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Onset of acetaminophen analgesia: comparison of oral and intravenous routes after third molar surgery

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Background. The purpose of this randomized double-blind study was to compare the efficacy and safety of propacetamol 2 g (an i.v. acetaminophen 1 g formulation) administered as a 2-min bolus injection (n=50) or a 15-min infusion (n=50) with oral acetaminophen 1 g (n=50) or placebo (n=25) for analgesia after third molar surgery in patients with moderate to severe pain after impacted third molar removal.

Methods. All patients were evaluated for efficacy during the initial 6 h period after treatment administration (T_0) and for safety during the entire week after T_0.

Results. The onset of analgesia after propacetamol was shorter (3 min for bolus administration, 5 min for 15-min infusion) than after oral acetaminophen (11 min). Active treatments were significantly better for all parameters (pain relief, pain intensity, patient's global evaluation, duration of analgesia) than placebo (P<0.05). Adverse events were more frequent after propacetamol, especially pain at the injection site. Propacetamol bolus resulted in a much higher incidence of local adverse events than the infusion (propacetamol bolus 90% *vs* propacetamol infusion 52%) with no clinically significant benefits in terms of analgesic efficacy.

Conclusion. I.V. propacetamol, administered as a 15-min infusion, is a fast-acting analgesic agent. It is more effective in terms of onset of analgesia than a similar dose of oral acetaminophen.

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Acetaminophen has a proven record in the management of postoperative pain, alone or in combination.[1–3] At recommended doses, acetaminophen is devoid of serious unwanted side-effects.[3 4] Surgical patients expect effective and fast-acting pain relief. When oral administration is not possible or rapid analgesia is needed, which is often the case following surgery, i.v. administration is the route of choice. Propacetamol, the water-soluble pro-drug of acetaminophen, was developed to offer i.v. administration of acetaminophen for postoperative pain. Propacetamol 2 g, equivalent to 1 g acetaminophen, has been shown to be effective in a variety of postsurgical pain models[5–9] and to have a faster onset of analgesia than oral acetaminophen.[5] The onset of analgesic action is an important factor when characterizing the clinical efficacy of analgesics, especially in the management of postoperative pain.[10] It is of significant clinical interest to know whether different routes of administration (i.v. *vs* oral) and different i.v. administration rates (2 min bolus *vs* 15 min infusion) influence the analgesic efficacy of acetaminophen.

The primary objective of this study was to determine the time to analgesia onset after i.v. administration of propacetamol 2 g by 2-min bolus injection or 15-min infusion compared with oral acetaminophen 1 g and placebo in patients with moderate to severe postoperative pain after impacted third molar surgery.

Methods

The study was completed in a single centre at the University Hospital of Aarhus, Denmark, between January 1997 and June 1997, according to the treatment practice outlined by the Declaration of Helsinki (update Hong Kong, September 1989) and the GCP Guidelines. The patients received oral and written information about the intention and nature of the study. Written informed consent was obtained from all patients.

Inpatients of either gender aged 18–50 years, classified as ASA I or II, were eligible for the study if they were scheduled for removal of an impacted mandibular third molar (and ipsilateral maxillary third molar if indicated) under standardized local anaesthesia and suffered moderate to severe pain (assessed on a four-point scale) within 4 h of surgery. Exclusion criteria included pregnant or breast-feeding women, alcohol or drug abuse, psychiatric or medical disorder able to modify patient compliance, history of complete non-responsiveness to acetaminophen or ibuprofen, history of hypersensitivity or serious adverse reactions to acetaminophen, non-steroidal anti-inflammatory drugs or local anaesthetic drugs, gastric or peptic ulcer disease, inflammatory bowel disease, blood coagulation abnormalities, pancreatic disease within the previous 12 months and impaired liver or kidney function. Treatment with analgesics was forbidden 12 h before and 6 h after administration of the study drug. Treatment with any investigational drug within the previous 30 days was forbidden.

The study was conducted according to a double-blinded design with treatments allocated randomly to four parallel groups of patients at a single centre. The target was to enrol 175 patients for evaluation (50 per group for the three active treatments and 25 for the placebo group). A computer-generated randomization schedule assigned treatments to sequential patients. Patients were stratified according to pain intensity at baseline (moderate or severe). The following treatments were administered: propacetamol 2 g as either a 2-min i.v. bolus injection or 15 min i.v. infusion, oral acetaminophen 1 g and placebo. A triple-dummy technique was used to blind the patients and the personnel conducting the study because of the different drug administration form. Prilocain 3% and felypressin 0.54 μg ml^{-1} (3.6–7.6 ml) were used for local anaesthesia. Third molar surgery was conducted according to a standardized procedure.[11] An i.v. cannula was placed in a superficial forearm vein in each arm immediately after surgery. Patients were enrolled and assigned medication if they rated their pain as moderate or severe within 4 h of surgery.

