Mainly on morphine and methadone and pain in palliative care in New Zealand in 2004

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In 2001 the *New Zealand Palliative Care Strategy*[1] marked the emergence of palliative care as a discipline in its own right. There are signs of a gradual increase in awareness of palliative care among individuals, families, health providers and doctors alike. Understanding what it all means takes time.

Yet there is an immediacy for general practitioners to be the capable and knowledgeable general practitioners that they usually are – and simultaneously to be fully informed of many things; not the least, the pharmacological options for managing pain relief for those 'under' palliative care. To that end, this paper looks at those options. The paper focuses on morphine and methadone, because they are commonly used, and within the scope of the general practitioner. By necessity, this paper leaves that important area of managing pain by non-pharmacological means, for another time and place. Also excluded is analgesia provided by epidural and spinal interventions, other nerve blocks, radiotherapy and palliative chemotherapy.

Pain in palliative care – what's the difference?

Pain is complex. Pain is personal. The International Association for the Study of Pain (IASP) proposed the following definition:

'Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.'

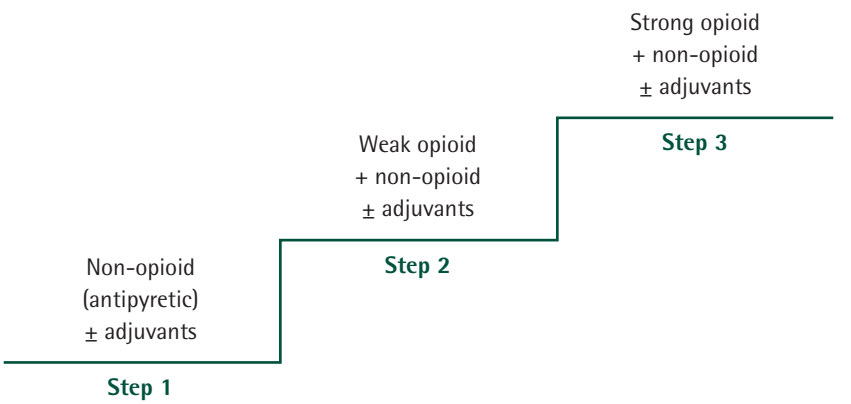
In palliative care, there is no avoiding the compounding factors, the roots of which may lie in social issues, existential, cultural and spiritual dimensions. As a person approaches the end of their life, all those contributing factors can no longer be partitioned, and referred to 'The Specialist'. They all rest in that one person who is in front of you and who is telling you unequivocally of their pain. And there is nowhere else to go. The patient is choosing to stay at home, and the pain is there. What are the options?

That we consider we can 'control' pain is ambitious if we dare to acknowledge the complexity of pain. Nonetheless we do endeavour. In that endeavour there are many options – outlined in this paper. Although morphine and methadone are detailed, brief mention is made of the other, no less important, agents for pain relief. The multiplicity of agents affirms, perhaps, the imperfectness of each agent alone, and the complexity of the neurophysiolgical processes, much less the non-physiological factors.

In principle

Managing the pain with the lowest dose of the most appropriate analgesic, given by the most effective route, is a laudable aim. For this reason, the model of the World Health Organization (WHO) analgesic ladder[2] remains useful (Figure 1). There are differing views on the value of Step 2, on pharmacological grounds.[3] Codeine is essentially a prodrug of morphine, and small doses of morphine can substitute for codeine. However, from the general practitioner's viewpoint, there is often value in having an intermediate step between paracetamol and morphine, as

Figure 1. The World Health Organization three-step analgesic ladder for cancer pain



many patients prefer to delay their starting on morphine.

The prescription of non-steroidal anti-inflammatories, low dose tricyclic anti-depressants, anti-convulsants, benzodiazepines, steroids and anti-arrhythmics (Boxes 1–4) are not exclusive to palliative care where they are largely used as analgesic adjuvants to paracetamol and strong opioids.

Using combinations of the above agents, modified according to tolerability of side effects, and effectiveness, is common. For example:

- Non-steroidal anti-inflammatories are effective for bone pain, but if given long-term require co-prescription of a gastroprotective agent and they may exacerbate renal impairment;
- Nerve pain is not always opioid responsive, and combinations of anticonvulsants +/- anti-arrhythmics +/- clonazepam may be more effective.

Strong opioids in New Zealand

Neither are opioids exclusive to palliative care, but the frequency and the way in which they are used, differ. There continues to be opiophobia among patients, families and doctors and nurses. However, with care and attention to managing side effects and titrating the dose against pain, much confidence can be gained by the prescribers and the patient.

Morphine remains the most commonly used strong opioid for pain relief in palliative care. Other strong opioids available in New Zealand are methadone, fentanyl, pethidine (Box 5). In essence, methadone is the most accessible alternative opioid, and being used more often as a second line opioid in palliative care.

