The rediscovery of methadone for cancer pain management

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Many patients with cancer require opioid analgesics at some stage of their illness. In Australia, morphine is commonly used for treatment of pain that is not controlled by non-opioid drugs. Other opioid analgesics are primarily second-line agents. Methadone has its niche in the therapy of pain poorly responsive or actually refractory to high doses of mu (μ) opioid receptor agonist analgesics, typified by neuropathic pain, particularly when dose-limiting side effects prevent escalation of the initial opioid dose. Most studies regarding methadone therapy for cancer pain are small and non-randomised, probably reflecting the urgency of symptom control and the short life expectancy of the patient population.

Methadone has been available for more than 50 years as a synthetic opioid drug with a long half-life. Though somewhat stigmatised by the medical and lay public as "the heroin addict's drug", it is used increasingly for treating chronic pain and cancer pain that is non-responsive or has lost responsiveness to high doses of μ-opioid receptor agonists (morphine, oxycodone, fentanyl, hydromorphone) because of tolerance or disease progression. Cross-tolerance between μ-receptor agonists is relatively common. Blocking N-methyl-D-aspartate (NMDA) receptors may reduce tolerance to opioids and improve responsiveness of neuropathic pain. Methadone is a non-competitive NMDA-receptor antagonist and μ-receptor agonist, which may explain its effectiveness in treating neuropathic pain and its incomplete cross-tolerance with μ-receptor agonists. It is structurally unrelated to the opioid derivatives, and so is a useful alternative when patients experience "morphine allergy" or intolerable side effects to morphine that do not respond to dose reduction.

Methadone is actually a racemic mixture of two isomers. The laevorotatory (L) isomer is the more potent analgesic, whereas the dextrorotatory (D) isomer has less potential for addiction and respiratory depression, but possesses antitussive behaviour.

Although previously discredited because of the risk of cumulative toxicity, this drug has been rediscovered following better knowledge of its pharmacokinetic properties and reports of more accurate, equianalgesic doses on conversion from other opioid drugs. Many narcotic conversion charts misrepresent the equipotency ratios of morphine to methadone, as they extrapolate single-dose effect and are not applicable to repeated therapy and its associated tissue accumulation. Adherence to new dosing guidelines could significantly diminish the risk of cumulative toxicity.

The benefits of methadone are summarised in Box 1, and the factors limiting its use in Australia are summarised in Box 2.

Pharmacological properties of methadone

Methadone is a basic and lipophilic drug that is avidly taken up such that the tissue level greatly exceeds the plasma level with repeated dosing. It has a large initial volume of distribution. With continued dosing, it has a long elimination half-life (up to 128 hours) resulting from slow tissue release into the bloodstream, in contrast to the short action of a single dose. This slow tissue release sustains the plasma level, which declines in a bi-exponential manner. The long half-life enables once- or twice-daily administration with repeated dosing, and explains the risk of cumulative toxicity.

Methadone can be administered via the oral, feeding tube, rectal, subcutaneous, intramuscular, intravenous and epidural routes. The high oral bioavailability (80%) makes this the route of choice. Analgesic effect begins between 30 and 60 minutes after a single dose, and duration of action is 4–6 hours. However, with repeated doses, the long terminal half-life of methadone and delayed consequences of dose changes make it less suitable for the treatment of breakthrough pain.

When appropriate, inexpensive custom-made methadone suppositories and micro-enemas can be used instead of oral and parenteral administration. Although local skin irritation and induration are recognised problems with continuous subcutaneous infusion of methadone, the admixed infusion of 1–2 mg/day of dexamethasone may alleviate this accumulation.
local reaction.\textsuperscript{25} At present, there is no information on the compatibility of methadone in solution with other drugs used in subcutaneous infusions for symptom control.