The primary efficacy variable was time to analgesia onset measured by the double-click stopwatch method developed by Siegel and colleagues.[12] This method is used to record the onset of analgesia objectively. It distinguishes between a sensation of perceptible pain relief (PPR) and the experience of meaningful pain relief (MPR) by recording the first onset of each with a different stopwatch. The procedure excludes invalid 'placebo' responses which result in a higher number of recorded PPRs than MPRs.[10] Simultaneously with study drug administration (T_0), two stopwatches were started and put beside the patient. Patients stopped one watch at the time of first PPR (when they 'felt that the drug was starting to work') and stopped the other watch to signal MPR (when they were 'sure that the drug was working'). The onset of analgesia was defined as the time to the first click if confirmed by a second click for MPR. In the absence of a second click, analgesia was considered not to have occurred and the time to onset was set to 2 h. Patients were encouraged to wait until at least 1 h before requesting rescue analgesia (ibuprofen 600 mg orally).

The secondary efficacy variables comprised pain relief, pain intensity, patients' global evaluation and duration of analgesia.

Pain relief (PR) was evaluated on a five-point categorical scale (none=0; a little=1; moderate=2; a lot=3; complete=4) at each evaluation time from $T_{15\ \mathrm{min}}$ to $T_{6\ \mathrm{h}}$. PR was expressed by the following derived scores: maximum PR (MaxPR), time of maximum PR (t_{MaxPR}) and a weighted sum of PR (TOTPAR) ($T_{15\,\mathrm{min}}$–$T_{6\,\mathrm{h}}$).

Pain intensity was evaluated on a 100-mm visual analogue scale (no pain=0 to worst possible pain=100) at each evaluation time from $T_{15\,\mathrm{min}}$ to $T_{6\,\mathrm{h}}$. Results were expressed by the following four derived scores: pain intensity difference from baseline (PAID), maximum PAID (MaxPAID), time of maximum PAID (t_{MaxPAID}) and a weighted sum of PAID (SPAID) ($T_{15\,\mathrm{min}}$–$T_{6\,\mathrm{h}}$).

Patients' global evaluation was rated on a four-point categorical scale (poor=0; fair=1; good=2; excellent=3) at the end of study ($T_{6\,\mathrm{h}}$) or when patients requested rescue analgesia (or withdrew from the study).

Duration of analgesia was estimated as the time after medication when 50% of patients in a treatment group requested rescue medication.

Time to remedication was set to 6 h for patients who did not request rescue medication. Baseline assessments of pain intensity (categorical and visual analogue scales) were made just before medication (time T_0), and pain relief and pain intensity were assessed 15 min, 30 min, 45 min, 1 h, 2 h, 3 h, 4 h, 5 h and 6 h after medication.

During the inpatient period and after hospital discharge, adverse events (AEs) and concomitant use of medication were recorded. An AE was defined as any untoward medical occurrence irrespective of causal relationship to the treatments. For each AE, the investigators rated the intensity, the outcome and the causal relationship to treatment. Vital signs were measured at T_0 just before ratings and medication, and at $T_{1\,\mathrm{h}}$ and $T_{6\,\mathrm{h}}$. Blood samples for laboratory variables (haematology and plasma biochemistry) were taken before and 48 h after medication.

