

# National Essential Medicine List Medication Review Process

## Adult Hospital Level

### Component: Pain

---

**Date:** July 18<sup>th</sup> 2015

**Medication:** Intravenous paracetamol

**Indication:** Analgesia during the perioperative period

#### **Introduction:**

Oral paracetamol (currently on the Essential Medicines List) and IV paracetamol are equally effective for the treatment of pain. The onset of action of IV paracetamol is quicker by 30 minutes but there is otherwise no difference between the analgesic actions of these two routes of administration.

However, there are circumstances in which oral paracetamol cannot be given and in these circumstances IV paracetamol is of value in the treatment of pain. These include (but are not limited to):

1. Patients who cannot swallow e.g. due to pathology or surgery of the gastrointestinal tract.
2. Patients who are unconscious e.g. due to trauma or anaesthesia
3. Patients who are vomiting.

This motivation is therefore for IV paracetamol for use in patients who are unable to take paracetamol tablets orally.

#### **Purpose of this Review:**

A previous motivation for IV paracetamol, by Reed and Llewellyn, has previously been submitted for review by the Adult Expert Review Committee. The purpose of this review is to supplement the previous review with articles not in the previous motivation for IV paracetamol, in order to provide additional evidence to confirm the efficacy and safety of IV paracetamol in the selected indications described above and in comparison to NSAIDs.

This is in keeping with the findings from the committee findings “Extracts from the Previous Adult Hospital Level Committee Minutes of the Meeting Regarding Paracetamol Intravenous. 7 Oct 2010, 24 Feb 2011, 31 March 2011, 3 Nov 2011, 19 Jan 2012, 16 Feb 2012,” in which it was stated that “robust data to support its use for the selected indication” (ie “patients that cannot safely receive postoperative opioids”) was required to support its inclusion in the Essential Medicines List. Also required in this report was “data comparing parenteral NSAIDs with IV paracetamol” and evidence that parenteral paracetamol confers “additional benefit over available pain therapies”.

## Evidence Synthesis

### *Benefit of IV Paracetamol in Trauma*

Trauma patients may be unable to take oral paracetamol because of depressed conscious level or due to vomiting. Vomiting may be as a consequence of acute pain, associated abdominal trauma or ingestion of emetogenic substances eg alcohol.

The articles below demonstrate that for trauma related pain IV paracetamol , is safe and efficacious International Experts in Emergency Medicine recommend its use.

In comparison with the use of opioids for trauma related pain, of note is the lack of side effects with IV paracetamol in contrast to the adverse side effects of opioids. IV opioids require titration by a health care practitioner trained in the IV administration of opioids and monitoring during and after its administration for opioids related side effects. Opioids require extra administrative practices as they are controlled drugs. IV paracetamol is not associated with these problems.

In comparison with NSAIDs, IV paracetamol showed better efficacy. Hypovolaemic patients are associated with renal damage if NSAIDs are given and, if due to haemorrhage, NSAIDs may increase the bleeding and hypovolaemia; IV paractamol is not associated with either of these two problems and has the benefit over NSAIDs in that it can be given to both hypovolaemic and bleeding patients.

Author	Type of article	Intervention	Primary Outcome	Results	Comments
Dijkstra 2014 <sup>1</sup>	Systematic review. 2328 studies found. 25 considered relevant.	Initial pharmacological interventions for trauma patients with pain	Efficacy and safety.	Paracetamol (oral and IV) safe and effective. NSAIDs mixed results for efficacy. Opioids effective but side effects of nausea and vomiting, drowsiness, confusion, hypotension, sedation.	NSAIDS not recommended (especially if hypovolaemia). Rectal paracetamol not recommended as variable bioavailability. Opioids safe if titrated to effect IV and respiratory and cardiovascular monitoring frequent.
Savoia (2015) <sup>2</sup>	Report of Italian Intersociety Consensus Conference	Pain management in emergency department	Efficacy and safety.	Level A recommendation for IV paracetamol for opioid sparing effects and reduction of opioid related adverse events.	
Craig (2012) <sup>3</sup>	Randomised double blind study. 55 adults with limb trauma and pain score $\geq 7/10$ .UK Emergency Department.	IV paracetamol 1g or IV morphine 10mg, over 15 mins.	Pain scores at 0,5,10,15,30,30 mins. Need for rescue analgesia. Adverse reactions.	Analgesic efficacy similar. More adverse reactions with morphine (P=0.03). Similar patients satisfaction.	IV paracetamol easier to administer as standard dose, morphine best titrated to effect, more adverse reactions and controlled drug.