Methadone toxicity responds to delaying the next dose and dose reduction, but in severe cases naloxone, in repeated doses or as an infusion, may be necessary.\textsuperscript{2} Abrupt discontinuation of methadone during chronic treatment should be avoided because of the risk of opioid withdrawal symptoms.\textsuperscript{15}

Methadone undergoes extensive liver metabolism to inactive metabolites that do not accumulate in renal failure.\textsuperscript{11}

Dosage

Commonly quoted equi-analgesic dose ratios for oral morphine to methadone are extrapolated from single-dose studies and mostly suggest a conversion ratio between 1:1 and 1:4 for all doses.\textsuperscript{16,22} In practice, this would be excessive for many patients. Supervised titration is necessary to avoid side effects, as there is wide interindividual variability.\textsuperscript{2,11,21,22} Paradoxically, the equi-analgesic dose of methadone is much lower in patients treated previously with very high doses of morphine or equivalent dose of another opioid.\textsuperscript{1,5,11,15,17} This fact and the usefulness of methadone for neuropathic pain is exhibited in our case series (Box 3). Plausible explanations for this relate to the type of pain, difficulties of identifying the dose at which morphine responsiveness was lost, and tolerance to the initial opioid.\textsuperscript{1,5,11} Escalating but ineffective doses of the initial opioid would frequently be used if morphine- or fentanyl-resistant pain were not identified. The methadone dose would thus be derived from an overestimated final dose of the previous narcotic, thereby risking toxicity. Plasma methadone levels should not be used to determine the required dose of methadone, as treatment is titrated to clinical effect and not drug level.

Protocols for use of methadone as second-line opioid

The Edmonton and Liverpool protocols are most notable for treatment of cancer pain with methadone. The Edmonton protocol\textsuperscript{11} means the patient's previous opioid by a third of the dose each day. Concurrently, methadone is commenced eight-hourly, using a dose of one-tenth of the daily oral morphine equivalent. The methadone dose is titrated according to pain relief and side effects.

Guidelines from Liverpool\textsuperscript{17} promote stopping the initial opioid and replacing it with a methadone dose of one-tenth of the previous daily oral morphine equivalent dose (if less than 300 mg) as required, up to three-hourly, but a methadone dose of 30 mg as required (maximum three-hourly) is substituted for daily oral morphine equivalent doses exceeding 300 mg. On Day 6, the total methadone requirement from the previous two days is divided by four to obtain the 12-hourly maintenance dose.

Royal Perth Hospital protocol

In July 1999, the palliative care team at Royal Perth Hospital, using a published conversion chart for morphine to

1: Favourable characteristics of methadone

- Well absorbed by oral and rectal routes.\textsuperscript{5,11}
- High oral bioavailability.\textsuperscript{18}
- Twice-daily dosing usually suitable for maintenance therapy.\textsuperscript{11,15,18}
- No known active metabolites. Relatively safe in renal failure as little active drug is excreted by the kidneys.\textsuperscript{11}
- Relatively safe in stable chronic liver disease,\textsuperscript{2} but needs titration to clinical effect.
- High potency compared with morphine.\textsuperscript{5,12,14,19}
- Low cost\textsuperscript{5,19,22} (a tenth of the cost of the equivalent dose of slow-release morphine at high dosages).\textsuperscript{15}
- Well tolerated by most patients.\textsuperscript{4} Side effect profile is similar to that of other opioids and often reflects toxic doses.
- Incomplete cross-sensitivity with morphine, so methadone can be used in patients intolerant of morphine.\textsuperscript{2,3}
- Useful for pain poorly responsive to morphine and transdermal fentanyl, particularly for neuropathic pain.\textsuperscript{1,10,14,17}