Statistical analyses

All analyses were conducted on the 'intent-to-treat' population, i.e. all patients who received the randomized medication, using SAS® Version 6.09. Demographic variables were tested by a one-way analysis of variance (ANOVA)[13] or the χ^2-test. A primary analysis of time to onset of analgesia was based on the Van Elteren test.[14] The Kaplan–Meier product-limit estimator[15] was used to derive the survival distribution and the median time to onset of analgesia with 95% confidence intervals (95% CI) for each treatment group. For patients who did not experience onset of analgesia within 2 h after dosing, time to onset was right censored and set to 2 h. A similar procedure was used to derive median time to escape medication, and median times to maximum PAID and PR. Time to remedication and times to maximum PAID and PR were compared using the Gehan–Wilcoxon test.[16] For patients who completed the 6-h evaluation period without the need for rescue medication, time to escape medication was right censored and set to 6 h. Treatment effects on the number of patients reporting analgesia onset and the number requesting rescue medication were compared using the Mantel–Haenszel test.[17] A two-way ANOVA model[13] with treatment effect and baseline pain intensity was used to compare treatment effects on pain relief and pain intensity differences, and effects on maximum and weighted sums of these variables. Missing data due to request for rescue medication were set to the last observation (LOCF). Missing or off-schedule assessments were interpolated from prior and subsequent assessments. Treatment effects on patients' global evaluation were compared using the Cochran–Mantel–Haenszel test.[18] All analgesic efficacy tests were stratified by baseline pain intensity and all tests were applied as Fisher's protected least significant difference procedure for pairwise.[19] Differences in the overall incidence of adverse events during treatment were compared using Fisher's Exact test. Shift tables were used with laboratory variables. For the sample size calculation, the null hypothesis assumed that the time to onset of analgesia would be distributed similarly for both i.v. treatments, except for a 10-min time shift. It was further assumed that 20% of patients in each treatment group would not meet the time to onset criteria. The Mann–Whitney *U*-test gave a minimum sample size estimate of 47 patients per group to demonstrate differences with 80% power between the two i.v. active treatments, with type I error rate (α) at 0.05, two-tailed.

Results

A total of 265 patients were enrolled and treatments were randomized between 175 patients, with 50 patients in each active treatment group and 25 in the placebo group. No patient withdrew from the study and all 175 were evaluated by the intent-to-treat analyses and for safety. Demographic and baseline characteristics of patients included in the four treatment groups are presented in Table 1.

A significantly higher proportion of patients reported analgesia onset after all three active treatments than after placebo.

The time to onset of analgesia yielded a significant ($P<0.001$) overall treatment effect (Table 2). Paired

Table 1 Patient and baseline characteristics. Data are presented as mean (SD) unless stated otherwise. PI, pain intensity (categorical scale, range 0–3); PAI, pain intensity (visual analogue scale, range 0–100)

	Propacetamol bolus injection (*n*=50)	**Propacetamol 15-min infusion (*n*=50)**	**Acetaminophen oral (*n*=50)**	**Placebo (*n*=25)**	***P*-value**
Age (yr) (range)	25.6 (20–42)	24.2 (18–39)	23.8 (19–36)	23.4 (20–29)	0.024
Sex					0.806
Male (no.) (%)	19 (38)	23 (46)	19 (38)	11 (44)	
Female (no.) (%)	31 (62)	27 (54)	31 (62)	14 (56)	
Body weight (kg)	66.8 (10.4)	68.8 (11.0)	66.6 (11.3)	70.9 (10.4)	0.328
Baseline PI					0.997
Mild (no.) (%)	2 (4)	1 (2)	1 (2)	1 (4)	
Moderate (no.) (%)	40 (80)	40 (80)	40 (80)	19 (76)	
Severe (no.) (%)	8 (16)	9 (18)	9 (18)	5 (20)	
Baseline PAI	59.9 (14.9)	58.1 (16.9)	58.2 (17.4)	60.6 (20.1)	0.894

Table 2 Onset and duration of analgesia. Data are expressed as median (95% CI) unless stated otherwise. *†‡Mean or median values associated with different symbols differ significantly from each other ($P<0.05$). MPR, meaningful pain relief

	Propacetamol bolus injection (*n*=50)	**Propacetamol 15-min infusion (*n*=50)**	**Acetaminophen oral (*n*=50)**	**Placebo (*n*=25)**	**Overall treatment effect *P*-value**
Onset of analgesia					
Patients experiencing onset (no. [%])	47* (94)	47* (94)	45* (90)	14† (56)	<0.001
Time to analgesia onset (min)	3* (2, 3)	5† (4, 7)	11‡ (7, 19)	13†‡ (3, >120)	<0.001
Time to MPR (min)	4* (3, 5)	8† (6, 13)	37‡ (24, 44)	14‡ (8,)	<0.001
Escape medication					
Time to rescue medication request (min)	180* (121, 237)	171* (138, 252)	278† (178, >360)	68‡ (60, 90)	0.023

