Intravenous Acetaminophen (Paracetamol): Comparable Analgesic Efficacy, but Better Local Safety than Its Prodrug, Propacetamol, for Postoperative Pain After Third Molar Surgery

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We compared an acetaminophen (paracetamol) 1 g (n = 51) formulation for infusion with propacetamol 2 g (n = 51) and placebo (n = 50) in a randomized, controlled, double-blind, parallel group trial in patients with moderate-to-severe pain after third molar surgery. Treatment efficacy was assessed in house for 6 h after starting the 15-min infusion. Significant effects versus placebo (P < 0.01) were obtained with both active treatments on pain relief, pain intensity difference on a 100-mm visual analog scale, and on a categorical scale (except for propacetamol at 6 h). No significant differences were noted between active groups except at 1 h. Six-hour weighted sums of primary assessments showed significantly better efficacy than placebo (P < 0.0001) and no difference between active treatments. Median stopwatch time to onset of pain relief for active treatment was 6–8 min after infusion start. Active treatments showed comparable efficacy with a significantly longer duration of analgesia and better patients’ global evaluation compared with placebo. The incidence of patients reporting local pain at the infusion site was significantly less frequent after IV acetaminophen or placebo (0%) in comparison with propacetamol (49%). In conclusion, acetaminophen 1 g and propacetamol 2 g were superior to placebo regarding analgesic efficacy, with a more frequent incidence of local pain at the infusion site for propacetamol.

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Effective postoperative pain control is essential for the optimal care of surgical patients. Nonsteroidal antiinflammatory drugs and acetaminophen (paracetamol) are commonly used in the management of moderate to severe pain alone or in combination with opioids (1). Conventional nonsteroidal antiinflammatory drugs may be associated with serious unwanted effects (such as bleeding or renal impairment) when used perioperatively. Short-term use of acetaminophen at adequate dosages has a well-established safety profile (2). IV administration is the route of choice when oral administration is not possible or when rapid analgesia is needed after surgery.

Acetaminophen is poorly water soluble and unstable in solution, making IV administration difficult. Propacetamol is an acetaminophen prodrug that is supplied as powder to be dissolved in saline or glucose immediately before infusion. Propacetamol has a proven efficacy and offers good general safety but is associated with pain at the infusion site (3,4). The reconstitution procedure of mixing powder and fluid includes the possibility of errors and the risk of contact dermatitis for the nursing staff (5).

A stable ready-to-use acetaminophen solution for infusion (IV acetaminophen) intended to reduce the disadvantages of propacetamol has been developed (5). The aim of this study was to compare the analgesic efficacy and safety of a single IV infusion of acetaminophen 1 g with propacetamol 2 g (equivalent to 1 g acetaminophen) and placebo in patients with moderate-to-severe pain after third molar surgery.

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Methods

The trial was completed in a single center at the University Hospital of Aarhus, Denmark between September and December 1999 after approval by the Scientific Ethical Committee for Aarhus County. Written informed consent was obtained from all patients. Inhouse patients aged 18 yr or older of either sex were eligible for the study if they were scheduled for elective removal of at least one impacted mandibular third molar requiring local anesthesia only, were classified as ASA risk class I, and were suffering from moderate to severe pain (assessed on a four-point verbal rating scale [VRS]) within 4 h after surgery. Patients were excluded from the study for the following reasons: other painful physical conditions, liver or advanced renal dysfunction, psychiatric or medical conditions, known drug abuse, contraindications to the study drugs, use of nonsteroidal antiinflammatory drugs or other analgesic drug within 12 h preceding study medication, concomitant use of sedatives or microsomal enzyme inducers, pregnancy, or women of childbearing potential not using adequate contraception.

The study was conducted as a controlled, randomized, double-blind, parallel-group study. Treatments were allocated according to block randomization (each block, n = 6). Treatments comprised a single 15-min IV infusion of IV acetaminophen 1 g, propacetamol 2 g, or placebo. A double-dummy method was used to preserve the double-blind design because the active drugs differed in appearance. IV acetaminophen was provided in a bottle containing 1 g acetaminophen in 100 mL solution. Propacetamol hydrochloride was presented as a 20 mL sterile vial containing 2 g propacetamol hydrochloride powder and a 100 mL bottle of 0.9% sodium chloride solution. During the trial period, the patients abstained from coffee, tea, or caffeine-containing beverages. Alcohol was not allowed from 12 h before drug administration until 48 h after medication. Local anesthesia only (prilocaine 3% and felypressin 0.54 μg/mL) ranging from 3.6 to 7.6 mL was used during standardized surgical procedures (6). An IV cannula for drug administration was placed in the cubital vein of each arm immediately after surgery in those patients who fulfilled inclusion criteria.

