Canterbury District Health Board
Te Poari Hauora ō Waitaha

Clinical Pharmacology Bulletin

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Paracetamol - oral or intravenous (iv)?

Use of iv paracetamol has increased from 1,160 of the 1 g infusions (cost of $4,928) in the financial year 2006/2007 to 20,600 (cost of $81,852) in the financial year 2012/2013. A dose of 1 g of paracetamol costs $2.25 iv and $0.02 oral.

PHARMAC Hospital Medicines List (HML) restricts the use of iv paracetamol in hospitals: only to be used where other routes are unavailable or impractical, or where there is reduced absorption. The need must be re-assessed 24 hourly.

In a recent hospital-wide HML education around, and evaluation of, the prescribing of iv paracetamol in Christchurch Hospital wards, 92 patients were prescribed it over a 2 week period. The majority of these were under the care of General Surgery (40 patients) mainly for abdominal issues and ICU/CICU (24 patients). Other specialities who prescribed it were Cardiothoracic, Vascular, Orthopaedic, Plastic and Dental Surgery, General Medicine, Neurology, Stroke Team and Urology.

Efficacy and adverse effects of paracetamol are reported to be similar for both the oral and the iv route. There are, advantages and disadvantages of each route. The iv preparation has disadvantages from safety, use of consumables and administration time perspectives. The oral route has the disadvantage of variable absorption. This bulletin compares these two routes and considers their place in therapy.

Pharmacokinetics

Paracetamol is mainly metabolised rather than renally excreted. Extensive liver metabolism occurs via glucuronidation (60-80%), sulphation (20-30%) and cytochrome P450 2E1 (< 4%). Less than 5% is excreted unchanged by the kidneys. The half life is 2 to 3 hours in adults, 1.5 to 4 hours in children and 4 to 11 hours in neonates.

Pharmacokinetic parameters are listed in the table below:

	oral	**iv**
availability	63-89%[#]	approx 100%
time to peak plasma concentrations	10-60 minutes	15-25 minutes (after the end of the infusion)
mean maximum plasma concentrations[*] (1g dose)	8-18 mg/L	28 mg/L

[#]Oral availability of paracetamol varies with the formulation, the rate of gastric emptying and body position.

[*]Although not clearly defined, concentrations required for analgesia are thought to be around 10 mg/L.

Maximum rather than mean paracetamol plasma concentrations have been reported to influence analgesia. This might indicate an advantage of the iv preparation over the oral preparation (maximum concentrations of 28mg/L and 18mg/L respectively). However from 1 hour to 24 hours post administration plasma concentrations for both oral and iv are similar.

Pharmacodynamics

The mechanism of action of paracetamol is poorly understood. The main analgesic effect of paracetamol is thought to be a central one perhaps via activation of descending pain pathways, particularly those involving serotonin and inhibition of central COX-2 or COX-3.

Adverse effects of paracetamol include hepatic damage (usually in overdose), gastrointestinal upset, haematological changes, pancreatitis and nephrotoxicity (prolonged use).

Efficacy of oral and iv paracetamol

In one randomised double blind placebo controlled study 1 g oral paracetamol was given to 34 patients with moderate to severe post-op dental pain. Pain at 4, 6 and 8 hours was significantly lower than with placebo.[1]

The 2007 Oxford league table of analgesic efficacy from Bandolier[2] reports that for every 4 patients with moderate to severe pain treated with a single dose of 1 g oral paracetamol 1 will have a 50% reduction in pain over 4 to 6 hours (i.e. number needed to treat of 4). NB iv paracetamol does not feature in the league table but similar efficacies as that of the oral would be expected.

Many of the studies that compare oral to iv administered paracetamol used the earlier available iv propacetamol – a paracetamol prodrug. In one randomised, double blind, placebo controlled study (n=265) comparing iv propacetamol with oral paracetamol in 3rd molar surgery, meaningful pain relief was reached in 8 minutes with iv and in 37 minutes with oral administration.[3] After 45 minutes however, there was no difference in pain between the two routes and, after 2 hours pain was less in the oral group. One published study carried out here recorded higher mean plasma paracetamol concentrations 30 minutes after arrival in recovery and non-statistically significant lower amounts of rescue fentanyl in recovery following iv paracetamol compared with oral.[4] There is also literature of mixed quality showing that the use of iv paracetamol either results in a reduction in post-operative opioid requirements[5,6] or increased analgesic satisfaction but no opioid sparing effects.[7]

In summary

- iv has a small therapeutic advantage over oral
- oral is preferred unless the patient is unable to swallow or absorb medicines or has nausea/vomiting
- iv has disadvantages - safety, consumables, time, cost
- iv is for patients where other routes are not feasible and its use should be reviewed 24 hourly

References **1.** Mehlish D R et al Clinical Therapeutics 2010;32 (5);882-894, **2.** Bandolier: /www.medicine.ox.ac.uk/bandolier/ **3.** Moller P L et al British Journal of Anaesthesia 2005:94(5); 642-648 **4.** Brett C N et al Anaesth Intensive Care 2012;40:166-171 **5.** NSW Therapeutic Advisory Group Inc Oct 2005 **6.** Hong J Y et al Anaesthesiology 2010:113(3);672-677 **7.**Cakan T et al Journal of Neurosurgical Anaesthesiology 2008:20(3):169-173