Drugs 2009; 69 (1): 101-113
0012-6667/09/0001-0101/$55.55/0

Intravenous Paracetamol (Acetaminophen)

Sean T. Duggan and *Lesley J. Scott*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Conshohocken, Pennsylvania, USA

Contents

Abstract

▲ Intravenous paracetamol (rINN)/intravenous acetaminophen (USAN) is an analgesic and antipyretic agent, recommended worldwide as a first-line agent for the treatment of pain and fever in adults and children.

▲ In double-blind clinical trials, single or multiple doses of intravenous paracetamol 1 g generally provided significantly better analgesic efficacy than placebo treatment (as determined by primary efficacy endpoints) in adult patients who had undergone dental, orthopaedic or gynaecological surgery.

▲ Furthermore, where evaluated, intravenous paracetamol 1 g generally showed similar analgesic efficacy to a bioequivalent dose of propacetamol, and a reduced need for opioid rescue medication.

▲ In paediatric surgical patients, recommended doses of intravenous paracetamol 15 mg/kg were not significantly different from propacetamol 30 mg/kg for the treatment of pain, and showed equivocal analgesic efficacy compared with intramuscular pethidine 1 mg/kg in several randomized, active comparator-controlled studies.

▲ In a randomized, noninferiority study in paediatric patients with an infection-induced fever, intravenous paracetamol 15 mg/kg treatment was shown to be no less effective than propacetamol 30 mg/kg in terms of antipyretic efficacy.

▲ Intravenous paracetamol was well tolerated in clinical trials, having a tolerability profile similar to placebo. Additionally, adverse reactions emerging from the use of the intravenous formulation of paracetamol are extremely rare (<1/10 000).

Features and properties of intravenous (IV) paracetamol (rINN)/ intravenous acetaminophen (USAN)	
Indication	
Short-term treatment of moderate pain and fever when administration by IV route is clinically justified	
Mechanism of action	
Inhibition of nitric oxide synthesis pathway; inhibition of prostaglandin synthesis	
Dosage and administration	
Adults weighing >50 kg	1 g (maximum 4 g/d)
Children weighing >33 kg, adolescents and adults weighing <50 kg	15 mg/kg (maximum 3 g/d)
Children weighing >10 to <33 kg	15 mg/kg (maximum 2 g/d)
Full-term newborn infants, infants, toddlers and children weighing <10 kg	7.5 mg/kg (maximum 30 mg/kg/d)
Route	15-min IV infusion
Minimum duration between doses	4–6 h
Pharmacokinetic properties (following 1 g infusion in healthy adult volunteers)	
Mean maximum plasma concentration	29.9 μg/mL
Mean area under the concentration time curve from time zero to infinity	57.6 μg • h/mL
Apparent volume of distribution	69.2 L
Systemic clearance	17.9 L/h
Mean elimination half-life	2.7 h
Tolerability profile	
Similar tolerability profile to placebo	

The recommended approach for postoperative pain management is to initiate therapy with analgesics, such as paracetamol (rINN) [acetaminophen (USAN)], NSAIDs and aspirin, followed by the adjunctive use of opioids to treat more acute pain symptoms. However, the adverse effects associated with opioid use are well established and include dose-dependent respiratory depression, nausea, vomiting, constipation, urinary retention and sedation.[1,2] NSAIDs are also associated with adverse events including dyspepsia, gastric mucosal damage, postoperative bleeding and renal effects,[3] highlighting a requirement for more tolerable pain relief agents.

Paracetamol has been widely used for over a century as an effective analgesic and as an antipyretic agent.[4] Its efficacy[5] and tolerability[6] are well established and in contrast with other analgesics, it has a favourable safety profile. Indeed, paracetamol is currently the most commonly prescribed drug for the treatment of mild to moderate pain in infants.[7]

Furthermore, paracetamol has the advantage of being the only non-opioid analgesic available in oral, rectal or intravenous formulations. The intravenous route is especially advantageous in postsurgical situations when oral (e.g. infections with severe fever or vomiting) or rectal (e.g. high variability in uptake and bioavailability)[4,8,9] routes are not suitable or effective. To date, only a limited number of analgesics are available for administration intravenously, including the NSAID ketorolac,[10] which carries special warnings for treatment-related adverse events including those mentioned above, and propacetamol, an intravenous prodrug version of paracetamol that requires metabolic activation *in vivo*.

Intravenous propacetamol, a soluble diethylglycidyl ester of paracetamol, has been used for over a decade in Europe and provides rapid and effective pain relief in the perioperative setting, but is not associated with the adverse effects of opioids and NSAIDs outlined here. However, propacetamol requires reconstitution and is associated with infusion-site adverse events and reactions.[2,11] More recently, a new formulation of intravenous paracetamol was introduced to replace propacetamol, which does not require reconstitution and is associated with fewer infusion-site reactions (see section 4). This profile reviews the clinical efficacy and tolerability of intravenous paracetamol in adult and paediatric patients with perioperative pain or infection-induced fever.

Medical literature referenced in this profile was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

The pharmacodynamic properties of intravenous paracetamol have been examined in both animal models[12,13] and in healthy adult volunteers,[14] and have been extensively reviewed elsewhere.[15,16] Despite more than 50 years of research, the precise mechanism underlying the analgesic and antipyretic activity of paracetamol is not fully understood.

- Paracetamol has been shown to act at both the central and peripheral components of the pain pathway.[17,18] One mechanism may be through the direct inhibition of the *N*-methyl-*D*-aspartate receptor, which stimulates the substance P-dependent synthesis of nitric oxide, a primary mediator of nociception.[12] Paracetamol has also been implicated in the inhibition of the cyclo-oxygenase 2 pathway involved in prostaglandin (PGE) synthesis.[16] A metabolite of paracetamol also sequesters reduced glutathione, a required cofactor for membrane bound PGE synthase, which is involved in the generation of PGE_2, another potent mediator of nociception.[16] Therefore, paracetamol may also contribute to the alleviation of pain by indirectly attenuating production of PGE_2.
- The analgesic effects of paracetamol may also involve the serotonergic system.[14] In healthy male adult volunteers, agonists of the serotonin $5\text{-}HT_3$ receptor, namely tropisetron and granisetron, completely blocked the analgesic effect of paracetamol, indicating an antinociceptive role for paracetamol.[14] In addition, in a rat model of tonic pain, paracetamol inhibited formalin-induced

responses by indirectly stimulating 5-HT_{1A} receptors, thereby activating 5-HT pathways that regulate spinal nociception.[19]

