Principles of Cancer Pain Management

Use of Long-acting Oral Morphine

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Oral morphine is increasingly recognized as the pharmacologic standard for cancer pain management. Yet for the primary care physician and oncologist alike, misconceptions of the safety and efficacy of oral morphine along with lack of recognized guidelines for use have often resulted in inadequate cancer pain therapy. Use of controlled-release oral morphine sulfate (MSC) requires additional guidelines for optimum analgesia. Proposed are ten principles of dosing oral morphine, especially MSC, which were followed in a clinical trial involving cancer patients. MSC dosed at 8-, 10-, and 12-hour intervals was compared with immediate-release morphine (IRMS) dosed every four hours, and with prestudy analgesics. Patients achieved satisfactory analgesia at daily doses (mean ± SE) of 118.0 ± 8.6 mg and 111.4 ± 12.6 mg ($P > .05$) for IRMS and MSC, respectively. Dosing endpoints were determined by titration with IRMS and MSC to a minimal and equivalent amount of supplemental short-acting analgesic. Side effects were typical for opioids and tolerated except for one dropout on IRMS (nausea and constipation). The ten principles have been incorporated into a dosing scheme as a practical guide for MSC therapy.

Recently oral morphine has been recognized as a standard pharmacologic intervention for the treatment of cancer pain.[1,2] Unfortunately, clinical use has been hampered by misunderstanding on the part of physicians and patients regarding the safety and efficacy of oral morphine, often resulting in inadequate therapy with alleged drug failure.[3] Moreover, the lack of recognized guidelines for use, especially for controlled-release oral morphine, has made it difficult for the family physician and oncology specialists alike to manage cancer pain in a collaborative and optimum fashion.

A fundamental misconception is that oral morphine is a poor analgesic. In fact, when dosed repeatedly, only three times as much oral morphine is required to achieve analgesia comparable to that from the parenteral route.[4] When inadequate analgesia occurs, physicians often add other opioids or shorten the dosing interval rather than make the correct initial adjustment of increasing the dose of morphine while maintaining the dosing frequency.[5] Yet the belief that increasing the dose of oral morphine is limited by a ceiling dose has never been substantiated. Data have shown that the amount of oral morphine needed to achieve adequate analgesia is patient dependent, and reported at nearly 2 g daily without unacceptable side effects.[6] The fear of toxic side effects with morphine has also limited prescribing by physicians. With titration of morphine to adequate dose, however, there have not been serious untoward effects such as respiratory depression.[3,7]

In this present study, controlled-release oral morphine (MSC) was evaluated for compliance, side effects, and analgesia. MSC was administered according to the following therapeutic principles:

1. Oral morphine can replace other analgesics to provide a single therapeutic agent of known pharmacology for moderate to severe pain.
2. Conversion to oral morphine can be accomplished easily using established opioid equianalgesic conversions that provide a starting dose of MSC.
3. For patients maintained on short-acting oral morphine every four hours, conversion to long-acting oral

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morphine (MSC) is simply a matter of dividing the daily dose by two, or perhaps three, and dosing every 12 or 8 hours.

4. If analgesia is inadequate, the amount of morphine in each dose, rather than the frequency of dosing, should be increased.

5. Increasing the dose of morphine is not limited by a ceiling dose; that is, titration should be continued until there is analgesia or unacceptable side effects.

6. The goal of titration with MSC should be complete analgesia requiring few or no rescue doses of short-acting supplemental analgesic.

7. During titration with MSC, pain should be treated as needed with a supplemental short-acting analgesic.

8. Breakthrough pain, that is, pain regularly occurring near the end of the dosing interval, should be eliminated by increasing the dose of MSC without shortening the dosing interval.

9. Incident pain, that is, occasional pain that results from circumstances such as physical activity or stress, should be treated with short-acting analgesics, and no adjustment should be made in the MSC regimen.

10. Side effects should be treated symptomatically. If they remain unresolved, they should be mitigated by dividing the total MSC dose in three doses to be administered every 8 hours. Alternatively, the MSC dose could be lowered while maintaining every 12-hour dosing and adjuvants added that have analgesic potential such as antidepressants, anticonvulsants, and nonsteroidal anti-inflammatory drugs.

