What is the evidence to support the use of IV paracetamol for the treatment of pain?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals
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Background

Intravenous (IV) paracetamol is licensed for the short-term treatment of moderate pain, especially following surgery and for the short-term treatment of fever. Use of the IV route is clinically justified by an urgent need to treat pain or pyrexia and/or when other routes of administration are not possible (1). There is however concern that the IV route may not always be chosen appropriately, due to:

- associated risks of infection or local pain and inflammation
- potential for overdose with concomitant orally administered medicines containing paracetamol
- failure to adjust the dose according to body weight or other patient-related factors
- increased nursing time and costs.

Answer

For some years paracetamol for IV use was only available (not licensed in the UK) in the form of propacetamol, a pro-drug of paracetamol. A dose of 2g of propacetamol is hydrolyzed to 1g of paracetamol (2) within 7 minutes of administration. Bioequivalence (3) and therapeutic equivalence (4) of 2g of IV propacetamol and 1g of IV paracetamol have been demonstrated. A large proportion of the efficacy data on IV paracetamol is derived from studies of IV propacetamol.

Post-operative pain

Pharmacokinetics

IV vs Oral

The manufacturer of IV paracetamol recommends the use of a suitable analgesic oral treatment as soon as this administration route is possible (1). There may be situations where this is not appropriate e.g. following abdominal or gastric surgery where normal stomach motility may not be restored for 15 hours or more, also after oral surgery, or if a rapid onset of action is required (5). Paracetamol is not absorbed in the stomach, therefore delays in gastric emptying decrease the transfer of drug to the small intestine, resulting in diminished peak plasma concentrations (6). A one-off dose of IV paracetamol in the immediate post-operative period has been suggested to achieve baseline analgesia in the sedated patient (5).

The onset of analgesia occurs rapidly within 5-10 minutes of IV paracetamol administration. The peak analgesic effect is obtained in 1 hour and its duration is approximately 4-6 hours (1,4). Although oral bioavailability is good (83-99%), early plasma concentrations following oral administration may vary, and in some cases may remain subtherapeutic (7). The minimum plasma paracetamol level required for analgesia and antipyresis is thought to be 10 mcg/mL (66 micromol/L) and although not clearly defined, the therapeutic range is usually considered to be 10-20 mcg/mL (66-132 micromol/L) (8).

In a small study comparing early bioavailability of paracetamol after oral or IV administration, 35 adult patients undergoing day surgery (5 groups of 7 patients) received either 1g or 2 g paracetamol tablets, 1g or 2g bicarbonate paracetamol tablets or 2g propacetamol. After 40 minutes IV propacetamol gave a median plasma concentration of 85 micromol/L (range 65-161). 11 out of 28 (40%) of the patients given paracetamol orally showed undetectable plasma concentrations of paracetamol after 40 minutes. At 80 minutes after oral paracetamol the median (range) plasma concentrations were 36 (0-90) and 129 (21-306) micromol/L for the 1- and 2-g groups respectively.

Three of fourteen patients who received 1g had a plasma paracetamol concentration of <10 micromol/L (8). The study did not report clinical outcomes i.e. pain relief, although pain was assessed by VAS and treated when VAS values were >4, but no details are given.

A recent systematic review and meta-analysis of single doses of propacetamol 2g IV and paracetamol 1g orally in 323 patients with moderate pain following hallux valgus plasty, showed a significantly greater and longer analgesic effect with the paracetamol form (9). Duration of follow-up was 6 hours.

IV vs Rectal

Absorption of paracetamol following rectal administration is slower and more variable than with IV or oral administration (5,7,10). High initial doses are needed to achieve therapeutic plasma concentrations (7) and therefore the rectal route is not the preferred route of administration of paracetamol for the immediate relief of post-operative pain (5). In the UK the acquisition cost of paracetamol suppositories may be higher than that of the injection, depending on brand and strength (11).

Therapeutic efficacy and tolerability

Paracetamol is a well-tolerated analgesic when used at normal dosages for the acute management of mild-to-moderate post-operative pain (5). Where alternative routes are unavailable, IV paracetamol is mostly used in association with NSAIDs and opioids to allow a reduced dose of these analgesics, that have a worse adverse effect profile, to be given (5), rather than as monotherapy (5,10). The Summary of Product Characteristics (SPC) states that ‘frequent’ adverse reactions at the injection site have been reported during clinical trials (pain and burning sensation) (11). However, the incidence of local adverse events such as injection-site pain and contact dermatitis is significantly lower with IV paracetamol compared with propacetamol (4,10) and comparable to placebo in two studies: 2% (4,12) and 0% (13).

