Fortnightly Review

Morphine in cancer pain: modes of administration

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Most cancer pain responds to pharmacological measures, and successful treatment is based on simple principles that have been promoted by the World Health Organisation[1] and extensively validated.[2,3] Oral administration of analgesic drugs is preferred, and analgesics are given regularly to prevent recurrence of pain, often for months or even years. A step by step approach to the choice of drug is recommended, based on the "analgesic ladder" (fig 1). The first step is a non-opioid analgesic such as aspirin, paracetamol, or a non-steroidal anti-inflammatory drug. At the second step a weak opioid such as codeine is added, and when this proves inadequate a strong opioid is substituted for the weak opioid.

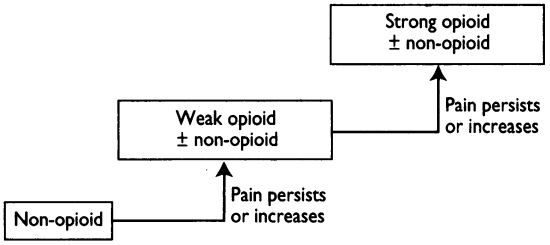

Fig 1—*Analgesic ladder for control of pain*

Morphine is the preferred strong opioid analgesic. The dose is titrated up to achieve adequate relief of pain. There is no upper limit. Dose requirements may vary 1000-fold, but few patients need daily doses above 200-300 mg.[4] Adjuvant analgesics such as antidepressant or anticonvulsant drugs, used alone or in conjunction with a conventional analgesic, have an important role in some patients.[5]

Unfounded fears associated with morphine

Morphine has long been feared by both the general public and doctors.[6] Underlying the fear is a mistaken belief that the problems associated with abuse of opioids are inextricably linked with their therapeutic use. Concerns about addiction, excessive sedation, and respiratory depression have resulted in widespread avoidance or underdosing. Yet extensive, carefully documented clinical experience has shown that these fears are unfounded.[7] Regular doses of morphine may be indicated and safely instituted early in the course of a patient's illness and continued for many months. Alternatively, some patients may be treated with morphine for short periods and, when their pain ameliorates, can reduce the dose and discontinue it without difficulty.

Daytime drowsiness, dizziness, or mental clouding commonly occur at the start of treatment but resolve when patients are stabilised, usually within a few days. Effects on cognitive and psychomotor function are minimal once patients are on a stable dose.[8] Similarly, nausea and vomiting, which may occur in up to two thirds of patients when morphine is started,[9] usually resolve. The main continuing adverse effect from morphine is constipation, and prophylactic use of laxatives is almost always required.

Modes of administration of morphine in treating cancer pain

Recently, there have been important developments in the ways in which morphine can be administered. Conflicting views about the usefulness and efficacy of these methods have resulted in considerable variations in practice even among specialists in palliative care and pain management.[10-12] New routes of administration have become fashionable but often lack kinetic and clinical logic,[13] and sensible advice on the best route is hindered partly by the lack of randomised controlled trials. To provide a consensus view of the available evidence, the European Association for Palliative Care convened a working group of experts from various disciplines and countries to draw up recommendations for the use of morphine for cancer pain. We produced a list of 20 recommendations.

(1) The optimal route of administration of morphine is by mouth. Ideally, two types of formulation are required: immediate release (for dose titration) and controlled release (for maintenance treatment)

(2) The simplest method of dose titration is with a dose of immediate release morphine given every four hours and the same dose for breakthrough pain. This rescue dose may be given as often as required (for example, every hour), and the total daily dose of morphine can be reviewed daily. The regular dose can then be adjusted according to how many rescue doses have been given

There is no such thing as a standard dose of morphine. The dose must be titrated against effect for each patient, and the starting dose will be determined by previous analgesic treatment. Patients changing from a weak opioid will usually start with 10 mg every four hours. If step two of the analgesic ladder is omitted 5 mg every four hours may suffice, whereas patients converted from another strong opioid may require more.