Morphine

Morphine is used for control of moderate to severe pain in accordance with the World Health Organization recommendations. It remains the most flexible opioid to use in the palliative care setting – with respect to range of formulations, cost, effectiveness, and known (often controllable) side effects.

Box 1. Paracetamol

- Mechanism of action central, but different to opioids – possible additive effect
- Antipyretic – no peripheral anti-inflammatory effect
- Hepatic damage with overdose
- In severe hepatic impairment, practice caution – reduce dose or stop
- Onset of action 15–30 mins; duration of action 4–6 hrs
- Dose 1g qid.

Box 2. Weak opioids

Codeine

- Weak opiod approximately 1/10 potency of morphine
- Opioid side effects similar to morphine
- PO bioavailability 40% (12–84%)
- Onset of action 30–60mins; duration of action 4–8 hours
- Usual dose 30–60mg q4–6h
- Use limited by dose ceiling and side effects.

Dihydrocodeine

- DHC continus – 12 hr slow release formulation
- Semi-synthetic analogue of codeine
- Similar side effects
- PO bioavailability 20%
- Dose 60–120mg bd.

Box 3. Tramadol

- Centrally active with opioid and non-opioid properties
- PO bio-availability 75%; and >90% with repeated doses
- Plasma half-life 6–8hrs; more than doubled in cirrhosis and severe renal failure
- By injection is 1/10 as potent as morphine
- By mouth is 1/5 as potent as morphine, because of the greater bioavailability of tramadol
- Usual dose 50–100mg PO q4–6 hourly (recommended maximum 400mg/24hrs) of short acting formulation
- Not funded in New Zealand.

Box 4. Adjuvant drugs

Added at any step of the WHO ladder and have a role in morphine insensitive pain and/or neuropathic pain and/or bone pain and/or visceral pain

- NSAIDs – gastroprotection needs to be considered
- Antidepressants (low dose tricyclics – e.g. amitriptilline)
- Anticonvulsants (carbamazepine, clonazepam, gabapentin – not funded for pain in New Zealand)
- Anti-arrhythmics (mexilitine – as membrane stabiliser)
- Ketamine – anaesthetic which is analgesic in low doses
- Steroids (e.g. prednsione, dexamethasone)
- IV bisphosphonates (pamidronate) – for bone pain.

Sevredol or morphine liquid may be used interchangeably for dose titration or breakthrough pain. Patient preference and dosage flexibility may determine which is used.

Morphine suppositories are not widely used, but can be used for breakthrough pain when oral formulations are not tolerated. The oral:rectal dose is 1:1.

Morphine sulphate and tartrate injections may be used interchangeably for dose convenience.

Initiating treatment in the morphine-naive patient

The aim is to titrate the dose against the pain (Box 7) – gradually increasing until the patient is comfortable, and, if possible, free of pain. Some people choose to experience a certain amount of pain, rather than abolish pain. And there are times when it is not possible to abolish pain with morphine.

Morphine for breakthrough pain

For breakthrough pain (see Box 8), 10 to 20% of the total daily dose of oral morphine, may be given up to hourly, between the regular long-acting morphine doses.

If this dose needs to be given more often than twice, at the hourly interval, a review of the pain and dose is warranted. It means the dose is too low, or the pain has changed, or both.

If this dose does not control the pain, or frequent doses are required, then a review is again needed. Both the long-acting and short-acting doses of morphine will need to be adjusted.

Conversion from oral to continuous subcutaneous infusion morphine (CSCI) via the syringe driver

The oral bioavailability of morphine is about 35% (range from 15–64%).[2]

The average relative potency of oral (PO) to subcutaneous (SC) morphine is between 1:2 and 1:3. When converting from oral (PO) to morphine (SC) in the syringe driver, use 30–50% of the total 24-hour oral dose.

The *'as required'* (PRN) dose for breakthrough pain, remains 10–20% of the total daily dose.

Box 5. Strong opioids, other than morphine, in New Zealand

- Methadone is fully funded, and is being used more often – particularly in the presence of renal impairment/failure; an intolerance of morphine; where there is nerve pain; or a combination of these factors.
- Fentanyl is available as a transdermal patch, or parenterally. It is not funded, and cost largely limits use in New Zealand. It is comparable to long acting morphine. It is possibly associated with less constipation, less sedation and the patch is non-invasive. It is not suitable for initial use or dose titration; nor for unstable pain. It can cause local skin reactions.
- Pethidine is fully funded, and largely avoided in palliative care, due to its short duration of action (2–4 hours) and the dose ceiling effect because of neurotoxic metabolites.