METHODS

The study was approved by the Institutional Review Board of the University Hospital of the New Jersey Medical School. Patients with serum creatinine levels > 132.6 μmol/L (1.5 mg/dL) and serum bilirubin > 34.2 μmol/L (2.0 mg/dL) were excluded from the study. After giving informed consent, cancer patients with poorly controlled moderate to severe chronic pain, but with relatively stable disease, were switched from their prestudy analgesics to immediate-release oral morphine sulfate tablets (IRMS) given every 4 hours. The opioid conversions were based on equianalgesic ratios[8] that included a one-to-three ratio of parenteral to oral morphine. The dose of IRMS was increased by 15 mg daily until patients were maintained on a stable 4-hour dose for at least 48 hours. Crossover to MSC was then accomplished by doubling the individual IRMS dose and giving this same amount of morphine as MSC every 8 hours. The dose of MSC was increased, if needed, by 30 mg daily until acceptable analgesia was obtained for 48 hours on the eight-hour regimen. For consenting patients, the dosing interval was extended to every 12 or 10 hours with further dose adjustment, if necessary. Patients were assessed daily for analgesia and side effects. Satisfactory analgesia was reached by titration with IRMS and MSC until need for supplemental analgesic was minimal.

TABLE 1. PATIENT DEMOGRAPHY

Characteristics	Value or Number of Patients
Sex	
Male	15
Female	10
Mean age (SE) in years	54.6 (2.4)
Location or type of oncologic disease	
Lung	5
Colon	4
Pancreas	3
Bladder	2
Cervix	2
Breast	2
Primary unknown	2
Prostate	1
Larynx	1
Small intestine	1
Mesothelcoma	1
Stomach	1

RESULTS

Twenty-eight cancer patients who were hospitalized, outpatients, or both during the study were enrolled, and 25 patients, whose characteristics and analgesic regimens are shown in Tables 1 and 2, respectively, were evaluated. Three patients did not complete the IRMS phase, one each because of poor compliance, intestinal obstruction, and nausea and constipation.

All patients were on prestudy analgesics as described in Table 2. The final controlled-release morphine regimens revealed a dosing range from 30 mg every 12 hours to 120 mg every 12 hours. Two of the 25 patients did not consent to dosing less frequently than every 8 hours. Of the 23 patients given MSC every 12 or 10 hours, 21 had adequate pain relief. The two patients who failed treatment at every 12 or 10 hours attained good control at every 8 hours. Because these two patients did not consent to upward titration of their 8-hour MSC dose when the dosing interval was extended, there resulted a reduced and ineffective daily dose of morphine.

The total daily doses of MSC and IRMS that provided comparable analgesia were not significantly ($P > .05$) different, 118.0 ± 8.6 mg and 111.4 ± 12.6 mg (mean ± SE), respectively. Mean durations of treatment were three days for IRMS followed by MSC for 17 days. This longer exposure to MSC was intended to establish that tolerance would not develop. During the last 48 hours of each treatment phase, one to several doses of acetamin-