2: Factors limiting widespread use of methadone for cancer pain

- Large interindividual variations in pharmacokinetics\textsuperscript{5,11,21,22} make individual dose titration necessary.
- Uncertainty about correct conversion ratios in patients taking other opioids. Many conversion ratio charts underestimate the potency of methadone and have resulted in toxicity with repeated dosing.\textsuperscript{1,5,11,22}
- If converting from high dose of other opioid, it is usually initiated as in-hospital therapy over at least 3–5 days.\textsuperscript{1,17,22}
- Long elimination half-life creates the potential for delayed toxicity.\textsuperscript{11,13} Features of toxicity include sedation, myoclonus, confusion, hallucination/delirium, constipation, nausea and vomiting, respiratory depression and (rarely) coma.
- Potential drug interaction — tricyclic antidepressant drugs, propranolol and phenothiazine derivatives can displace methadone from its plasma protein binding, but do not result in significant enhancement of methadone effect.\textsuperscript{5} Fluvoxamine may increase plasma methadone levels.\textsuperscript{19} Phenytoin, spironolactone, rifampicin and verapamil may increase methadone metabolism and hence reduce its levels.\textsuperscript{2,11,21} Caution is required with concurrent sedating drugs and alcohol.
- Elderly patients (> 65 years old) have reduced methadone clearance, necessitating cautious dosing and close supervision.\textsuperscript{21}
- Experience is limited to few clinicians\textsuperscript{19} (unlike wide experience with morphine and, increasingly, with oxycodone and transdermal fentanyl).
- Presentation of tablets in Australia is currently only 10 mg (but it can be broken, crushed, made into a suspension and administered into a feeding tube).
methadone, treated a patient suffering severe neuropathic pain with methadone in substitution for high dose parenteral morphine. The result was excellent analgesia over the next two days, followed by near-fatal toxicity. This event prompted a prospective study of methadone dose conversion ratios (see Box 3), guided by two small series. For the next six months, all patients referred to the palliative care team with severe cancer and non-cancer pain that could not be controlled with other opioids without unacceptable side-effects were switched to methadone. Fourteen consecutive patients fulfilling the above criteria were studied. The most common reason for conversion to methadone was escalating but ineffective doses of other opioids in a patient with neuropathic pain. Findings include improved analgesia within one day in 79%, considerably lower equi-analgesic dose of oral methadone in patients treated previously with high doses of other opioids, and achievement of maintenance dose within three days in 64% of patients. Previous side effects were generally relieved. Significant sedation was seen only in the two patients commencing methadone via the subcutaneous route.

Our protocol starts with a loading dose and titration to pain score and side effects over the next few days. The predicted maintenance dose is calculated from the conversion ratios in Box 4, after determining the oral morphine equivalent. The original opioid is discontinued when commencing methadone. For the first two days, a loading dose of 25%–50% extra is used, allowing saturation of body tissues. This loading dose is omitted for frail and elderly patients and those taking long-acting sedating medications. The initial dosing interval is six hours, increasing to eight or 12 hours over several days. Example: A patient is taking slow-release morphine 300 mg twice a day. The predicted maintenance dose is 60 mg of methadone daily. A loading dose of 80 mg per day is given as 20 mg four times a day for the first two days, reducing to 20 mg three times a day on Day 3, simplified to 30 mg twice a day on Day 5. Analgesia for breakthrough and activity pain is provided with short-acting opioids (eg, morphine elixir or oxycodone). Non-opioid analgesics and adjuvant drugs (TCAs, certain anticonvulsants) have a synergistic effect and should be continued.

Initiation of treatment with methadone and dose increments (if necessary) are best undertaken in the morning for ease of monitoring the effect, although dose reductions must necessarily occur as clinical parameters demand. Attention to pain score, respiratory rate, level of alertness/sedation, and presence of confused speech, disorientation and myoclonus enhance early identification of toxicity and simplify dose adjustments over the initial days of therapy. An alert patient with ongoing pain during treatment with methadone can usually tolerate a dose increase.