- The onset of analgesia occurs rapidly within 5–10 minutes of intravenous paracetamol administration.[17] The peak analgesic effect is obtained in 1 hour and its duration is approximately 4–6 hours.[17]
- The antipyretic effects of intravenous paracetamol are also rapid, with fever reduction occurring within 30 minutes of administration and lasting at least 6 hours.[17]

2. Pharmacokinetic Profile

The pharmacokinetic properties of intravenous paracetamol have been evaluated in both single-dose[20,21] and multiple-dose[22,23] trials. These studies included both healthy volunteers[20,22,23] and patients undergoing hip arthroplasty.[21] In addition, a comparative pharmacokinetic study of oral and intravenous paracetamol is also discussed,[24] as is the relative bioavailability of intravenous paracetamol versus propacetamol.[25] This section summarizes these studies, two of which are available as abstract and/or poster presentations,[21,24] with supplemental data derived from the manufacturer's prescribing information.[17]

General Profile

- Paracetamol displays linear pharmacokinetics at dosages of 4–8 g per day.[22] In healthy adult volunteers, following a single dose of paracetamol 1 g, the mean maximum plasma concentration (C_{max}) was 29.9 μg/mL at the end of the 15-minute infusion period, with a mean area under the plasma concentration-time curve (AUC) from time zero to infinity of 57.6 μg • h/mL.[25] In patients who had undergone hip arthroplasty, the mean AUC from 0 to 24 hours was 59.7 μg • h/mL.[21]
- As might be expected, C_{max} was approximately 2-fold higher after intravenous paracetamol than after oral paracetamol, while AUC and volume of distribution values were similar between the two routes of administration in healthy volunteers (no specific data reported).[24]
- The mean volume of distribution for intravenous paracetamol 1 g was 85.0 L in patients who had undergone hip arthroplasty[21] and 69.2 L in healthy adult volunteers.[25] Paracetamol exhibits rapid penetration into the cerebrospinal fluid[20,26] and does not extensively bind to plasma proteins.[17]
- Therapeutic doses of paracetamol are metabolized predominantly in the liver by glucuronidation and sulfation.[22,27] At higher doses, paracetamol is metabolized by the cytochrome P450 (CYP2E1) pathway to produce the reactive intermediate *N*-acetyl-*p*-benzoquinone (NAPQI).[28] NAPQI rapidly forms conjugates with glutathione to generate nontoxic thiol metabolites.[29] At very high doses, far exceeding the recommended therapeutic doses of paracetamol (section 5), as seen during events of acute overdose, glutathione stores may be depleted by this pathway, allowing the accumulation of NAPQI, which could potentially lead to hepatotoxicity.[22] Although there is a potential for hepatotoxicity at supratherapeutic doses, it can be treated by the administration of the antidote N-acetylcysteine, ideally within 10 hours of overdose.[17]
- The metabolites of paracetamol are predominantly excreted in the urine as glucuronide (60–80%) and sulfide (20–30%) conjugates, with less than 5% of the drug excreted unchanged.[17] This ratio is similar between oral and intravenous formulations.[24,27] Less than 1% of an paracetamol dose is recovered in the bile.[30] The elimination half-life ($t_{½β}$) of paracetamol 1 g is 2.7 hours and its rate of systemic clearance is 17.9 L/h.[25]
- In patients with severe renal failure (creatinine clearance 10–30 mL/min [0.6–1.8 L/h]), $t_{½β}$ increases to 2.0–5.3 hours; thus, the dosage interval should be increased from 4 to 6 hours.[17] The pharmacokinetics of paracetamol are not changed in elderly subjects.[17]
- Concomitant use of probenecid (4 g/day for ≥4 days) causes an almost 2-fold reduction in paracetamol clearance by inhibiting glucuronidation.[31] Therefore, a reduction in paracetamol dose should be considered when these agents are used concomitantly.[17] Additionally, salicylamide may prolong the $t_{½β}$ of paracetamol.[17]

• Concomitant use of paracetamol with oral anticoagulants may lead to slight variations of international normalized ratio (INR) values. In this case, increased monitoring of INR values should be conducted during the period of concomitant use and for 1 week after paracetamol treatment is discontinued.[17]

In Paediatric Populations

The pharmacokinetic properties of intravenous paracetamol have also been evaluated in neonates and children in both single-dose[32-34] and multiple-dose[35,36] studies. These studies include both healthy neonates,[32] neonates admitted to intensive care,[34,36] infants undergoing major cranial facial surgery,[35] and children and adolescents undergoing major surgery.[33]

• The pharmacokinetic properties of paracetamol in children are generally similar to those in adults with the exception of $t_{1/2\beta}$, which is slightly shorter in children (1.5–2.0 hours).[17] By contrast, the $t_{1/2\beta}$ in neonates (3.5 hours)[32] is longer than that in adults (2.7 hours).[25]

• Neonates and children up to 10 years of age excrete less glucuronide conjugates and more sulphate conjugates than adults.[17,34,35] This is consistent with findings suggesting that young children are more resistant to paracetamol-induced hepatotoxicity as a result of the preference for metabolism through sulfation over glucuronidation and the resulting reduction in NAPQI generation.[37]

• In a study in neonates (n = 50) with a median gestational age (GA) of 38.6 weeks and a mean weight of 2.9 kg, the systemic clearance rate of intravenous paracetamol (10, 12.5 or 15 mg/kg for neonates aged 28–32 weeks, 32–36 weeks and ≥36 weeks, respectively) was estimated to be 5.24 L/h/70 kg (i.e. data were standardized for a 70 kg person), with a volume of distribution of 76 L/70 kg.[36] Clearance rates increased with increasing GA, from 4.4 L/h/70 kg for 34-week GA neonates to 6.3 L/h/70 kg for 46-week GA neonates.[36]

• In a study in children and adolescents (n = 7), the pharmacokinetics of intravenous paracetamol were best described by a two-compartment model, with a clearance rate of 13.2 L/h/70 kg and an intercompartmental clearance rate of 45.7 L/h/70 kg.[33] The volume of distribution in these subjects was 13.3 L/70 kg, with a peripheral volume of distribution of 33.0 L/70 kg.[33]

3. Therapeutic Efficacy

In Adults

Several large (n > 150), randomized, double-blind, placebo-controlled trials in adult patients who had undergone dental or various surgical procedures have investigated the use of intravenous paracetamol in the management of postoperative pain (table I).[2,38-40] Two of these trials also included a propacetamol comparator arm.[2,40] These data are supported by two smaller placebo-controlled trials.[41,42] Of note, two placebo-controlled trials in postoperative patients were terminated early because the placebo vehicle contained particulate matter;[43,44] these trials are not tabulated or discussed further.

