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Opioid analgesics for cancer pain in primary care

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Each year, around 140,000 people die from cancer in England and Wales,[1] about one-quarter of them in the community.[2] Two crucial goals in the palliative care of such people are to enhance quality of life and control symptoms. Of particular importance, more than two-thirds of patients with cancer will require opioid analgesics to control pain.[3] Since many patients with cancer, including those with advanced disease, aim to spend more time at home rather than in hospital, the primary care team has an important role in managing pain. The team, supported by community clinical nurse specialists and specialist palliative care units, is often responsible for initiating analgesic therapy and for ongoing assessment of patients' pain and analgesic requirements. Here we discuss key issues in using opioids for cancer-related pain in primary care.

The WHO analgesic ladder

Standard practice in the drug treatment of cancer pain is based on the concept of an 'analgesic ladder' formulated by the World Health Organization (WHO).[3,4] This is a stepwise approach to the use of analgesic drugs. However, it is only one part of a comprehensive strategy for managing cancer pain, which also involves disease-modifying treatments and non-drug analgesic measures.

What does the ladder involve?

Step 1 on the ladder involves giving non-opioid analgesics, such as paracetamol or an NSAID. Step 2 involves adding an opioid for mild-to-moderate pain (e.g. codeine, dihydrocodeine, tramadol), and is used when the pain is persisting or increasing. Step 3 involves substituting the 'weaker' opioid with a 'stronger' opioid for moderate-to-severe pain (e.g. morphine, fentanyl, hydromorphone, oxycodone), and is used when step 2 fails to relieve the pain. Oral morphine is generally accepted as the first-line drug in the management of moderate-to-severe cancer pain.[3,5] Other drugs may be necessary to enhance pain relief (e.g. a tricyclic antidepressant for neuropathic pain);[6] to treat the unwanted effects of analgesics (e.g. an anti-emetic); or to treat psychiatric problems (e.g. an antidepressant).

Does the ladder work?

Retrospective and prospective observational studies, but no randomised controlled trials, have assessed the effectiveness of the WHO analgesic ladder in the management of cancer pain.[7,8] Data from these studies (which included a total of 7,633 patients) suggest that, when the ladder is used as recommended, it enables patients with advanced cancer "to receive adequate pain treatment" at home.[7,8]

Starting an opioid

The optimal starting dose of an opioid is determined by previous analgesic requirements and, particularly for stronger opioids, should be the minimum needed by the patient for effective symptom control. The drug should be given at fixed intervals and the dose increased gradually until the patient is comfortable.[3] The next dose should be given before the effect of the previous one has fully worn off.[3] Where high doses of stronger opioids are being prescribed, it is sensible to contact the specialist palliative care team for advice and support, wherever feasible. Involvement of different healthcare professionals could lead to a patient with cancer receiving opioids from more than one source. So, it is good practice for one professional in a locality to take on the co-ordinating role to avoid oversupply and to help maintain patient and public safety.[9]

Morphine

Adult patients moving up from a step 2 opioid will usually need to start on normal-release (immediate-release) oral morphine at a dose of 5–10mg every 4 hours.[5,10,11] However, a lower starting dose may be needed if step 2 is omitted (e.g. because the pain is very severe), or if the patient is elderly, frail or has liver disease or impaired renal function.[5,10,11] If the morphine is being given to replace another step 3 opioid, then a dose of 10–20mg or more may be needed,[5] and the appropriate equivalent dose should be checked, particularly where the conversion ratio is not simple (e.g. with transdermal fentanyl). The dose should then be increased as appropriate for the individual patient to achieve maximum analgesia with minimum unwanted effects. For children, the recommended starting

dose of normal-release oral morphine, given up to every 4 hours, for those aged 1–12 months is 80μg/kg, 1–2 years 200–400μg/kg, 2–12 years 200–500μg/kg[12] and 12–18 years 5–15mg.[4,12]

