Anti-Cancer Drugs 1995, **6**, Suppl 3, pp. 4–13

Misconceptions and controversies regarding the use of opioids in cancer pain

Kathleen M Foley
Memorial Sloan-Kettering Cancer Center, New York, USA.

The WHO has created a Cancer Pain Relief Programme and developed guidelines for the treatment of cancer pain. Implementation of the analgesic guidelines, assurance of drug availability (specifically opioids), education of healthcare professionals, and designating cancer pain as a priority for all national cancer control programmes are the major goals. Recent studies of medical students, physicians, nurses and state medical boards demonstrate a significant lack of knowledge with regard to the theoretical and practical understanding of the use of analgesic drugs, particularly opioids, in the management of cancer pain. Communication between physicians and patients about pain symptoms has also been shown to be problematic. Limited availability of opioids, their excessive regulation, and the lack of use of alternatives to systemic analgesics also prevent adequate management. Although analgesic drug therapy is the mainstay of treatment, opioid use remains a controversial issue. Some of the controversies include their role in the management of neuropathic pain, which has been suggested to be 'opioid-resistant', as well as the choice of opioid drug. A third controversy is the route of administration. The impetus for the development of novel routes has come from the goals of maximising analgesia, minimising side effects, and providing convenient dosing schedules for patients who require parenteral administration. Other important controversial issues are the development of tolerance and the relationship of pain management to patient requests for physician-assisted suicide and euthanasia.

Introduction

Advances in the evaluation and treatment of pain in patients with cancer have led to a series of clinical guidelines which define a comprehensive approach to the management of this difficult medical problem.[1,2] Of particular importance has been the unique opportunity that this population has provided as a natural experiment to study the chronic administration of analgesic drugs, specifically the opioids, to non-addict populations, providing insight as well as controversy in their appropriate use.

Numerous national and international surveys report that one-third of patients receiving active therapy and two-thirds of patients with advanced disease report pain.[3,4] Tumour infiltration of bone, nerve, soft tissue or viscera is the most common cause of pain, accounting for 65%–75% of patients.[5,6] Pain as a result of cancer therapy (surgery, chemotherapy or radiation) account for 15%–25% of patients, while 5%–10% of patients report pain independent of their cancer or cancer therapy.[5,6] Various factors influence the prevalence of pain including the primary tumour type, stage and site of disease, and patient variables, especially psychological factors.[7–12]

To address the need to provide appropriate pain management to patients with advanced cancer, the World Health Organization (WHO) Cancer and Palliative Care Unit has created a Cancer Pain Relief Program and through a series of expert panels has developed guidelines for the treatment of cancer pain.[1,2] The programme has achieved a broad international consensus based on the concept that analgesic drug therapy is the mainstay for the majority of patients with cancer pain. Field testing of the WHO guidelines in conjunction with clinical experience has shown that 80%–90% of cancer patients' pain can be controlled using a simple inexpensive method described as the three-step analgesic ladder.[13] This approach is based on the use of a combination of non-opioid, opioid and adjuvant drugs titrated to the individual needs of the patient, according to the severity of pain and its pathophysiology. Implementation of the analgesic guidelines, assurance of drug availability (specifically opioids), the education of healthcare professionals, and designating cancer pain a priority for all national cancer control programmes are the major goals of the WHO's effort.[14] However, several controversies have arisen that have influenced the wide application of this pharmacotherapy.[15]

Correspondence to KM Foley
Memorial Sloan-Kettering Cancer Center
1275 York Avenue, New York, NY 10021, USA

Barriers to effective cancer pain treatment

Although not well appreciated initially, the WHO has demonstrated that undertreatment of cancer pain remains a serious medical problem. They report that 4.3 million cancer patients die each year with inadequate control of cancer pain.[2] Numerous barriers have been documented that prevent patients from receiving effective treatment and healthcare professionals from providing such care.[16,17] The knowledge and attitude of healthcare professionals toward pain and its impact on the patient is particularly important, since both of these factors influence the priority both they and their patients place on pain treatment. Recent studies of medical students, physicians, nurses, and state medical boards, as well as broad national and international studies, demonstrate a significant lack of knowledge in both the theoretical and practical understanding of the use of analgesic drugs, particularly the opioids, in cancer pain management.[16–22] Patient–physician communications about pain symptoms have been shown to be problematic, particularly when patients report pain as moderate to severe. Physicians consistently underestimate patients' physical pain and overemphasise the psychological components.[21,22]

