



Frequently Asked Questions on oral Morphine Usage

NCG Palliative Care Committee

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Frequent questions asked by the patient/ relative

Q1. Can I take this tablet on empty stomach?

Yes. It does not have any side effects like acidity / gastritis if taken on empty stomach.

Q2. What is the duration of this treatment? After how many days will I be pain free without medicine?

This is not a course of treatment. These medicines must be continued as long as the disease that causes this pain persists.

Q3. Will my mother get addicted once we start this medicine?

Patient with advanced cancer - For all practical purposes, NO. The way this medicine is used for pain relief, the possibility of addiction is remote.

Patient with chronic painful condition – For all practical purposes, NO. With the careful processes that we use, for evaluation, monitoring and review, the possibility of addiction is remote.

Q4. Will she become drowsy and bedridden once we start this medicine?

Most people continue their regular work, driving and social activities. Up to 1/3rd of people may have some sleepiness with this medicine, especially in the 1st few days. If it is excessive, the dose would be reviewed and adjusted by the doctor.

Q5. Will she become confused? Will she start talking irrelevantly?

Not ordinarily. If there is irrelevant talk or confusion, the dose probably has to be reviewed.

Q6. Will it harm kidney / liver?

NO

Q7. Will she die earlier because of Morphine?

No. Morphine does not disturb activity of any vital organ to cause premature death. However, the medicine can cause dangerous adverse effects if used without due caution. This medicine is being prescribed as it is safe, and effective in the dose that I have prescribed for the type of pain your mother has. When used in in this type of severe pain, and monitored and reviewed carefully as we have agreed together, and used as per instructions given to you here on this prescription, we ensure that her pain is relieved to a milder level and nothing un-towards happens to her.

Acknowledgement to Dr Robert Twycross

We acknowledge Dr Robert Twycross, Emeritus Clinical Reader in Palliative Medicine, Oxford University - UK, for allowing excerpts of Frequently Asked Questions from his work - *Oral Morphine in Advanced Cancer, Indian edition 2005* to appear in this compilation.

Frequently Asked Questions by Professionals¹

For convenience of discussion, oral Morphine is used as the prototype.

Q1. What are the indications for morphine in advanced cancer?

| Main | Subsidiary |
|---|------------|
| Pain | Cough |
| Dyspnea | Diarrhea |
| NOTE: Morphine should not be used as a primary sedative | |

Q2. Why use morphine? What about other opioids?

Morphine is a versatile drug. By mouth, it has an average duration of action of 4-5 hours and, except in patients with renal failure, there is no danger of drug cumulation. It is also inexpensive.

Pethidine is available only in injectable form in India. It has a shorter duration of action. Its main metabolite is norpethidine which can cause tremor, twitching, agitation, and even seizures.

Pentazocin has short duration of action. Besides it has nausea and dysphoria as common side effects.

Tramadol 400mg/day by mouth is claimed to be equivalent to about morphine 80mg/day by mouth and can therefore substitute for morphine for moderate pains. It causes nausea and has a pro-convulsant action.

Transdermal Fentanyl is an alternative to morphine in continuous stable pain, but, is considerably more expensive.

¹ Oral Morphine in Advanced Cancer, Indian edition 2005, Robert Twycross DM, FRCP
Emeritus Clinical Reader in Palliative Medicine, Oxford University, UK

Methadone, a step 3 analgesic is now available in India. It is very effective in patients with neuropathic component in pain. Also, it is safe to use Methadone in those with renal impairment. Titration and optimization of Methadone dose in an individual patient is a complex process.

Q3. Is Morphine the panacea for all Cancer Pains? Are there morphine non-responsive pains?

Not all pains respond equally well to morphine. The following pains should be regarded as morphine non-responsive:

1. Tension headache
2. Muscle spasm (cramp)
3. Biliary colic

Movement-related pain often does not respond well to oral morphine. Here, such a high dose of morphine is required for relief during activity that the patient becomes unacceptably drowsy at rest. The dose of morphine is therefore titrated against rest pain rather than pain on movement.