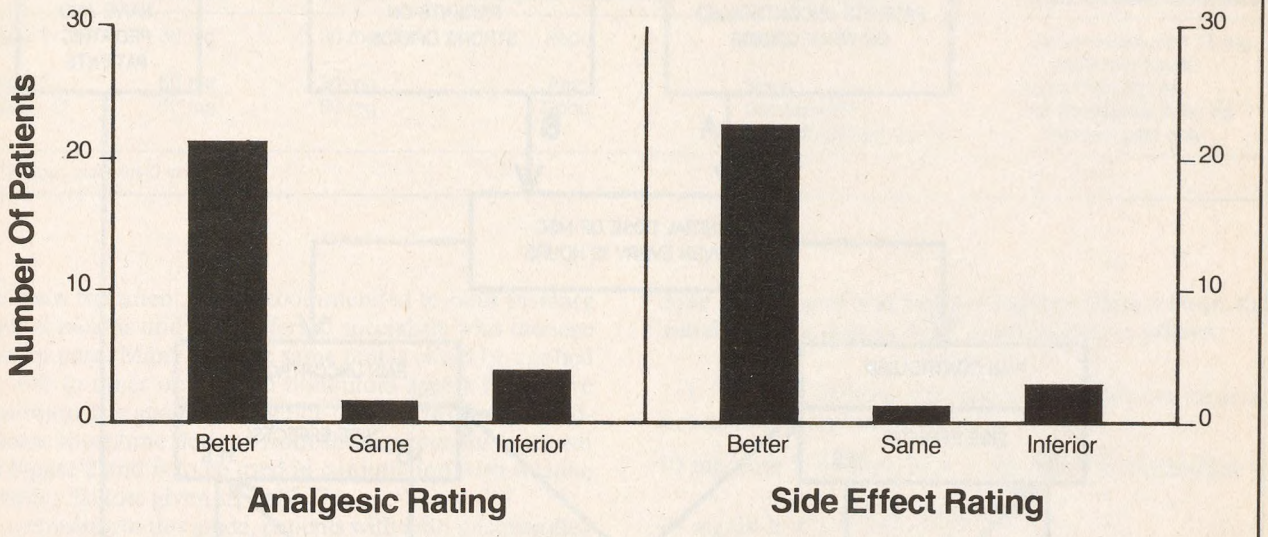

Figure 1. The analgesic and side effect ratings of controlled-release morphine sulfate (MSC) compared with prestudy analgesics are displayed in terms of the number of patients having found MSC to be better, the same, or inferior.

ophen were required as supplemental analgesic by four patients on IRMS and two patients on MSC. This minimal and essentially equivalent requirement for rescue assured the analgesic equivalence of both test regimens in steady state.

That satisfactory efficacy and side-effect endpoints were achieved with MSC treatment is shown in Figure 1. Patients' daily records revealed that MSC provided better analgesia with fewer side effects than was achieved with their prestudy analgesics, although the prestudy regimens may not have been dosed adequately.

Adverse events attributed to MSC were seen in four patients. There were two cases of severe constipation, one of nausea, and one of hallucinations.

DISCUSSION

The principles presented for the optimal use of morphine given in a controlled-release form were implemented successfully and conveniently in this study. Principle 1, that morphine can replace other analgesics, was substantiated by data in Table 2. A diversity of opioids and one nonopioid were easily replaced by immediate-release and controlled-release morphine (IRMS and MSC). Principle 2, conversion to oral morphine using standard equianalgesic ratios for opioids, assuming the ratio of parenteral to oral morphine to be one to three, was successful for all but one patient, who developed an unacceptable side effect on IRMS.

TABLE 2. ANALGESIC REGIMENS (dosing ranges low to high doses for patient group)

No. of Patients	Prestudy	End of Study—MSC
8	Oxycodone, 5 mg, with aspirin or acetaminophen, 325 mg every 6 h to 2 × dose every 3.5 h	30 mg to 90 mg every 12 h
6	Hydromorphone, 2 mg every 6 h to 4 mg every 3 h	30 mg to 90 mg every 12 h
6	Acetaminophen, 325 mg, with codeine, 30 mg every 4 h	30 mg to 120 mg every 12 h
1	Oxycodone, 7.5 mg every 6 h	30 mg every 12 h
1	Levorphanol, 2 mg every 6 h	30 mg every 12 h
1	Methadone, 10 mg, and hydromorphone, 2 mg every 6 h	60 mg every 8 h
1	Codeine, 60 mg every 3 h	90 mg every 12 h
1	Diflunisal, 250 mg every 6 h	30 mg every 12 h

Principle 3, the ease of conversion from IRMS to MSC, was supported by the daily amounts of morphine required in each treatment, which did not differ significantly. The total daily morphine dose given as IRMS in six divided doses was given as effectively in two to three divided doses as MSC. That two patients did not achieve adequate an-

