Special Article

Opioid Use in Advanced Malignant Disease: Why Do Different Centers Use Vastly Different Doses? A Plea for Standardized Reporting

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Abstract
This paper reviews several recent publications concerning the use of opioids to control cancer pain and highlights the wide variation in mean daily dose. Present methods of reporting do not provide an explanation for these widely different doses used. It is essential that we understand the circumstances in which high doses are required, as higher doses are associated with greater toxicity and higher cost. Several factors that may influence the dose of opioid required are discussed. It is suggested that reporting of cancer pain, patient population, pharmacological and nonpharmacological interventions, and toxicity be standardized to allow for rational guidelines to be established for opioid use in pain due to advanced cancer. J Pain Symptom Manage *1995;10:632–638.*

Key Words
Cancer, opioid, pain, tolerance, parenteral infusion

Introduction

Recent publications concerning the use of opioids to control cancer pain reveal a surprising variation in mean daily dose.[1–9] This is an important observation because higher doses are associated with increased toxicity and higher costs, without apparent improvement in pain control. Although comparisons of opioid doses and toxicity across studies must be interpreted with care because of the differences in case selection and dose reporting methods, it is useful to summarize these data to draw attention to apparent differences in prescribing practices and their consequences. Guidelines for specific opioid therapies, such as subcutaneous infusions,[7] have begun to appear, but are premature given our current lack of understanding of the reasons for these differences. This observation is not an indictment of centers using high doses, but rather a call for the use of a standardized taxonomy of cancer pain; standardized reporting of patient populations, pharmacological interventions, and toxicity; and recognition of the role of nonpharmacological influences on cancer pain.

More than 30 years ago, Dr. Cicely Saunders reported that 70% of her terminally ill cancer patients achieved pain control with the equivalent of 180 mg of oral morphine daily,[10] and only very rarely did she require a dose greater than 360 mg per day.[11] Similarly, Twycross[12] reported a median maximum daily dose of 90 mg oral morphine, with 98% of his terminally

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Table 1
Mean Doses and Effects

	Low dose								High dose			
	Bruera 1990	Drexel	Gomez-Batiste	Melzack	Schug	Scott	Sitil	Royal Victoria	Bruera 1988	Ferris	Kerr	Moulin
No. of patients	100	—	—	33	550	44	60	75	108	135	18	60
Oral morphine	—	—	—	133[c]	117[a]	—	—	63[a]	—	—	—	—
Continuous SC morphine	44[c,d]	22[c]	112[c]	—	77[b]	—	140[b,c]	32[a]	305[a]	695[c,e]	523[a]	—
Oral hydromorphone	—	—	—	—	—	—	—	13[a]	—	—	—	—
Continuous SC hydromorphone	—	—	—	—	—	25[f]	—	26[a]	310[a]	568[c,e]	656[a,e]	578[a]
% with good pain relief	—	100	—	85	80	—	93	—	80	86	90	80
% toxicity	—	3	—	5	5[g]	—	2	—	10	20	10	20

[a] Mean maximal dose.
[b] Mean final daily dose.
[c] Mean daily dose.
[d] Parenteral equivalents, not all continuous or parenteral.
[e] Subcutaneous and intravenous infusions.
[f] Median maximal daily dose.
[g] % of time on oral morphine.

ill patients requiring 1200 mg of oral morphine or less per day. In 1979, 85% of patients with advanced malignant disease on the Royal Victoria Hospital Palliative Care Unit reported good pain control with mean oral daily doses of morphine of 133 mg.[6] More recently, a retrospective review of the charts of cancer patients followed by the Royal Victoria Hospital Palliative Care Service who were admitted and died in the first 6 months of 1993 revealed that the mean maximum daily dose had dropped to 63 mg oral morphine and 32 mg for subcutaneous morphine. Similarly low doses were used by the few patients given hydromorphone, with a mean maximum daily dose of 13 mg for oral hydromorphone and 26 mg for subcutaneous hydromorphone. Seven other centers treating cancer pain report using similar daily doses: 22–117 mg oral morphine; 44–140 mg subcutaneous morphine; and 25–26 mg subcutaneous hydromorphone[2,3,5,6] (Downing, personal communication; Gomez-Batiste et al., personal communication; Scott, personal communication).