Neuropathic pains and bone pains may respond only partially to opioids and may require adjuvant medications for their control.

Oral morphine is a useful medicine without which life would be extremely uncomfortable for many patients in pain. It must be used correctly with an awareness of its limitations and with regular supervision for each patient.

Q4. Are there any other important reasons for pain being poorly responsive to Morphine?

There are several other circumstances in which pain appears to be non-responsive to morphine. These include:

- Under-dosing (dose too small or given only as needed)
- Poor alimentary absorption
- Ignoring psychological, social and spiritual factors.

Q5. Can psychological factors really inhibit the action of morphine?

Morphine (or any other analgesic) should be given only within the context of comprehensive bio-psychosocial (whole-person) care. If psychological factors are ignored, pain may well prove intractable.

A 55-year-old man with cancer of the oesophagus was still in pain despite receiving slow-release morphine tablets 600 mg twice a day. Following inpatient admission, after rehabilitation, he became pain-free on 30mg twice a day and diazepam 10mg at bedtime. When he returned home, he converted an under-used room into a workshop, and spent many happy hours there. The key to success was listening, explaining and setting positive rehabilitation goals.

Achieving a good night's sleep may require measures other than morphine as for e.g. attention to psychosocial concerns.

The first step is to break the vicious cycle of pain, sleeplessness, exhaustion, increasing pain and increasing distress.

An antidepressant should be prescribed if the patient is clinically depressed. Initially it is impossible to distinguish between clinical depression and demoralisation secondary to insomnia and exhaustion caused by long-continued pain and despair. Generally, clinical depression should be diagnosed only after steps have been taken to relieve persistent severe pain and the associated insomnia. With pains expected to respond to morphine, lack of success is one pointer to depression, or another major negative psychological factor.

Short term anxiolytics may be necessary in indicated patients.

Q6. Can I ever be confident that the use of morphine in a particular patient will result in good relief?

Yes; if the pain is morphine-responsive. Partial relief obtained with a weak opioid or when morphine is first prescribed often indicates that the pain is morphine-responsive.

Doctor: 'With your present tablets [weak opioid], how soon do you get relief?'

Patient: 'After 20-30 minutes.'

Doctor: 'How long does the relief last?'

Patient: 'About one and a half to two hours.'

Doctor: 'How much of the pain is relieved by the tablets? 25%, 50%, 75%?'

Patient: 'I would say about 50%; they make it bearable.'

Doctor: 'That's good, because it means that you have a pain which responds to this group. What we have to do now is to use something stronger, something which will give you relief that is satisfactory to you.'

In the above situation, the doctor can be confident that the use of morphine will achieve much greater, possibly complete, relief.

Overwhelming pain

Some patients present a picture of 'It's all pain, doctor.' This can be caused by the pathophysiological response to prolonged unrelieved pain in which case we can expect quick and dramatic improvement with analgesics. But this state may also indicate an anxious, demoralised patient, possibly exhausted from pain-related insomnia. If anxiety or depression appears to be a predominant factor, then simultaneous assessment of psychosociospiritual status should be considered along with prescription of morphine. If there is clear panic, a small dose of anxiolytic [Lorazepam 0.5 mg or 1 mg S/L] may be given. Review by the doctor after two hours and again after 4 hours is not excessive. Subsequent doses of both drugs depend on the initial response.

Overwhelming pain is usually the result of weeks or months of unrelieved severe pain. *It should be regarded as a medical emergency.* Best results are obtained if *one doctor* (or at most two) accepts responsibility for frequent review and prescribing.

Q7. Is an anti-emetic always necessary?