Successful outpatient methadone therapy requires a

### Table 3: Summary of a prospective study of use of methadone in patients with severe pain

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Type of pain</th>
<th>Original opioid</th>
<th>Oral Morphine Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>M</td>
<td>Melanoma, bone metastases</td>
<td>Neuropathic</td>
<td>S/c morphone 380 mg/d</td>
<td>1140 mg</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>F</td>
<td>Ca breast, bone metastases</td>
<td>Neuropathic + somatic</td>
<td>Transdermal fentanyl 175 µg/h + s/c fentanyl 800 µg/d</td>
<td>960 mg</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>M</td>
<td>Ca lung, bone metastases</td>
<td>Neuropathic + somatic</td>
<td>Oral morphine 600 mg/d</td>
<td>600 mg</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>M</td>
<td>Ca prostate, bone metastases</td>
<td>Neuropathic + somatic</td>
<td>Transdermal fentanyl 100 µg/h + oral morphine 100 mg/d + s/c morphine 30 mg/d</td>
<td>590 mg</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>F</td>
<td>Ca caecum, nerve infiltration</td>
<td>Neuropathic + somatic</td>
<td>Oral morphine 560 mg/d</td>
<td>560 mg</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>M</td>
<td>Ca tonsil, bone metastases</td>
<td>Neuropathic + somatic</td>
<td>Transdermal fentanyl 75 µg/h + s/c fentanyl 800 µg/d</td>
<td>560 mg</td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>F</td>
<td>Myeloma</td>
<td>Neuropathic + somatic</td>
<td>Transdermal fentanyl 75 µg/h + s/c morphine 60 mg/d + oral morphine 40 mg/d</td>
<td>520 mg</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>F</td>
<td>Ca breast, bone metastases</td>
<td>Neuropathic + somatic</td>
<td>Oral morphine 500 mg/d</td>
<td>500 mg</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>M</td>
<td>Ca lung, bone metastases</td>
<td>Somatic</td>
<td>Oral morphine 350 mg/d</td>
<td>350 mg</td>
</tr>
<tr>
<td>10</td>
<td>54</td>
<td>F</td>
<td>Ca rectum, nerve infiltration</td>
<td>Neuropathic + somatic</td>
<td>Oral oxycodone 180 mg/d + transdermal fentanyl 25 µg/h + IM pethidine 200 mg/d</td>
<td>300 mg</td>
</tr>
<tr>
<td>11</td>
<td>47</td>
<td>M</td>
<td>HIV-associated painful peripheral neuropathy</td>
<td>Neuropathic</td>
<td>Oral morphine 300 mg/d</td>
<td>300 mg</td>
</tr>
<tr>
<td>12</td>
<td>49</td>
<td>F</td>
<td>Angiosarcoma</td>
<td>Neuropathic + somatic</td>
<td>Transdermal fentanyl 50 µg/h + oral morphine 20 mg/d</td>
<td>220 mg</td>
</tr>
<tr>
<td>13</td>
<td>66</td>
<td>M</td>
<td>Forsteri's disease</td>
<td>Neuropathic</td>
<td>Transdermal fentanyl 50 µg/h</td>
<td>200 mg</td>
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<tr>
<td>14</td>
<td>51</td>
<td>M</td>
<td>Osteomyelitis, painful diabetic peripheral neuropathy</td>
<td>Somatic + neuropathic</td>
<td>Codeine phosphate 240 mg/d</td>
<td>30 mg</td>
</tr>
</tbody>
</table>

Key: 1 = side effects of original narcotic. 2 = escalating but ineffective dose of narcotic. 3 = neuropathic pain. 4 = other. VAS = visual analogue scale.

### Table 4: Morphine–methadone conversion ratios

<table>
<thead>
<tr>
<th>Daily oral morphine dose</th>
<th>Approximate conversion ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 mg</td>
<td>3:1</td>
</tr>
<tr>
<td>101–300 mg</td>
<td>5:1</td>
</tr>
<tr>
<td>301–600 mg</td>
<td>10:1</td>
</tr>
<tr>
<td>601–800 mg</td>
<td>12:1</td>
</tr>
<tr>
<td>801–1000 mg</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt;1001 mg</td>
<td>20:1</td>
</tr>
</tbody>
</table>

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partnership with the patient. Adequate education of patient (and carer) regarding possible signs of toxicity simplifies continuation and adjustment of methadone therapy following discharge home. Self-administration is not appropriate for unsupervised patients incapable of managing their own medications at home.