In striking contrast, four authors have recently reported subcutaneous doses many times higher (mean maximum daily dose of *subcutaneous* morphine equivalents range from 300 to 523 mg; mean maximum daily doses of subcutaneous hydromorphone range from 310 to 626 mg.[1,4,5,7] Table 1 lists the average doses of morphine and hydromorphone calculated using data in these reports. When available, the mean maximal daily dose of all patients receiving opioids was included in Table 1. When this information was not available, the mean final daily dose or mean or median daily dose was used, as indicated in the legend.

Although all centers report pain control in 80%–100% of patients, the prevalence of side effects such as respiratory depression, seizure, myoclonus, severe sedation, hallucinations, and skin problems appears to increase in incidence with increasing dose (Tables 1 and 2). Bruera et al.[1] and Kerr et al.[5] report a 10% prevalence of toxicity while Moulin et al.[7] and Ferris et al.[4] report toxicity in 20% of patients. Those using lower doses report symptoms that are less severe and toxicity in fewer patients (2%–5% where reported). Fifteen of 16 instances of myoclonus reported by Ferris et al.[4] were in patients receiving hydromorphone subcutaneously at doses ranging between 60 and 200 morphine equivalent mg/hr. In addition to toxicity, the financial burden associated with higher doses and more expensive drugs must be considered.

Potential Explanations for Reported Differences in Opioid Dose

Until more precise studies are carried out, we can only speculate as to the reasons for these different prescribing practices.

Table 2
Toxicity

	Low dose				High dose			
	Drexel	Melzack	Schug	Royal Victoria	Bruera 1988	Ferris	Kerr	Moulin
Respiratory depression	—	—	—	—	X	X	—	X
Seizure	—	—	—	—	—	X	X	—
Confusion or severe sedation	—	X	—	—	X	X	—	X
Myoclonus	—	—	—	—	—	X	—	X
Skin irritation	—	—	—	—	X	X	X	X
Nausea and/or vomiting	X	X	X	X	—	X	X	—
Mild or moderate sedation	X	X	X	X	—	X	X	—
Constipation	X	—	X	X	—	X	X	—

Patient Characteristics

Differences in patient selection may account for the differences in dose in these reports. As described in the published papers, however, the samples do not appear significantly dissimilar. The mean patient ages are similar in reports that describe low opioid doses (mean age ranges from 53 to 61 years) and relatively high opioid doses (mean age ranges from 49 to 59 years). The patients in the Melzack et al. study[6] all had advanced cancer and had been referred to the Palliative Care Service of the Royal Victoria Hospital, a tertiary care teaching hospital with an active oncology program. The 1993 Royal Victoria Hospital data include all patients with cancer referred to the Palliative Care Service and who died in a 6-month period, (including those with neuropathic pain and incident pain). The patients of Scott (personal communication, 1993) and Gomez-Batiste et al. (personal communication, 1993) were all advanced cancer patients. The sample of Schug et al[8] consists of "patients with advanced cancer who were treated by the pain management unit." Bruera et al.[2] report on patients with cancer pain. The patients of Drexel et al.[9] had cancer pain that "could not be controlled by causal antitumor therapy... nor by local measures confined to one site," for whom "non-opioid and weak analgesics do not control pain." The sample of Sitl et al.[9] were "oncological out-patients" for whom "oral therapy according to the step scheme of the WHO was no longer possible." Bruera et al.[1] report on "patients with pain due to advanced cancer requiring parenteral narcotics." The patients of Moulin et al.[7] were seen in "neuro-oncologic consultation for cancer pain" and required high doses of opioid despite the fact that "patients with primarily neuropathic pain or pain related to movement (incident pain) were usually excluded, because these pain syndromes generally respond poorly to narcotic analgesics." Ferris et al.[4] report on oncology inpatients who received one or more narcotic infusions with a minimum of 6 days duration during the first 3 years of an infusion program. The sample of Kerr et al.[5] consists of "patients with poorly controlled cancer pain or significant side-effects from regular administration of various narcotics."

Pharmacology

Previous opioid use and concurrent use of adjuvant and antiinflammatory drugs may be related to the dose of opioid required to obtain adequate analgesia. This information is almost always available and should be included in all reports to enhance interpretation of reported results. Alterations in liver and kidney function could also influence the required dose of opioid and should be reported when available and assessed in all studies that include patients who are likely to have such alterations.