During dose titration it is preferable to use a formulation of morphine that has a rapid onset, a predictable effect, and a short duration of action to allow steady state to be achieved as quickly as possible. The so called immediate release formulations fulfil these requirements. Peak plasma concentrations usually occur within the first hour after oral adminis-

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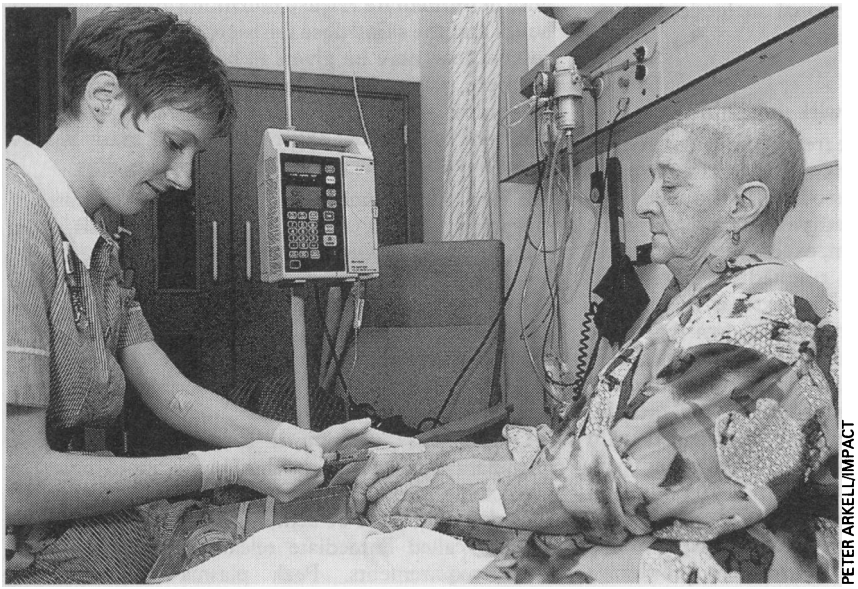
tration of morphine in solution[14] and slightly later with immediate release tablets.[15] Both formulations have a rapid effect, and analgesia lasts for about four hours (table 1). In contrast, controlled release morphine tablets produce delayed peak plasma concentrations after two to four hours,[16] the peak is attenuated,[16] and analgesia usually lasts for 12 hours.[17] This means that, with controlled release morphine, it is more difficult to assess the adequacy of analgesia and to adjust the dose during the dose finding period and to make rapid changes in dose.

Table 1—*Time (hours) to peak plasma concentration, elimination half life, and duration of analgesia after single doses of immediate release and controlled release morphine formulations in patients with normal renal and hepatic function*

	Formulation	
	Immediate release	**Controlled release**
Time to peak plasma concentration	0·25-1·0	2-4
Elimination half life	2-4	2-4
Duration of analgesia	4	12

The plasma elimination half life of morphine is two to four hours, and steady state is reached within four to five half lives (that is, within 24 hours)[15] after the start of treatment and every dose adjustment. This is an important interval at which to re-evaluate a patient and adjust the daily dose. This method of dose titration avoids the need to remember predetermined increments and has been shown to be safe and effective.

Various fractions of the regular dose have been recommended for treating breakthrough pain, but there is no logic to using a smaller rescue dose. The full dose is more likely to be effective, and any dose related adverse effects will be insignificant. If patients experience breakthrough pain once they have been stabilised they can be allowed to continue to take extra doses of immediate release morphine as required. Patients stabilised on a four hourly regimen should continue to use the same dose for breakthrough pain. For patients maintained on a 12 hourly regimen of controlled release morphine, the appropriate rescue dose of an immediate release formulation will be one third of the regular dose (that is, equivalent to the four hourly dose of morphine).



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Intravenous administration may be necessary in patients with poor peripheral circulation

(3) If pain returns consistently before the next regular dose is due the regular dose should be increased. In general, immediate release morphine does not need to be given more often than every four hours and controlled release morphine more often than every 12 hours

It is important to keep the drug regimen as simple as possible. Increasing the dose invariably allows a four hourly or 12 hourly regimen to be achieved without producing troublesome adverse effects associated with the increase in peak blood concentrations. There is no advantage in increasing the frequency of administration and a considerable disadvantage to the patient in terms of convenience and compliance.

(4) Several countries do not have an immediate release formulation of morphine (though such a formulation is necessary for optimal management). A different strategy is needed if treatment is started with controlled release morphine

Total daily dose requirements are estimated on the basis of previous analgesic intake. Breakthrough pain is managed with single doses of a non-steroidal anti-inflammatory drug as required, or with another short lasting strong opioid available for oral administration (such as oxycodone), or with oral or rectal administration of morphine injection solution.

(5) For patients receiving immediate release morphine every four hours, a double dose at bedtime is a simple and effective way of avoiding being woken by pain

No formal investigations of this practice are available. However, it has been widely adopted[18] and seems to work without causing problems.[19]

(6) Administration of controlled release morphine every eight hours may be occasionally necessary or preferred

Controlled release morphine tablets are designed to be given every 12 hours.[20] Randomised controlled trials confirm that almost all patients can be maintained with twice daily dosing.[17 21] A few patients, however, do not seem to achieve a 12 hour duration of analgesia and require administration every eight hours. Occasionally, patients requiring a high dose prefer dosing every eight hours to avoid taking too many tablets at a time, particularly in countries where no high dose formulations are available.