Conclusion

The routine use of methadone as a first-line opioid drug for cancer pain can not currently be advocated. Methadone is, however, a valuable addition to the armamentarium of clinicians treating severe cancer pain, particularly neuropathic

<table>
<thead>
<tr>
<th>Reason for change</th>
<th>Initial</th>
<th>Oral morphine to methadone ratio</th>
<th>Pain score 1–10 (VAS)</th>
<th>Days to decrease pain score</th>
<th>Days to final morphine dose</th>
<th>Final morphadone dose (mg)</th>
<th>Final methadone ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+2+3</td>
<td>40 mg</td>
<td>28:1</td>
<td>Severe</td>
<td>1</td>
<td>12</td>
<td>200 mg (s/c)</td>
<td>1:10</td>
</tr>
<tr>
<td>2+3</td>
<td>6 mg</td>
<td>24:1</td>
<td>Severe</td>
<td>1</td>
<td>6</td>
<td>50 mg</td>
<td>1:4</td>
</tr>
<tr>
<td>2+3</td>
<td>85 mg</td>
<td>10:1</td>
<td>Severe</td>
<td>1</td>
<td>3</td>
<td>85 mg</td>
<td>1:4</td>
</tr>
<tr>
<td>2+3</td>
<td>45 mg</td>
<td>20:1</td>
<td>Severe</td>
<td>1</td>
<td>3</td>
<td>65 mg</td>
<td>1:3</td>
</tr>
<tr>
<td>1+2+3</td>
<td>60 mg</td>
<td>12:1</td>
<td>Mild</td>
<td>1</td>
<td>4</td>
<td>40 mg</td>
<td>1:3</td>
</tr>
<tr>
<td>1+2+3</td>
<td>80 mg</td>
<td>11:1</td>
<td>Mild</td>
<td>1</td>
<td>3</td>
<td>80 mg</td>
<td>1:3</td>
</tr>
<tr>
<td>1+2+3</td>
<td>55 mg</td>
<td>17:1</td>
<td>Mild</td>
<td>1</td>
<td>3</td>
<td>55 mg</td>
<td>1:3</td>
</tr>
<tr>
<td>2+3</td>
<td>80 mg</td>
<td>8:1</td>
<td>0-1</td>
<td>&lt;1</td>
<td>4</td>
<td>80 mg</td>
<td>1:3</td>
</tr>
<tr>
<td>1+2</td>
<td>65 mg</td>
<td>7:1</td>
<td>Mild</td>
<td>&lt;1</td>
<td>3</td>
<td>65 mg</td>
<td>1:3</td>
</tr>
<tr>
<td>3+4</td>
<td>60 mg</td>
<td>6:1</td>
<td>0-1</td>
<td>&lt;1</td>
<td>3</td>
<td>60 mg</td>
<td>1:3</td>
</tr>
<tr>
<td>1+2+3</td>
<td>60 mg</td>
<td>5:1</td>
<td>0-1</td>
<td>&lt;1</td>
<td>3</td>
<td>60 mg</td>
<td>1:3</td>
</tr>
<tr>
<td>2+3</td>
<td>40 mg (s/c)</td>
<td>15:1</td>
<td>0-1</td>
<td>&gt;12</td>
<td>7</td>
<td>40 mg</td>
<td>1:3</td>
</tr>
<tr>
<td>2+3</td>
<td>60 mg</td>
<td>5:1</td>
<td>2-3</td>
<td>&lt;1</td>
<td>2</td>
<td>60 mg</td>
<td>1:3</td>
</tr>
<tr>
<td>1+3</td>
<td>20 mg</td>
<td>2:1</td>
<td>0-2</td>
<td>&lt;1</td>
<td>6</td>
<td>20 mg</td>
<td>1:3</td>
</tr>
</tbody>
</table>

