CURRENT THERAPEUTIC RESEARCH

VOLUME 66, NUMBER 4, JULY/AUGUST 2005

Effects of Single-Dose Injectable Paracetamol Versus Propacetamol in Pain Management After Minor Gynecologic Surgery: A Multicenter, Randomized, Double-Blind, Active-Controlled, Two-Parallel-Group Study

Jean Marty, MD[1]; Dan Benhamou, MD[2]; Dominique Chassard, MD[3]; Nicole Emperaire, MD[4]; Alain Roche, MD[5]; Annick Mayaud, MD[6]; Dominique Haro, MD[7]; Xavier Baron, MD[8]; and Odile Hiesse-Provost, MD[9]

[1]Department of Anesthesia Reanimation, Hôpital Beaujon, Clichy, France; [2]Department of Anesthesia Reanimation, Hôpital Antoine Béclère, Clamart, France; [3]Department of Anesthesia Reanimation, Hôtel Dieu, Lyon, France; [4]Department of Anesthesia Reanimation, Hôpital La Conception, Marseille, France; [5]Department of Anesthesia Reanimation, Centre Hospitalier Universitaire, Saint André, Bordeaux, France; [6]Department of Anesthesia Reanimation, Centre Hospitalier de Caen, Caen, France; [7]Department of Anesthesia Reanimation, Clinique Mutualiste Eugène André, Lyon, France; [8]Department of Anesthesia Reanimation, Centre Hospitalier Saint Louis, La Rochelle, France; and [9]Bristol-Myers Squibb Company, Rueil-Malmaison, France

ABSTRACT

Background: Intravenous administration is the route of choice for drug therapy in the immediate postoperative period. Propacetamol (ProAPAP), an injectable prodrug of paracetamol requiring reconstitution, has demonstrated efficacy in managing acute pain and fever. However, it has been associated with pain at the injection site. A stable, ready-to-use formulation of paracetamol solution infused intravenously (IV-APAP) has been developed and might be associated with less pain at the injection site compared with ProAPAP.

Objective: The objective of this study was to assess the tolerability and efficacy of a single dose of IV-APAP 1 g compared with those of a single dose of ProAPAP 2 g in patients with moderate to severe pain after minor gynecologic surgery.

Methods: This single-dose, randomized, double-blind, active-controlled, 2-parallel-group study was conducted at 23 hospitals and outpatient clinics in France. After minor gynecologic surgery, patients reporting moderate to severe pain were randomized to receive a single 15-minute infusion of IV-APAP 1 g or ProAPAP 2 g (bioequivalent doses). Tolerability was monitored using local and systemic adverse event (AE) reporting, clinical examination including vital sign

This study was presented in part in poster form at the 45th Congress of the Société Française d'Anesthésie Réanimation, Paris, France, 2003.

Accepted for publication May 17, 2005.
doi:10.1016/j.curtheres.2005.08.007

0011-393X/05/$19.00

measurement, and patients' ratings of acceptability of the infusion. Efficacy end points included pain intensity at 0, 1, 2, 4, and 6 hours; median time to rescue medication (defined as the time at which 50% of patients requested rescue medication); and percentage of patients requesting rescue medication. Patients' satisfaction with the study drugs was assessed using patient's global evaluation (PGE) and the percentage of patients willing to receive the treatment again.

Results: Of the 163 women who were randomized, 161 received the study medication. The IV-APAP group comprised 80 patients (mean [SD] age, 38.3 [12.8] years [range, 18.0–69.0 years]; mean [SD] weight, 61.1 [11.0] kg [range, 49.0–90.0 kg]), and the ProAPAP group comprised 81 patients (mean [SD] age, 33.9 [12.0] years [range, 18.0–67.0 years]; mean [SD] weight, 61.6 [10.2] kg [range, 42.0–95.5 kg]); the difference in mean age between the 2 groups was statistically significant ($P < 0.05$). The incidence of local treatment-emergent AEs (TEAEs) was significantly lower in the IV-APAP group compared with that in the ProAPAP group (7.5% vs 38.3%; $P < 0.001$). No between-group differences in the incidence of systemic TEAEs was found. All patients in the IV-APAP group found the infusion tolerable, compared with 95% of patients in the ProAPAP group. The median time to rescue medication was not evaluated because <50% of the patients in each group requested it. No significant differences in mean pain intensity score or percentage of patients requesting rescue medication were found between the 2 groups at any time point. The percentages of patients in the IV-APAP and ProAPAP groups who rated the study medication as good or excellent on the PGE (83.6% vs 75.6%; $P < 0.05$) and who were willing to receive the same treatment again (96.0% vs 81.0%; $P = 0.005$) were significantly higher with IV-APAP compared with ProAPAP.

