



Step III Pain Control with Oral Morphine in Terminally Sick Cancer Patients

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Introduction

Terminal medical illness is a disease status which has progressed beyond the stage at which treatment aimed at remission is feasible. This state may exist (persist) for variable period of time and majority of cancer patients suffer from pain during this period. Though, impending death is foreign to our goals, frame-work and training yet the responsibilities and obligations of the clinician do not end when physical disease eludes cure (1). Data from several prospective surveys suggest that 70-90% of patients with cancer pain could attain adequate relief if guidelines of WHO (WHO ladder) and/or US agency for Health Care Policy and Research are followed with judicious use of opioids/oral morphine (2,3). The hard fact is that more than 40% patients with pain are under-treated (4,5), which usually leads to development of chronic pain syndrome manifesting in; Depression, Dependency, Disability, Disuse, Drug misuse Drug abuse, Doctor shopping/Hypochondriasis.

Pain has been regarded as a form of punishment for sinful activity (6,7). Infact, the word pain comes from the Latin word "poena" meaning "punishment"(8). Pain is a common feared symptom in cancer patients. It occurs in 50-80% of patients with advanced cancer (9-11). Terminally sick patients often report the fear of intractable pain and loosing self-control more than they fear dying. They frequently express the desire to have an open dialogue with medical faculty about pain and want to be involved fully, with self control, in planning their pain management (12). Though reassurance is helpful, Collusion and false hope must be avoided at all

costs in order to preserve trust. Because, having promised to keep the patient relatively pain-free, it is paramount to meet this promise. Attempt and treatment goal should be prevention of pain because, it is easier to check than to relieve pain in cancer and drug(s) should be prescribed on a prophylactic basis with no other consideration than maintaining the best possible quality of life; adding life to remaining days rather than adding merely days to life of a terminally sick cancer patient (13).

We, at our Institute started using oral morphine in terminally sick cancer patients with pain for last 4-5 years. This review is a gist of experience of various authors and our own to encourage the clinicians. Procedures for pain management in terminal Sickness:-

Cancer pain can be controlled in most patients by relatively cheaper oral drug(s) after a detailed assessment of pain, using different pain scoring scales (Visual Analogue, Numerical scale, etc), and analysis of the suitability of analgesic(s) (14).

Approch to Terminally Sick Cancer Patient

- a) Establish the cause of the pain which may be due to cancer or due to treatment related side effects make a full assessment of all contributing factors. Differentiate between acute, chronic, nociceptive and neuropathic pain.
- b) Try to use minimum number of drugs in the most acceptable form. Assess prior treatment as a guideline to future treatment
- c) Use of WHO analgesic ladder to guide systematic pain relief is recommended but one has to be

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vigilant as other treatments (surgery, nerve blocks, radiotherapy etc) may also contribute in alleviating the pain (15,16)

- d) Choice of drug(s) should be based on the severity of pain Step up to higher step when lower step analgesics have failed.(Figure-1)
- e) Use drug(s) by the mouth; by the clock; by the ladder; for the individual with attention to detail
- f) Adjuvant drugs i.e anxiolytics may be added which augments the analgesic effect.
- g) Prescribe not only to cover continuous background pain felt by the patient but also for breakthrough that occurs with everyday activities such as walking or omitting a prescribed dose . The aim is keep the patient pain-free both when sitting at home but also when undertaking normal daily activities.
- h) Regular review is essential to ensure that treatment goals are being met and side-effects avoided

Strong opioids (Step III pain control) - Oral morphine

Opioids have been consistently under-used in the treatment of cancer pain because the general population ,physicians, and paramedical staff share many of the common myths which include;

- a) Opioids cause addiction
- b) Opioids cause frequent respiratory depression
- c) Opioids decrease survival
- d) Physical dependence and addiction is same

Counter Common Myths & Misunderstandings

- a) Under normal prescription opioids are not normally addictive. Dose reduction of morphine is possible if other measures counter the cause of the pain.
- b) Respiratory depression is not usually a common problem with oral morphine. Pain tends to counter this effect.
- c) At the correct dose patients can continue with normal activities. Initial sedation may occur but, it usually settles within 48 hours
- d) Patients are normally maintained for several weeks on a constant dose and significant tolerance to morphine does not usually develop (17,18)

Dose Titration

“There is no standard dose of morphine. The dose needs adjustment against effect for each patient individually with starting dose determined roughly by previous analgesic treatment”.

Guideline for Dose Titration

- a) For a naive patient starting dose for opioid is usually 5-10mgs.adminstered at 4 hourly interval .We,at our centre, have used 10 mgs 6 hourly schedule in our patients with good pain relief and most of these patients stayed pain free for an appreciable length of time before dose escalation or frequency reduction to 4 hourly schedule.We have found 6 hrly schedule most acceptable amongst our patient population.
- b) For ‘breakthrough pain’ extra doses of the same size is administered.
- c) Many Hospice centres give double dose at bedtime to avoid waking-up from sleep.
- d) After 24 hours total the previous day’s intake 4 hourly/6 hourly dose requirement is calculated thus, adjusting the regular dose needed.
- e) If oral route is not possible the best alternative routes are sub-cutaneous and/or rectal
- f) The relative potency ratio of oral morphine to rectal morphine is 1:1
- g) The relative potency ratio of oral morphine to sub-cutaneous morphine is 1:2.
- h) The relative potency ratio of oral to I/V morphine is 1:3
- i) Sublingual or transdermal use of other opioids may be an alternative to subcutaneous injection (19).