s/c = subcutaneous. IM = intramuscular. Ca = cancer

5: Indications for use of methadone in managing cancer pain

- Severe neuropathic pain requiring high dose opioid drug therapy, particularly when addition of a tricyclic antidepressant or anticonvulsant has not been beneficial.
- Persistent, unacceptable side effects of morphine at low dose, particularly when alternative opioids are either unavailable or are too expensive.
- Hypersensitivity or anaphylactoid reactions to morphine, where other opioids are either unavailable or are too expensive.
- Escalating dose of maintenance morphine, fentanyl or oxycodone, where a dose increase would only result in adequate analgesia at the cost of intolerable side effects.
- Very high doses of morphine, oxycodone or transdermal fentanyl at significant financial cost to the patient.

pain. Pain which is poorly responsive to morphine should be identified quickly so that futile morphine dose escalations can be avoided. Methadone may prove effective in some cases, as indicated in Box 5.

Acknowledgements

We would like to thank Natalie Panizza, Clinical Nurse Specialist in Palliative Care (RPH), for assistance with data compilation.

References


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**BOOK REVIEWS**


**ANYONE INVOLVED in the diagnosis or treatment of sporting injuries would be delighted to find this book under their Christmas tree. Its main strength is the superb quality of the plain x-ray reproductions, complemented by an impressive array of ultrasound, computed tomography, magnetic resonance and nuclear medicine images.**

**Arranged by anatomical order, the book covers normal skeletal anatomy in virtually all the standard radiographic projections. It then encompasses the gamut of bone and soft tissue abnormalities, occasionally branching out to embrace less obviously sporting problems such as avascular necrosis of the hip. More contemporary (and contentious) issues, including rotator cuff disorders, groin strain and entrapment syndromes, are addressed with precision and clarity.**

**And so to the authors. Jock Anderson is a luminary in the field of musculoskeletal radiology, recognised in his selection to oversee diagnostic imaging for the Sydney Olympic Games. John Read is the man who made joint and soft tissue ultrasound fashionable in this country. Working closely with both clinicians and equipment manufacturers, he has raised ultrasound to new heights, beating down the sceptics with the high quality of his work. Jeff Steinweg, a sports physician, adds the clinical input so necessary to lend relevance and balance, a feature often lacking in similar overseas texts.**

**In 10 years' time this book will still lie within my easy reach. Quality is quality, and at less than $100 it's an absolute bargain. Mad if you don't.**

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**What should I do?**


**READING A TEXT on ethics requires a particular orientation. A textbook is normally judged by scientific comprehensiveness and quality of presentation; reporting on contemporary facts and theories. Ethics is not, in the ordinary sense, factual. Ethics is about conflicting values (mostly positive values) such as autonomy versus beneficence.**

**When reading about ethics the focus is on the quality of the argument and drawing out of key issues rather than specific conclusions. Ethics considers precedents set in law and other issues that can alter a person's perceptions. This third edition of the book sets the same high standards as its previous two editions. There are six new chapters that are relevant to contemporary clinical practice and mental health management and policy. They cover genetics, resource allocation and community psychiatry. A practitioner may not come to the same conclusions as the authors on every issue, but his or her thinking about difficult ethical issues will doubtless be enhanced by this reference book.**

**My only criticism is the interchangeable use of the words "privacy" and "confidentiality" throughout the book. Confidentiality is a professional issue with its associated responsibilities, whereas privacy relates to an individual's choice on disclosure of information and remains in the person's own domain. However, as medicine is increasingly involved in complex legal processes, the separate issue of privacy is worthy of consideration.**

**This is the benchmark ethics textbook for mental health workers and administrators and is relevant to any clinician or ethicist.**

**Psychiatric ethics** is well written and good value for money.

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**Robert F Loneragan**

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