Patients were enrolled if their postoperative pain intensity (PI) reached moderate or severe within 4 h after surgery on a four-point VRS as follows: 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Baseline assessments of pain intensity (VRS and visual analog scale [VAS]) were made just before administration of trial medication. Posttreatment observations began simultaneously with drug administration (T0). PI and pain relief (PR) were assessed at baseline (T0, start of infusion) and at 15 min, 30 min, 45 min, 1 h, 2 h, 3 h, 4 h, 5 h, and 6 h postmedication. Pain assessments were also made when a patient requested rescue analgesia (ibuprofen 400 mg tablet). A patient’s global evaluation was required at 6 h postmedication.

The primary efficacy variable, PR, was rated on a 5-point verbal scale (0 = none, 1 = a little, 2 = moderate, 3 = a lot, and 4 = complete). Secondary variables were the derived scores: maximum PR (MaxPR), time of maximum PR (tMaxPR), and weighted sum of PR (TOTPAR), i.e., the sum of scores weighted for time elapsing between observations T15min to T6h. Two types of PI scales were used. PI was categorized on a four-point VRS similar to that at enrollment time and on a VAS PI scale (PAI) ranging from 0 mm (no pain) to 100 mm (worst possible pain). The following scores were derived from both the PI and the PAI: PI difference from baseline (PID/PAID), maximum difference (MaxPID/MaxPAID), time of maximum difference (tMaxPID/tMaxPAID), and a weighted sum of differences (SPID/SPAID) from T15min to T6h. The onset of PR was timed by patients using two stopwatches and was defined as the time to stop of the first watch, indicating the first perceptible PR, only if confirmed by a stop of the second watch indicating meaningful PR (7). In the absence of stop of the second watch, the onset of PR was censored. The time of rescue medication was recorded as the actual time of request. A global evaluation scale was used to categorize treatment satisfaction at 4 levels (0 = poor, 1 = fair, 2 = good, 3 = excellent).

Safety variables comprised adverse events (AEs), vital signs (arterial blood pressure and heart rate), and laboratory variables (hematology and plasma biochemistry). AEs were assessed before surgery on Day 0 and up to Day 6. Vital signs were measured at T0 just before ratings and medication and at 1 h and 6 h postmedication. Blood samples for laboratory variables were drawn between Day −6 and Day −1 and at 48 h postmedication.

The null hypothesis was the absence of statistical difference between treatment groups and between T0 and T6h in terms of PR (the primary efficacy variable) and supported by other variables. The comparison between IV acetaminophen and propacetamol was a secondary objective. The study was powered toward (β = 10%) demonstrating superiority of both active treatments over placebo, defined by a population difference of one categorical step (equal to 1) on the PR scale. A minimum sample size of 48 patients per group was estimated using the method provided by PASS 6.0 for a one-way analysis of variance with a two-sided α = 5% and assuming a common standard deviation of 1.2 on the basis of previous experience using the same trial method.

All patients who received at least one dose of randomized medication were evaluated by intention-to-treat (ITT) analyses. Data from patients who requested rescue medication were carried forward from the last valid assessment. Treatment effects at each time point,
for all pain variables except timed data, were analyzed by a one-way covariance analysis model that used treatment as a fixed effect and PAI as covariate. All multiple pairwise treatment comparisons were performed using Fisher’s protected least significant difference procedure. For the number of patients experiencing onset of analgesia and the number of patients requiring rescue medication, χ² or Fisher’s exact tests were used. For survival type data, the percentiles of the survival distribution were calculated using the Kaplan-Meier product limit estimator. Times of maximum effects and time-to-onset data were analyzed by the Gehan-Wilcoxon test. Time to request for rescue medication was analyzed by the log-rank test. Patient’s global evaluation was analyzed by the Cochran Mantel-Haenszel test. The incidence of patients with at least one treatment-emergent AE was compared between treatment groups using Fisher’s protected least significant difference procedure. Shift tables were used with laboratory variables.