In addition, several, randomized, active comparator-controlled trials have evaluated the efficacy of intravenous paracetamol relative to that of propacetamol,[45] parecoxib,[46] ibuprofen[47] or morphine[48] in surgical patients. In one of these head-to-head trials,[46] there was also a dipyrone (metamizole) comparator group; dipyrone is no longer approved in the US and is prohibited in numerous other countries.[49] The use of intravenous paracetamol in combination with intravenous tramadol in cardiac surgery patients[50] or with patient-controlled intravenous morphine in women who had undergone a Caesarean section[47] has been evaluated in separate randomized, double-blind trials.

Furthermore, two randomized, placebo-controlled trials have evaluated the efficacy of intravenous paracetamol in the management of preoperative pain associated with the administration of the anaesthesia induction agent, propofol.[51,52]

Trials were conducted at a single institution[39,45,51,52] or as part of a multicenter

Table I. Efficacy of intravenous paracetamol (PAR) in adult patients with postoperative pain. Summary of randomized, double-blind, placebo (PL)-controlled, multi-[2,38,40] or single-centre[39] studies in adult patients (pts) who had undergone third molar extraction,[39,40] knee or hip replacement,[2] or gynaecological surgery.[38] All agents were given as intravenous infusions

Study	No. of pts	Treatment regimen (g)	Mean pain relief[a]			Mean TOTPAR[b]			Mean SPID[c]			Median time to rescue medication[d] (h)
			15 min	1 h	6 h	6 h	24 h	48 h	6 h	24 h	48 h	
Dental (single dose)												
Juhl et al.[39][e]	132	PAR 1				7.1***[f]			2.2***			3.23***
	33	PL				2.8[f]			−0.6			1.03
Moller et al.[40]	51	PAR 1	2.1**[f]	2.0**†[f]	0.8**[f]	6.9*			2.2*			2.08***
	51	PRO 2	2.08**[f]	1.5**[f]	0.7**[f]	7.7*			2.4*			3.00***
	50	PL	0.8[f]	0.6[f]	0.1[f]	1.7			−0.4			0.70
General surgery (multiple doses)[g]												
Candiotti et al.[38][h]	162	PAR 1					50.1*	106.9*		1793[f]	3612[f]	2.90**[i]
	159	PL					46.6	99.4		1845[f]	3718[f]	1.70[i]
Sinatra et al.[2]	49	PAR 1	1.0*[f]	1.6*[f]	0.8*[f]	6.6*			2.3*			3.00***
	50	PRO 2	1.0*[f]	1.5*[f]	0.8*[f]	7.5*			2.5*			2.60***
	52	PL	0.6[f]	0.7[f]	0.2[f]	2.2			−0.6			0.80

a Scores assessed using a 5-point verbal scale (0 = no relief to 4 = complete pain relief).[2,40] Active treatments were significantly better than PL at all timepoints during the assessment period, with no significant differences between active treatment groups except at the 1-h timepoint in the Moller et al. study.[40] All data were estimated from graphs, intermediate timepoints not presented here.

b Sum of pain relief scores, assessed on a 4- or 5-point verbal scale (0 = no pain to 4 = worst possible pain).

c Sum of pain intensity scores, assessed using a 100 mm visual analogue scale (0 = no pain to 100 mm = worst possible pain).

d Time elapsed from initiation of treatment until actual time of request for rescue medication by the patient.

e The PAR 2 g group from this study is not tabulated as this dosage is not recommended.[17]

f Primary endpoint.

g One dose every 6 h for 24[2] or 48 h.[38]

h Data available in poster form only.

i Values are the mean time to rescue medication.

PRO = propacetamol; **SPID** = sum of pain intensity difference; **TOTPAR** = sum of pain relief score; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs PL; † $p < 0.05$ vs PRO.

study.[2,38,40] Apart from one study (abstract plus poster presentation),[38] all studies have undergone peer review. Inclusion criteria for nearly all of the studies required postoperative pain to be rated at least moderate to severe on a 4-point verbal rating scale (VRS).[2,38-40,45,51]

Agents were administered pre-,[51,52] intra-[46,48] or post-operatively[2,38-40,45] and were delivered as a 15-minute intravenous infusion,[2,38-40,45] except for the treatment of preoperative pain associated with propofol injection, where paracetamol was administered as a bolus injection.[51,52] For multiple dose studies, infusions were administered every 6 hours for the duration of the study.[2,38] Discussion focuses on trials that used the recommended dosages of intravenous paracetamol (see section 5).

Primary efficacy endpoints included pain relief at various timepoints from 15 minutes to 6 hours,[2,40] the sum of the pain relief score over the 6-hour period after treatment (TOTPAR6)[39] and the sum of pain intensity difference (SPID) over a 24-[38] or 48-hour[38] period after treatment (see table I for details).

Treatment of Dental Pain

- In two single-dose trials, intravenous paracetamol 1 g provided significantly greater pain relief than placebo in patients undergoing third molar extraction (table I), as assessed by mean

pain relief[40] and TOTPAR6[39] scores (primary endpoints).

- Other endpoints also indicated that intravenous paracetamol 1 g generally provided better pain relief than placebo treatment, including TOTPAR6 scores,[40] SPID scores over a 6-hour period[39,40] and the median duration of analgesia (measured by the time taken until rescue medication) [table I].[39,40]
- In addition, patient global treatment satisfaction was greater with intravenous paracetamol 1 g, with a significantly ($p < 0.001$) higher percentage of patients rating the treatment as 'good' or 'excellent' in this group than in the placebo group (40% vs 12%[40] and 39% vs 9%[39]).
- Generally, intravenous paracetamol 1 g was not significantly different from a bioequivalent dose of propacetamol (2 g), according to primary and secondary endpoints (table I).[40]