The systemic bioavailability of oral morphine is variable (15–64%),[10] which partly explains why the effective analgesic dose of normal-release morphine for patients with cancer pain can range from 5mg to 1,000mg every 4 hours.[3] However, most patients need no more than 200–300mg of oral morphine daily.[13] All patients should have immediate access to analgesia for breakthrough pain, in the form of normal-release morphine. During the dose-titration phase, the current 4-hourly dose of normal-release morphine should be used as 'rescue' treatment for such pain, and can be taken as often as hourly.[11] The total daily dose of morphine taken (i.e. 4-hourly plus breakthrough-pain doses) should be reviewed every day and the regular 4-hourly dose adjusted to take into account the total amount of 'rescue' morphine used.[11] An additional dose of normal-release morphine should also be given 30 minutes before any manoeuvre or procedure expected to cause pain, with the next regular dose being taken at the usual time.[5]

Modified-release formulations

Modified-release morphine formulations are sometimes used when starting a patient on oral morphine. However, the slower onset of action and later peak effect of such formulations makes it harder than when using normal-release morphine to rapidly assess efficacy and safety, and appropriately adjust the dose during the dose-titration period.[11] On the other hand, once patients are stabilised on a 4-hourly regimen of normal-release morphine, they can be switched to morphine taken as a 12-hourly formulation (e.g. Morphgesic SR, MST Continus, Zomorph) or a 24-hourly formulation (e.g. Morcap SR, MXL), if this is the preferred option.[5] Compared with the previous 4-hourly dose, the twice-daily dose with a 12-hourly formulation will be three times higher, and the once-daily dose with a 24-hourly formulation will be six times higher.[10] Patients should be provided with normal-release morphine for support during the switchover, and as cover from breakthrough pain, at a dose of one-sixth of the total daily dose.

A meta-analysis of 69 pharmacokinetic studies involving 2,146 participants found no evidence of significant differences between various modified-release oral formulations (tablets, capsules, liquids) in terms of their potency or duration of effect.[14] However, because the pharmacokinetic profiles of these formulations can differ,[15] it is best to keep a patient on the same brand throughout treatment.[10]

Alternatives to oral morphine

Morphine can be given via a parenteral route to patients unable or unwilling to take oral morphine, for example, because of uncontrolled vomiting, difficulty in swallowing or gastrointestinal obstruction. However, for treatment by injection, diamorphine is preferred to morphine because it is more soluble and can be given in a smaller volume via continuous subcutaneous infusions using a syringe driver.[5] The equivalent 24-hour dose of subcutaneous diamorphine is about a third of the total 24-hour dose of oral morphine. Suppositories of morphine are also available. Their bioavailability and duration of effect are similar to those of oral normal-release morphine,[16] but they are rarely used in clinical practice in the UK.

Unwanted effects

Opioid analgesics have many unwanted effects in common, the most frequent being constipation, nausea and vomiting, and drowsiness. Opioid-related constipation is a persisting effect. Therefore, from the start of treatment, patients taking opioids should be prescribed daily laxatives with both softening and stimulant actions, such as co-danthramer alone or docusate sodium plus a senna preparation.[5,10] The laxative dose should be titrated up to ensure that the patient's normal pattern of bowel-opening is maintained. On starting morphine, up to two-thirds of patients develop nausea and vomiting,[11] which usually resolve within a few days. In general, patients should be given an anti-emetic drug such as cyclizine, metoclopramide or haloperidol for the first week of opioid treatment. Where the patient is known to have had problematic nausea while on a weaker opioid, the anti-emetic should be continued daily throughout treatment.[5,10] Daytime drowsiness and mental clouding may occur at the start of treatment, but these symptoms usually resolve within days once the dose is stabilised.[10] Effects on cognitive function are minimal for most patients on stable doses of morphine. For example, a case-control study involving 49 patients reported that driving ability was not significantly impaired in alert people receiving a stable dose.[17] However, patients receiving an opioid for the first time, or having their dose increased, should be warned that sedation may occur and about the risks of driving or using machinery.