### *Benefit of IV Paracetamol in the Perioperative Period*

Patients who are anaesthetised are unable to swallow. Whilst oral paracetamol can be given preoperatively for perioperative analgesia, if the operation finishes before 6h after the oral paracetamol was given (the maximum duration of action of oral paracetamol), then further paracetamol will be required to maintain its effect before emergence from anaesthesia. This is of particular importance for patients in whom opioid related side effects need to be prevented postoperatively. These patients include (but are not limited to) those with:

- A high risk of opioid related postoperative nausea and vomiting (PONV) e.g. previous PONV with opioids.
- A high risk of postoperative complications with vomiting (jaws wired, oesophageal surgery, intraocular surgery).
- Respiratory disease.
- Obesity.

In these patients IV paracetamol can be used before emergence from anaesthesia to prevent pain occurring (pain in itself can cause vomiting) or to treat acute postoperative pain in the recovery room.

IV paracetamol can be administered postoperatively until the patient is able to take oral paracetamol.

In comparison with NSAIDs for pain relief in the early postoperative period, IV paracetamol is safer as it is associated with less hypotension (1% for paracetamol and 10% for an NSAID;  $P=0.02$ )<sup>6</sup> and less postsurgical bleeding.<sup>8</sup> Furthermore, there are many patients in whom NSAID's cannot be used eg history of peptic ulcer disease, asthma, bleeding risk, renal disease, hypovolaemia. Due to the risk of platelet dysfunction and bleeding, there are types of surgeries in which bleeding can have severe consequences and in these postoperative NSAIDs are avoided (e.g. intracranial or spinal surgery) but paracetamol can be used.

Many studies have shown that paracetamol can reduce postoperative opioid requirements by about 30% (see below). NSAIDs can also reduce postoperative opioid requirements by 30-50%<sup>4</sup>. The anomaly is that with NSAIDs this reduction in opioid requirements has been demonstrated in several studies to reduce opioid related adverse events such as sedation, nausea and vomiting but for paracetamol, it has only been shown to reduce opioid adverse effects in one study by Memis (2010). **Error! Bookmark not defined.** (It is known that IV paracetamol reduces the risk of PONV but this has been attributed to its analgesic action rather than an opioid sparing effect.<sup>5</sup>) This paucity of studies is probably because many previous studies on IV paracetamol have focused on measuring a reduction in opioid dose rather than a reduction in opioid side effects; further studies are required to confirm what is a reasonable clinical assumption that reducing the dose of a drug will reduce the incidence of its clinically relevant side effects and the results of the Memis (2010) study.

In the meanwhile, it is reasonable to use paracetamol (IV until the oral route is available) for patients at high risk of adverse consequences from opioids in the postoperative period, particularly if NSAIDs are contraindicated.