Up to 1/3rd of opioid-naïve patients may have nausea / vomiting after the 1st dose. If the patient vomits after taking morphine, the morphine will not be absorbed, the patient remains in pain and she / he loses confidence in the treatment. To avoid this, some authorities recommend an anti-emetic routinely for the first three days (and thereafter PRN) when morphine is prescribed. If this is not done, an anti-emetic medication must be available on order for PRN administration.

Prophylactic anti-emetic may be needed

Prophylactic anti-emetic may not be needed

- | | |
|---|--|
| <ul style="list-style-type: none"> • those who are already experiencing nausea and vomiting from another cause. • those who are experiencing nausea and vomiting with codeine or other step II opioid. • those who vomited when given a step III opioid in the past. | <ul style="list-style-type: none"> • those with no nausea and vomiting on step II opioids. • those taking a weak or alternative strong analgesic regularly without nausea or vomiting. |
|---|--|

Q8. Can the anti-emetic be stopped?

For many patients, vomiting with morphine is an initial effect. If an anti-emetic was prescribed prophylactically, and not to relieve pre-existing nausea and vomiting, it is good practice to stop it after the patient has been on a steady dose of morphine after about three days. Remember: about 2/3 of patients receiving morphine never need an anti-emetic. If necessary, the anti-emetic can be restarted, and continued indefinitely.

Q9. Do patients on Morphine become confused?

Yes, a few; and this would indicate a relative overdose. This is particularly likely in the elderly, who are more sensitive to the effects of morphine. It will be necessary to titrate the dose of morphine more slowly in these patients, possibly starting on a lower dose, or prescribing every 6–8 hours initially. Patients over 70 years old should be warned that they may become muddled at times during the first few days and will need review and dose adjustment.

Confusion (delirium) may be caused by the concurrent use of morphine and psychotropic drugs and/or anti-muscarinic drugs. If the confusion persists, a reduction in concurrent medication should be considered.

Q10. What's so special about 'every 4 hours'?

Clinical experience in countless countries has shown that increasing the dose of morphine solution to provide relief for 4 hours achieves the optimum balance between relief, practical convenience, and undesirable effects.

Giving more at less frequent intervals will provide comfort for a longer period, but only at the price of more troublesome undesirable effects, particularly drowsiness and nausea.

Giving less at more frequent intervals simply makes the regular taking of morphine more tedious for the patient, particularly at night. Compliance is then reduced and more pain is the

result. The general rule is: *give morphine regularly every 4 hours (or twice a day if a slow-release preparation is used)*.

Q11. For ordinary morphine tablets and solution, are there any exceptions to the 'every 4 hours' rule?

Regular morphine is indicated for continuous pain but not for occasional pain. Other circumstances in which it may be desirable to prescribe morphine solution *less often* include:

- the very old (75+)
- patients with only night pain
- Patients in renal failure.

Q12. How about driving while taking regular oral Morphine?

Most patients receiving morphine are not well enough to drive, and have no wish to do so. Those who are stronger may still want to drive their car, particularly if they are continuing to work. Patients who wish to drive should be assessed first for any period of confusion and need specific advice. They are also more likely than others to sleep while driving.

Box -1 Advice for patients wishing to drive while taking oral morphine

The medicines you are taking do *not* automatically disqualify you from driving.

However, the speed of your reactions and general alertness may be adversely affected by your medication.

It is important that you take the following precautions, particularly if you have not driven for some weeks because of ill health:

do not drive in the dark or when conditions are bad

do not drink alcohol

check your fitness to drive in the following way:

Choose a quiet time of the day when the light is good

Choose an area where there are several quiet roads

Take a companion (husband, wife, friend)

Drive for 10–15 minutes on quiet roads

If both you and your companion are happy with your attentiveness, reactions and general ability, *then it is all right to drive for short distances*

Do not exhaust yourself by long journeys.

Q13. Don't patients stay doped or die more quickly once morphine has been prescribed?

There is a misconception, that patients stay sleepy / doped when given Morphine for pain relief in an appropriate manner.