A number of systematic reviews have assessed the effectiveness of adding a non- opioid to (PCA) morphine for pain relief and reduction of morphine-related side effects following surgery (14). These are briefly summarised below:

Paracetamol plus morphine

Remy et al(15) showed that paracetamol (including propacetamol) combined with PCA morphine results in a pooled mean reduction of 9mg in morphine consumption in the first 24 hours after surgery (95% CI: -15 to -3) equivalent to a 20% reduction. Seven RCTs, mainly in orthopaedic and spinal surgery, were included. Five studies used IV paracetamol, one used oral and one used IV plus rectal paracetamol. There were 265 patients in the group with PCA morphine plus paracetamol and 226 patients in the group with PCA morphine alone. There was no statistically significant reduction in morphine-related adverse effects including urinary retention, pruritus and sedation (OR 1.3 for sedation; 95% CI 0.79 TO 2.16; P=0.3). Paracetamol administration resulted in a non-significant reduction in PONV (OR = 0.99; 95% CI, 0.64 to 1.55; P=0.98). Patient satisfaction as assessed by verbal rating scales did not differ between the groups.

Elia et al (16) showed that paracetamol (including propacetamol) reduced 24-hour morphine consumption by 8.3mg (95% CI: -10.9 to -5.7). However, there was no statistically significant reduction in PONV or sedation (16). Fifty-two RCT (4,893 patients undergoing orthopaedic, abdominal, gynaecological, spinal or thoracic surgery) were included. This review also assessed the effect of NSAIDs and COX-2 inhibitors. These were associated with a statistically significant increase in adverse effects: surgical bleeding complications and renal failure, respectively. No adverse effects were noted for paracetamol (16).

A more recent systematic review compared the effectiveness of paracetamol, NSAIDs and COX-2 inhibitors in reducing cumulative morphine consumption for the first 24 hours after surgery, and associated adverse effects, when used as part of multimodal analgesia following major surgery (14), including thoracic, orthopaedic, gynaecological, obstetric and general surgery. Sixty studies were identified of which were from the previous view (16) and 20 new trials. Only 5 studies were identified that directly compared paracetamol and NSAIDs. Seven studies compared paracetamol vs. placebo. Of the 12 paracetamol studies, 9 used IV paracetamol and 3 used oral and/or rectal administration. Data was combined from 56 trials that randomised patients to four treatments including placebo. The main analysis was mixed treatment comparison (MTC) evaluating the relative effects of the four treatment classes: paracetamol, NSAIDs, COX-2 inhibitors and placebo. The mean
difference in 24h morphine consumption for paracetamol was -6.34mg; 95% CI -9.02 to -3.65. NSAIDs and COX-2 inhibitors were more effective than paracetamol, but the differences were small and probably of limited clinical significance. Paracetamol was well-tolerated, with no reports of surgical bleeding, compared to 2.4% of participants receiving a NSAID, based on 6 trials (n = 695) NSAIDs were only slightly more superior to paracetamol in reducing PONV (RR 0.78; 95% CI 0.51 to 1.20) and sedation (RR 0.35; 95% CI 0.04 to 3.00) in patients on PCA morphine.

There are other studies of IV paracetamol for post-operative pain which did not meet the inclusion criteria for these systematic reviews (14). Some of these are summarised below.
### Table 1. Studies of IV paracetamol for pain relief after cardiac surgery