Treatment of Perioperative Pain

- In two multi-dose trials, the pain relief induced by intravenous paracetamol was significantly greater than with placebo following major orthopaedic surgery,[2] but was not significantly different from that with placebo following gynaecological surgery,[38] according to primary endpoints (table I). The authors of the gynaecological surgery study suggested that the lack of statistical significance with the primary endpoint was due to the high pain intensity experienced by patients prior to treatment and the high variability in pain intensity experienced postoperatively.[38]
- In both trials, intravenous paracetamol 1 g every 6 hours was also better than placebo treatment in terms of secondary endpoints, TOTPAR scores and median time to rescue medication (table I).[2,38] Patient global treatment satisfaction was also greater with paracetamol, with a higher percentage of patients in the paracetamol than in the placebo group rating the treatment as 'fair' or 'excellent' at 24 hours following treatment initiation (80% vs 65%; $p < 0.01$) in one study.[2] Similarly, in the other study,[38] overall patient global treatment satisfaction was significantly greater with intravenous paracetamol treatment than with placebo at both 24 ($p < 0.01$) and 48 hours ($p < 0.05$) following treatment initiation.[38]
- The use of intravenous paracetamol 1 g every 6 hours was also generally associated with morphine-sparing effects.[2,38] In the orthopaedic study,[2] a significant ($p < 0.01$) reduction in morphine consumption (9.7 vs 17.8 mg for placebo) was observed over 6 hours following a single dose of intravenous paracetamol, and was maintained for 24 hours following repeated doses of intravenous paracetamol (38.3 vs 57.4 mg for placebo; p-value not reported). In patients who underwent gynaecological surgery,[38] the difference in morphine consumption between treatment groups did not reach statistical significance at 48 hours post-treatment (48.3 mg with intravenous paracetamol vs 52.1 mg with placebo), although the time to rescue medication was significantly longer for patients treated with intravenous paracetamol (table I).
- Several head-to-head studies have compared the efficacy of intravenous paracetamol with other analgesics.[2,45-48] Intravenous paracetamol 1 g was not significantly different from intravenous propacetamol 2 g in providing pain relief in patients after orthopaedic[2] (table I) and soft-tissue surgery.[45] In patients following gynaecological surgery, no significant between-group differences in mean pain scores (assessed using a 100 mm visual analogue scale [VAS]: 0 = no pain to 100 mm = worst possible pain) were observed with intravenous paracetamol or propacetamol treatments for the 6-hour study duration (mean VAS scores at 6 hours: 15 vs 23 [data estimated from a graph]).[45]
- Intravenous paracetamol 1 g was also not significantly different from intravenous parecoxib 40 mg, according to changes in mean pain scores (36.4 vs 32.5; assessed using a 100 mm VAS) immediately upon arrival to the postanaesthesia care unit, but neither was as effective as dipyrone 1 g (mean VAS score 14.2; $p < 0.05$) in a double-blind trial in patients undergoing unilateral microsurgical lumbar discectomy ($n = 80$).[46]
- In combination with patient-controlled intravenous morphine, intravenous paracetamol 1 g was not significantly different from oral ibuprofen 400 mg in providing pain relief after a Caesarean section in 45 women participating in

a randomized, double-blind trial.[47] There were no significant between-group differences observed in VAS scores (estimated marginal means: 1.4 vs 1.9 for intravenous paracetamol and ibuprofen; assessed using a 10-point scale) or postoperative morphine requirement (cumulative dose 98 vs 93 mg) throughout the duration of the 48-hour assessment period. There were also no significant between-group differences in postoperative sedation scores (3-point scale).[47]

- Intravenous paracetamol 1 g was not significantly different from that of morphine 0.1 mg/kg in patients (n = 84) after undergoing arthroscopic knee surgery.[48] Patients receiving intravenous paracetamol experienced similar pain relief immediately upon arrival in the recovery room and for the next 4 hours compared with those treated with morphine (for example the number of patients providing a VRS score of 0 at 4 hours was 41 vs 39; assessed using a 5-point VRS [data estimated from a graph]).[48]
- In patients who had undergone cardiac surgery (n = 113), intravenous paracetamol 1 g as adjunctive treatment to intravenous tramadol (30-minute infusion of tramadol 200 mg immediately before the first dose of the study drug, followed by a 300 mg infusion over 24 hours) was better than placebo in treating postoperative pain.[50] Intravenous paracetamol recipients experienced significantly less pain at 12, 18 and 24 hours following surgery than placebo recipients (10 cm VAS score 1 vs 2 for all timepoints; $p < 0.01$), with no between-group differences seen for the remaining assessment period (72 hours).[50] No significant between-group differences were observed in postoperative morphine consumption over the 72-hour assessment period (48 vs 97 mg for intravenous paracetamol and placebo recipients), although numerically fewer intravenous paracetamol recipients (14.2%) requested morphine compared with placebo recipients (24.5%).[50]
- In two smaller randomized, double-blind, placebo-controlled studies in patients who had undergone tonsillectomy[41] (n = 76) or endoscopic sinus surgery[42] (n = 74), intravenous paracetamol 1 g significantly reduced the patient's requirement for rescue medication. Compared with placebo, intravenous paracetamol recipients required significantly fewer doses of pethidine 1 mg/kg (mean over 24 hours 0.5 vs 2.2 doses; $p < 0.001$)[41] or oxycodone 2 mg (mean over 4 hours 0.5 vs 1.5 doses; $p < 0.01$).[42]
- Two studies have compared intravenous paracetamol with other analgesics in reducing injection site pain associated with propofol administration.[51,52] Propofol is an anaesthetic commonly used for the induction of general anaesthesia. In both studies, a bolus of intravenous paracetamol 1 g was significantly ($p < 0.05$) more effective at reducing injection site pain than placebo, with fewer intravenous paracetamol recipients experiencing pain with propofol administration (46%[52] and 22%[51]) compared with placebo recipients (64% in both studies).[51,52] The efficacy of intravenous paracetamol was not significantly different from lidocaine 40 mg in one study (pain incidence 22% vs 8%),[51] but not the other study (pain incidence 46% vs 32%; $p < 0.05$).[52] In addition, in one study, intravenous paracetamol was less effective than lidocaine fentanyl treatment at reducing injection site pain (pain incidence 46% vs 30%; $p < 0.05$).[52]

In Paediatric Patients

The therapeutic efficacy of intravenous paracetamol 15 mg/kg for the management of perioperative pain (in paediatric patients aged 1–12 years,[11] 3–16 years,[53,54] or 2–5 years[55]) and fever (in paediatric patients aged 1 month to 12 years)[56] has been evaluated in several randomized, single-[55] or double-blinded,[11,53,54,56] active comparator-controlled trials.

Studies were conducted at single institutions[53-55] or as part of a multicenter study;[11,56] all studies are fully published. Inclusion criteria were for postoperative pain to be >30 mm on a 100 mm VAS[11] or the patient had to be scheduled for surgery.[53-55] Agents were administered intra-[53-55] or post-operatively,[11] or immediately after obtaining an initial body temperature reading,[56] as a 15-minute intravenous infusion.