This is not true. Many patients with advanced disease, who are bedridden mainly due to severe pain, become more comfortable after starting oral morphine and survive the rest of their lives for months or years with greater comfort and better quality of life. They are able to participate in daily living because they are able to rest, sleep and eat better. They are also able to resume their normal activities at work and at home and develop a renewed interest in life.

When morphine is prescribed when someone is very near death, the morphine may get blamed for hastening the process of dying. Hence it is necessary to warn the family first about the advanced state of the disease and possibility of imminent death.

Q14. When the patient is close to death and unconscious, should morphine be stopped?

No, because semiconscious patients in pain are restless. Or the patient may simply be unable any more to complain or express what they feel. Further, physical dependence develops after several weeks of oral morphine therapy. If morphine is stopped abruptly, the patient will get withdrawal symptoms and would be restless, sweaty, and may develop faecal incontinence secondary to rebound hyperperistalsis. However, smaller analgesic dose is sufficient to maintain pain relief and prevent opioid withdrawal phenomena. It is conventional to reduce the dose of morphine by one-third to half in such situations, particularly considering that the renal function is likely to deteriorate too.

Q15. Can Narcotics be weaned when no longer required?

It is possible that the pain may disappear during the course of treatment, as for example with palliative radiation or palliative surgery. If pain disappears, the dose of opioids can be decreased and stopped altogether in the following steps:

- if a patient has been entirely pain-free for > 4 weeks on a regular unchanged dose of morphine, decrease the dose on a trial basis by 20–50%.
- if the pain recurs, increase the dose back to the original level.
- if the pain does not return, the dose of morphine should be decreased every 1-2 weeks until the morphine is completely curtailed, or until the pain recurs.
- When the pain recurs, increase the dose to the previously satisfactory dose.

Q16. Do patients die of morphine-induced respiratory depression?

No, because pain antagonises the central depressant effects of morphine. When morphine is used in the way described here, clinically important respiratory depression is rarely seen.

Should it occur,

- reduce the dose of morphine
- consider using an opioid antagonist, e.g. naloxone 20 microgram IV every 2 minutes until the patient's respiratory status is satisfactory; this is rarely necessary.

The dose of Naloxone - 1 ml = 0.4 mg is diluted 10 times and is given incrementally only for reversal of respiratory dysfunction and not to reverse analgesia. This may precipitate severe pain and sympathetic overactivity. The patient may be allowed to sleep off the excessive sedation' as that by itself is not life threatening, taking care to monitor respiration and maintain hydration in the meantime.

However, iatrogenic over dosage and respiratory depression can occur in deliberate (suicidal) or accidental over dosage.

Q17. How about the allegation that use of morphine tantamount to prescribing a living death?

Many doctors and nurses have strongly negative attitudes towards the medicinal use of morphine. For example, comments from colleagues may be as follows:

'What about the inoperable cancer patient who may not die for months and is suffering agonies from chronic pain? Is a doctor justified in prescribing morphine when he knows full well he will be sentencing his patient to a kind of living death?'

'I try to postpone giving morphia until the very end and am best pleased if the first dose is also the last.'

These views stem from ignorance about the correct use of morphine in cancer patients with pain. **Indeed, the patients who are truly sentenced to a kind of living death are the ones who are not prescribed adequate doses of morphine.**²

² <http://www.lifebeforedeath.com/movie/short-films/36-poetryinmotion.html>

A young architect had attempted suicide because of unrelieved cancer pain. The subsequent correct use of morphine enabled this patient to get back to productive life, finish his construction project and make provisions for his family before he eventually died. This kind of meaningful life on opioids has proved true for many others too.

Q18. Wouldn't injections generally be better?

No. Injections are *not* generally better, and can be uncomfortable. Regular injections tie the patient to professional help, generally a nurse, because someone else is needed to administer the medication. This precludes home based care and increases the overall cost.