In one study of cancer patients' reports of pain and the concurrent observations of the physicians and nurses, the correlates of the nurse, house officer, and oncology fellow differed significantly from that of the patient, with an overall correlation of 13% for patients reporting moderate to severe pain.[22] These observations have been confirmed by others who have studied responses from 1,177 American physicians (65% response rate) through a survey of the Eastern Cooperative Oncology Group (ECOG).[18] Eighty-five per cent of the respondents who care for over 70,000 cancer patients agreed that the majority of cancer patients with pain were undermedicated, with poor pain assessment (76%) and lack of knowledge about analgesic drug therapy as the common barriers to adequate treatment. At both national and international levels, the limited availability of opioids, excessive regulation of opioids, and the lack of use of alternatives to systemic analgesics, such as nerve blocks, palliative neurosurgery and behavioural treatments, also prevent adequate treatment.[14] Recent cancer pain initiatives from the Philippines, China, Japan, Argentina, France and Germany have facilitated opioid drug availability.[23–30] For example, in Japan there has been a 17-fold increase in morphine consumption since the introduction of the WHO Cancer Pain Relief Program.[25] The increase in opioid availability worldwide for medical use has not been associated with an increase in the illicit market.[29] This latter concern has been a major one, one of the principal controversies being that drug diversion would result from wider availability of opioids for medical use.

In a special report of the International Narcotics Control Board (INCB), which addressed the demand and supply of opioid drugs for medical and scientific needs, the INCB strongly endorsed the WHO Cancer Pain Relief Program, and recommended that governments develop guidelines for the rational use of opioids for the treatment of painful medical conditions.[30] These cumulative survey data provide a powerful incentive for the implementation of broad educational efforts to improve the knowledge about cancer pain and its treatment in both healthcare professionals and patients, and to dispel some of their concerns on controversial issues. Attempts to remedy the situation include major educational efforts by various national and international professional societies.

In the United States, the American Pain Society, the American Society of Clinical Oncology and the Oncology Nursing Society have developed broad curriculum guidelines, as well as guidelines for use for the treatment of cancer pain.[31–33] Furthermore, in the United States, 25 states have started cancer pain initiatives to increase awareness and disseminate information to patients and healthcare professionals.[34] Although curricula have been developed, undergraduate and graduate medical programmes have not yet implemented formal curricula to meet these educational needs, although such curricula have been suggested for implementation by medical oncologists.[32]

At an international level, numerous countries have incorporated cancer pain relief into their cancer control programmes, and governments have developed specific strategies to provide effective relief for cancer patients. Such model programmes include those in France, the Philippines and Japan.[23,25,27] These countries serves as different models for developing broad educational programmes that implement the WHO guidelines for cancer pain relief.

Specific controversies in the clinical use of opioids in cancer pain

Although analgesic drug therapy is the mainstay of treatment, opioid use remains a controversial issue.[15] Controversies have arisen over their use in various types of pain, the specific choice of opioid drug, the use of sequential trials of opioids, routes of administration, the development of tolerance, economic factors influencing these controversies, and the concern that pain management is a form of euthanasia.