Conclusion: In these patients with moderate to severe pain after minor gynecologic surgery, a single dose of IV-APAP was associated with better local tolerability, similar analgesic efficacy, and greater patient satisfaction compared with a single bioequivalent dose of ProAPAP. (*Curr Ther Res Clin Exp.* 2005;66:294–306)

Key words: paracetamol, propacetamol, intravenous, acetaminophen, postsurgical pain management, gynecologic surgery.

INTRODUCTION

Intravenous administration is the route of choice for drug therapy in the immediate postoperative period. However, because of its poor solubility, paracetamol (acetaminophen), a commonly used analgesic agent, was not available as an injectable formulation until recently. Propacetamol (ProAPAP), an injectable prodrug of paracetamol that requires reconstitution, has been available since 1985 and is used for managing acute pain and fever. In the blood, ProAPAP is rapidly cleaved by plasma esterases into paracetamol and an inactive promoiety (diethylglycine); 2 g of ProAPAP provides 1 g of paracetamol by the end of infusion.

A stable, ready-to-use formulation of intravenous paracetamol (IV-APAP) has been developed, allowing for IV administration of paracetamol itself. It is provided in a 100-mL vial containing 1 g of paracetamol or a 50-mL vial containing 500 mg of paracetamol diluted in water for injection. IV-APAP does not require reconstitution and thus might decrease the risks for contamination and dosage error.[1]

The pH and osmolarity of ProAPAP (3.5 and 410 mOsm/L, respectively) are far from those of plasma (ranges, 7.3–7.4 and 275–295 mOsm/L, respectively). Thus, ProAPAP has been associated with pain at the injection site.[2] In contrast, the pH and osmolarity of IV-APAP (5.5 and 290 mOsm/L, respectively) are more similar to those of plasma, which might lead to less pain at the injection site compared with ProAPAP.

In a pharmacokinetic study with a randomized, open-label, 3-period, crossover design, Flouvat et al[3] compared the pharmacokinetic properties of 2 different doses of IV-APAP with those of ProAPAP in 24 healthy volunteers. Single doses of IV-APAP 0.5 g, IV-APAP 1 g, and ProAPAP 2 g were given, with a 1-week washout period between doses. After the administration of IV-APAP 0.5 and 1.0 g, the pharmacokinetic properties of paracetamol were found to be linear. The 90% CIs for the C_{max} and $AUC_{0-\infty}$ ratios of IV-APAP to ProAPAP were within acceptable bioequivalence ranges, indicating that IV-APAP 1 g is bioequivalent to ProAPAP 2 g. Pain at the infusion site was found in 2% of patients receiving IV-APAP versus 20% receiving ProAPAP. Randomized clinical trials of IV-APAP in adults with postoperative pain after dental[4] and orthopedic[5] surgery and children after hernia repair[6] have also shown improved local tolerability and similar efficacy compared with ProAPAP.

The objective of this study was to assess the tolerability and efficacy of a single dose of IV-APAP 1 g compared with those of a single dose of ProAPAP 2 g in patients with moderate to severe pain after minor gynecologic surgery.

PATIENTS AND METHODS

This single-dose, randomized, double-blind, active-controlled, 2-parallel-group study was conducted at 23 hospitals and outpatient clinics in France. It was conducted in accordance with the Good Clinical Practice guidelines[7] and the Declaration of Helsinki and its amendments.[8] The protocol was approved by an independent ethics committee (Comité de Protection des Personnes de Paris Bichat-Claude Bernard, Paris, France). Patients were enrolled from March 2001 to February 2002.