Treatment of Perioperative pain

For the treatment of perioperative pain in paediatric patients, the primary efficacy endpoints

were pain intensity (assessed by pain intensity difference [PAID] from baseline until 6 hours postdose, maximum PAID, time to maximum PAID and weighted sum of PAID),[11] and time to first rescue medication assessed using Kaplan-Meier plots (see table II for details).[55] Pain evaluations using the VAS were assessed by an investigator or by the patient when possible.

- A single preoperative dose of intravenous paracetamol 15 mg/kg appeared to provide less initial pain relief than a single dose of intramuscular pethidine 1 mg/kg after dental surgery (table II).[54] Pain relief was significantly better in patients receiving pethidine during the first 10 minutes of the recovery period, although these patients also experienced significantly more sedation during this period, which may possibly account for this effect (table II).[54] However, there were no significant differences in objective pain scale (OPS) and sedation scores during the final 20 minutes of the 30-minute recovery period (table II). The sedative effects of pethidine were also reflected in a longer median time to readiness for discharge in these patients than in those receiving intravenous paracetamol (table II), although there was no between-group difference in the actual time to discharge (34 vs 32 minutes).[54] Other endpoints showed no statistical differences between groups.[54]
- The analgesic efficacy of intravenous paracetamol 15 mg/kg was not significantly different from that of intramuscular pethidine 1 mg/kg after tonsillectomy (table II).[53] Both analgesics produced OPS scores that did not differ significantly beginning at the time of admission to the recovery room (table II) and for the 40-minute duration of the study. Recipients of intravenous paracetamol were significantly less sedated than

Table II. Efficacy of intravenous (IV) paracetamol (PAR) in paediatric patients (pts) with postoperative pain. Fully published, randomized, double-blind, multi-[11] or single-centre[53-55] studies in paediatric pts who had undergone dental restoration,[54] inguinal hernia repair,[11] tonsillectomy[53] or adenotonsillectomy[55]

Study	No. of pts	Regimen (mg/kg)	Mean PAID[a,b]		Mean pain score (OPS)[a,c]				Median time to rescue medication[e] (h)	Mean Ramsay sedation score[d]				Time to readiness to discharge[f] (min)
			30 min	6 h	0 min	10 min	30 min	40 min		0 min	10 min	30 min	40 min	
Alhashemi and Daghistani[54]	20	PAR IV 15			4.0[g]	3.5[g]	3.2[g]		0.08	2.0[g]	2.1[g]	3.0[g]		5
	20	PET IM 1			2.5[g]	2.5*[g]	2.0[g]		0.17	3.5*[g]	3.1*[g]	3.2[g]		16**
Alhashemi and Daghistani[53]	40	PAR IV 15			3.1[g]		2.7[g]	3.2[g]	0.30	3.3[g]		2.5[g]	2.3[g]	15
	40	PET IM 1			2.1[g]		2.0[g]	2.0[g]	NR	4.3*[g]		2.7[g]	2.7[g]	25**
Capici et al.[55]	23	PAR IV 15							7.00[h]					
	23	PAR PR 40							10.00*[h]					
Murat et al.[11]	95	PAR IV 15	37[h,g]	42[h,g]					>4.00[i]					
	88	PRO IV 30	38[h,g]	36[h,g]					>4.00[i]					

a Data were rated by the investigator.[11,53-55]

b Scores are for time after treatment, assessed using a 100 mm visual analogue scale (0 = no pain to 100 mm = worst possible pain). Higher PAID scores represent greater pain reduction.

c Scores are for time after admission to recovery room, calculated using a 10-point scale based on scores for five categorical scales: blood pressure, crying, movement, agitation and body language.[53,54] Lower scores indicate greater pain reduction.

d Scores are for time after admission to recovery room.[53]

e Time elapsed from initiation of treatment until actual time of administration of rescue medication.

f Time taken to achieve an Aldrete score of 10 (based on Kaplan-Meier survival curves).

g Data estimated from a graph, intermediate timepoints not presented here.

h Primary efficacy endpoint.

i Mean time to rescue medication.

IM = intramuscular; **NR** = not required; **OPS** = objective pain scale; **PAID** = pain intensity difference from baseline until 6 hours postdose; **PET** = pethidine; **PR** = rectal; **PRO** = propacetamol; * $p < 0.05$; ** $p < 0.01$ vs PAR.

those receiving pethidine at the time of admission to the recovery room (table II) and during the initial recovery period (0–5 minutes).[53] Consistent with this finding, patients receiving intravenous paracetamol experienced a significantly shorter duration in the time to readiness to discharge from the recovery room (table II).[53]

- Compared with propacetamol 30 mg/kg, intravenous paracetamol 15 mg/kg did not differ significantly in efficacy in the reduction of pain intensity (PAID) scores after inguinal hernia repair (table II).[11] There were also reportedly no between-group differences in the time to peak PAID, maximum PAID and the weighted sum of PAID.[11] Mean PAID values in the intravenous paracetamol and propacetamol groups did not differ significantly during the first 30 minutes and remained so for the duration of the 6-hour assessment period (table II).[11] There were also no significant differences between secondary efficacy endpoints such as the proportion of patients using rescue medication (approximately 20% in both groups), mean time to rescue medication (table II) and global assessment of treatment rated as 'excellent' by the investigator (76% of intravenous paracetamol recipients vs 63% of propacetamol recipients).[11]
- Intravenous paracetamol 15 mg/kg was associated with a shorter median time to rescue medication than rectal paracetamol 40 mg/kg in a small (n = 46), single-blind, single-centre trial in patients after adenotonsillectomy (table II).[55] Nonetheless, no between-group differences in comfort at home scores were observed (assessed over the 24-hour period after discharge using six separate measures, each with a 4-point VRS), with 61% of patients receiving intravenous paracetamol recording a score of ≤4 compared with 78% of rectal paracetamol recipients.[55] As previously noted, the bioavailability and absorption of paracetamol after rectal administration shows a high degree of interpatient variability, which may in part explain the longer median time to rescue medication.[4,8,9]

Treatment of Fever

A double-blind noninferiority study compared the single-dose efficacy of intravenous paracetamol 15 mg/kg (n = 33) with propacetamol 30 mg/kg (n = 32) in the treatment of paediatric patients with acute fever due to infection.[56] Patients were included if they had acute fever attributable to infection and a body temperature of 38.5–41°C.[56] The primary efficacy endpoint in this trial was the maximum body temperature reduction over the 6-hour assessment period following infusion of the drug. Intravenous paracetamol was shown to be noninferior to propacetamol if the upper boundary of the 95% confidence interval for the difference in maximal body temperature reduction (propacetamol minus paracetamol) was less than the noninferiority margin of 0.5%.[56]