Results

Treatments were randomized among 152 patients (IV acetaminophen n = 51, propacetamol n = 51, placebo n = 50). No patient withdrew from the study and all 152 were evaluated for efficacy (ITT analyses) and for safety. The treatment groups were comparable with respect to demographics, number of teeth removed, and initial PI. Patients were aged 24.4 ± 3.1 yr and were mainly females (64.5%), with one tooth removed for 60.5% of patients and two teeth removed for 39.5%. Mean PI at baseline on the 100-mm VAS was 52.0 ± 13.5 mm (Table 1). The baseline pain assessed on a verbal scale was considered as mild for 3.3% of patients, moderate for 92.8%, and severe for 4.0%.

The time course of the primary effect variable PR for IV acetaminophen, propacetamol, and placebo during the 6-h observation period is shown in Figure 1. The overall treatment effect for PR up to 6 h was significant (P = 0.0001). Paired comparisons demonstrated that PR was greater after IV acetaminophen and propacetamol than placebo at all assessment times and that IV acetaminophen did not differ significantly from propacetamol except at T₁h. Corresponding results were obtained for MaxPR (Table 2) and TOTPAR (Table 3).

PID showed a significant (P ≤ 0.0002) overall treatment effect up to 6 h and PID was greater after IV acetaminophen and propacetamol as compared with placebo at all assessment times except at T₀h for propacetamol. IV acetaminophen did not differ significantly from propacetamol. Corresponding results were obtained for MaxPID (Table 2) and SPID (Table 3).

The analog scale PAID also showed a significant (P ≤ 0.0035) overall treatment effect at each assessment time up to 6 h (Fig. 2). Paired comparisons demonstrated that PAID was greater after IV acetaminophen and propacetamol than placebo at all assessment times. IV acetaminophen did not differ significantly from propacetamol. Corresponding results were obtained for MaxPAID (Table 2) and SPAID (Table 3).

The time-to-onset of analgesia, measured by the double stopwatch method, indicated a significant (P = 0.0001) overall treatment effect. Paired comparisons showed that the median time-to-onset of analgesia was significantly earlier after either active treatment than after placebo (P = 0.0001), whereas IV acetaminophen and propacetamol did not differ significantly from each other (IV acetaminophen, 8 min; 95% confidence interval, 5–12; propacetamol, 6 min; 95% confidence interval, 5–7; placebo was not estimable as <50% of patients experienced onset of analgesia). The number of patients experiencing an onset of analgesia was significantly larger with IV acetaminophen (80.4%) and propacetamol (88.2%) than with placebo (38.0%; P = 0.001 in both cases).

The median duration of analgesia, as measured by the time elapsing to a request for rescue medication was significantly longer (P = 0.0001) after IV acetaminophen (125 min; 95% confidence interval, 84–204 min) and propacetamol (180 min; 95% confidence interval, 102–216 min) than after placebo (42 min; 95% confidence interval, 30–48 min). The corresponding overall treatment effect was significant (P = 0.0001) and the 2 active treatments did not differ significantly from each other. Fewer patients requested rescue medication after IV acetaminophen (82.4%) as compared with placebo (98.0%; P = 0.016). Six hours after medication, more patients rated their global treatment satisfaction as good-to-excellent after IV acetaminophen (40%) and propacetamol (49%) than after placebo (12%). The corresponding overall treatment effect was significant (P = 0.001).

In total, 90 treatment-emergent AEs were reported by 38.8% of patients (Table 4). The most frequent AEs were local pain at the infusion site (15.8% of patients), postoperative pain (8.6%), and dizziness (7.9%); none was serious and no patient was withdrawn because of an AE. The proportion of patients with AEs was significantly smaller (P = 0.001) with IV acetaminophen (27.5%) than withpropacetamol (60.8%) and the proportion was similar with placebo (28.0%). This was attributed to a frequent incidence of application site disorders (local pain at the infusion site (15.8% of patients), which did not occur with IV acetaminophen or placebo infusions. The intensity of application site disorders led to interrupted infusions in 36% of patients experiencing local pain. The infusion was resumed in all patients when the pain disappeared, after 2 to 14 min. Other AEs did not differ significantly between groups. Laboratory tests and vital signs showed no clinically important changes (data not shown).
Discussion

Despite a wide use of acetaminophen, no injectable form has been available because of instability in aqueous solution (8,9). Recently, an aqueous solution of acetaminophen has been developed by controlling hydrolysis through adding a pH buffer to maintain a stable pH and oxidation through the addition of a powerful antioxidant and through an oxygen-free manufacturing process. These processes result in an infusible formulation of acetaminophen that does not need reconstitution and that overcomes the disadvantages of the former available prodrug, propacetamol (i.e., injection site pain, the risk of making errors during the reconstitution procedures, and risk of contact dermatitis for the nursing staff) (5).