Inclusion and Exclusion Criteria

Patients aged 18 to 70 years scheduled for elective minor gynecologic surgery to be performed using standardized general anesthesia and who were to receive postoperative care in a hospital or outpatient clinic for at least 6 hours after study drug administration were eligible for the study. Additional inclusion criteria were as follows: body weight 50 to 100 kg; American Society of Anesthesiologists[9] physical status P1 or P2 (healthy or mild systemic disease);

and ability to understand the study procedures, including the use of pain scales after training was given. Except for patients undergoing elective abortion, women of childbearing potential were to have been using oral, implanted, or injectable contraceptive hormones or mechanical contraceptive products and to have a negative urinary pregnancy test within 72 hours before study drug administration. Eligible patients provided written informed consent to participate.

Exclusion criteria included a history of known or suspected alcohol or drug abuse, psychiatric disease, or medical conditions that might invalidate participation in the trial; a history of complete nonresponse to paracetamol or NSAIDs when seeking pain relief; poor venous access; and participation in another clinical study within the 30 days before the study. Patients with any contraindication to the study drugs or any painful physical condition (other than postoperative pain) were also excluded. Patients were excluded if they had a known hypersensitivity to ProAPAP, paracetamol, phenacetin, anesthetics and related compounds, or the inactive ingredients in the study medications.

Patients who had used paracetamol or any NSAID or analgesic within 12 hours before study drug administration, or any concomitant treatment that might confound the quantification of analgesia, and patients treated with corticosteroids within 7 days before surgery were ineligible. Patients were also excluded if they were treated with any microsomal enzyme inducer (eg, barbiturates, isoniazid, anticonvulsants) before the study. Finally, patients with cysteinic lithiasis, impaired hepatic function, advanced renal dysfunction, or chronic malnutrition were excluded from the study.

Anesthesia and Study Drug Administration

During the screening visit, which was scheduled within 21 days before surgery, informed consent and medical history were obtained by the investigator; physical examination and laboratory testing (renal and hepatic function tests) were performed. Training in the use of pain scales was provided to patients.

On the day of surgery, patients received standardized general anesthesia (premedication using hydroxyzine or midazolam; induction with propofol, fentanyl, or alfentanil; intubation with curare as needed; and maintenance with propofol or halogenated gas as required), without any epidural or intrathecal opioids or local anesthetics for postoperative pain control.

After surgery, on recovery of consciousness, patients were asked by the study observer to rate the intensity of their pain using a 4-point verbal scale (0 = none; 1 = mild; 2 = moderate; and 3 = severe). Patients who rated their pain intensity as moderate to severe were randomly assigned, in a 1:1 ratio according to a computer-generated list of random numbers, to 1 of 2 treatment groups: IV-APAP 1 g or ProAPAP 2 g.

The study medications were prepared by an unblinded hospital pharmacist or nurse who was not involved in the data collection. The study medications were

administered as a 100-mL solution infused over 15 minutes through a cannula dedicated to the study medications. To properly assess the tolerability of the medication at the infusion site, no other drugs were administered through the cannula.

In case of insufficient pain relief with the study medications, patients were allowed to receive the usual rescue medication used in each center. Patients were encouraged to wait for at least 1 hour after the start of the infusion before requesting rescue medication.

Tolerability Assessments

Adverse events (AEs) were monitored throughout the 6-hour study period using patient interview and spontaneous reporting. The severity of systemic AEs was assessed by a blinded investigator. In cases of spontaneous reporting of pain at the infusion site, local pain intensity, as assessed by the patient using a 4-point verbal scale (0 = none; 1 = mild; 2 = moderate; and 3 = severe), was recorded. Vital signs, including blood pressure, heart rate, and respiratory rate, were measured at 2 and 6 hours after dosing. Blood pressure was measured with the patient in the supine position, using a mercury sphygmomanometer or an automated blood pressure cuff.

Immediately after study drug administration, patients were asked to evaluate the acceptability of the infusion by answering the question, "Was the infusion tolerable for you?"

Biochemical parameters were not assessed in this study because the biological safety of the study drugs has been shown previously.[2,4,5]

Efficacy Measurements

For the efficacy assessment, patients were asked to rate their pain intensity, both on the 4-point verbal scale and on a 100-mm visual analog scale (VAS) (0 = no pain to 100 = worst possible pain). Pain intensity was assessed at 0 (immediately before infusion; baseline), 1, 2, 4, and 6 hours after dosing. Time to request for rescue medication was recorded. Patients' satisfaction with the study drug was assessed using a patient's global evaluation (PGE) scale (0 = poor; 1 = fair; 2 = good; and 3 = excellent) and their willingness to receive the same treatment again. This assessment was performed at 6 hours after dosing, time rescue medication was requested, or time of study withdrawal.