Tolerance

Differences from center to center in the prevalence of tolerance might also explain the need for high doses. Differences in tolerance could be related to the opioid, route of admin-

istration, behavioral conditioning, or prescribing practices. It is generally accepted that tolerance is not a clinically significant problem when morphine is administered orally at regular intervals in individually adjusted doses so as to consistently just prevent pain.[13] Many of the "high dose" reports involve the use of parenteral administration and hydromorphone. The prevalence of tolerance has not been defined in this situation. Differences in psychosocial support between the reporting programs may also explain the large differences in the doses of opioid used. These possibilities are discussed in greater detail below.

Tolerance: Type of opioid. Is the risk of tolerance higher with some opioids? Table 1 shows the mean daily dose of morphine and hydromorphone used in several centers. It appears that when hydromorphone is administered continuously subcutaneously, a dose almost as high as morphine is required, despite the fact that it is reported to be six to eight times as potent as morphine.[14–16] Insufficient information is given concerning reasons for selection of a particular opioid to determine whether patient selection alone may account for this difference. The use of higher relative doses of hydromorphone may be related to its greater solubility, which sometimes makes it the drug of choice for those requiring high doses. It seems possible, however, that this only partially explains the need for relatively high doses of hydromorphone, as the majority of patients are prescribed hydromorphone for reasons other than solubility.[4,7]

In recent years, the dose equivalency of hydromorphone to morphine cited in the literature has dropped from 6 or 8 to 1 to a ratio of 4 or 5 to 1.[4,7,17,18] This has occurred without support by specific clinical data. This apparently benign detail leads to an increase of up to 33% in the doses prescribed (e.g., 2 mg instead of 1.5 for 10 mg of morphine). As tolerance is reported to be related to the number of agonist molecules bound to the receptors, both in vitro and in vivo,[19,20] a 33% increase in hydromorphone dose levels from initiation of its use might increase the likelihood of tolerance.

Tolerance: Route of administration. Is tolerance more likely with one route of administration than another? Cox[19] has suggested that tolerance is more likely to develop when receptors are continually bathed with the drug. Intravenous infusion of opioids is thought to contribute to the development of tolerance in some patients.[21] With both intravenous administration and subcutaneous infusion, the receptors are continually bathed with the drug.

Tolerance: Behavioral conditioning. Is the need for higher doses partly due to behavioral conditioning? The animal literature suggests that the equipment used for subcutaneous opioid infusion can potentially come to have an anti-opioid effect. In animals, the effect of behavioral conditioning is so strong that much of the observed tolerance to the analgesic effect of opioids disappears when environmental factors are controlled. When the level of analgesia is measured in the same environment in which the animal received the opioid, marked tolerance is observed. However, if the same "tolerant" animal is given the same dose of opioid but tested for analgesia in an environment different from that in which it had previously received the drug, little or no tolerance is observed.[22] This is true not only for the analgesic dose but also for the lethal dose of morphine.[23] The effects of behavioral conditioning are so strong that animals with a *longer* history of exposure to morphine may actually develop tolerance *more slowly* than animals who have *less* experience with morphine, if they are explicitly given the drug in an environment distinct from the test environment.[24]

Environmental stimuli that are associated with a period *without* pain begin to act as a "safety signal." This "safety signal" has an anti-opioid effect: rats exposed to this "safety signal" along with morphine exhibit little or none of the usual analgesic effect of morphine. This anti-opioid effect is mediated by the release of cholecystokinin in the spinal cord.[25] It would be in keeping with the experimental data cited above if a stimulus as obvious and omnipresent as a subcutaneous infusion pump or syringe driver were to act as a "safety signal" and have a similar anti-opioid effect which *decreased* the analgesic potency of the drug being infused.

Psychosocial Factors

Differences in the psychosocial status of the patient populations may also explain the difference in dose requirement between centers.