Author	Type of article	Intervention	Primary Outcome	Results	Comments
McNicol 2011 <sup>6</sup>	Systematic Review and meta-analysis	IV paracetamol or proparacetamol as single dose for postoperative pain.	Pain relief at 4 and 6 hours	For IV paracetamol: 32% had ≥50% pain relief at 4 hours (nnt 3.4: CI 95% 2.8-4.5). Used less IV morphine than patients receiving an NSAID.	Few adverse events with paracetamol. Noted that IV paracetamol has superior safety profile over IV NSAID's and IV morphine.
Koh 2015 <sup>7</sup>	Review article	IV paracetamol or IV ibuprofen for perioperative pain.	Efficacy and safety	IV paracetamol safe and effective for treatment of acute peri-operative pain. Can be effectively used alone or in combination with IV ibuprofen.	Best effect if given before onset of pain. Also reduces postoperative nausea and vomiting as consequence of pain relief. Adverse reactions < 1/10,000. Reduces opioid consumption.
Maund (2010) <sup>8</sup>	Systematic review of RCT's 2003-9,	Adults in the 24h postoperative period using PCA morphine and non-opioids.	Compared with placebo, 24h morphine consumption with paracetamol, (also compared NSAIDS and Cox 2 inhibitors)	Of 60 trials included, 12 were of paracetamol or proparacetamol. PCA with paracetamol used significantly less morphine (6.34mg).	NSAIDs reduced pain more than paracetamol (morphine reduction 10.92mg/24h) but at expense of increased risk of postsurgical bleeding (2.4% with NSAID, 0.4% with placebo).
Saurabh (2015) <sup>9</sup>	Retrospective study. Patients who had laparoscopic Roux-en-Y gastric bypasses for severe obesity.	IV paracetamol with PCA for 24h postop (183 patients) compared to historical control of PCA morphine with no IV paracetamol (229 patients).	First 24hr postoperative morphine use.	Demand for PCA morphine reduced by 25% (P<0.05) and dose of opioid reduced by 20% (<0.05)	Opioid reduction important in severely obese patients as at high risk of opioid related respiratory depression and sleep apnoea. Often unable to use the oral route for paracetamol in the first 24h postoperatively.
Gonzalez (2015) <sup>10</sup>	Retrospective study in patients having bariatric surgery.	IV paracetamol and opioids in first 24h postoperatively (38 patients) compared to historical control who had only opioids (47 patients).	First 24hr postoperative morphine use.	With IV paracetamol used 99.5mg opioid compared to 164.6mg opioid without paracetamol (ie 39.5% less)	As described above. Obese patients at risk with opioids.
Memis (2010) <sup>11</sup>	Randomised double blind controlled trial. 40 adults admitted to ICU for postoperative ventilation after major abdominal/pelvic surgery.	IV paracetamol 1g with IV pethidine 100mg 6hourly or IV saline with IV pethidine 100mg 6 hourly for 24 hours.	Time to extubation. Rescue analgesia. PONV.	Less time to extubation with paracetamol group (64.3 vs 204.5 minutes; P<0.01). Less PONV in paracetamol group 1/20 vs 8/20 patients: P<0.05)	No adverse effects attributed to paracetamol use.

### *Benefit of IV Paracetamol in Renal Colic*

Renal colic is frequently associated with vomiting and if this occurs oral paracetamol cannot be given. Owing to the severity of renal colic pain, the faster onset of action of IV paracetamol compared to oral paracetamol is also of advantage. A single dose of IV paracetamol has been shown to be as efficacious as IV morphine and NSAIDs in the treatment of this condition with fewer side effects than either drug.

IV paracetamol is an important addition to the drugs that can be used to treat this acutely painful condition, particularly in those patients in whom opioids and/or NSAIDs must be avoided. These include pregnant patients with renal colic (NSAIDs can cause premature closure of the fetal patent ductus arteriosus) and suspected drug abusers (who may present with fictitious renal colic in order to obtain opiates).

Author	Type of article	Intervention	Primary Outcome	Results	Comments
Grissa (2009) <sup>12</sup>	Randomised controlled trial. 100 patients with acute renal colic.	Single dose IV paracetamol 1g or IM piroxicam 20mg.	Pain relief at 90 minutes ie 50% less pain than initial pain score.	80% had pain relief with paracetamol and 48% with piroxicam (P=0.002).	Analgesia obtained earlier with paracetamol.
Kaynar (2015) <sup>13</sup>	Randomised trial. 182 patients with acute renal colic.	IV paracetamol 1g, acupuncture or IM diclofenac 75mg	Pain scores at 0,10,30,60,120 minutes.	On admission pain scores 9/10. Paracetamol and diclofenac had similar good effect with pain scores at 60 and 120 minutes (3.46 and 2.1 for paracetamol and 2.78 and 2.75 for diclofenac)	Acupuncture resolved pain quicker than either drug but at 60 and 120 minutes not as effective as the medications.
Bektas (2009) <sup>14</sup>	Randomised double blind placebo controlled trial. 165 adults with acute renal colic	IV paracetamol 1g or Morphine 0.1mg/kg or placebo.	Pain relief at 15 and 30 minutes after drug administered using 100mm visual analogue scale.	Similar pain relief with both drugs and better than placebo; reduction on VAS 43mm paracetamol, 40mm for morphine, 27mm for placebo.	Fewer adverse events with paracetamol than morphine.
Masoumi K (2014) <sup>15</sup>	Randomised, double blind controlled trial. 108 patients with renal colic.	IV paracetamol 1g or 0.1mg/kg morphine.	Pain at 15, 30, 45, 60 minutes.	Pain relief at 30 minutes higher with paracetamol (P = 0.0001). (study confounded after 30 minutes as rescue analgesia then given )	Patients with paracetamol could be discharged earlier and had fewer adverse events.
Azizkhani (2013) <sup>16</sup>	Randomised double blind controlled trial. 124 patients with renal colic.	IV paracetamol 1g or IV morphine 0.1mg/kg	Pain score after 30 minutes.	Morphine and paracetamol were effective at relieving pain with greater pain relief with morphine.	Morphine caused more hypotension and dizziness.