Statistical Analysis

It was calculated that a sample size of 80 patients per group was required to detect a 50% reduction in the proportion of patients experiencing local AEs for IV-APAP versus ProAPAP, with 80% power and $\alpha = 0.05$, based on an anticipated rate of 40% to 50% of patients in the ProAPAP group and 20% to 25% in the IV-APAP group experiencing local AEs.

All analyses were performed in the intent-to-treat (ITT) population (patients who received the study treatment).

The incidence of AEs was analyzed using the χ^2 test or the Fisher exact test, and descriptive statistics were used to analyze the changes in vital signs.

Mean pain intensity scores were calculated and compared using analysis of covariance, adjusting for baseline pain intensity score. Median time to rescue medication, defined as the time at which 50% of the patients had requested it, was treated as a survival-type response and was analyzed using the stratified Gehan-Wilcoxon test,[10] with baseline pain intensity (verbal scale) as the stratum variable. In comparing the 2 treatment groups, the Cochran-Mantel-Haenszel test stratified by baseline pain intensity (verbal scale) was used for analysis of the need for rescue medication, PGE, and patients' willingness to receive the treatment again.

Statistical analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina). $P < 0.05$ was considered statistically significant.

RESULTS

Study Population

A total of 163 women were enrolled, and 161 received the single infusion of study medication. Two patients did not receive study medication (1 did not comply with the study protocol, and 1 discontinued). All 161 patients, including 2 patients (1 in each group) who did not meet eligibility criteria (mild pain instead of moderate or severe pain) but were inadvertently included in the study, were included in the ITT population and analyses of demographic characteristics, tolerability, and efficacy.

The IV-APAP group comprised 80 patients (mean [SD] age, 38.3 [12.8] years [range, 18.0–69.0 years]; mean [SD] weight, 61.1 [11.0] kg [range, 49.0–90.0 kg]), and the ProAPAP group comprised 81 patients (mean [SD] age, 33.9 [12.0] years [range, 18.0–67.0 years]; mean [SD] weight, 61.6 [10.2] kg [range, 42.0–95.5 kg]); the difference in mean age between the 2 groups was statistically significant ($P < 0.05$). Mean baseline pain intensity scores were statistically similar between the 2 treatment groups (**Table I**).

Six patients received the entire infusion of study drug but did not complete the trial (IV-APAP: 1 patient due to noncompliance with trial instructions, and 2 patients due to AEs [both, postoperative uterine hemorrhage]; ProAPAP: 1 patient due to withdrawal of consent, and 2 patients due to AEs [1 patient each, postoperative uterine bleeding and uterine pain]).

Tolerability

AEs were reported by significantly fewer patients in the IV-APAP group compared with the ProAPAP group (14 [17.5%] vs 43 [53.1%]; $P < 0.001$). The percentage of patients who reported AEs considered related to the study medication was significantly lower in the IV-APAP group compared with the ProAPAP group (5 [6.3%] vs 35 [43.2%]; $P < 0.001$).

Local treatment-emergent AEs (TEAEs) (pain and reaction at the injection site) occurred in a significantly lower number of patients in the IV-APAP group

(6 [7.5%] patients, all with pain) compared with the ProAPAP group (31 [38.3%] patients, 27 with pain and 4 with reaction) ($P < 0.001$) (**Table II**). These local TEAEs were considered treatment related in 5 of 6 patients in the IV-APAP group and in all 31 patients in the ProAPAP group. In most patients, local TEAEs were mild (IV-APAP, 5 [83.3%] patients; ProAPAP, 16 [51.6%] patients). Local TEAEs were reported as severe by 2 (6.5%) ProAPAP-treated patients. One (1.2%) patient in the ProAPAP group discontinued treatment 10 minutes after the start of the 15-minute study drug infusion due to pain at the infusion site. The residual volume of the infused medication was 50 mL (1 g ProAPAP).