- Intravenous paracetamol was shown to be noninferior to intravenous propacetamol at reducing mean maximum body temperature (reduced by 1.92 vs 2.05°C; between-group difference 0.13°C [95% CI –0.25, 0.54]).[56]
- Additionally, there was no significant difference in the numbers of patients in each group who achieved a normal body temperature of 38°C (79% vs 75% of intravenous paracetamol and propacetamol recipients).[56] The median time to reach normal body temperature was 2 hours for each group and the investigators' global evaluation of 'good' or 'excellent' was achieved in 73% versus 65% of patients in the intravenous paracetamol and propacetamol groups.[56]

4. Tolerability

Single and multiple doses of intravenous paracetamol were generally well tolerated in adult and paediatric patients participating in the clinical trials discussed in section 3.[2,11,33,36,40,45,56,57]

In Adult Patients

- In large placebo-controlled trials (see table I for dosage and design details),[2,38-40] the tolerability profile of intravenous paracetamol was generally similar to that of placebo. As is the case with all formulations of paracetamol, adverse drug reactions with the intravenous formulation of paracetamol are rare (i.e. malaise, hypotension and increased levels of hepatic transaminases

[>1/10 000, <1/1000]) or very rare (i.e. hypersensitivity reaction and thrombocytopenia [<1/10 000]).[17]

- Intravenous paracetamol was better tolerated than bioequivalent doses of intravenous propacetamol, with a significantly ($p < 0.05$) lower incidence of infusion-site treatment-emergent adverse events in intravenous paracetamol than in propacetamol groups in multicentre trials.[2,40,45] For example, in adult patients who underwent orthopaedic surgery, infusion-site adverse events occurred in 2% of paracetamol recipients compared with 38% of patients receiving propacetamol ($p < 0.001$); the incidence in the placebo group was 2%.[2] The nature and incidence of other adverse events was generally similar in the paracetamol and propacetamol groups.[2,40,45]
- At recommended doses, intravenous paracetamol was not associated with hepatotoxicity, based on a pooled analysis of phase II and III clinical trials ($n > 1000$; elevations in transaminase enzyme levels occurred in 3.1% of paracetamol recipients vs 6.3% of placebo recipients) [only available as a poster].[57]

In Paediatric Patients

- In several controlled studies in paediatric patients discussed in sections 2 and 3, a similar safety profile to that seen in adults was observed, with single and multiple doses of intravenous paracetamol 15 mg/kg generally well tolerated.[11,33,36,56]
- In two comparator-controlled studies in paediatric patients, recommended doses of intravenous paracetamol were generally better tolerated than bioequivalent doses of intravenous propacetamol, with significantly ($p < 0.01$) fewer incidences of infusion-site treatment-emergent adverse events in paracetamol than in propacetamol groups.[11,56] For instance, in patients who underwent inguinal hernia repair, infusion-site adverse events occurred in 15% of paracetamol recipients compared with 36% of patients receiving propacetamol,[11] while the nature and incidence of other adverse events was generally similar in both groups.
- In a retrospective study in 149 neonates (5–182 days of age), intravenous paracetamol (initial dose of 20 mg/kg, followed by 10 mg/kg every 6, 8 or 12 hours for neonates with a GA of >36 weeks, 31–36 weeks and <31weeks, respectively) was not associated with hepatotoxicity, with no changes in hepatic enzyme profiles observed during the treatment period and for up to 2 days after the last dose.[7] Similarly, in a safety and pharmacokinetic study in neonates ($n = 50$) from an intensive care unit, multiple doses of intravenous paracetamol administered at recommended doses were not associated with hepatotoxicity, according to liver function tests (ALT, ALP and γ-glutamyl transferase).[36]

5. Dosage and Administration

Intravenous paracetamol is approved for the treatment of pain and fever in several countries worldwide.[58,59] For example, in the UK, intravenous paracetamol has been approved for the short-term treatment of moderate pain, especially following surgery, and for the short-term treatment of fever, when administration by intravenous route is clinically justified by an urgent need to treat pain or hyperthermia, and/or when other routes of administration are not possible.[17]

Intravenous paracetamol is administered as a 15-minute infusion. The recommended dosage in adults and adolescents weighing >50 kg is 1 g up to four times per day, with a minimum interval of 4 hours between doses and a maximum daily dose of 4 g.[17] In children weighing >33 kg, and in adolescents and adults <50 kg, the recommended dosage is 15 mg/kg up to four times per day, with a minimum interval between doses of 4 hours and a maximum daily dose of 60 mg/kg (without exceeding 3 g).[17] In children weighing >10 and <33 kg, the recommended dosage is 15 mg/kg up to four times per day, with a minimum interval between doses of 4 hours and a maximum daily dose of 60 mg/kg (without exceeding 2 g).[17] In full-term newborn infants, infants, toddlers and children weighing less than 10 kg (up to ≈1 year of age), the recommended dosage is 7.5 mg/kg up to four times per day, with a minimum interval of 4 hours between doses and a maximum daily dose of 30 mg/kg.[17]

In patients with severe renal impairment (creatinine clearance rates of ≤30 mL/min [1.8 L/h]), the minimum interval between each administration should be increased to 6 hours. No dosage adjustment is required for treatment in the elderly and in patients with liver disease.[17]

Local prescribing information should be consulted for detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

6. Intravenous Paracetamol: Current Status

Intravenous paracetamol has been approved for the short-term treatment of moderate pain and fever in both adult and paediatric patients in numerous countries worldwide[59] and is currently in preregistration with the US FDA.[58] In several large well designed trials in adult patients, single or multiple doses of intravenous paracetamol 1 g generally provided more effective postoperative analgesia than placebo after various surgical procedures. The use of intravenous paracetamol for postoperative analgesia generally reduced the requirement for morphine and other opioid rescue medication. Intravenous paracetamol showed generally similar postoperative analgesic efficacy to a bioequivalent dose of propacetamol in adult and paediatric patients. In paediatric patients, intravenous paracetamol was no less effective than propacetamol for the treatment of fever.

Intravenous paracetamol was very well tolerated in clinical trials. It is rarely associated with significant adverse events, including those associated with opioid and NSAID analgesics, such as nausea and sedation, or gastrointestinal and cardiovascular complications. Notably, intravenous paracetamol was associated with significantly fewer adverse infusion-site reactions than intravenous propacetamol.