The pain perceived by these patients is "total pain"[11] and is greatly influenced by its meaning and effect on their lives. As Foley writes when describing different groups of patients with cancer pain:

> Group IV is the dying patient with pain...in the author's experience they can represent special management problems. Within this group of dying patients are a number of relatively young patients in whom no analgesic regimen is sufficient to control their pain and rapid escalation of narcotic therapy, usually by the intravenous route, provides pain relief only at doses that are associated with excessive sedation or obtundation. 'Suffering' plays a major role in this group of patients and identification of such a factor will provide insight into the aspects of pain in this group of patients.[20]

Similarly, Twycross writes:

> If the pain is not relieved after one or two increments of 100 per cent (for a low starting dose) or 50 per cent (for a high starting dose), it is probable that the patient has a narcotic non-responsive pain..., and the use of a 'co-analgesic' and non-drug measures should be considered. Alternatively, it may indicate a higher than average psychological component to the pain, which will demand more time, more psychotherapeutic support, and probably the prescription of an anxiolytic or antidepressant.[12]

Some of those requiring exceedingly high doses may also manifest alexithymia which goes unrecognized. Alexithymics have no words for their feelings and may not recognize their emotions. Typically alexithymia "refers to a group of patients who have an impoverished fantasy life, exhibit difficulty in communicating emotion, use action to avoid conflict, rarely dream, rarely cry, or display inappropriate copious crying, and tend to focus self-reports on physical symptoms and trivial environmental detail."[27] Tourian[28] questions "why only 1–5 % of nervous system damaged patients suffer from chronic pain and what is different about this small subcategory of patients from all others whose damage does not result in a chronic deafferentation pain." He notes "a dramatically striking prevalence of impaired ability to communicate emotion ... in a certain subset of patients who develop deafferentation pain. A developmental history of abandonment by parents, psychological, physical, and sometimes sexual abuse seems to punctuate the life experiences of this subcategory of patients."

Questions in Need of Answers

Unfortunately, the foregoing discussion is merely speculative because hard data are lacking. Rigorous studies are required to determine the factors responsible for the reported difference in prescribing practices and provide guidelines for the use of opioids in this patient population. Some of the unresolved questions include the following:

- Are we treating different patient populations? To know this, we need a more detailed evaluation system for pain in the patient with cancer. This system should consider (a) the etiology of the pain; (b) the severity and frequency of the pain; and (c) psychological, social, financial, and spiritual contributing factors for each patient.
- Is there more rapid tolerance for one opioid than another? To answer this, we would need to define reasons underlying opioid selection or randomize choice of opioid.
- Is there more rapid tolerance with one route of administration compared to another? To answer this, we would need to know the rationale for choice of route or randomize choice of route.
- Does concomitant use of adjuvant analgesics vary across centers? Schug et al.[8] report a low average opioid dose and used adjuvants on 93% of the days opioids were used. They suggest that this may explain why they require lower doses of opioids to achieve similar pain control to those using higher doses. Ferris et al.[4] used high doses of opioids and suggest that "adjuvant therapies were not used as frequently as might be warranted."
- Does the use of nonpharmacological pain-decreasing procedures vary across centers? For example, as pain has a psychological component, we need to know not only the differences in pharmacological prescribing practices between centers but also whether there are differences in psychological support.
- Does the timing of the intervention differ

in different centers? Possibly, intervention before the pain is severe might result in the need for lower doses of analgesic, similar to the "pre-emptive analgesia" described for postsurgical pain (for review see Coderre et al.[20]). Are "low-dose" programs initiating multidimensional therapy earlier in the pain trajectory?

- How many cases of paradoxical pain do we see after high doses of opioid? In the animal literature, high doses of opioids have been shown to produce hyperalgesia and allodynia. Hydromorphone produces this effect at lower doses than morphine, and morphine-3-glucuronide is more potent in eliciting this effect than either hydromorphone or morphine.[30–32] In humans, paradoxical pain has been reported following high dose intrathecal morphine,[33,34] intravenous hydromorphone,[18] and intravenous morphine.[35] Recent evidence suggests that paradoxical pain is related to a high plasma ratio of morphine-3-glucuronide to morphine plus morphine-6-glucuronide.[36]

As some reports suggest that relatively low doses of opioid are sufficient to control pain due to advanced cancer, it is imperative that we understand the need documented in other reports for much higher doses with associated higher toxicity. Multicenter studies to answer the questions listed above are required.

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