Table I. Baseline demographic and clinical characteristics of the study patients (N = 161).

Characteristic	IV-APAP (n = 80)	ProAPAP (n = 81)
Age, y		
Mean (SD)	38.3 (12.8)	33.9 (12.0)*
Median	38.0	31.0
Range	18.0–69.0	18.0–67.0
Weight, kg		
Mean (SD)	61.1 (11.0)	61.6 (10.2)
Median	57	60
Range	49.0–90.0	42.0–95.5
Surgery type, no. (%)		
Hysteroscopy	28 (35.0)	23 (28.4)
Elective abortion	19 (23.8)	25 (30.9)
Celioscopy	10 (12.5)	12 (14.8)
Curettage	10 (12.5)	7 (8.6)
Conization	6 (7.5)	7 (8.6)
Other	3 (3.8)	3 (3.7)
Aspiration	2 (2.5)	1 (1.2)
Hysterectomy	1 (1.3)	2 (2.5)
Laser treatment for condyloma	1 (1.3)	1 (1.2)
Pain intensity at the surgical site		
Verbal scale, no. (%)		
Mild	7 (8.8)	4 (4.9)
Moderate	68 (85.0)	67 (82.7)
Severe	5 (6.3)	10 (12.3)
VAS score,† mean (SD), mm	37.7 (19.4)	41.1 (20.5)

IV-APAP = injectable paracetamol; ProAPAP = propacetamol; VAS = visual analog scale.
*$P < 0.05$ versus IV-APAP.
†Scale: 0 = no pain to 100 = worst possible pain.

Table II. Incidence of treatment-emergent adverse events (TEAEs) reported by >5% of patients (N = 161). Values are presented as no. (%) of patients unless otherwise specified.

TEAE	IV-APAP (n = 80)	ProAPAP (n = 81)
Local		
Pain	6 (7.5)	27 (33.3)*
Reaction	0	4 (4.9)
Total local TEAEs, no.	6	31
Total severe local TEAEs, no.	0	2
Total patients with ≥1 local TEAE	6 (7.5)	31 (38.3)†
Systemic		
Nausea	3 (33.3)	5 (26.3)
Vomiting	3 (33.3)	5 (26.3)
Uterine hemorrhage	2 (22.2)	1 (5.3)
Migraine	1 (11.1)	0
Abdominal pain	0	3 (15.8)
Back pain	0	1 (5.3)
Other gastrointestinal disorders‡	0	1 (5.3)
Uterine atony	0	1 (5.3)
Uterine disorders	0	1 (5.3)
Pyrexia	0	1 (5.3)
Total systemic TEAEs, no.	9	19
Total severe systemic TEAEs, no.	0	3
Total patients with ≥1 systemic TEAE	8 (10.0)	15 (18.5)
Total TEAEs	15	50
Total patients with ≥1 TEAE	14 (17.5)	43 (53.1)†

IV-APAP = injectable paracetamol; ProAPAP = propacetamol.
*One patient withdrew due to this TEAE.
†$P < 0.001$ versus IV-APAP.
‡Includes intestinal transit disorders.

There were no between-group differences in the incidence of systemic TEAEs, with 8 (10.0%) patients in the IV-APAP group having reported at least 1 systemic TEAE compared with 15 (18.5%) patients in the ProAPAP group. Systemic TEAEs were reported as severe by 3 (15.8%) patients treated with ProAPAP (uterine hemorrhage, abdominal pain, vomiting). None of the patients discontinued the study due to a systemic TEAE. No significant changes in vital signs were observed.

All patients in the IV-APAP group found the infusion acceptable compared with 77 (95.0%) patients in the ProAPAP group.

Efficacy

There were no significant differences in mean scores on the verbal scale (**Figure 1**) or VAS (**Figure 2**) between the 2 treatment groups at any time point. At ≥1 hour after dosing, the mean VAS scores were <30 mm (considered the threshold for clinically significant pain).

No statistically significant differences in the numbers of patients requesting rescue medication were found between the 2 groups at any time during the study (at study end, 20 [25.0%] vs 27 [33.3%]) (**Figure 3**). The median time to rescue medication was not evaluated because <50% of the patients in either group requested rescue medication.