Role of opioids for treatment of nociceptive and neuropathic pain

Although previously well recognised, recent attention has focused on the observation that the pathophysiological mechanisms of pain influence analgesic responsiveness. Based on neuroanatomical and neurophysiological correlates, two types of pain, nociceptive (somatic and visceral) and neuropathic, occur in cancer patients. Each type results from activation and sensitisation of nociceptors and mechanoreceptors by compression, infiltration or disruption due to surgically-induced nerve injury, chemotherapy or radiation therapy. Cancer patients commonly have multiple sites and types of pain.[3–6] It has been suggested that neuropathic pain, which accounts for 10%–20% of difficult to manage pain problems, is 'opioid resistant' and that opioid drugs should not be used in this population.[35,36] Studies in cancer patients with both nociceptive and neuropathic pain, as well as controlled studies in non-malignant neuropathic pain, demonstrate the variable responsiveness of neuropathic pain to opioid analgesics.[37–42] The concept of a continuum of opioid responsiveness, rather than an all or none quantal phenomenon, has been clearly observed. Opioid responsiveness is defined as the degree of analgesia achieved during dose escalation to either intolerable side effects or adequate analgesia.[38] Patient characteristics, pain-related factors, as well as drug-selective effects, influence this variable responsiveness. A wide range of adjuvant analgesics, including the tricyclic antidepressants, anticonvulsants, corticosteroids, benzodiazepines, oral and parenteral local anaesthetics, etc. have been suggested to provide analgesia.[43] Controlled studies assessing the efficacy of opioids and the adjuvant analgesics in various cancer pain syndromes are critical to resolve the controversy and to provide scientifically based guidelines for analgesic drug therapy.

Choice of opioid drug to manage cancer pain

Morphine

The WHO Cancer Pain Guidelines designated morphine as the drug of choice in its Cancer Pain Relief Program. The choice was based on practical, not scientific, considerations. At the time of the decision in 1982, morphine was on the Essential Drug List of the WHO. It was thought to be widely available, familiar to physicians for acute pain management, had been demonstrated to be effective in hospices for the treatment of chronic cancer pain, and its clinical pharmacology was believed to be fully defined. These considerations were not totally correct. The introduction of the WHO Program rapidly demonstrated the limited availability of morphine worldwide for oral treatment of chronic cancer pain.[29] Moreover, the expanded use of morphine, combined with new formulations and new information about the analgesic activities of its metabolites, focused renewed attention on its clinical pharmacology, with recognition of morphine-6-glucuronide (M6G) as an active metabolite.[44–46] Animal studies demonstrate that M6G, but not morphine-3-glucuronide (the second major metabolite), binds to the opioid receptor and, compared to morphine, is twice as potent subcutaneously, 90 times as potent intracerebroventricularly, and 650 times as potent intrathecally.[47,48] Human studies have shown that M6G is analgesic in man and appears in the plasma and cerebrospinal fluid (CSF) of patients receiving morphine systemically.[49–53]

The half-life of morphine and M6G are 108 and 120 min respectively, with clearances of 132 and 1,093 ml/min respectively (unpublished data). This small clearance for M6G reflects its limited volume of distribution compared to morphine. Current studies demonstrate that the MG6 : morphine ratio (mean molar ratio = 1.2) is independent of morphine dose in patients with normal renal function. In renal dysfunction, M6G has an increased elimination half-life and decreased clearance, confirming a true delay in elimination of the compound, leading to an increase in the M6G : morphine ratio during chronic therapy.[53,54]

Adverse effects (nausea and respiratory depression) have been attributed to plasma concentrations of the metabolite, particularly in patients with renal failure.[45,55,56] In a more recent study, attempts to correlate M6G levels, M6G : morphine or M6G : M3G ratios to side effects, such as cognitive impairment or myoclonus, have not been possible.

Plasma levels of M6G predict CSF distribution.[52] Although the steady-state levels of M6G are always greater than those of morphine (approximately twice as much), the distribution of M6G in CSF averages only one-third to one-fifth that of morphine.[53] These data are consistent with the different physicochemical properties of the parent drug and its metabolite, and the observation that M6G is much more potent when introduced directly into the CSF of animals.[48] To date, there is no evidence of central nervous system (CNS) production of M6G after intrathecal morphine or of peripheral reconversion of M6G to morphine.

Various factors may influence the levels of both M6G and M3G, including route (increased M6G following oral administration), age (increased M3G

and M6G if > 70 years), male sex (decreased morphine and M6G plasma concentrations), concurrent use of tricyclic antidepressants (increased M3G), and use of ranitidine (increased morphine).[54,56,57]

Controlled-release oral morphine is currently available in a wide range of doses, from 15–200 mg for every 12 h administration. These preparations provide comparable analgesia to immediate-release forms, but offer increased convenience, improved compliance and a reduction in duration of pain. These quality of life issues have not been analysed fully in a cost–benefit analysis, and controversy remains regarding the cost of controlled-release compared to immediate-release morphine preparations. Although the oral, intramuscular, subcutaneous, and intravenous routes are the common methods of morphine administration, preparations are currently available for rectal, epidural, intrathecal and intraventricular administration.