Pharmacokinetic comparison of 1 g IV acetaminophen with 2 g propacetamol in 24 healthy volunteers showed bioequivalence (10). Therefore, all pharmacokinetic, efficacy, and general safety data of propacetamol can be applied to IV acetaminophen. The analgesic superiority of propacetamol to placebo is documented for patients with moderate-to-severe postoperative orthopedic and abdominal pain (3,4,11). It also provides an opioid-sparing effect of up to 46% in several types of postoperative pain (12–15). Oral acetaminophen 1 g administered

Table 1. Mean Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Acetaminophen (n = 51)</th>
<th>Propacetamol (n = 51)</th>
<th>Placebo (n = 50)</th>
<th>Overall (n = 152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>24.5 ± 2.9</td>
<td>24.3 ± 3.6</td>
<td>24.5 ± 2.8</td>
<td>24.4 ± 3.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.5 ± 10.5</td>
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<td>67.3 ± 10.7</td>
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</tr>
<tr>
<td>PAI (VAS) (mm)</td>
<td>51.1 ± 12.2</td>
<td>53.8 ± 14.2</td>
<td>51.2 ± 14.2</td>
<td>52.0 ± 13.5</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (31.4%)</td>
<td>22 (43.1%)</td>
<td>16 (32.0%)</td>
<td>54 (35.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>35 (68.6%)</td>
<td>29 (56.9%)</td>
<td>34 (68.0%)</td>
<td>98 (64.5%)</td>
</tr>
</tbody>
</table>

Values are mean ± sd or n (%).
PAI = pain intensity analog scale; VAS = visual analog scale.

Table 2. Maximum Pain Relief and Pain Intensity Difference Ratings

<table>
<thead>
<tr>
<th></th>
<th>Acetaminophen (n = 51)</th>
<th>Propacetamol (n = 51)</th>
<th>Placebo (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MaxPR</td>
<td>2.3 ± 1.0</td>
<td>2.4 ± 1.2</td>
<td>1.0 ± 1.2</td>
</tr>
<tr>
<td>MaxPID</td>
<td>1.1 ± 0.5</td>
<td>1.1 ± 0.7</td>
<td>0.3 ± 0.6</td>
</tr>
<tr>
<td>MaxPAID</td>
<td>32.9 ± 15.6</td>
<td>34.7 ± 21.0</td>
<td>11.0 ± 16.4</td>
</tr>
</tbody>
</table>

When the global test among all treatment groups was significant, individual treatment group comparisons were examined. Means and medians associated with different symbols are significantly different. Differences are differences from baseline at successive posttreatment times, i.e., pretreatment scores minus posttreatment scores (T15m to T6h). MaxPR = maximum pain relief; MaxPID = maximum pain intensity difference (categorical scale); MaxPAID = maximum pain intensity difference (analog scale).

Figure 1. Mean scores of pain relief (PR). Abscissa: time (h); ordinate: pain relief (mean score). **P < 0.01, acetaminophen versus placebo and propacetamol versus placebo; ¥P < 0.05, acetaminophen versus propacetamol. ▲ = acetaminophen; ◦ = propacetamol; ■ = placebo.
as single (16,17) and repeated doses (18) shows analgesic superiority to placebo in alleviating pain after third molar surgery, which is recognized as one of the most consistent and sensitive pain models for evaluating analgesic drugs (19–22).

The present study was the first comparing IV acetaminophen and propacetamol for postoperative pain after oral surgery. It showed the superior analgesic effect of IV acetaminophen 1 g and propacetamol 2 g as compared with placebo on pain after third molar surgery. Analgesia was demonstrated by the primary efficacy variable PR and supported by the secondary efficacy variables PID and PAID assessed between 15 minutes and 6 hours after the start of infusions compared with baseline values. These findings were supplemented by efficacy scores derived from each scale comprising peak effects and sums of scores. These differences regarding analgesic efficacy between the active groups and the placebo group confirm the analgesic efficacy of propacetamol and validate the study.