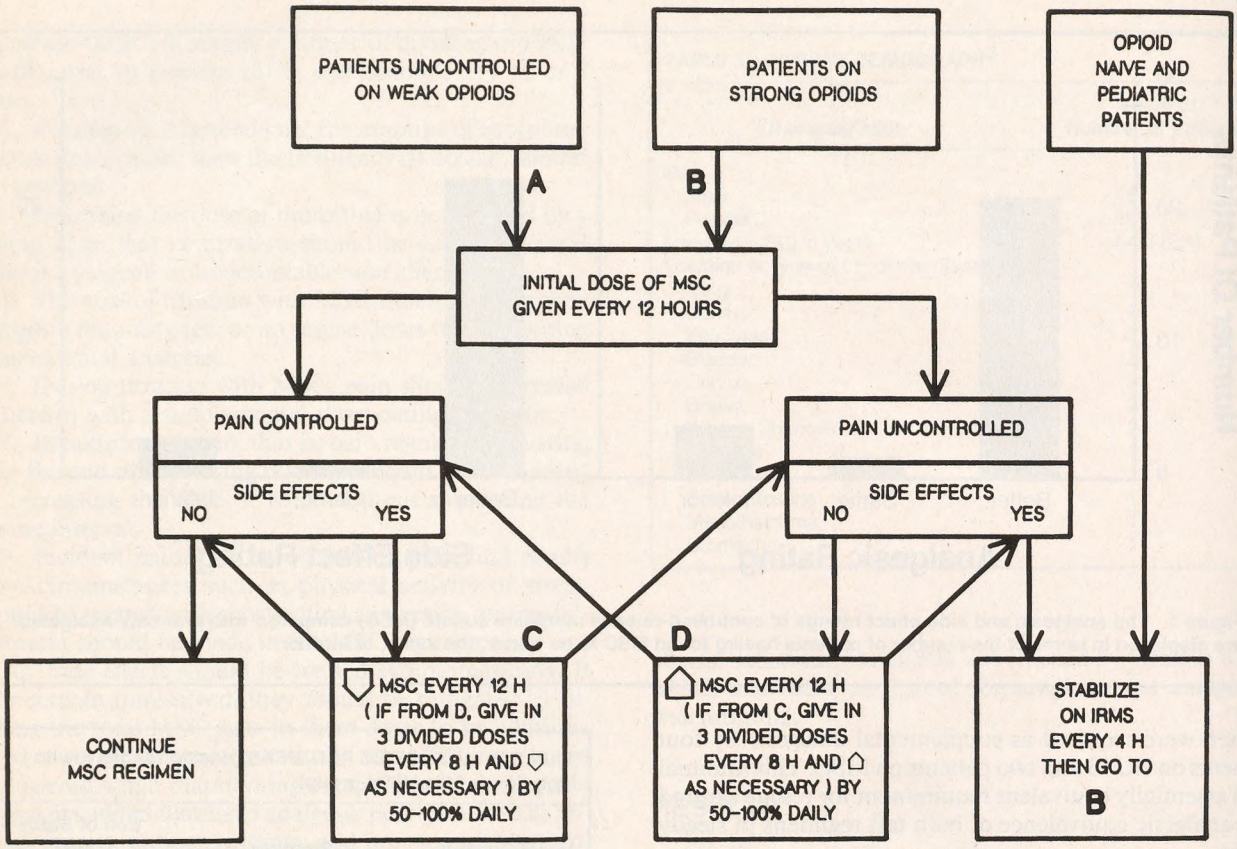

Figure 2. Guide for use of controlled-release morphine. (A) Start with controlled-release morphine sulfate (MSC) at 30 mg every 12 hours. (B) Calculate the total daily dose of each opioid being taken, then multiply each daily dose by the relative potency factor (Table 3) and sum these morphine equivalences. Administer total in two divided doses of MSC every 12 hours. (C and D) 50 to 100% provides a range of dose titration determined by clinical status. Supplemental short-acting analgesic, such as immediate-release morphine sulfate (IRMS) as solution or tablets, should be available as needed for breakthrough and incident pain. Nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and anticonvulsants may be added to enhance analgesia (eg, NSAIDs in bone metastases)

algesia during less frequent MSC dosing underscores principle 4, which calls for increasing the amount in each dose if analgesia is not satisfactory. For these two patients, the dose was not increased as their dosing interval was extended beyond every 8 hours. Following the fifth principle of titrating to effect resulted in MSC doses that ranged from 60 mg to 240 mg/24 h. Furthermore, other data exist of dosing with oral morphine at levels many times higher than the upper value in this study.[9]

According to principles 6 and 7, short-acting supplemental analgesic was employed until titration with MSC was completed. Breakthrough and incident pain were also treated with rescue analgesia according to principles 8 and 9. In this study, side effects were not unusual in kind or severity and required no more than symptomatic therapy as called for in principle 10.

These 10 principles, based on the clinical pharmacology of morphine and extrapolated from experience with can-

TABLE 3. RELATIVE POTENCIES OF OPIOIDS

Opioid Administered	Relative Potency Factor	
	IV or IM	po or pr
Codeine	0.25	0.15
Meperidine	0.4	0.1
Pentazocine	0.50	0.17
Oxycodone	NA	1
Morphine	3	1
Methadone	3	1.5
Nalbuphine	3	NA
Levorphanol	15	7.5
Butorphanol	15	NA
Hydromorphone	20	4
Buprenorphine	75	NA

IV—intravascular, IM—intramuscular, po—by mouth, pr—by rectum, NA—not applicable
Derived from relative potency studies[11,12] and assuming that morphine given IV or IM is 3 times more potent than when given orally or rectally[8]