Maintenance Dose

- a) Once pain relief is satisfactory and stable ; patient can be switched to sustained release preparations to allow 8 or 12 hourly dosing.
- b) Any breakthrough pain not associated with unusual activity should be treated with morphine elixir or ordinary morphine sulphate tablets at 1/6 total daily dose.

Side Effect Profile

- a) Use of lowest necessary dose with minimum side effects is recommended.
- b) Sedation - usually subsides within a few days.
- c) Nausea and vomiting are common but these usually settles within a few days but can be prevented using antiemetic (e.g.metoclopramide, Ondansterone etc).We have used Ondesterone in our patients for initial week or so and later discontinued the antiemetic gradually.
- d) Constipation and abdominal discomfort is frequent



side effect. Laxative like Bisacodyl should be prescribed prophylactically. We, at our Institute, avoid using bulk laxatives as it can aggravate the clinical situation. Case report of pseudo intestinal obstruction has been reported (20).

- e) The sequelae of dry mouth is easily controlled by good mouth care: frequent sips of iced drinks, salivary stimulants.etc
- f) For pruritis which in our observation is very infrequent, oral antihistamine are recommended.
- g) Bronchoconspasm, again an infrequent side effect in our observation, may necessitate use of parenteral antihistaminic and bronchodilator(s) and switch over to other safer opioid such as methadone.
- h) Over dose symptom(s)/sign(s) appear as confusion, agitation, hallucinations, vivid dreams and myoclonic jerks. Worsening renal or hepatic function will alter the metabolism of morphine and may cause accumulation and toxicity. Consider adjusting dose downwards or increasing dose interval (21).
- i) Remember that :- Pain is the best antidote of morphine.

Dependency Versus Addiction

One of the most mis-understood but much highlighted aspect of narcotic analgesics has been their addictive potential. One needs to clarify the demarcation between addiction and dependence. The dependence simply means a patient needs the drug to prevent his distressing symptoms secondary to the absence of the drug--a withdrawal/an Abstinence reaction. This has medical dimension and implications. Addiction, on the other hand has social implications alone. Addicts devote all their resources to the drug they must have sacrificing every thing they value.; they give up their enjoyment of family, food, sex and personal freedom to the drug in question— Their main focus being procuring and taking the drug. Cosequently, the two terms need to be separated apart and need not to be used interchangeably. A patient may be dependent but not an addict. It is therefore unlikely that a cancer patient in pain will become a street addict(22).

Recent Clinical Evidence

Oxycodone controlled-release (CR) has been shown efficacious and well tolerated as a first-line strong opioid for the treatment of moderate-to-severe cancer-related pain (23). In an open-label, multicenter study assessed the efficacy & tolerability of once-daily OROS hydromorphone therapy in patients with chronic cancer pain.

Figure 1:-WHO Analgesic Ladder

Step 1	
Non-opioid+/-adjuvant Pain persisting or increasing?	
Step 2	
Opioid for mild to moderate pain +/-non-opioid +/-adjuvant Pain persisting or increasing?	
Step 3	
Opioid for moderate to severe pain +/-non-opioid +/-adjuvant Objective: Freedom from pain	
Adjuvant Drugs for Cancer Pain	
Drugs category	Indications
<i>Non-Steroidal Anti-Inflammatory</i>	Bone pain Soft tissue infiltration Hepatomegaly
<i>Steroids</i>	Raised ICT Soft tissue infiltration Nerve compression Hepatomegaly
<i>Anticonvulsants and Antidepressants</i>	Nerve compression Paraneoplastic neuropathies
<i>Bis-phosphonates</i>	Bone pain

The OROS hydromorphone dose titrated over 3- 21 days to achieve effective analgesia and maintained for up to 14 days has been shown efficacious. Adverse events were as expected & there were no clinically significant changes in vital signs (24). In an other study to assess the effect and tolerability of oral normal-release morphine during the initial phase of treatment in patients with moderate-to-severe cancer pain results in rapid and satisfactory pain control, and is well tolerated (25).

The European Association for Palliative Care guidelines for treatment of cancer pain recommend a double dose (DD) of immediate-release morphine at bedtime instead of single doses (SD) repeated every four hours throughout the night. Where as, a open controlled study reported more side effects after DD than after SD. However, a randomized, double-blind, crossover study indicated the two procedures to be clinically equivalent (26). The oral “around-the clock” administration of sustained-release strong opioids has been recommended for the long-term treatment of patients suffering from chronic severe pain. No relevant differences between the different strong opioids with respect to efficacy and tolerability exist. However, hydromorphone and oxycodone appear to be advantageous over morphine due to a lack of immunosuppression. Hydromorphone has the additional benefit of a lower risk of intoxication by accumulation of active metabolites in patients with decreased renal function. As a result, although morphine has been



regarded as the standard for the treatment of chronic severe pain, hydromorphone and oxycodone may be better and safer alternatives for certain patient groups (e.g. older age, multimorbidity, cancer) (27).

Conclusion

Opioids remain one of the most effective treatment for cancer pain. Cancer patients have unique problems that require special consideration in the use of opioids, including chronic nausea, poly-pharmacy; associated comorbid condition(s). Current guidelines recommend the regular use of oral opioid agonists, on WHO guidelines, with titration of dose according to analgesia and side effects. Lately, modified release preparations of oral morphine have been synthesized and used by several authors with encouraging results. These preparations are prescribed at 12-24 hours schedules leading to a better patient compliance. Most of patients require alternative routes of opioid delivery before death. The sub-cutaneous and rectal routes are simple, safe, effective and economical in this setting particularly for patients in a Hospice or receiving home care.

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