Acknowledgements

The manuscript was reviewed by: **B. Bannwarth**, Department of Rheumatology, Victor Segalen University, Bordeaux, France; **G.G. Graham**, Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

References

1. Walder B, Schafer M, Henzi I, et al. Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain. Acta Anaesthesiol Scand 2001; 45 (7): 795-804
2. 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 Apr; 102 (4): 822-31
3. Haas D. An update on analgesics for the management of acute postoperative dental pain. J Can Dent Assoc 2002; 68 (8): 476-82
4. Malaise O, Bruyere O, Reginster JY. Intravenous paracetamol: a review of efficacy and safety in therapeutic use. Future Neurol 2007; 2 (6): 673-88
5. Kehlet H, Werner MU. Role of paracetamol in acute pain management. Drugs 2003; 63 (Spec. Iss. 2): 15-22
6. Graham GG, Scott KF, Day RO. Tolerability of paracetamol. Drugs 2003; 63 (Spec. Iss. 2): 43-6
7. Allegaert K, Rayyan M, De Rijdt T, et al. Hepatic tolerance of repeated intravenous paracetamol administration in neonates. Paediatr Anaesth 2008 May; 18 (5): 388-92
8. Holmer Pettersson P, Jakobsson J, Owall A. Plasma concentrations following repeated rectal or intravenous administration of paracetamol after heart surgery. Acta Anaesthesiol Scand 2006 Jul; 50 (6): 673-7
9. Arana A, Morton NS, Hansen TG. Treatment with paracetamol in infants. Acta Anaesthesiol Scand 2001 Jan; 45 (1): 20-9
10. Electronic Medicines Compendium. Ketorolac 30 mg/ml solution for injection (Beacon pharmaceuticals): summary of product characteristics [online]. Available from URL: http://emc.medicines.org.uk/emc/assets/c/html/DisplayDoc.asp? DocumentID=20922 [Accessed 2008 Dec 12]
11. Murat I, Baujard C, Foussat C, et al. Tolerance and analgesic efficacy of a new i.v. paracetamol solution in children after inguinal hernia repair. Paediatr Anaesth 2005; 15 (8): 663-70
12. Bjorkman R, Hallman KM, Hedner J, et al. Acetaminophen blocks spinal hyperalgesia induced by NMDA and substance P. Pain 1994 Jun; 57 (3): 259-64
13. Muth-Selbach US, Tegeder I, Brune K, et al. Acetaminophen inhibits spinal prostaglandin E2 release after peripheral noxious stimulation. Anesthesiology 1999 Jul; 91 (1): 231-9
14. Pickering G, Loriot MA, Libert F, et al. Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. Clin Pharmacol Ther 2006 Apr; 79 (4): 371-8

15. Aronoff DM, Oates JA, Boutaud O. New insights into the mechanism of action of acetaminophen: its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. Clin Pharmacol Ther 2006 Jan; 79 (1): 9-19
16. Graham GG, Scott KF. Mechanism of action of paracetamol. Am J Ther 2005; 12 (1): 46-55
17. Electronic Medicines Compendium. Perfalgan 10 mg/ml solution for infusion: summary of product characteristics [online]. Available from URL: http://emc.medicines.org.uk/emc/assets/c/html/DisplayDoc.asp?DocumentID=14288 [Accessed 2008 Aug 19]
18. Bonnefont J, Courade JP, Alloui A, et al. Mechanism of the antinociceptive effect of paracetamol. Drugs 2003; 63 (Spec. Iss. 2): 1-4
19. Bonnefont J, Daulhac L, Etienne M, et al. Acetaminophen recruits spinal p42/p44 MAPKs and GH/IGF-1 receptors to produce analgesia via the serotonergic system. Mol Pharmacol 2007 Feb; 71 (2): 407-15
20. Kumpulainen E, Kokki H, Halonen T, et al. Paracetamol (acetaminophen) penetrates readily into the cerebrospinal fluid of children after intravenous administration. Pediatrics 2007 Apr; 119 (4): 766-71
21. Viscusi E, Royal M, Leclerc A, et al. Pharmacokinetics, efficacy and safety of IV acetaminophen in the treatment of pain following total hip arthroplasty: results of a double-blind, randomized, placebo-controlled, single-dose study [abstract no. 215 plus poster]. 24th Annual Meeting of the American Academy of Pain Medicine; 2008 Feb 12-16; Orlando (FL)
22. Gelotte CK, Auiler JF, Lynch JM, et al. Disposition of acetaminophen at 4, 6, and 8 g/day for 3 days in healthy young adults. Clin Pharmacol Ther 2007 Jun; 81 (6): 840-8
23. Gregoire N, Hovsepian L, Gualano V, et al. Safety and pharmacokinetics of paracetamol following intravenous administration of 5 g during the first 24 h with a 2-g starting dose. Clin Pharmacol Ther 2007 Mar; 81 (3): 401-5
24. Schutz RA, Fong L, Chang Y, et al. Open-label, 4-period, randomized crossover study to determine the comparative pharmacokinetics of oral and intravenous acetaminophen administration in healthy male volunteers [poster only]. 32nd Annual Regional Anesthesia Meeting; 2007 Apr 19-22; Vancouver (BC)
25. 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 Jan; 42 (1): 50-7
26. Bannwarth B, Netter P, Lapicque F, et al. Plasma and cerebrospinal fluid concentrations of paracetamol after a single intravenous dose of propacetamol. Br J Clin Pharmacol 1992; 34 (1): 79-81
27. Clements JA, Critchley JA, Prescott LF. The role of sulphate conjugation in the metabolism and disposition of oral and intravenous paracetamol in man. Br J Clin Pharmacol 1984; 18 (4): 481-5
28. Manyike PT, Kharasch ED, Kalhorn TF, et al. Contribution of CYP2E1 and CYP3A to acetaminophen reactive metabolite formation. Clin Pharmacol Ther 2000; 67 (3): 275-82
29. Koch-Weser J. Medical intelligence: drug therapy. N Engl J Med 1976; 295 (23): 1297-300
30. Jayasinghe KSA, Roberts CJC, Read AE. Is biliary excretion of paracetamol significant in man? Br J Clin Pharmacol 1986; 22 (3): 363-6
31. Abernethy DR, Greenblatt DJ, Ameer B, et al. Probenecid impairment of acetaminophen and lorazepam clearance: direct inhibition of ether glucuronide formation. J Pharmacol Exp Ther 1985; 234 (2): 345-9
32. Levy G, Khanna NN, Soda DM, et al. Pharmacokinetics of acetaminophen in the human neonate: formation of acetaminophen glucuronide and sulfate in relation to plasma bilirubin concentration and D-glucaric acid excretion. Pediatrics 1975 Jun; 55 (6): 818-25
33. Wurthwein G, Koling S, Reich A, et al. Pharmacokinetics of intravenous paracetamol in children and adolescents under major surgery. Eur J Clin Pharmacol 2005 Feb; 60 (12): 883-8
34. van Lingen RA, Deinum JT, Quak JM, et al. Pharmacokinetics and metabolism of rectally administered paracetamol in preterm neonates. Arch Dis Child Fetal Neonatal Ed 1999 Jan; 80 (1): F59-63
35. van der Marel CD, Anderson BJ, van Lingen RA, et al. Paracetamol and metabolite pharmacokinetics in infants. Eur J Clin Pharmacol 2003 Jul; 59 (3): 243-51
36. Palmer GM, Atkins M, Anderson BJ, et al. I.V. acetaminophen pharmacokinetics in neonates after multiple doses. Br J Anaesth 2008 Oct; 101 (4): 523-30
37. Pineiro-Carrero VM, Pineiro EO. Liver. Pediatrics 2004 Apr; 113 (4 Suppl): 1097-106
38. Candiotti K, Singla N, Wininger S, et al. A randomized, double-blind, placebo-controlled, multi-center, parallel-group, multiple-dose study of the efficacy and safety of intravenous acetaminophen over 48 hours for the treatment of postoperative pain after gynecologic surgery [abstract no. A-13 plus poster]. 33rd Annual Regional Anesthesia Meeting; 2008 May 1-4; Cancun
39. Juhl GI, Norholt SE, Tonnesen E, et al. Analgesic efficacy and safety of intravenous paracetamol (acetaminophen) administered as a 2 g starting dose following third molar surgery. Eur J Pain 2006 May; 10 (4): 371-7
40. Moller PL, Juhl GI, Payen-Champenois C, et al. Intravenous acetaminophen (paracetamol): comparable analgesic efficacy, but better local safety than its prodrug, propacetamol, for postoperative pain after third molar surgery. Anesth Analg 2005 Jul; 101 (1): 90-6
41. Atef A, Fawaz AA. Intravenous paracetamol is highly effective in pain treatment after tonsillectomy in adults. Eur Arch Otorhinolaryngol 2008 Mar; 265 (3): 351-5
42. Kemppainen T, Kokki H, Tuomilehto H, et al. Acetaminophen is highly effective in pain treatment after endoscopic sinus surgery. Laryngoscope 2006; 116 (12): 2125-8
43. Gimbel J, Royal M, Leclerc A, et al. Efficacy and safety of IV acetaminophen in the treatment of pain following primary total hip arthroplasty: results of a double-blind, randomized, placebo-controlled, multiple-dose, 24 hour study [poster only]. 24th Annual Meeting of the American Academy of Pain Medicine; 2008 Feb 12-16; Orlando (FL)