Methadone

Another drug that has been proposed as a drug of choice for cancer pain management is methadone.[58] This proposal again stemmed from the wide availability of this agent. The WHO guidelines suggest that methadone represents a second-line drug in patients who have had prior exposure to opioids.[1] It is a relatively inexpensive oral analgesic preparation, but its name has negative connotations for cancer patients who view methadone as a drug used to treat addicts.

The bioavailability of methadone is higher than that of morphine – 85% vs 35% respectively. Its analgesic potency also differs, with a parenteral to oral ratio of 1 : 2 in contrast to 1 : 6 with morphine. Moreover, the plasma half-life of methadone is 17–24 h, with reports of up to 50 h in some cancer patients, but with a duration of analgesia of only 4–8 h.[59] Significant adverse effects have also been reported in cancer patients receiving methadone by various routes.[60]

The discrepancy between the analgesic duration and plasma half-life of methadone has made it a difficult drug to use because of the need for careful titration.[61] Investigators using an intravenous infusion technique to evaluate the clearance of methadone and its minimal effective analgesic concentration demonstrated that they could effectively titrate patients to adequate pain control. However, such methodologic expertise is not widely available.

Of particular interest, a number of case reports have highlighted the possible greater analgesic potency of methadone than the often quoted 1 : 1 equivalency with morphine. Rogers reported a 50-year old female with chronic cancer pain, poorly controlled on a 300 mg dose of parenteral morphine. Good pain control was achieved with methadone at an equivalent dose of 90 mg.[62] Galer *et al.* assessed the individual variability and response to different opioids and reported three patients who were switched from levorphanol and morphine to methadone because of inadequate pain control.[41] In all cases the amount of methadone required was far below the estimated equianalgesic dose.

Methadone can be administered by a variety of routes – subcutaneously, intravenously, rectally, epidurally and intrathecally. Several studies have demonstrated its efficacy by these routes of administration, but have also reported adverse effects, such as cutaneous hypersensitivity, by the subcutaneous route.[58] At the current time the controversies about its equianalgesic dose and the appropriate interval of administration remain important ones. Due to its long half-life, some authors have suggested its use on a 8–12 h basis, whereas others have demonstrated analgesic efficacy and safety in acute 3–4 h dosing intervals.[61] Therefore, the timing of methadone dosing remains controversial, in which issues of peak and trough effects have not been fully studied.

In summary, the most important controversial issue is the adverse effects which occur with methadone treatment. Future studies need to address the issues of its equianalgesic dose compared to other opioids, its appropriate interval for administration, and its place in the management of cancer pain. These factors should be considered before advocating its role as first-line rather than second-line treatment for cancer pain patients.

Oxycodone

Oxycodone is commonly used to manage cancer pain in both steps II and III of the WHO analgesic ladder. It is used most often in patients with moderate to severe pain. Due to its availability as 5 mg tablets, used either alone or in combination with acetaminophen or aspirin, it is more commonly used in step II of the analgesic ladder.

Recent studies have shed further light on the pharmacokinetics of oxycodone, and results from a series of patients with postoperative pain[63–65] have suggested that it may produce less sedation and fewer hallucinatory effects compared to morphine.

The metabolism of oxycodone to its active metabolite oxymorphone is dependent upon the P450 2CDA enzyme.[66] Certain drugs can interfere with its metabolism, and therefore may potentially interfere with its analgesic effectiveness in certain patient populations. Some studies have demonstrated that

free oxymorphone levels in plasma after the administration of oxycodone are negligible.[64] These preliminary studies suggest that oxycodone may have a more acceptable spectrum of side effects compared to the other currently used analgesic drugs. If this is true, these observations may lead to a broader use of oxycodone in chronic cancer pain management.[67] At the current time, slow-release oxycodone preparations are being investigated.