(7) Several controlled release formulations are available. There is no evidence that they are substantially different in their duration of effect and relative analgesic potency

Most of the clinical and pharmacokinetic investigations of controlled release morphine have used the original formulation (MST Continus, MS Contin, MOS-Contin). Several new formulations are now available. While in principle it is unwise to change between preparations when using modified release products because of possible variations in release profiles and oral bioavailability, there is no consistent evidence that more recent formulations (designed for administration every 12 hours) have a different pharmacokinetic or pharmacodynamic profile in patients.

(8) If patients are unable to take drugs orally the preferred alternative routes are rectal and subcutaneous

(9) The bioavailability of morphine by rectal and oral routes is the same, and the duration of analgesia is also the same

(10) The relative potency ratio of oral morphine to rectal morphine is 1:1

Immediate release morphine is effective when given rectally in solution or in suppository form, with similar

Recommendations for use of morphine for cancer pain

(1) The optimal route of administration of morphine is by mouth. Ideally, two types of formulation are required: immediate release (for dose titration) and controlled release (for maintenance treatment)

(2) The simplest method of dose titration is with a dose of immediate release morphine given every four hours and the same dose for breakthrough pain. This rescue dose may be given as often as required (for example, every hour), and the total daily dose of morphine can be reviewed daily. The regular dose can then be adjusted according to how many rescue doses have been given

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(10) The relative potency ratio of oral morphine to rectal morphine is 1:1

(11) Controlled release morphine tablets should not be crushed or used for rectal or vaginal administration

(12) Morphine may be given subcutaneously either as bolus injections every four hours or by continuous infusion

(13) The relative potency ratio of oral morphine to subcutaneous morphine is about 1:2

(14) There is generally no indication for giving morphine intramuscularly for chronic cancer pain because subcutaneous administration is simpler and less painful

(15) Other opioids may be preferred to morphine for parenteral use because of their greater solubility: diamorphine in Britain and hydromorphone elsewhere

(16) Subcutaneous administration of morphine may not be practical in patients
(a) with generalised oedema
(b) who develop erythema, soreness, or sterile abscesses with subcutaneous administration
(c) with coagulation disorders
(d) with very poor peripheral circulation
In these patients intravenous administration is preferred. Intravenous administration may also be the best parenteral route in patients who, for other reasons, have an indwelling central or peripheral line

(17) The relative potency ratio of oral to intravenous morphine is about 1:3

(18) The above guidelines produce effective control of chronic cancer pain in about 80% of patients. In the remaining 20% other methods of pain control must be considered, including spinal administration of opioid analgesics alone or in combination with local anaesthetics or other drugs. There is insufficient evidence to allow recommendations about precise indications for these routes of administration

(19) The buccal, sublingual, and nebulised routes of administration of morphine are not recommended because there is presently no evidence of clinical advantage over conventional routes

(20) Sublingual or transdermal use of other opioids may be an alternative to subcutaneous injection

Table 2—*Relative potency ratios for oral administration of morphine by different routes of administration*

Oral morphine to	Ratio
Rectal morphine	1:1
Subcutaneous morphine	1:2
Intravenous morphine	1:3
Subcutaneous diamorphine	1:3

bioavailability to oral morphine and a similar duration of action (four hours).[22] The relative potency of morphine by this route is disputed, but anecdotal evidence (supported by pharmacokinetic data) suggests that the ratio of rectal morphine to oral morphine is 1:1 (table 2). Morphine suppositories are commercially available in several doses in many countries or can be prepared easily in hospital pharmacies.

(11) Controlled release morphine tablets should not be crushed or used for rectal or vaginal administration

Crushing controlled release morphine tablets alters their dissolution and absorption characteristics and should be avoided. Liquid controlled release formulations are now available for patients who have difficulty swallowing. Recent formulations of capsules containing granules allow the granules to be sprinkled on food without loss of the controlled release characteristics.

There are anecdotal reports of rectal and vaginal administration of controlled release morphine in patients unable to take drugs orally. However, pharmacokinetic studies of rectally administered tablets of controlled release morphine indicate a reduced bioavailability and haphazard absorption,[23] suggesting that a predictable sustained effect by this route cannot be assumed. There are no published studies of vaginal administration, but similar limitations probably apply.