comparisons showed a significantly earlier median onset of analgesia after propacetamol bolus than after propacetamol infusion, oral acetaminophen or placebo ($P \leq 0.004$). In addition, the median time to onset of analgesia was earlier after propacetamol infusion than after oral acetaminophen ($P=0.004$). The median time to MPR also yielded a significant ($P<0.001$) overall effect (Table 2). Paired comparisons showed an earlier median time to meaningful analgesia after propacetamol bolus than after propacetamol infusion ($P<0.001$), and earlier times of both i.v. treatments compared with oral acetaminophen ($P<0.001$) or placebo (bolus, $P<0.001$; infusion, $P=0.032$). The median time to MaxPR (Table 3) occurred significantly later after oral acetaminophen (1 h; $P<0.001$) than after either propacetamol or placebo (all 15 min). The corresponding overall treatment effect was significant ($P=0.017$). The same trend was observed with the median time to MaxPAID, although the overall treatment effects were not statistically significant (Table 3).

Table 3 also shows that with all three active treatments maximum scores and weighted sums of PR and PAID scores differed significantly from placebo, but not from each other. Significant ($P<0.01$) overall treatment effects were found on all these variables. The temporal pattern of response was different with oral acetaminophen. Paired comparisons showed that up to $T_{45\,\mathrm{min}}$, oral acetaminophen analgesia was significantly inferior to both propacetamol treatments with respect to PR and PAID. From $T_{45\,\mathrm{min}}$ to $T_{2\,\mathrm{h}}$, there was no difference between both propacetamol groups and oral acetaminophen. Global results in terms of analgesia in the oral acetaminophen group are superior to results of the propacetamol groups for PR (Figs 1 and 2). Scores for PR and PAID following propacetamol were significantly superior to placebo score up to 3 h for PR and 4 h for PAID. None of the three treatments differed significantly from placebo between $T_{5\,\mathrm{h}}$ and $T_{6\,\mathrm{h}}$ on any of the variables.

The duration of analgesia was significantly longer after all three active treatments than after placebo (Table 2). The two propacetamol groups did not differ significantly from each other. The duration of analgesia was significantly longer after oral acetaminophen than after any other treatment.

Table 3 Time to peak pain scores (median [95% CI]), maximum pain scores [mean (SD)] and summed pain scores [mean (SD)]. *†Mean or median values associated with different symbols differ significantly from each other ($P<0.05$). ‡Weighted by time elapsing between observations, e.g. Σpain relief×time (hours since previous observation). t_{MaxPR}, time to maximum pain relief; t_{MaxPAID}, time to maximum pain intensity difference (visual analogue scale); MaxPR, maximum pain relief; MaxPAID, maximum pain intensity difference (visual analogue scale); AUC, area under curve; TOTPAR, sum of pain relief scores; SPAID, weighted sum of pain intensity difference (visual analogue scale)

	Propacetamol bolus injection (*n*=50)	**Propacetamol 15-min infusion (*n*=50)**	**Acetaminophen oral (*n*=50)**	**Placebo (*n*=25)**	**Overall treatment effect *P*-value**
Time to peak					
t_{MaxPR}	0.25* (0.25, 0.27)	0.25* (0.25, 0.48)	1.00† (0.73, 1.00)	0.25* (0.25, 0.50)	0.017
t_{MaxPAID}	0.75 (0.50, 0.75)	0.50 (0.48, 0.75)	1.50 (1.00, 2.00)	0.25 (0.25, 0.75)	0.752
Maximum score					
MaxPR	2.66* (1.02)	2.70* (0.86)	2.64* (1.17)	1.44† (1.04)	<0.001
MaxPAID	39.86* (19.35)	39.55* (18.25)	39.70* (24.18)	21.48† (21.78)	<0.001
Weighted sum (AUC: $T_{15\,\mathrm{min}}$–$T_{6\,\mathrm{h}}$)‡					
TOTPAR	9.35* (6.19)	8.78* (4.88)	9.70* (5.73)	5.02† (5.49)	0.005
SPAID	117.39* (126.85)	110.17* (104.14)	125.32* (140.69)	31.67† (138.02)	0.007