<table>
<thead>
<tr>
<th>Ref</th>
<th>Trial design</th>
<th>Trial population</th>
<th>Treatment</th>
<th>Primary outcome(s)</th>
<th>Results</th>
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<tr>
<td>Eremenko 2008&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Randomised blind, placebo-controlled trial</td>
<td>45 patients after CABG</td>
<td>Paracetamol 1g IV (&lt;sup&gt;n=22&lt;/sup&gt;) 30 min before extubation and then every 6h for 18h</td>
<td>Use of rescue analgesic (promedol IM 10mg)</td>
<td>36% reduction in mean total use of promedol (p=0.019).</td>
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<td>Lahtinen 2002&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Randomised, double blind, placebo-controlled trial</td>
<td>79 patients after CABG</td>
<td>Propacetamol 2g (&lt;sup&gt;n=40&lt;/sup&gt;) IV 6-hourly for 72h</td>
<td>Mean cumulative oxycodone consumption via PCA device at the end of 72h</td>
<td>Reduction in oxycodone dose of 18.3 mg; 95% CI (-6.1 to -42.7) propacetamol vs placebo, (p=0.15).</td>
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<td>Petterson 2005&lt;sup&gt;19&lt;/sup&gt;</td>
<td>RCT</td>
<td>80 patients after CABG</td>
<td>Paracetamol 1g IV(&lt;sup&gt;n=39&lt;/sup&gt;) or PO(&lt;sup&gt;n=38&lt;/sup&gt;) every 6h after extubation for 15h or 14h</td>
<td>Mean cumulative ketobemidone administration during the study period VAS pain scores and PONV</td>
<td>Mean dose of ketobemidone : IV paracetamol 17.4 ± 7.9mg vs PO paracetamol 22.1 ± 8.6mg (p=0.016). No difference in incidence of PONV &amp; in VAS scores</td>
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<td>Cattabriga 2007&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Randomised, double blind, placebo-controlled trial</td>
<td>113 patients after cardiac surgery. All patients received tramadol for 72h.</td>
<td>Paracetamol 1g IV (&lt;sup&gt;n=56&lt;/sup&gt;) or placebo (&lt;sup&gt;n=57&lt;/sup&gt;) 15 min before the end of surgery and every 6h for 72h.</td>
<td>Pain as assessed by VAS. Cumulative dose of rescue IV morphine over 72h</td>
<td>At 12, 18 and 24 h, pain scores significantly lower in paracetamol group (p=0.0041, 0.0039, 0.0044 respectively) 48mg vs 97mg (p=0.274) paracetamol vs placebo</td>
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Table 2. Studies of IV paracetamol for pain relief in other types of surgery

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<tr>
<th>Ref</th>
<th>Trial design</th>
<th>Trial population</th>
<th>Treatment</th>
<th>Primary outcome(s)</th>
<th>Results</th>
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<tr>
<td>Van Aken</td>
<td>Double blind RCT</td>
<td>95 patients undergoing third-molar surgery</td>
<td>IV propacetamol 2 g (n=31), vs. IM morphine 10 mg (n=30) vs. placebo (n=34). Five hours later, readministered at half of the previous dosages</td>
<td>Pain relief scores at 10 hours and other measures of analgesia</td>
<td>No significant differences were found between propacetamol and morphine, both of which were better than placebo. Adverse events were significantly less frequent in the propacetamol than in the morphine group (p&lt;0.027)</td>
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<tr>
<td>Varrassi</td>
<td>Double blind RCT</td>
<td>200 women after hysterectomy</td>
<td>Two IV doses of propacetamol 2 g (n=87) or ketorolac 30mg (n=89)</td>
<td>Total dose of PCA morphine over 12h</td>
<td>Propacetamol 10.6 ± 4.8mg vs. ketorolac 10.2 ± 4.4mg (mean ± SD). Incidence of AE was similar. NS prolongation of bleeding time with ketorolac. NS reduction of gastric pain with paracetamol</td>
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<tr>
<td>Zhou</td>
<td>Double blind RCT</td>
<td>164 patients after hip or knee replacement surgery</td>
<td>IV propacetamol 2 g (n=57), IV ketorolac 30mg (n=27), 15mg (n=28), placebo (n=52)</td>
<td>Pain intensity over 6h assessed by VAS and VRS and pain relief assessed by a categorical scale</td>
<td>Pain relief scores for propacetamol superior to placebo (p&lt;0.001) and similar to ketorolac 15mg and 30mg (p &lt;0.05) from 0.75 h to 5h.</td>
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Glossary

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<tr>
<th>Acronym</th>
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<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
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<td>VRS</td>
<td>Verbal Rating Scale</td>
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<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
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<td>PCA</td>
<td>Patient-controlled analgesia</td>
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<td>CI</td>
<td>Confidence intervals</td>
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<td>PONV</td>
<td>Post-operative nausea and vomiting</td>
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<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<td>RR</td>
<td>Risk Ratio</td>
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<tr>
<td>CABG</td>
<td>Coronary artery bypass graft</td>
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<tr>
<td>NS</td>
<td>Not Significant</td>
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<td>AE</td>
<td>Adverse effects</td>
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Renal colic