Less common unwanted effects with opioids include dry mouth, hypotension, respiratory depression, poor concentration, gastroparesis, urinary hesitancy or retention, and itching. Patients who have a dry mouth should be encouraged to take regular sips of cool water, and the use of other drugs that can cause dry mouth should be avoided wherever possible. Worries about dependence, respiratory depression and excessive sedation have sometimes resulted in inappropriate avoidance of opioid use and underdosing. However, clinical experience has shown that these fears are largely unjustified when opioids are used correctly with proper dose-titration and adjustment for changing circumstances. The dose may need to be increased, but can also be decreased or stopped as other therapy begins to act,[11] and many patients with stable disease can remain on the same dose for weeks or months.[3] To avoid withdrawal symptoms when stopping treatment, the dose should be decreased gradually over 2–4 weeks.

When morphine is unsuitable

There is no reliable way of predicting which patients are likely to benefit from taking morphine. Around 10–30% of patients cannot be successfully treated with oral morphine because of a poor analgesic response at a dose which is producing unacceptable unwanted effects.[18] It is common practice to switch such patients from morphine to another strong opioid. However, this may be unsuccessful.

Evidence on the effectiveness of opioid-switching in the management of cancer pain is limited to data other than from randomised controlled trials.[19] In one prospective survey of 100 patients with cancer pain, 20% of patients required two or more switches to alternative opioids before a satisfactory outcome was achieved.[20] Patients who need to switch to an alternative opioid should be referred to, or at least discussed with, a specialist in the management of cancer pain. There are an increasing number of alternative strong opioids to morphine for cancer pain available in the UK, but these are generally more expensive options.

Hydromorphone and oxycodone

Hydromorphone and oxycodone are semi-synthetic congeners of morphine. They are available as both normal-release and modified-release oral formulations. Hydromorphone is around 7.5 times more potent than morphine (on a mg for mg basis) and has similar pharmacokinetic properties.[21] Oxycodone is around twice as potent as morphine (mg for mg) when given orally, and has a more predictable systemic bioavailability than morphine.[22] Randomised controlled trials suggest that both drugs resemble morphine in terms of analgesic efficacy and tolerability.[21–23]

Fentanyl

Fentanyl is a lipid-soluble synthetic opioid that can be delivered transdermally via a skin patch, with one patch lasting for up to 72 hours.[24] Prospective surveys[25,26] and randomised controlled trials[27] have suggested that transdermal fentanyl is as effective as oral morphine in the treatment of cancer-related pain, and may be less likely to cause constipation and somnolence.[26–28] However, case reports of opioid toxicity have been reported when transdermal fentanyl has been prescribed in patients with unstable pain,[29] and specialists recommend that it is best reserved for patients who have stable opioid requirements.[11] Dosing is less flexible than with oral morphine because the limited number of different patch strengths means that small changes in dose are not possible. The dose is effectively doubled when increasing from a 25μg/hour to a 50μg/hour patch. There is a lag time of up to 12 hours to onset of action after application of the first patch.[10] The patch dose should not be increased for at least 48 hours until peak blood levels are reached, so titration is slow.[10] When transdermal fentanyl is discontinued, significant levels of the drug persist in the blood for 24 hours or more after the patch has been removed.[10] Used patches still contain fentanyl. So, the patient information leaflet (PIL) recommends that these patches should be folded with the adhesive side inwards and discarded with domestic rubbish.

Fentanyl citrate is available as an oral transmucosal formulation (a lozenge), which acts within 15 minutes of taking the dose.[30] It is licensed, and shown to be effective, for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain.[31–34] However, the formulation's effects are short-lasting and it is expensive (one lozenge of any strength costs around £6.20).

Methadone

Methadone appears to have a similar analgesic effect and unwanted-effects profile to morphine.[35] However, methadone has complex pharmacokinetics, which vary between different individuals, and its long half-life carries the risk of drug accumulation to toxic concentrations.[35] Therefore, only physicians experienced in its use should initiate, titrate and monitor treatment with the drug.