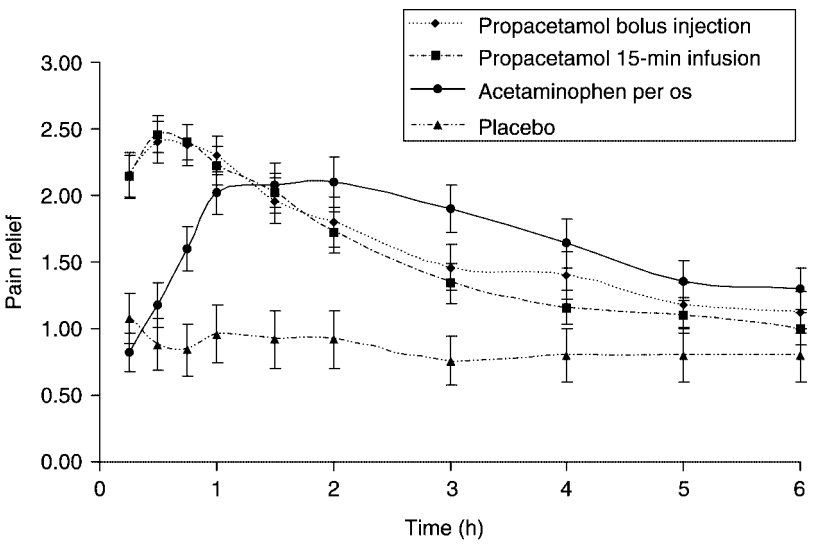

Fig 1 Pain relief.

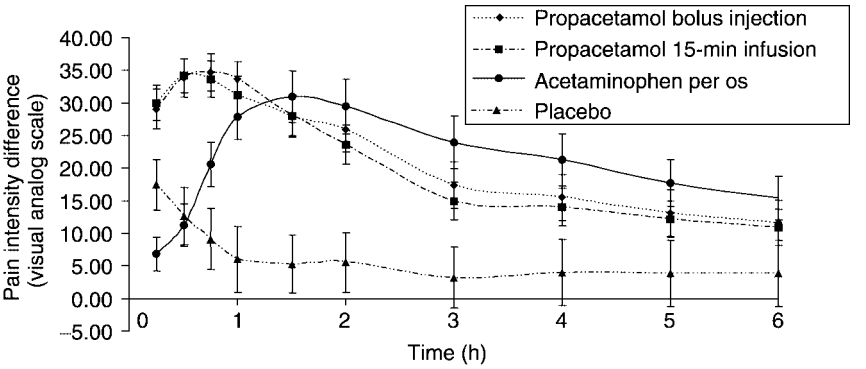

Fig 2 Pain intensity difference (visual analogue scale).

Table 4 Adverse events (AEs)

	Propacetamol bolus injection (*n*=50)	Propacetamol 15-min infusion (*n*=50)	Acetaminophen oral (*n*=50)	Placebo (*n*=25)	Overall treatment effect *P*-value
Patients with ≥1 AE (no. [%])	49 (98)	38 (76)	21 (42)	12 (48)	<0.001
Total AEs	170	88	55	19	
Related to treatment (no. [%])	129 (76)	48 (55)	15 (27)	7 (37)	<0.001
Description of disorder					
Administration site disorders (no. [%])	45 (90)	26 (52)	6 (12)	1 (4)	
Injection site pain (no. [%])	39 (78)	22 (44)	4 (8)	1 (4)	<0.05
Injection site reaction (no. [%])	12 (24)	7 (14)	4 (8)	0	<0.05
General disorders presented by >10% patients					
Periodontal destruction (no. [%])	13 (26)	6 (12)	5 (10)	3 (12)	
Nausea (no. [%])	13 (26)	9 (18)	0 (0)	1 (4)	<0.05
Dizziness (no. [%])	34 (68)	7 (14)	2 (4)	2 (8)	<0.05
Headache (no. [%])	5 (10)	4 (8)	5 (10)	2 (8)	
Malaise (no. [%])	10 (20)	2 (4)	1 (2)	0	<0.05
Fatigue (no. [%])	1 (2)	1 (2)	4 (8)	0 (0)	
Postoperative pain (no. [%])	5 (10)	3 (6)	3 (6)	1 (4)	
Skin cold and clammy (no. [%])	6 (12)	1 (2)	0 (0)	0 (0)	<0.05

Six hours after medication, more patients rated their global treatment satisfaction as 'good' to 'excellent' after receiving active treatments (40–56%) than after placebo (12%). The corresponding overall treatment effect was significant ($P<0.001$).