Box 6. Morphine preparations available

Short-acting morphine

Onset of pain relief in 20–30 minutes; duration of action 3–4 hours

- Morphine hydrochloride elixir (RA-Morph)
- Morphine sulphate tablets (Sevredol)
- Morphine sulphate suppositories

Long-acting morphine

Morphine sulphate - can be given 8 hourly, 12 hourly or 24 hourly

- m-Eslon* capsules (12 hourly, may be needed 8 hourly)
- MST tablets (12 hourly, may be needed 8 hourly)
- Kapanol capsules (12 hourly, at times 24 hourly)

Note: from 1/2/04 m-Eslon is the only fully funded long-acting morphine in NZ*

Parenteral morphine

- Morphine sulphate and tartrate injections

Box 7. Starting morphine

- Titrate dose with short acting morphine (morphine liquid or Sevredol tablets)
- Start with 5–10 mg 4 hourly. In the elderly consider 2.5–5mg 4 hourly
- If not fully effective, increase next dose by 25–50%
- When pain is controlled and dose stable, convert to long-acting morphine.
- Divide the total daily dose of short-acting morphine into 2 doses 12-hours apart.

For example:

- Patient's long acting morphine PO/24hrs – 100mg morphine
- Converts to syringe driver (SC) morphine – 30–50mg SC/24hrs
- With PRN dose for breakthrough pain – 3–5mg SC or 6–12mg PO.

Morphine side effects

The nausea, vomiting, constipation and sedation are well known to doctors and patients alike. The former three symptoms can often be satisfactorily managed with other agents. Nausea and sedation can subside once a person has been taking morphine for several days, or several days after a dose increase (Box 9).

Less well recognised are cognitive blunting, confusion and hallucinations. Patients may not spontaneously report hallucinations, for a number of reasons (including embarrassment) and it is worthwhile specifically asking after them. Allodynia (pain due to an innocuous stimulus - e.g. light brushing of skin) and mycolonus has been seen after high dose intrathecal

and intravenous morphine. At moderate doses the presence of myoclonus indicates toxicity.

Morphine and renal impairment

In 1898 Toogood[3] stated *'Of all the lessons which were hammered into me during my hospital career, none was more persistently driven home than the fact that it is extremely dangerous to administer morphia in kidney disease.'* Some mysterious communication breakdown in medical education circles between 1898 and the 1960s and later must have happened, as it is a point oft overlooked these days.

Morphine's glucuronidated metabolites are excreted by the kidneys, and they accumulate in renal impairment/failure. The consequence of this is increasing morphine toxicity – with more nausea, more constipation, more hallucinations and/or confusion, mycolonic jerks, respiratory depression – unless the frequency of administration and/or dose is reduced.

There are no established guidelines yet, for the prescription of morphine in the presence of renal impairment. There are however a number of management options (Box 10)

Methadone

The initial stabilisation of a patient on methadone requires careful supervision. There is increasing familiarity in palliative care units, with its use both in community and in-patient settings as it is in essence the only easily accessible, fully funded alternative strong opioid at present.

Indications for methadone use

Indications for methadone use include:

- Morphine toxicity or intolerable morphine-related side effects (nausea, vomiting, hallucinations, myoclonus, allodynia, hyperalgesia, confusion);
- Pain no longer morphine responsive (the process is then described as 'opioid switching');
- Neuropathic pain not controlled by morphine/NSAID/tricyclic antidepressant/anti-epileptic regimen;
- Renal impairment and failure (Box 10).

Switching from morphine to methadone

There are different models for switching from morphine to methadone. Many palliative medicine specialists in New Zealand and palliative care units in the United Kingdom use guidelines proposed by Morley and Makin.[2]

These guidelines (Box 12) take into account the long and variable half-life (eight to 80 hours); the lipid solubility, and the large volume of distribution; all of which result in several days' delay before a steady state is achieved. They also minimise the development of methadone accumulation associated with undue drowsiness, progressing to reduced consciousness and respiratory depression.

The Morley and Makin model for switching from morphine to methadone is more easily managed in the inpatient setting than in the community. Commonly when opioid switching is considered, pain is complex, morphine doses can be high (often greater than 300mg morphine daily); and managing the conversion in the home setting requires meticulous

Box 8. Breakthrough and incident pain

BREAKTHROUGH PAIN is an intermittent transient recurrence or exacerbation of severe pain in a patient who is taking regular analgesic medication and who has good pain relief most of the time.[3]

The essence of breakthrough pain is in its unpredictability.

Predictable, movement-related pain is better called **INCIDENT PAIN** (e.g. with pathological fracture of humerus). Such pain is difficult to manage pharmacologically, and non-pharmacological means need to be considered. Management is decided on a case-by-case basis.