A significantly higher number of patients in the IV-APAP group assessed the treatment they received as good or excellent on the PGE compared with that in the ProAPAP group (66 [83.6%] vs 59 [75.6%]; $P < 0.05$), with the remainder of patients assessing the treatments as fair or poor. Similarly, a significantly higher percentage of patients in the IV-APAP group were willing to receive the same treatment again compared with that in the ProAPAP group (76 [96.0%] vs 64 [81.0%]; $P = 0.005$).

DISCUSSION

In this comparison of the tolerability and efficacy of IV-APAP and ProAPAP, ProAPAP was chosen as the comparator because it was the only injectable formu-

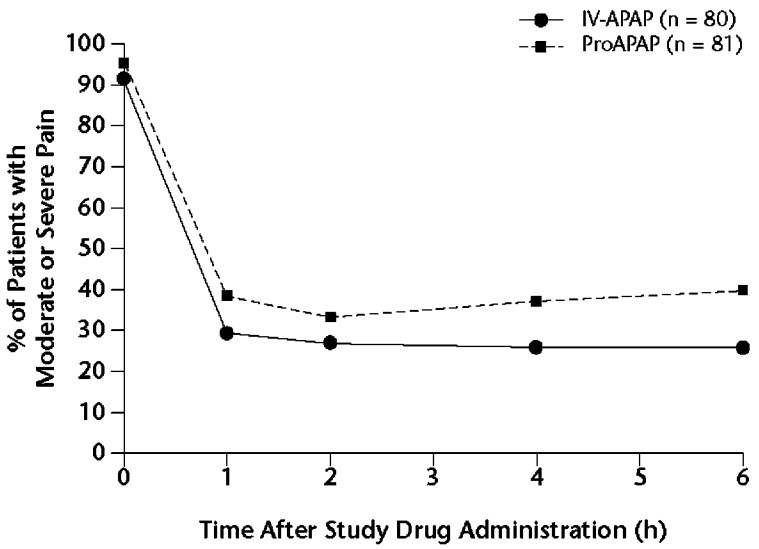

Figure 1. Percentages of patients who rated pain as moderate to severe after receiving a single dose of injectable paracetamol (IV-APAP) or propacetamol (ProAPAP) for postsurgical pain management. No significant between-group differences were found.

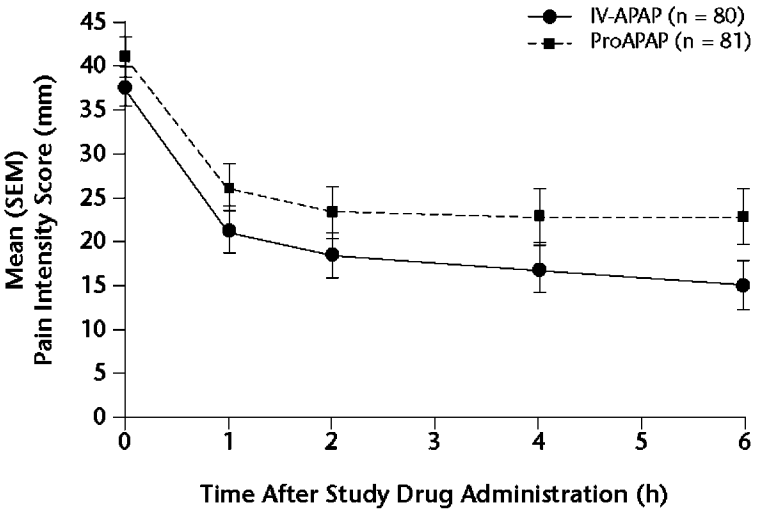

Figure 2. Mean pain intensity scores, as measured on a 100-mm visual analog scale (0 = no pain to 100 = worst possible pain), in patients receiving a single dose of injectable paracetamol (IV-APAP) or propacetamol (ProAPAP) for postsurgical pain management. No significant between-group differences were found.