In total, 332 AEs were reported by 69% of patients, and 60% of AEs were related to treatments. Only one patient experienced a serious AE in the propacetamol bolus group (postoperative haemorrhage unrelated to treatment). No patient was withdrawn because of an AE. The proportion of patients reporting AEs was higher with propacetamol than with oral acetaminophen or placebo. Moderate to severe AEs were more frequent after propacetamol bolus (81%) than after propacetamol infusion (57%), oral acetaminophen (56%) or placebo (68%). Ninety per cent of patients receiving a bolus injection of propacetamol experienced an administration site disorder (pain or local reaction). This was less frequent after propacetamol infusion (52%), oral acetaminophen (12%) or placebo (4%). Dizziness, nausea, malaise and cold clammy skin were more frequent among patients receiving propacetamol than after oral acetaminophen or placebo (Table 4). The overall treatment effect was statistically significant for all AEs mentioned above. The remaining AEs did not differ significantly between groups. Laboratory tests and vital signs showed no clinically important changes (data not shown).

Discussion

This study compared i.v. administration of acetaminophen, as its prodrug propacetamol, with oral acetaminophen. Oral acetaminophen had already demonstrated its analgesic efficacy in a pain model of postoperative pain following third molar surgery,[20] although a recent publication argues that oral acetaminophen kinetic data are unpredictable in patients scheduled for surgery.[21] The use of a placebo group was considered to be necessary to assess the sensitivity of the study methods and therefore to validate the study.[22,23] However, for ethical reasons, an unbalanced randomization scheme was used in order to decrease the number of patients exposed to placebo.

The present study demonstrated significantly greater analgesia after i.v. propacetamol or oral acetaminophen following third molar surgery than after placebo, with an earlier onset of analgesia as measured by time to onset, time to meaningful pain relief and time to maximal pain relief.

Even if the statistically significant difference between propacetamol infusion and oral acetaminophen is low (5 min for the 15-min propacetamol infusion group *vs* 11 min for the oral acetaminophen group), the difference can be considered as clinically significant when considering the time to meaningful pain relief (8 min in the 15-min infusion propacetamol group *vs* 37 min in the oral acetaminophen group) or when considering the time to maximal pain relief (15 min for both i.v. administrations *vs* 1 h for oral administration).

These results correlate with those obtained in another study comparing propacetamol 2 g, administered as a 15-min infusion, with oral acetaminophen 1 g and placebo in postoperative pain following hallux valgus surgery.[5] In this study, in addition to a faster onset of action, propacetamol 2 g (equivalent to acetaminophen 1 g) provided superior analgesia to oral acetaminophen 1 g over the 4-h period following the start of infusion.

This delayed onset of analgesia has already been shown in a previous study with acetaminophen tablet administration.[20] This result could be explained by the fact that passage through the blood–brain barrier could be concentration dependent, with the rate of concentration increase and the initially high concentration secondary to i.v. injection being taken into account.[24]

Ninety per cent of patients receiving propacetamol bolus injection experienced an administration site problem (pain or a local reaction). These events were less frequent after propacetamol infusion (52%) and far less so after the double-dummy i.v. treatments associated with oral acetaminophen (12%) and placebo (4%). Injection site pain after propacetamol infusion has been reported in previous studies[5 6] and is related to pH and osmolarity of the propacetamol solution (pH 3.5; osmolarity 410 mOsmol litre^{-1}), which differs greatly from plasma characteristics (pH 7.3–7.4; osmolarity 275–295 mOsmol litre^{-1}). Other AEs (e.g. dizziness, nausea, malaise and cold clammy skin) occurred more frequently after propacetamol bolus than after infusion, and only occasionally after oral acetaminophen or placebo. These adverse events are classically described with propacetamol and may be attributable to the injection site pain inducing these reactions. This poor local tolerance confirms the recommendation to infuse propacetamol solution over 15 min.[25]

Propacetamol may be replaced by a ready-to-use i.v. formulation of acetaminophen which is much better tolerated at the site of injection.[26–28] The bioequivalence of i.v. acetaminophen 1 g and propacetamol 2 g has been demonstrated.[26]

I.V. propacetamol is a fast-acting analgesic agent, superior to placebo on all measures of pain and producing significantly earlier pain relief than oral acetaminophen. I.V. propacetamol administered by bolus injection provided no clinically relevant important advantages over 15-min i.v. infusion in terms of analgesia. The more rapid bolus injection resulted in a much higher incidence of AEs, in particular injection site pain. Thus the 15-min i.v. infusion could be considered as the route of choice for i.v. administration of acetaminophen for acute pain relief in the postoperative setting where rapid onset of action is required.

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