Canterbury District Health Board
Te Poari Hauora o Waitaha

Clinical Pharmacology Bulletin

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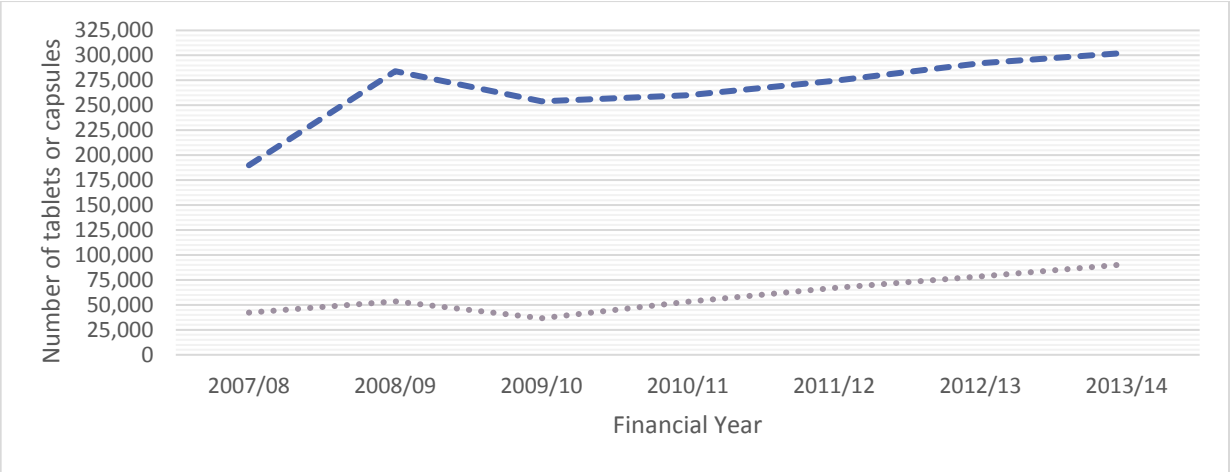
Codeine and tramadol

The use of opioids has been of interest both nationally and locally. Codeine is the most commonly used opioid from step 2 of the WHO analgesic ladder within CDHB hospitals. The use of codeine and another step 2 analgesic, tramadol, are increasing in the CDHB.

Solid oral dose forms of codeine (blue dashes) and of tramadol (brown dots):



Indications

- both are used for the relief of acute, chronic, peri-operative, malignant and non-malignant pain
- codeine is also used in the treatment of diarrhoea

Pharmacodynamics

- both are prodrugs
- both parents (extent is likely minimal – see affinities below) and active metabolites are mu opioid receptor agonists, have similar efficacy, and minimal activity on other opioid receptors
- compared with morphine the parent codeine has 1/200th the affinity for the mu opioid receptor and 1/50th the intrinsic activity, while the parent tramadol has 1/6000th the affinity and its active metabolite M1 has 1/30th the affinity.
- the parent tramadol also inhibits serotonin and noradrenaline reuptake in the spinal cord pain pathways

Adverse effects

- constipation (may be less with tramadol)
- nausea and vomiting
- sweating, dizziness (especially tramadol)
- drowsiness
- confusion
- hallucinations
- CNS depression (enhanced by other CNS depressants e.g. cyclizine)

NB. Tolerance to analgesic effects, and the majority of adverse effects, develops over days with the exception of constipation. Co-prescription of prophylactic laxatives should always be considered on initiation. Anti-emetics may also be required initially.

Dosing (oral)

- **immediate release** 4 to 6 hourly
- **slow release** **(tramadol only)** 12 to 24 hourly

Maximum Dose

- **codeine** 240 mg/24 hours
- **tramadol** 400 mg/24 hours

Pharmacokinetics

	codeine	tramadol
oral bioavailability	50%	70%
half-life	3 hours	6 hours
metabolism	Mainly CYP2D6	Mainly CYP2D6

Metabolism

Both codeine and tramadol are considered to be prodrugs. Metabolism is mainly by cytochrome P450 2D6. CYP2D6 metabolises codeine to its active metabolite morphine-6-glucuronide (~10% of the dose) while tramadol is metabolised to o-demethyl tramadol (M1). The affinity of M1 for the mu opioid receptor is ~ 200 times that of the parent. Metabolism of both is subject to pharmacogenetics. Both will produce little if any analgesia in slow metabolisers of CYP2D6 substrates and in those with concomitant CYP2D6 inhibitors. Conversely ultrarapid metabolisers of CYP2D6 substrates may experience increased effects and toxicity.

CYP3A4 is also involved in the metabolism of both. Codeine is metabolised to norcodeine by this route while tramadol is metabolised to O,Ndidemethyltramadol. The activity of these metabolites is unclear.

Renal dysfunction

Both morphine-6-glucuronide and M1 are excreted renally. Patients with poor renal function should be monitored closely for signs of toxicity e.g. CNS depression.

Drug interactions

Both are affected by CYP2D6 inhibitors as above (e.g. fluoxetine) and will also interact with other CNS depressant drugs. Tramadol also interacts with other serotonergic drugs e.g. citalopram which has been reported to result in serotonin toxicity. The use of ondansetron with tramadol is reported to attenuate its analgesic effect.

Costs/maximum dose

	immediate release oral	slow release oral	injection
codeine (240 mg)	$0.48	-	-
tramadol (400 mg)	$0.24	$0.44	$7.28

Summary

The use of both codeine and tramadol is increasing within CDHB hospitals with codeine being used more than tramadol.