(12) Morphine may be given subcutaneously either as bolus injections every four hours or by continuous infusion

(13) The relative potency ratio of oral morphine to subcutaneous morphine is about 1:2

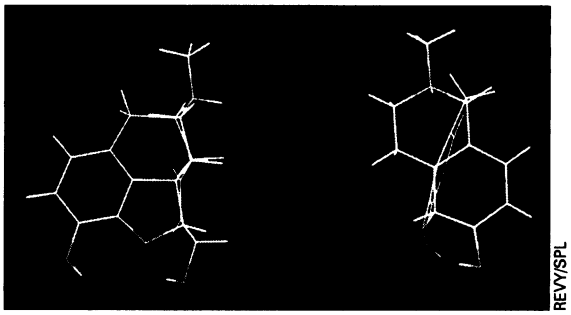
(14) There is generally no indication for giving morphine intramuscularly for chronic cancer pain because subcutaneous administration is simpler and less painful

The relative potency ratio of oral to parenteral morphine has been highly controversial.[24-27] It seems that the relative potency ratio varies according to the circumstances in which morphine is used. It also varies between individual patients. While exact figures cannot be given, guidance is necessary for clinical practice. When converting from oral morphine to subcutaneous morphine for chronic cancer pain, the dose should be divided by two to get a roughly equianalgesic effect (the precise ratio probably lies somewhere between 1:2 and 1:3) (table 2).

(15) Other opioids may be preferred to morphine for parenteral use because of their greater solubility: diamorphine in Britain and hydromorphone elsewhere

Only 1·6 ml of water is needed to dissolve 1 g of diamorphine hydrochloride, whereas morphine sulphate requires about 20 ml to dissolve 1 g.[28] Hydromorphone is almost as soluble as diamorphine. Neither drug is more effective than morphine or less likely to produce adverse effects, though both are more potent. The relative potency ratio of oral morphine to subcutaneous diamorphine is 1:3.[28]

(16) Subcutaneous administration of morphine may not be practical in patients
(a) with generalised oedema
(b) who develop erythema, soreness, or sterile abscesses with subcutaneous administration
(c) with coagulation disorders



Morphine's atomic backbone

(d) with very poor peripheral circulation

In these patients intravenous administration is preferred. Intravenous administration may also be the best parenteral route in patients who, for other reasons, have an indwelling central or peripheral cannula

(17) The relative potency ratio of oral to intravenous morphine is about 1:3

Subcutaneous infusions have several advantages over intravenous infusions: venous access is not required, close supervision is unnecessary, and infection is unlikely. Thus, subcutaneous infusion of morphine is generally preferred for chronic cancer pain in patients unable to take oral drugs.[29] However, intravenous infusion may have advantages in the specific circumstances listed above.

Intravenous morphine is likely to be more potent than subcutaneous morphine, so the relative potency ratio of oral to intravenous morphine is probably nearer 1:3, and recent data confirm this ratio.[30] The ratio will be higher still with bolus intravenous doses of morphine because of greater peak effects.

(18) The above guidelines produce effective control of chronic cancer pain in about 80% of patients. In the remaining 20% other methods of pain control must be considered, including spinal administration of opioid analgesics alone or in combination with local anaesthetics or other drugs. There is insufficient evidence to allow recommendations about precise indications for these routes of administration

If patients derive inadequate analgesia or suffer intolerable adverse effects despite the optimal use of systemic opioids, spinal administration (epidural or intrathecal) should be considered. The use of spinal opioids is highly controversial,[31-34] but it is generally agreed that such routes are second line options in managing cancer pain.

(19) The buccal, sublingual, and nebulised routes of administration of morphine are not recommended because there is presently no evidence of clinical advantage over conventional routes

The absorption of morphine by these routes is unpredictable,[35,36] and they are best avoided.

(20) Sublingual or transdermal use of other opioids may be an alternative to subcutaneous injection

The highly lipophilic drugs methadone, fentanyl, and buprenorphine are well absorbed sublingually,[35] and buprenorphine is commonly used by this route. Sublingual buprenorphine may be a useful alternative to low dose oral morphine for patients who have difficulty swallowing,[37] but experience of long term use of this drug in cancer pain is limited.

A transdermal system for drug delivery has been developed for fentanyl. The system is designed to provide continuous, controlled systemic delivery of fentanyl for 72 hours, and it seems to be effective and well tolerated.[38,39] It is too early to determine where this method of strong opioid delivery will fit in the routine management of cancer pain.

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