Hydromorphone

Hydromorphone, like oxycodone, is a morphine congener, and is five times more potent than morphine. Its bioavailability varies from 30%–40%, with a parenteral to oral ratio of 5 : 1.[68] Studies to date report that it produces excellent analgesia, with a shorter latency to effect and reduced incidence of side effects compared to morphine. It is available for oral, rectal, subcutaneous, intramuscular and intravenous administration and a concentrated 10 mg/cc parenteral dosing form is available for subcutaneous administration.[69] There is some evidence to suggest that hydromorphone may play an important role in the management of patients with cancer pain, specifically the elderly, because of its short half-life. More recent observations, however, suggest that it has a series of metabolites which may accumulate in patients with neural disease and produce CNS toxicity.[70] However, at the present time, the lack of direct studies comparing hydromorphone to morphine or oxycodone prevent anything other than empirical consideration to help support the choice of an analgesic regimen for cancer pain patients. Slow-release hydromorphone preparations are currently being tested.

Levorphanol

Levorphanol is a synthetic opioid analgesic, also a congener of morphine. It is used commonly as a second-line agent in patients with chronic cancer pain who cannot tolerate morphine because of inadequate analgesia and excessive side effects. Dose titration needs to be undertaken carefully, particularly in opioid-naïve patients, because although it produces analgesia for only 4–6 h, it has a half-life that varies from 12 to 17 h. In contrast to the other opioid drugs commonly used in cancer pain, which are predominantly μ agonists, levorphanol has a greater affinity for the delta receptor. This observation suggests that it may provide greater analgesia in patients tolerant to morphine or other μ agonist drugs.[71] Its parenteral to oral ratio is 1 : 2 and it is available in oral and parenteral forms for acute and chronic administration.[72,73] As with the other drugs, it represents an alternative analgesic, but comparative studies of its side effect spectrum have not been done.

Meperidine

There is good evidence to suggest that meperidine, a synthetic opioid with anticholinergic properties, should not be used chronically in the management of patients with cancer pain. Meperidine has a poor parenteral to oral ratio (1 : 4). It is available for the oral and intramuscular routes but repetitive intramuscular administration is associated with local tissue fibrosis and sterile abscess. Repetitive dosing of meperidine (> 250 mg/day) can lead to normeperidine accumulation – an active metabolite which can produce CNS hyperexcitability.[74] This hyperirritability is characterised by subtle mood effects, followed by tremors, multifocal myoclonus and occasionally seizures. It occurs commonly in patients with renal disease, yet can occur following repeated administration in patients with normal renal function. The factors associated with meperidine-induced CNS excitation include the plasma normeperidine level, plasma normeperidine : meperidine ratio, compromised renal function, duration of meperidine administration, and meperidine dose. Naloxone does not reverse meperidine-induced seizures and its use in meperidine toxicity is controversial; there have been some case reports that the use of naloxone has precipitated generalised seizures in individual patients. In rare instances, CNS toxicity characterised by hyperpyrexia, muscle rigidity, and seizures have been reported following the administration of a single dose of meperidine to patients receiving treatment with monoamine oxidase inhibitors.

Fentanyl

This opioid analgesic has been used effectively in cancer pain patients and the recent development of a novel transdermal patch has broadened its clinical usefulness.[75,76] The half-life of fentanyl ranges from 3 to 12 h. It is metabolised by the liver and N-dealkylated to norfentanyl and other inactive metabolites. Seventy-five per cent of the dose is excreted in the urine. Its relative potency compared to parenteral morphine varies from 1 to 20 in non-tolerant acute pain patients. In chronic cancer pain, relative potency comparisons have not been fully established. The uniqueness of this preparation, a different opioid analgesic administered by a novel route, facilitates the management of patients who are unable to take drugs by mouth by providing them with continuous opioid analgesia. Patches are currently available in 25 to 100 μg/h doses. Fentanyl can also be used intravenously and

epidurally. Oral transmucosal formulations have demonstrated effectiveness in breakthrough pain in cancer patients but are not available for clinical use. Direct comparisons of this drug to the other commonly used opioids remain to be undertaken.