### **Summary**

IV paracetamol can provide safe and efficacious analgesia in trauma patients, the perioperative period and for patients with renal colic, with a safety profile superior to NSAIDs and opioids.

Affordability of paracetamol, IV will determine whether the agent is included on the Essential Medicines List.

## References

- <sup>1</sup> Dijkstra BM, et al. Review on pharmacological pain management in trauma patients in (pre-hospital) emergency medicine in the Netherlands. *Eur J Pain* 2014; 18: 3-19.
- <sup>2</sup> Savoia G et al. Italian Intersociety Recommendations on pain management in the emergency setting (SIAARTI, SIMEU, SIS 118, AISD, SIADER, SICUT, IRC). *Minerva Anestesiol* 2015; 81(2): 205-25.
- <sup>3</sup> Craig M et al. Randomised comparison of intravenous paracetamol and intravenous morphine for acute traumatic limb pain in the emergency department. *Emerg Med J* 2012; 29: 37-39.
- <sup>4</sup> Marret E et al. Effects of nonsteroidal anti-inflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. *Anesthesiology* 2005; 102: 1249-60.
- <sup>5</sup> Apfel A et al. Intravenous acetaminophen reduces postoperative nausea and vomiting: a systematic review and meta-analysis. *Pain* 2013; 154: 677-689.
- <sup>6</sup> McNicol BD et al. Single dose paracetamol or proparacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis, *Br J Anaesth* 2011; 106:764-75.
- <sup>7</sup> Koh W et al. Intravenous non-opioid analgesia for peri- and postoperative pain management: a scientific review of intravenous acetaminophen and ibuprofen. *Korean J Anesthesiol* 2015; 68(1): 3-12.
- <sup>8</sup> Maund E et al. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review. *Br J Anaesth* 2011; 106(3):292-7.
- <sup>9</sup> Saurabh S et al. Scheduled intravenous acetaminophen reduces postoperative narcotic analgesic demand and requirement after laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2015; 11(2): 424-30.
- <sup>10</sup> Gonzalez AM et al. Intravenous acetaminophen in bariatric surgery: effects on opioid requirements. *J Surg Res* 2015; 195(1): 99-104.
- <sup>11</sup> Memis D et al. Intravenous paracetamol reduced the use of opioids, extubation time, and opioid related adverse effects after major surgery in intensive care unit. *Journal of Critical Care*(2010); 25: 458-462
- <sup>12</sup> Grissa MH et al. Paracetamol vs piroxicam to relieve pain in renal colic. Results of a randomized controlled trial. *American Journal of Emergency Medicine* 2011; 29: 203-206.
- <sup>13</sup> Kaynar M et al. Comparison of the efficacy of diclofenac, acupuncture, and acetaminophen in the treatment of renal colic. *American Journal of Emergency Medicine* 2015; 33: 749-753.
- <sup>14</sup> Bektas F et al. Intravenous paracetamol or morphine for the treatment of renal colic; a randomized, placebo-controlled trial. *Ann Emerg Med* 2009; 54: 568-574.
- <sup>15</sup> Masoumi K et al. Comparison of clinical efficacy of intravenous acetaminophen with intravenous morphine in acute renal colic: a randomized, double-blind, controlled trial. *Emergency Medicine International* 2014, Article ID571326.
- <sup>16</sup> Azizkhani R et al. Comparing the analgesic effect of intravenous acetaminophen and morphine on patients with renal colic pain referring to the emergency department: a randomized controlled trial. *J Res Med Sci* 2013; 18(9): 772-776.