A RCT in 165 patients admitted with suspected renal colic compared single IV doses of paracetamol 1g, morphine 0.1mg/kg and placebo for pain relief. Patients were excluded if they needed rescue anesethetics within the first 30 minutes of the study, so 146 patients were included in the final analysis. The mean reduction in VAS pain intensity scores at 30 minutes was 43 mm for paracetamol (95% CI 35 to 51mm), 40 (29 to 52 mm) for morphine, and 27 (19 to 34 mm) for placebo. There was no difference in pain intensity reduction between paracetamol and morphine. At least one adverse event was experienced by 11(24%) receiving paracetamol 16(33%) receiving morphine and 8(16%) in the placebo group (24).

- Adverse effects/precautions/potential risks

Cases of accidental overdose have been reported during treatment with IV paracetamol 10mg/mL solution for infusion. In most cases this occurred in infants and neonates (25). However there are reports of clinical incidents involving paracetamol overdose in adult patients weighing less than 50kg, where the dose was not adjusted according to the patient’s weight (26,27). Failure to reduce the dose appropriately may result in paracetamol-induced liver toxicity. This could lead to hepatic failure and death (26,27). The British National Formulary (BNF) advises that the maximum daily dose of infusions should be also reduced to 3 g for patients with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition, or dehydration (11). In addition, since the infusion is presented in a rigid container (glass bottle), close monitoring is needed during administration and it must be stopped at the end of the infusion when the bottle is empty, in order to avoid air embolism (1,28).

Summary

- Intravenous (IV) paracetamol is licensed for the short-term treatment of moderate pain, especially following surgery, and for the short-term treatment of fever, when administration by the IV route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible.

- The main advantages of IV paracetamol are: when GI motility is reduced in the immediate post-operative period or when rapid establishment of analgesia is required. Studies have shown a reduction in morphine/opiod requirements; however sedation and post-operative nausea and vomiting are not reduced

- IV paracetamol has been shown to achieve therapeutic plasma concentrations well above the therapeutic range within 40 minutes of administration, whereas early plasma concentrations following oral administration of paracetamol may vary, and in some cases may remain subtherapeutic, unless a loading dose has been given. Absorption of paracetamol following rectal administration is slower and more variable than with IV or oral administration therefore this is not a suitable alternative if the oral route is not appropriate

- A large proportion of the efficacy data on IV paracetamol is derived from studies of IV propacetamol, a pro-drug of paracetamol. 2g IV propacetamol has been shown to be therapeutically equivalent to 1g IV paracetamol.

- There are several studies of the use of IV paracetamol in patients with severe pain post surgery as an opioid-sparing agent and a number of systematic reviews have assessed the effectiveness of adding paracetamol to (PCA) morphine for pain relief and reduction of morphine-related side effects following surgery. IV paracetamol was used in most of the included studies. Paracetamol reduced the mean 24 hour morphine consumption by 6 to 9mg, but overall there was no statistically significant reduction in post-operative nausea and vomiting. Paracetamol was well tolerated, compared to NSAIDs and COX-2 inhibitors.

- Caution must be used when IV paracetamol is given to children or adults weighing less than 50kg, as the dose has to be adjusted according to body weight. The dose should also be reduced in patients with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition, or dehydration. Failure to reduce the dose appropriately may result in paracetamol-induced liver toxicity. This could lead to hepatic failure and death.

- IV paracetamol has been shown to be effective and well-tolerated in the management of moderate pain immediately after surgery, but care must be taken to dose according to the licensed recommendations (see above).

Limitations

This Q&A discusses the evidence from studies in adults. The use in infants and children is not discussed. For full prescribing information please refer to the Summary of Product Characteristics

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Acknowledgements

Dr Hannah Blanshard, Consultant Anaesthetist, Bristol Royal Infirmary

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Quality Assurance

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30th December 2010

Search strategy
• Medline: exp *ACETAMINOPHEN and [ exp *INFUSIONS, INTRAVENOUS or exp *INJECTIONS, INTRAVENOUS] or "paracetamol infusion".ti,ab or "paracetamol injection".ti,ab [Limit to: Humans]