reduce opioid-related AEs.5,6

Table 5. Summary of Local Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>1 g Intravenous Acetaminophen</th>
<th>2 g Propacetamol</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td>49</td>
<td>50</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Total No. of patients with ≥1 local AE, n (%)</td>
<td>1 (2.0)</td>
<td>21 (42.0)</td>
<td>1 (1.9)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Injection site pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>1 (2.0)</td>
<td>19 (38.0)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Extravasation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. of patients with serious local AEs, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. of patients who discontinued because of local AEs, n (%)</td>
<td>0</td>
<td>1 (2.0)</td>
<td>3 (6.0)</td>
<td></td>
</tr>
<tr>
<td>No. of patients with ≥1 related local AE, n (%)</td>
<td>1 (2.0)</td>
<td>21 (42.0)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
</tbody>
</table>

* Pairwise comparisons: intravenous acetaminophen vs. placebo: P = 0.610; propacetamol vs. placebo: P = 0.001; intravenous acetaminophen vs. propacetamol: P = 0.001.

AE = adverse event.

It is possible that earlier administration of intravenous acetaminophen, starting the morning of surgery and continuing for up to 48 h, could have further reduced opioid consumption to the point that significant reductions in nausea and constipation could have been detected. Morphine has been considered the accepted standard of analgesia. In the immediate postoperative setting, optimal analgesia cannot always be achieved with intravenous opiates used as monotherapy. As noted previously, the global measures of efficacy over 6 h were equivalent in the intravenous acetaminophen and propacetamol groups and superior to those reported in the placebo group (P < 0.05). A balanced, multimodal approach may therefore provide better efficacy results.

This study and numerous other studies report that pain intensity scores are significantly reduced in patients treated with intravenous acetaminophen, propacetamol,16 COX-2 inhibitors,29,30 or NSAIDs7 as adjuncts to...
PCA morphine compared with PCA morphine alone. Zhou et al. reported lower pain intensity scores in patients treated with either ketorolac or propacetamol compared with placebo, despite the fact that all patients treated could self-administer additional PCA morphine and theoretically achieve equivalent levels of analgesia. The risks and benefits of any treatment must be considered before implementation. Although NSAIDs and COX-2 inhibitors offer effective augmentation of opioid-based analgesia, concerns have been raised regarding their use perioperatively. NSAIDs inhibit platelet function, increase perioperative bleeding, and have been shown to have nephrotoxic effects in patients with and without preexisting renal insufficiency. Selective COX-2 inhibitors have been associated with salt and water retention and hypertension and inhibit bone remodeling in animal models. This latter observation has raised concerns of impaired healing and nonunion after various forms of orthopedic surgery. Recently, a greater incidence in sternal wound infection and proportionately greater incidences of other serious AEs, including cerebrovascular complications, myocardial infarction, and renal dysfunction, have been reported with COX-2 inhibitors in patients undergoing coronary artery bypass surgery. Acetaminophen offers a historically low incidence of adverse effects and untoward drug interactions. However, higher-than-recommended doses have been associated with hepatotoxicity and hepatic failure. When used according to the labeling, propacetamol has been associated with liver dysfunction in less than 1 case per 500,000 treated patients (postmarketing surveillance). A similar safety record has been observed with intravenous acetaminophen during the 2 yr after its availability in the European Union. Consistent with this historic safety profile, there was no difference in this study between groups regarding clinically significant increases in liver function test results in patients receiving up to four doses of active study medication or placebo over the 24-h evaluation interval.

Intravenous acetaminophen was well tolerated in the elderly and high-risk (American Society of Anesthesiologists physical status II and III) population included in the current study. As reported previously, AEs with propacetamol and the need to discontinue therapy were primarily related to pain at the infusion site. In contrast, and in accord with a previous clinical trial, the incidence of local AEs with intravenous acetaminophen was similar to that observed with placebo and significantly lower than that noted in the propacetamol group. In addition to providing comparable analgesic efficacy and an improved local safety profile, advantages of intravenous acetaminophen over propacetamol include ease of use and cost effectiveness. In conclusion, 1 g intravenous acetaminophen administered as a single infusion and repeated infusions in patients with moderate to severe postoperative pain after major orthopedic joint replacement surgery is effective, safe, and well tolerated. Intravenous acetaminophen, 1 g, was similar to 2 g propacetamol with regard to efficacy and was superior to propacetamol with regard to local AEs (pain at infusion site), a significant advantage for the patients in terms of tolerance and compliance. These data suggest that intravenous acetaminophen is a useful component of the multimodal analgesia model, especially after major orthopedic surgery.

Appendix: Participating Centers
Raymond S. Sinatra, M.D., Ph.D., Professor, Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut (10 patients); Jonathan S. Jahr, M.D., Professor, University of California, Sacramento, California (65 patients); Lowell W. Reynolds, M.D., Associate Professor, Center for Pain Management, Loma Linda, California (49 patients); Robert Mandel, M.D., Attending Anesthesiologist, Department of Anesthesiology, Cooper Hospital, Camden, New Jersey (1 patient); Brian Ginsberg, M.D., Professor of Anesthesiology, Duke University School of Medicine, Durham, North Carolina (3 patients); Eugene R. Viscusi, M.D., Associate Professor, Department of Anesthesiology, Jefferson Medical College, Philadelphia, Pennsylvania (16 patients); Scott B. Groudine, M.D., Associate Professor, Department of Anesthesiology, Albany Medical College, Albany, New York (12 patients).