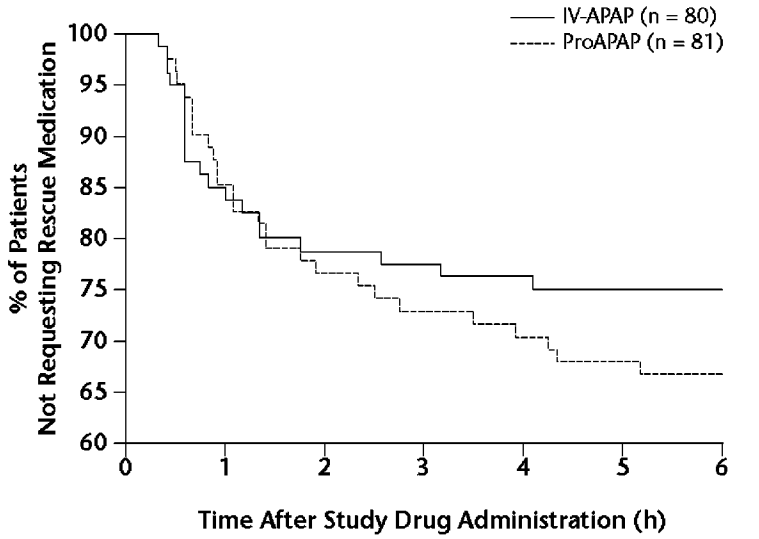

Figure 3. Percentages of patients who did not request rescue medication after receiving a single dose of injectable paracetamol (IV-APAP) or propacetamol (ProAPAP) for postsurgical pain management. Because <50% of patients requested rescue medication, the median time to rescue medication use was not assessable. No significant between-group differences were found.

lation of paracetamol commercially available in Europe at the time of the study. The amount of 2 g of ProAPAP was chosen because it has been shown to be bioequivalent to 1 g of paracetamol.[3] No placebo group was included because the main objective of the study was the tolerability assessment, and both ProAPAP and IV-APAP have shown significant analgesic efficacy compared with placebo.[2,4,5,11,12]

We found that IV-APAP was well tolerated in the study population. As reported in previous clinical trials,[3–5] a significantly smaller percentage of patients experienced local TEAEs in this group compared with the ProAPAP group (7.5% vs 38.3%; $P < 0.001$). This difference was likely due to the pH and osmolarity of IV-APAP, which are closer to those of plasma than are the pH and osmolarity of ProAPAP. As reported previously,[2] pain at the infusion site was the most common TEAE associated with ProAPAP.

The analgesic efficacy of IV-APAP, as measured by pain intensity score, was similar to that of ProAPAP, supporting (in this first study comparing these drugs in the treatment of postoperative pain management after minor visceral surgery in adults) previous studies that have shown the analgesic efficacy of IV-APAP after dental[4] and orthopedic surgery.[5] Regarding the magnitude of the analgesic effect, at ≥1 hour after dosing, the mean VAS scores were <30 mm—the value commonly considered to be the threshold for clinically significant pain.[13]

In addition to better local tolerability and comparable analgesic efficacy, the potential advantages of IV-APAP over ProAPAP include decreased risks for contamination and dosage error, as well as reduced nurse's time and need for ancillary products, because reconstitution is not required. Finally, occupational contact dermatitis, a risk for health care providers who handle ProAPAP, is unlikely to occur with IV-APAP.[1]

The general tolerability of both medications was good, supporting the good general safety profile of paracetamol, which has a historically low incidence of AEs (with hepatotoxicity and hepatic failure being associated only with higher-than-recommended doses) and untoward drug–drug interactions.[14] Paracetamol has not been found to induce nausea, vomiting, or respiratory depression (which are commonly induced by opioids), making it useful in the postoperative setting. Paracetamol also has not been found to be associated with deleterious gastrointestinal effects; inhibition of platelet function; increased risk for perioperative bleeding; nephrotoxicity observed with NSAIDs[15–18]; salt or water retention or hypertension described with selective cyclooxygenase-2 inhibitors.[19] Furthermore, paracetamol has not been shown to interact with drugs commonly used in the postoperative setting.[20]

After treatment with IV-APAP, patients' satisfaction with treatment was considered better with IV-APAP, as suggested by the PGEs of the study drug and their willingness to receive the same treatment again. Therefore, the results of the present study, which showed the better local tolerability and similar analgesic efficacy of IV-APAP compared with ProAPAP, suggest that IV-APAP is a viable option in postsurgical pain management.

CONCLUSION

In these patients with moderate to severe pain after minor gynecologic surgery, a single dose of IV-APAP was associated with better local tolerability, similar efficacy, and greater patient satisfaction compared with a single bioequivalent dose of ProAPAP.