TABLE 4. TITRATING CONTROLLED-RELEASE ORAL MORPHINE SULFATE (MSC) FOR OPTIMUM ANALGESIA*

	AM Dose	PM Dose	Analgesia With MSC	Side Effects	Supplemental Analgesic
Day 1	30 mg	30 mg	Poor	None	Morphine solution 15 mg every few hours
Day 2	60 mg	30 mg	Fair	None	Less than above
Day ≥3	60 mg	60 mg	Good	Constipation (treat with laxatives)	An occasional dose for incident pain only

* Follows guideline D in Figure 2

cer pain treatment,[10] are recommended to both primary care clinicians and their referred specialists who manage cancer pain. Many of these same tenets could be applied as well to other opioid and nonopioid agents to achieve optimum safe analgesia. A guide for the use of controlled-release morphine derived from these principles is shown as Figure 2 and is to be used in conjunction with relative potency factors given in Table 3.

According to this guide, patients with pain uncontrolled with weak opioids such as formulations containing codeine or pentazocine should be switched to MSC 30 mg every 12 hours. For patients who were treated successfully or not with stronger opioids, the initial 12-hour dose of MSC should be calculated using relative opioid potency factors (Table 3) as will be illustrated in an example to follow. If the initial 12-hour regimen controls pain, the dose is not changed unless there are unacceptable side effects. If so, the dose is decreased by 50 to 100 percent daily while the 12-hour regimen is maintained. However, some patients might benefit from dosing every 8 hours with one third the daily dose, as shown in Figure 2.

If the initial MSC regimen does not control pain, the dose should be increased by 50 to 100 percent daily while maintaining the 12-hour regimen. Some subjects whose pain is then controlled but who also experience side effects might benefit from dosing every 8 hours with one third the daily dose.

Patients not on opioids, pediatric patients, and patients on an initial 12-hour MSC regimen whose pain is uncontrolled and who also have unacceptable side effects should have their treatment regimen converted to immediate-release morphine sulfate solution or tablets and stabilized at every 4-hour dosing before attempting conversion to MSC.

As mentioned above, to switch patients being treated with strong opioids to MSC, an equipotent dose of oral morphine should be calculated using relative opioid potency factors (Table 3). The total daily dose of each opioid is calculated separately, and each daily dose is multiplied by its respective relative potency factor; then these oral morphine equivalences are summed. The total 24-hour amount of oral morphine would then be administered in two divided doses of MSC every 12 hours and dose adjustments made as previously described.

As an example, for a patient on 10 mg of oral methadone and 2 mg of oral hydromorphone every 6 hours the initial 12-hour dose of MSC is calculated as follows:

1. Convert 24-hour amount of methadone to equivalent as oral morphine:

$$10 \text{ mg/dose} \times 4 \text{ doses/24 h} = 40 \text{ mg/24 h methadone}$$

$$40 \text{ mg/24 h} \times 1.5 \frac{\text{oral morphine}}{\text{oral methadone}} = 60 \text{ mg/24 h morphine}$$

2. Convert 24-hour amount of hydromorphone to equivalent as oral morphine:

$$2 \text{ mg/dose} \times 4 \text{ doses/24 h} = 8 \text{ mg/24 h hydromorphone}$$

$$8 \text{ mg/24 h} \times 4 \frac{\text{oral morphine}}{\text{oral hydromorphone}} = 32 \text{ mg/24 h morphine}$$

3. Add 24-hour amounts of oral morphine equivalencies:

$$60 \text{ mg/24 h} + 32 \text{ mg/24 h}$$

$$= 92 \text{ mg/24 h morphine (approximate as 90 mg/24 h)}$$

4. MSC is to be started as 45 mg every 12 hours.

Since only 30-mg and 60-mg tablets are available at this time, dosing could be initiated asymmetrically with 30 mg and 60 mg, the latter given during the 12 hours of greater discomfort. Alternatively, 30 mg every 12 hours could be started and dosing adjusted, as in the following case in which it is assumed that pain is uncontrolled and there are no side effects. A possible titration scenario that follows guideline D in Figure 2 is shown in Table 4.

Aside from issues of efficacy and safety, cost is a factor in the equation determining therapy of choice. Of the commonly prescribed opioid analgesics, as in Table 2, only methadone has a lower factory cost (adjusted wholesale price from Redbook, 1988) for equianalgesic doses. Lower doses of methadone, however, are often used along with other more expensive opioids. This practice, as well as the inherent pharmacologic difficulty of using metha-

done because of plasma accumulation,[13] is a factor favoring use of controlled-release morphine sulfate.

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