Q19. When should we consider using injectable opioids?

| Main | Subsidiary |
|---|---|
| <ul style="list-style-type: none"> • Intractable vomiting. • Inability to swallow. • Unconscious or semiconscious patient who has non-verbal expressions of severe pain. | <ul style="list-style-type: none"> • Some patients who do not respond well to oral Morphine due to genetic predisposition, may do well on injectable Morphine. • Conditions with poor alimentary absorption |

If regular injections become necessary, the best option is a *continuous subcutaneous infusion* of morphine (preferably using a battery-driven or clockwork portable syringe driver) but this is not always possible. An indwelling butterfly cannula to give injections every 4 hours is another option. *The dose of morphine should be halved when changing to the subcutaneous route.*

The Indian Association of Palliative Care has made a position statement endorsing administration of injectable opioids by the patients' family under medical guidance³

³ <http://www.jpalliativecare.com/article.asp?issn=0973-1075;year=2007;volume=13;issue=1;spage=21;epage=21;aualast=Indian>

Q20. Once on injections, is it possible to change back successfully to the oral route?

Yes, once vomiting has been relieved with parenteral anti-emetics, it is often possible to revert to the oral route. It may be wise to convert in stages, e.g. first establish control with oral anti-emetic, and then, the next day, change the route of morphine if there is no recurrence of vomiting.

Q21. Is it possible to achieve pain relief initially with an injection and then change over to oral Formulation?

Yes. This is through Parenteral Morphine Trial⁴. –described below.

⁴ Harris JT, Sureshkumar K, Rajagopal MR. Intravenous morphine for rapid control of severe cancer pain. Palliative Medicine, 2003; 17:248-256

Parenteral Opioid Titration For Treatment of a Severe Pain Emergency

Advantages

- Immediate relief.
- Improved patient confidence.
- Index of Opioid sensitivity (drowsiness without pain relief indicates poor opioid sensitivity).
- Index of oral opioid requirement.

Procedure for Morphine Titration

1. Check vital signs.
2. Secure an intravenous access
3. Note the patient's pain score using numerical rating scale (0-10)
4. Give an antiemetic e.g. 10mg metoclopramide IV /SC. If there is colic, use antiemetic without prokinetic effect e.g. Ondansetron.
5. Dilute one ampule of morphine to 10ml (depending on the available formulation, the result may be 1mg or 1.5mg per ml). Label the syringe.
6. Give the diluted morphine 1ml (1 to 1.5 mg) IV/SC every 10 minutes. The bolus dose should be 0.5 mg per bolus for elderly
7. Check pain score, vital signs and check for drowsiness before every dose.
8. End point: Pain relief to a score of ≤ 3 or significant drowsiness.
9. At end point, stop giving bolus dose and note the total dose.
10. Note: Drowsiness without adequate pain relief indicates poor opioid sensitivity and is an indication to stop continuation of opioid titration.

The Oral Dose Requirement of morphine

In opioid titration in an opioid naïve patient, the injectable opioid is required to build up the opioid concentration in the body from 0 level.

The usual conversion ratio for parenteral to oral dose [1: 2] does not apply here. It is applicable only for conversion of a stable 24 hour requirement of parenteral to oral Morphine dose which has established satisfactory and continuous pain relief.

We have found that the oral morphine requirement after an IV trial, may be anywhere from 0.4 to 2.2 times the intravenous dose requirement with the initial titration. For practical purposes, if satisfactory pain relief is achieved with 5 mg of IV

morphine, the patient may be started on 5 mg of oral morphine after 2 hours of the trial and then Q4H by clock and then the oral dose is titrated up or down.

If 13 mg of IV Morphine relieved the pain, then give 15 mg 4 hourly with same dose as SOS for breakthrough [if systemic functions are normal]. Review after 4-6 hours, 12 hours, 24 hours, 48 hours and adjust the dose, side effects and signs of effectiveness.