ACKNOWLEDGMENT

The authors thank Laurence Saya, MD, of Altius Pharma CS, Paris, France, for assistance in the preparation of the manuscript.

REFERENCES

1. Schmitt E, Vainchtock A, Nicoloyannis N, et al. Ready-to-use injectable paracetamol: Easier, safer, lowering workload and cost. *Eur J Hosp Pharm.* 2003;9:96–102.
2. Zhou TJ, Tang J, White PF. Propacetamol versus ketorolac for treatment of acute postoperative pain after total hip or knee replacement. *Anesth Analg.* 2001;92: 1569–1575.
3. Flouvat B, Leneveu A, Fitoussi S, et al. Bioequivalence study comparing a new paracetamol solution for injection and propacetamol after single intravenous infusion in healthy subjects. *Int J Clin Pharmacol Ther.* 2004;42:50–57.
4. Moller PL, Juhl GI, Payen-Champenois C, Skoglund LA. IV acetaminophen (paracetamol): Comparable analgesic efficacy, but better local safety than its prodrug, propacetamol, for postoperative pain after third molar surgery. *Anesth Analg.* 2005;101: 90–96.
5. Sinatra RS, Jahr JS, Reynolds LW, et al. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. *Anesthesiology.* 2005;102:822–831.
6. Murat I, Baujard C, Foussat C, et al. Tolerability and analgesic efficacy of a new i.v. paracetamol solution in children after inguinal hernia repair. *Pediatr Anaesth.* 2005; 15:663–670.
7. European Agency for the Evaluation of Medicinal Products, International Conference on Harmonisation-World Health Organization. Guideline for Good Clinical Practice. ICH Topic E6 [EMEA Web site]. London, United Kingdom: EMEA; 2002. Available at: http://www.emea.eu.int. Accessed June 21, 2005.
8. World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects [WMA Web site]. Ferney-Voltaire, France: WMA; 1989. Available at: http://www.wma.net. Accessed June 21, 2005.
9. American Society of Anesthesiologists. ASA Physical Status Classification System [ASA Web site]. Available at: www.asahq.org/clinical/physicalstatus.htm. Accessed June 21, 2005.
10. Cox DR, Oakes D. *Analysis of Survival Data.* New York, NY: Chapman and Hall; 1984.
11. Jarde O, Boccard E. Parenteral versus oral route increases paracetamol efficacy. *Clin Drug Invest.* 1997;14:474–481.
12. Van Aken H, Thys L, Veekman L, Buerkle H. Assessing analgesia in single and repeated administrations of propacetamol for postoperative pain: Comparison with morphine after dental surgery. *Anesth Analg.* 2004;98:159–165.

13. EuroPain Task Force. European minimum standards for the management of postoperative pain. Montreal, Quebec, Canada: Pegasus Healthcare International, Ltd; September 1998.
14. Sheen CL, Dillon JF, Bateman DN, et al. Paracetamol toxicity: Epidemiology, prevention and costs to the health-care system. *QJM.* 2002;95:609–619.
15. Haas DA. An update on analgesics for the management of acute postoperative dental pain. *J Can Dent Assoc.* 2002;68:476–482.
16. Patel NY, Landercasper J. Ketorolac-induced postoperative acute renal failure: A case report. *Wis Med J.* 1995;94:445–447.
17. Strom BL, Berlin JA, Kinman JL, et al. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. A postmarketing surveillance study. *JAMA.* 1996; 275:376–382.
18. RuDusky BM. Severe postoperative hemorrhage attributed to single-dose parenteral ketorolac-induced coagulopathy. *Angiology.* 2000;51:999–1002.
19. Wright JM. The double-edged sword of COX-2 selective NSAIDs. *CMAJ.* 2002;167:1131–1137.
20. Toes MJ, Jones AL, Prescott L. Drug interactions with paracetamol. *Am J Ther.* 2005; 12:56–66.

Address correspondence to: Odile Hiesse-Provost, MD, Bristol-Myers Squibb Company, 3 rue Joseph Monier-BP 325, 92500 Rueil-Malmaison, France. E-mail: odile.hiesse-provost@neuf.fr