WHO Analgesic Ladder: which weak opioid to use at step two?

In BPJ 16 (September 2008) we discussed the management of chronic pain. The World Health Organisation (WHO) analgesic ladder is the framework used to guide the pharmacological treatment of pain in chronic pain and palliative care patients.

In general, at step one, paracetamol and NSAIDs are recommended. At step two weak opioids are introduced and at step three the weak opioid is stopped and a strong opioid started. Another option is to start low doses of a strong opioid, such as morphine, at step two.

Chronic opioid therapy may have fewer life-threatening risks than long-term daily use of NSAIDs

Recent guidelines for treating musculoskeletal pain, for example osteoarthritis and low back pain, recommend NSAIDs and COX-2 inhibitors only in strictly defined circumstances, at the lowest effective dose and for the shortest possible time. It is now considered that, especially for many elderly people, chronic opioid therapy may have fewer life-threatening risks than the long-term daily use of NSAIDs. Recent guidelines focus more on the use of paracetamol and opioids. This has led to more interest in how to choose between the opioids available, particularly at step two.

Opioids at step two – comparing apples with pears

All opioids are not the same. They differ in their pharmacodynamics and pharmokinetics, and clinically in their range of effects (Table 1).

Table 1: Commonly used opioid analgesics compared to morphine

	Codeine & dihydrocodeine	Tramadol	Morphine
Metabolised by	CYP2D6 to morphine	CYP2D6 and CYP3A4	glucuronidation
Main action	mu-opioid	mu-opioid & monoaminergic	mu-opioid
Constipation	●●●	●	●●
Nausea & vomiting	●●	●●●●	●●
Sedation	●●●	●●●●	●●●
Dizziness	●●	●●●	●●
Addiction risk	●●	●	●●
Respiratory depression	●●	●	●●
Serotonin toxicity		●●	
Seizures	●	●●	●
Major contraindications		MAOIs history of seizures	
Maximum daily dose	240 mg/day = morphine 24 mg	400 mg/day* = morphine 80 mg	no practical limit

Adapted from Rodriguez et al

*300 mg/day in people aged >75 years

Codeine is a prodrug that must be metabolised to morphine by the liver enzyme CYP2D6 to achieve most of its analgesic effect. Because of genetic differences some individuals (e.g. 6–10% of Caucasians) lack the enzyme CYP2D6 and cannot metabolise codeine effectively and therefore obtain limited pain relief while experiencing all the adverse effects.

Dihydrocodeine is similar to codeine in both its structure and its analgesic effect. It is primarily metabolised by CYP2D6 and CYP3A4 to dihydromorphine and nordihydrocodeine, however it is unclear whether the parent drug, metabolites or a combination of both result in dihydrocodeine's analgesic activity.

Tramadol is chemically unrelated to morphine. Tramadol is also metabolised by CYP2D6 and CYP3A4. Similar to codeine and dihydrocodeine some individuals tolerate tramadol poorly and may have increased adverse effects.

Tramadol and its metabolites have combined opioid and monoaminergic properties. Less than half of the analgesic effect is via the mu-opioid receptors. The remainder is from inhibiting the re-uptake of noradrenaline and serotonin. This dual action produces a different analgesic effect compared with the simple opioid analgesics and less respiratory depression or risk of addiction compared with the strong opioids. However, there is also a wider range of side effects, with the additional risk of serotonin toxicity (see BPJ 8 for details) and a reduced seizure threshold. For this reason tramadol is contraindicated in individuals taking MAOIs and those with epilepsy. It should also be used with caution, or avoided if possible, in those already taking a serotonergic medication (e.g. most antidepressants) or in people taking drugs that reduce seizure threshold (e.g. TCAs). In general, tramadol is associated with less constipation but increased nausea and vomiting, sedation, dizziness and orthostatic hypotension when compared to other step two opioids.

Is tramadol an option at step two?

Tramadol has been shown to be no more effective than other weak opioids but adverse effects may be problematic and drug interactions need to be considered. Tramadol is not currently subsidised and so cost to the patient is also a factor.

The most recent Scottish Intercollegiate Guidelines Network (SIGN) publication for the treatment of cancer pain suggests that there is still insufficient evidence available to make a recommendation on the use of tramadol.

For many patients, codeine when used concurrently with paracetamol will be as effective as tramadol and may be better tolerated.

Strong opioids such as morphine are more effective for severe pain and this combined with the fact that tramadol has a ceiling dose of 400 mg/day means that it is not considered an alternative to morphine for severe pain.

The choice

The final choice of which opioid to prescribe, after contra-indicated drugs are excluded, will come down to a balance between possible adverse effects and the desired analgesic effect.

Although it is often not possible to predict beforehand how an individual will tolerate a particular opioid, asking about response to previous trial of codeine may help exclude codeine and tramadol in those patients who are poor metabolisers. For these patients starting on a low dose of morphine may be the preferred option.

All step two opioids have active metabolites that are excreted renally and therefore require reduced doses and increased monitoring in elderly people and in people with reduced renal function.

As with all opioids "start low and go slow".
Remember **ABC**:
Antiemetic for the first week,
Breakthrough medication
Laxatives for **C**onstipation

see BPJ 16 for further information on the treatment of chronic pain.

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