Procedure for Fentanyl Titration

In the case of fentanyl, the advantage is that the trial is quicker compared to morphine, may be used in patients who have mild dehydration or have poor renal function. The disadvantage is the higher cost.

The ampule of fentanyl is usually 50µg / ml. It is diluted so that 1 ml contains 10 micro grams. 1ml is given every 3 minutes.

As a starting point, the fentanyl/morphine conversion ratio is 1:60 (For example 100 microgram of fentanyl is considered equivalent to 6 mg of morphine).

Q22. Can morphine be given by suppository?

Yes. Suppositories are a useful alternative to injections, particularly in the home. The *oral to rectal potency ratio is 1:1*; i.e. the same dose is given per rectum as by mouth.

Unfortunately, morphine suppositories are not available in India and many palliative care units manage by using tablets rectally.

If administration every 4 hours proves difficult, it is possible to give slow-release morphine tablets *per rectum* every 12 hours. Pharmacokinetic studies have demonstrated that they are equally well absorbed by this route.

Q23. Why do some people need more morphine than others?

There are many reasons, including:

- Differences in pain threshold and the intensity experienced.
- Older people tend to need less
- Concurrent use of adjuvant drugs and non-drug measures
- Pharmacokinetic differences:
 - Absorption
 - 'first-pass' hepatic metabolism
 - Plasma half-life
 - Renal function

- Genetic differences in patient's pain tolerance threshold (relates to CNS endorphin stores)
- Differences in patient's pain threshold
- Duration of treatment (the dose tends to increase with pain as the disease progresses)
- Adequacy of management of other symptoms.

Q24. When treating the pain in a cancer patient, what else must I bear in mind?

Because pain is a somato-psychic experience, its intensity is modified by the patient's mood and morale, and the meaning of the pain for the patient.

Those caring for the patient with cancer must be aware of the many factors which influence the patient's perception of discomfort. A doctor should be prepared to address the many factors influencing the perception of pain, when planning to include morphine in his prescription.

Q25. How is morphine used to relieve intractable dyspnoea in advanced disease?

Patients with dyspnoea caused by irreversible malignant chest disease often benefit from oral morphine. The aim is to reduce the *sensation* of breathlessness. If the subjective discomfort of breathing worsens with minimal exertion to a level which is distressing to the patient, it should be treated. The use of morphine for dyspnoea is appropriate only after:

- The impact of dyspnoea has been discussed with the patient and family and, when relevant, the nature of respiratory panic attacks has been explored and coping strategies devised.
- General guidance about coping with activity-related dyspnoea has been given, e.g. introducing periods of rest between necessary activities (sometimes called 'pacing').
- Contributing co-morbidities have been assessed and optimized e.g. bronchospasm/ infection / heart failure.

There is high levels of respiratory inspiratory drive is seen in patients with diffuse pulmonary disease. This is possibly in response to ineffective ventilation due to multiple areas of dysfunction / disease / atelectasis. This is when the body is deconditioned and debilitated due to the advanced disease and has worsening fatigue. Here any increase in metabolism e.g. rising CO₂ levels when getting out of bed - could excessively stimulate inspiratory drive and give rise to overwhelming fatigue and panic.

Much of the benefit from morphine may relate to a net reduction of respiratory inspiratory drive. Opioids appear to act as dampeners or modulators of a complex system and offsets particular response cascades. The modified respiratory drive seem to optimize the dead space to alveolar ventilation, and the Tidal Volume, leading to decreased sensation of distress.

Q26. What is the right dose of morphine for dyspnoea?

The optimum dose of morphine for dyspnoea is generally less than that for pain relief:

- Begin with a test dose of 2.5 – 5 mg continue with 2.5 – 5 mg every 4 hours during the daytime, and 5-10mg at bedtime
 - At each stage, benefits must be weighed against undesirable effects. The aim is a more relaxed patient who is not cyanosed and is mentally clear. If a patient is already receiving morphine as an analgesic, the dose should be increased by 50% on a trial basis.
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