The statistically significant difference in PR at 1 hour between propacetamol and acetaminophen was not confirmed at other time points. In addition, another study performed in patients with postoperative pain after orthopedic surgery demonstrated no difference between IV acetaminophen and propacetamol regarding PR at any time (23).

The median time to onset of analgesia occurred very shortly after the active drug infusion start, whereas the corresponding median time-to-onset of analgesia after placebo was not estimable because <50% of the patients experienced onset of analgesia. Such a fast onset of action of the active drugs is remarkable and is of particular interest in the postoperative setting.

The end-point used to assess the duration of analgesia was the elapsed time until a request for rescue medication. This end-point, recommended by regulatory agencies, is restrictive, as all patients, even non-responders, are included in the analysis. This may explain the relatively short duration of action observed with both active drugs. During the 6 hours

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**Table 3. Weighted Sum of Pain Ratings over 6 Hours**

<table>
<thead>
<tr>
<th></th>
<th>Acetaminophen (n = 51)</th>
<th>Propacetamol (n = 51)</th>
<th>Placebo (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTPARK</td>
<td>6.9 ± 5.9*</td>
<td>7.7 ± 5.5*</td>
<td>1.7 ± 3.4†</td>
</tr>
<tr>
<td>SPID</td>
<td>2.2 ± 3.1*</td>
<td>2.4 ± 2.8*</td>
<td>−0.4 ± 2.9‡</td>
</tr>
<tr>
<td>SPAID</td>
<td>88.1 ± 109.3*</td>
<td>91.0 ± 98.7*</td>
<td>−12.4 ± 86.0‡</td>
</tr>
</tbody>
</table>

*When the global test among all treatment groups was significant, individual treatment group comparisons were examined. Means and medians associated with different symbols are significantly different. Sums are weighted by time elapsing between observations; e.g., ∑Pain relief × time (hours since previous observation).

TOTPAR = weighted sums of pain relief; SPID = weighted sums of pain intensity differences (categorical scale); SPAID = weighted sums of pain intensity differences (analog scale).

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**Figure 2.** Mean scores of pain intensity difference (visual analog scale). Abscissa: Time (h); ordinate: pain intensity analog scale (mean score). **P < 0.01, acetaminophen versus placebo and propacetamol versus placebo. ▲ = acetaminophen; ● = propacetamol; ■ = placebo.**
after the infusions, fewer patients requested rescue medication in the IV acetaminophen group as compared with the placebo group. In this study, a significant difference was observed between both active drugs and placebo up to 6 hours postmedication, which is consistent with the duration observed in routine practice (4 to 6 hours).

Satisfaction was similar between the 2 active drugs (40% of patients rating the treatment as good or excellent in the IV acetaminophen group, 49% in the propacetamol group) and statistically significantly better than placebo (12%) in this model. The discrepancy between this result and the percentage of 65% of patients rating the treatment as good or excellent in an orthopedic study (4) is probably related to the model.

AEs after IV acetaminophen 1 g occurred with the same frequency as in the placebo group and were significantly less frequent than after propacetamol 2 g. Most of the AEs with propacetamol were local pain at the infusion site (49.0%), as reported previously (3,4). These local AEs led to interruption of the infusion in nine patients (17.6%) in the propacetamol group, whereas there were no treatment interruptions in the IV acetaminophen group. This lack of infusion interruption seen with IV acetaminophen administered as a single dose in this study could be especially beneficial and associated with better patient compliance in the case of repeated administration in clinical practice.

Local AEs did not occur with IV acetaminophen1 g or placebo. The difference between IV acetaminophen and propacetamol is probably attributable to the pH and osmolarity of IV acetaminophen (5.5 and 290 mOsmol/L, respectively) that are closer to plasma characteristics (7.3–7.4 and 275–295 mOsmol/L) than are those of propacetamol (3.5 and 410 mOsmol/L). In addition to comparable analgesic efficacy and a better local safety profile, the advantages of IV acetaminophen over propacetamol include ease of use (no need for previous reconstitution) and cost effectiveness (reduction in nurse’s time and ancillary products) (3,5).

In conclusion, IV acetaminophen 1 g and propacetamol 2 g were superior to placebo regarding efficacy after third molar surgery. No application site disorder was reported after IV acetaminophen infusions. Acetaminophen IV demonstrated a tolerability profile comparable to that of placebo and significantly better than propacetamol 2 g, which caused local pain at the infusion site for 49% of the patients, leading to infusion interruption for 17.6% of them.

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**References**