

Paracetamol - oral or intravenous (iv)?

Intravenous paracetamol was first prescribed in Christchurch Hospital in 2006. Its use has been steadily increasing with 1,160 infusions used in the financial year 2006/2007 at a cost of \$4,928 and 28,300 infusions in 2009/2010 at a cost of \$110,878. Costs per 1g of paracetamol are currently \$3.96 for the iv formulation and \$0.02 for oral tablets. A recent audit of 60 Christchurch Hospital inpatients who had surgery found that 55% received paracetamol intravenously in theatre or recovery and 30% received it in the 5 days post-op.

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)	8-18mg/L	28mg/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 10mg/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 1g oral paracetamol was given to 34 patients with moderate to severe post-op dental pain. Pain relief at 4, 6 and 8 hours was significantly higher than with placebo.¹

The 2007 Oxford league table of analgesic efficacy from Bandolier² reports that for every 4 patients with moderate to severe pain treated with a single dose of 1g oral paracetamol 1 will have a 50% reduction in pain over 4 to 6 hours (i.e. number needed to treat of 4).

Bandolier does not feature iv paracetamol in their league table although it would be expected to result in similar efficacies as that of the oral as it is the same drug. Many of the studies that compare oral to intravenously 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 Maximum pain relief occurred at 15 minutes with iv and at 1 hour with oral administration. After 45 minutes however, there was no difference in analgesia between the two routes and, interestingly after 2 hours analgesia was greater in the oral group. There is also some literature of mixed quality that has shown either that the use of iv paracetamol results in a reduction in post-operative opioid requirements^{4,5} or no opioid sparing effects but a increased analgesic satisfaction.⁶

In summary

- there is little therapeutic advantage of iv paracetamol over oral
- oral is the preferred route unless the patient is unable to swallow or absorb oral paracetamol or has nausea/vomiting
- iv has disadvantages in terms of safety, consumables, time and cost
- iv should be reserved for those patients where other routes are not feasible

References

1. Mehlish D R et al Clinical Therapeutics 2010;32 (5):882-894,
2. Bandolier: /www.medicines.ac.uk/bandolier/
3. Moller P L et al British Journal of Anaesthesia 2005;94(5): 642-648
4. NSW Therapeutic Advisory Group Inc Oct 2005
5. Hong J Y et al Anaesthesiology 2010;113(3):672-677
6. Cakan T et al Journal of Neurosurgical Anaesthesiology 2008;20(3):169-173