44. Minkowitz H, Royal M, Leclerc A, et al. Efficacy and safety of IV acetaminophen in the treatment of pain following vaginal hysterectomy: results of a double-blind, randomized, placebo-controlled, multiple-dose, 24 hour study [poster only]. 24th Annual Meeting of the American Academy of Pain Medicine; 2008 Feb 12-16; Orlando (FL)
45. Marty J, Benhamou D, Chassard D, et al. 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. Curr Ther Res Clin Exp 2005 Jul; 66 (4): 294-306
46. Grundmann U, Wornle C, Biedler A, et al. The efficacy of the non-opioid analgesics parecoxib, paracetamol and metamizol for postoperative pain relief after lumbar microdiscectomy. Anesth Analg 2006 Jul; 103 (1): 217-22
47. Alhashemi JA, Alotaibi QA, Mashaat MS, et al. Intravenous acetaminophen vs oral ibuprofen in combination with morphine PCIA after Cesarean delivery. Can J Anaesth 2006 Dec; 53 (12): 1200-6
48. Khan ZU, Iqbal J, Saleh H, et al. Intravenous paracetamol is as effective as morphine in knee arthroscopic day surgery procedures. Pakistan J Med Sciences 2007; 23 (6): 851-3
49. Arellano F, Sacristan JA. Metamizole: reassessment of its therapeutic role. Eur J Clin Pharmacol 1990; 38 (6): 617-9
50. Cattabriga I, Pacini D, Lamazza G, et al. Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: a double blind randomized controlled trial. Eur J Cardiothorac Surg 2007 Sep; 32 (3): 527-31
51. Canbay O, Celebi N, Arun O, et al. Efficacy of intravenous acetaminophen and lidocaine on propofol injection pain. Br J Anaesth 2008 Jan; 100 (1): 95-8
52. El-Radaideh KM. Effect of pretreatment with lidocaine, intravenous paracetamol and lidocaine-fentanyl on propofol injection pain: comparative study. Rev Bras Anestesiol 2007; 57 (1): 32-8
53. Alhashemi JA, Daghistani MF. Effects of intraoperative i.v. acetaminophen vs i.m. meperidine on post-tonsillectomy pain in children. Br J Anaesth 2006 Jun; 96 (6): 790-5
54. Alhashemi JA, Daghistani MF. Effect of intraoperative intravenous acetaminophen vs. intramuscular meperidine on pain and discharge time after paediatric dental restoration. Eur J Anaesthesiol 2007 Feb; 24 (2): 128-33
55. Capici F, Ingelmo PM, Davidson A, et al. Randomized controlled trial of duration of analgesia following intravenous or rectal acetaminophen after adenotonsillectomy in children. Br J Anaesth 2008 Feb; 100 (2): 251-5
56. Duhamel JF, Le Gall E, Dalphin ML, et al. Antipyretic efficacy and safety of a single intravenous administration of 15 mg/kg paracetamol versus 30 mg/kg propacetamol in children with acute fever due to infection. Int J Clin Pharmacol Ther 2007 Apr; 45 (4): 221-9
57. Singla N, Viscusi E, Candiotti K, et al. A review of the intravenous acetaminophen placebo-controlled clinical trial safety experience: a focus on hepatic transsaminases [poster only]. 33rd Annual Regional Anesthesia Meeting; 2008 May 1-4; Cancun
58. Cadence Pharmaceuticals Inc. Cadence pharmaceuticals announces FDA concurrence with clinical development plan for acetavance™ [online]. Available from URL: http://cadx. client.shareholder.com/releases.cfm [Accessed 2008 Sep 1]
59. Electronic medicines compendium. Perfalgan 10 mg/ml solution for infusion, 50 ml vial: patient information leaflet [online]. Available from URL: http://xpil.medicines.org.uk/ViewPil. aspx?DocID=19321 [Accessed 2008 Aug 19]

Correspondence: *Sean T. Duggan*, Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand. E-mail: demail@adis.co.nz