Box 9. Side effects of morphine

Constipation

Affects almost all patients
Prescribe regular laxative
Best with combination of stimulant+ softener (e.g. doccusate+senna)

Nausea and vomiting

Affects 30–50% of patients
About 30% will need regular anti-emetic
Consider trial off anti-emetic after 7–10 days
Haloperidol low dose, metoclopramide and cyclizine effective for opioid induced nausea

Drowsiness, sedation

Usually self limiting after 2-3 days
If persistent and distressing, review dose

Hallucinations, agitation, paranoia, cognitive blunting, confusion, myoclonus

Review dose. Consider morphine toxicity aggravated by renal impairment. Consider reducing dose or alternative opioid

Respiratory depression

If respiratory rate is less than 8/minute and there are pinpoint pupils, and undue sedation, consider morphine excess/overdose; or acute renal decompensation

Box 10. Options for morphine in renal impairment

- Manage the side effects (e.g. with anti-emetics, anti-psychotics) and continue with the same dose. This may be sustainable particularly if no increase in analgesia is needed.
- Reduce the dose (e.g. by 30–50%; or to the dose at which there were no side effects) – and use other pharmacological or non-pharmacological means of pain relief.
- Change the opioid – to methadone or fentanyl (see Box 5).
- Discuss with local palliative medicine specialist.

documentation, and a sound understanding of the concept of titrating the methadone to the pain.

Any switch must be closely supervised, and unless familiar with its use, seek palliative medicine specialist advice.

Subcutaneous methadone

There is a wide variability (40–100%) in oral bioavailability of methadone.[2] As a result, there are differing practices in converting from PO to SC methadone. A conservative conversion is to halve the PO dose, to get the SC dose. If this is done, it is important to bear in mind that some patients may need a higher dose. It will be most helpful to speak with the palliative medicine specialist in your region if confronted with this need.

Continuous subcutaneous methadone in a syringe driver may be limited by skin irritation at the injection site, and uncertainty about the compatibility with other commonly used medications.

Skin irritation can be reduced by:

- Changing the site every day
- Saline 0.9% is used as diluent
- Using a more dilute solution in a 20ml or 30ml syringe
- Changing the syringe eight or 12 hourly
- Adding 1mg of dexamethasone to the syringe prescription is practised by some centres – although the research to support this, has not yet been completed.

Box 11. Starting oral methadone[4]

- Start on methadone 5mg q12h ***and*** 5mg q3h PRN
- If pain relief remains minimal, consider increasing to 10mg q12h after one to two days (and 5mg PRN), but generally do ***not*** increase the regular dose for one week
- If necessary, continue to titrate the regular dose upwards by 1/3 to 1/2 once a week
- With higher regular doses, increase the PRN dose to 1/4 of the q12h dose

Box 12. Switching from oral morphine to oral methadone (after Morley and Makin 1998)

- Stop the long-acting morphine (i.e. stop completely – no down-titration)
- Give q3h PRN doses of PO methadone 1/10th of the previous 24h PO morphine dose, up to a maximum of 30mg.
- On Day 6, the amount of methadone taken over the previous two days is noted and divided by four to give a regular q12h dose, with 1/4th of the regular q12h dose q3h PRN.
- If two or more doses/day of PRN methadone continue to be needed, the dose of regular methadone should be increased by 1/3rd to 1/2 once a week.

Box 13. Managing breakthrough pain while on methadone

PRN Morphine

Better option if normal renal function, and morphine tolerated

Avoids concern about accumulation of methadone if frequent PRN use needed

The morphine dose is 10–20% of the former 24 hour PO morphine dose

The PRN dose may be up or down-titrated according to need

PRN Methadone

For patients with established renal failure, or who are intolerant of morphine

There are no clinical trials to indicate the actual PRN dose

Clinical experience suggests 10–20% of the total 24 hr PO dose, but no more than three hourly

The PRN dose may be up or down-titrated according to need.

If additional analgesia is needed within three hours, options are:

- Methadone 5–10mg q1h PRN (i.e. a small fixed dose)
- The former PRN dose of morphine if on morphine formerly
- An alternative (paracetamol, tramadol)

In conclusion

General practitioners care for an average of three to four terminally ill people each year, and not all patients will have pain. It is entirely possible that in the interval the general practitioner has between managing patients with pain (in a palliative care setting) that better or other pain management options have emerged. This paper just touches on what is practised in New Zealand at present – and acknowledges ongoing refinements from year to year.

Among the many on-line resources available, a helpful one is www.palliativedrugs.com. This contains a very active Bulletin Board on all matters pharmacological and palliative. Further it contains the full version of *The palliative care formulary, second edition* – a main reference for this paper. It is accessible to all, and easily understandable.

As palliative medicine comes of age, there is a gradual increase in the body of knowledge and emerging research. There are now palliative medicine specialists the length and breadth of New Zealand – and they form a small but approachable group. Although many details about morphine and methadone are outlined here, sometimes, if in doubt, there is nothing better than talking with a colleague palliative medicine specialist.

References

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