Buprenorphine

▼Transdermal buprenorphine is licensed for moderate to severe cancer pain[36] and has been shown to be more effective than placebo in a double-blind randomised controlled trial.[37] However, it is unclear how its efficacy for this indication compares with that of oral morphine. Buprenorphine has both opioid agonist and antagonist properties. Its duration of analgesic effect is 6–8 hours, and transdermal buprenorphine is about half as potent (mg for mg) as transdermal fentanyl.[10]

Cost

Approximate cost* of typical treatments for 28 days

Opioid	Strength	Brand	Cost†
Normal-release formulations			
morphine	10mg tablets	Sevredol	£16.80
	10mg in 5mL solution	Oramorph	£13.20
oxycodone	5mg capsules	OxyNorm	£33.30
	5mg in 5mL solution	OxyNorm	£31.70
hydromorphone	1.3mg capsules	Palladone	£26.50
methadone	5mg tablets	Physeptone	£13.30
Modified-release formulations			
morphine (twice daily)	30mg tablets	Morphgesic SR	£9.20
	30mg tablets	MST Continus	£13.70
	30mg capsules	Zomorph	£9.60
morphine (once daily)	60mg capsules	Morcap SR	£13.20
	60mg capsules	MXL	£15.00
oxycodone (twice daily)	15mg (5mg + 10mg tablets)	OxyContin	£48.60
hydromorphone (twice daily)	4mg capsules	Palladone SR	£28.80
Patches			
fentanyl transdermal	25μg/hour††	Durogesic	£51.40
▼buprenorphine transdermal	35μg/hour	Transtec	£54.10

* Based on information in *Drug Tariff* and *Chemist & Druggist*.

† Doses equivalent to about 60mg oral morphine daily (††except for fentanyl transdermal 25μg/hour which is equivalent to 90mg oral morphine daily).

Advice to patients

Patients with cancer pain who are taking an opioid at home need to be given advice and supporting information to ensure they can take it safely and to best effect. Ideally, when the medicine is first started, the patient should be given a practical information leaflet covering general issues on controlled drugs, in addition to the PIL supplied with the product by the drug company.[9] This additional leaflet should give clear advice about whom to contact if problems arise, outline the roles and responsibilities of various members of the healthcare team and of patients and carers, and should summarise systems for the safe

use of controlled drugs. It should also emphasise the need for safe storage and appropriate procedures for drug disposal (e.g. return to a pharmacy).[9]

Conclusion

Many people with advanced cancer develop pain, which can often be managed in primary care. In most cases, this symptom can be controlled using the principles outlined by the World Health Organization analgesic ladder, which comprises three steps. Step 1 involves giving a non-opioid analgesic, step 2 involves adding in an opioid analgesic for mild-to-moderate pain, and step 3 involves substituting this 'weaker' opioid with an opioid for moderate-to-severe pain.

Morphine is the first-line drug in the management of moderate-to-severe cancer pain. Whenever possible, normal-release (immediate-release) oral morphine should be used initially until the patient's pain is controlled. At that point, patients can be switched to a modified-release morphine product, if this is preferred. The drug should be given at fixed intervals and the dose tailored to the individual patient's needs. It is crucial to inform patients about, and to minimise the likelihood of, potential unwanted effects of opioid therapy (e.g. constipation, drowsiness, nausea and vomiting).

Where appropriate analgesic doses are used, oral hydromorphone and oxycodone appear to be similar to morphine in terms of efficacy and tolerability and can be tried when a patient has intolerable unwanted effects with morphine. Transdermal fentanyl is best reserved for patients whose opioid requirements are stable. Primary care doctors should, ideally, only use those drugs with which they are familiar, and should seek advice from specialists in pain management before attempting to switch opioids.

[M=meta-analysis; R=randomised controlled trial]

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