This brief discussion of some of the commonly used opioid analgesics in cancer pain management reveals the lack of information regarding the wide variability in analgesia and the side effects experienced in the clinical setting. In a recent study by Cherny *et al.*, the course of cancer pain pharmacotherapy was evaluated in a longitudinal survey of strategies used by pain service physicians, and the clinical practices and rationale for opioid therapy applied by a specialised pain service were reviewed.[77] Of particular interest, 100 consecutive inpatients were evaluated prospectively. Eighty of the 100 patients underwent a total of 182 changes in route of administration or both drug type and route of administration prior to discharge or death. The major reasons for change were to improve the convenience of the treatment regimen while providing adequate pain relief (31.4%), diminish side effects while controlling pain (25%), reduce the invasiveness of therapy (19.3%), and simultaneously improve pain control and reduce opioid toxicity (17.7%). In these patients, when opioid toxicity was the main reason for change, physicians changed the opioid drug in 71% of the cases and the route in 29%. When convenience or invasiveness were targeted, the physicians changed the route in 61% of cases and the opioid in 39%. Of particular note, 44 patients required one or more changes of opioid, and 20 required two or more changes (range 2–6). At the time of discharge (n = 82), morphine was more commonly selected than hydromorphone or fentanyl (39% vs 23% vs 17%), and the routes of administration were oral (57%), transdermal (18%), intravenous (18%), subcutaneous (5%) and intraspinal (4%). Therapeutic changes were associated with an improvement in physician-recorded pain intensity and a lower prevalence of cognitive impairment, hallucinations, nausea and vomiting, and myoclonus among patients discharged from hospital. These data, demonstrating improved outcomes from multiple trials with opioid analgesics in cancer pain management, suggest the potential value of clinical protocols based on these patterns of care. Further studies are necessary to address the development of specific analgesic protocol guidelines that will take advantage of individualising opioid pharmacotherapy, while at the same time attempting to carefully assess the appropriate rationale for the choice and route of administration in this population of patients. Such studies may help to better define some of the controversies, with a critical goal of providing patients with adequate analgesia and minimal side effects. Thus, the controversy regarding the choice of drug is not a trivial one in clinical decision making.

Route of administration

A third controversy involves the choice of the route of administration. Although the oral route represents the simplest and most commonly used approach, the impetus for the development of novel routes of administration has come from the goal of maximising analgesia, minimising side effects, and providing convenient dosing schedules for patients who require parenteral drug administration. Survey data demonstrate that the majority of patients with progressive disease and pain will require at least two, and in at least 25% of cases, three routes of drug administration.[78] What remains controversial is the logic of both patient selection and timing, and implementation of these alternative routes.[79] Risk–benefit and cost–benefit analyses are beginning to address these issues. Various factors, including the availability of oral opioids, the expertise of the treating physician (internist, oncologist, anaesthesiologist), the nature of the pain, and the financial resources of the patient have confounded the true assessment of the 'best approach'. The key concept in considering alternative routes is the effectiveness and appropriateness of an intervention. The crucial factor regarding appropriateness of novel routes is the associated adverse effects. The golden rule for comparison of adverse effects of two analgesic interventions is that the comparison should be made at the same level of analgesic effect. Such a comparison of adverse effects at equianalgesic doses has not been done in the earlier work with spinal administration of different opioids, as well as for some of the newer more novel routes, such as transdermal administration.[80]

The development of tolerance

The chronic use of opioids in cancer pain patients has provided a unique natural experiment to study tolerance development to opioid analgesia and side effects in a medical setting. Previous studies of tolerance in humans have focused on the neuroadaptation of mood and autonomic effects in addict populations and have not addressed tolerance to analgesia in acute and chronic pain patients. From a series of studies assessing the patterns of opioid drug use in cancer pain patients, it is evident that the role

of tolerance development varies enormously among patients and is influenced by numerous environmental, behavioural, pharmacological, pain and patient-related factors.[81–87] Several patterns of opioid use have been described:

1. Rapidly escalating doses of opioids associated with escalating pain and/or psychological distress;
2. Stable doses of opioids for long periods of time (weeks to months) with effective analgesia with no need for dose escalation or reduction;
3. Reduction in or discontinuation of opioid drugs with effective analgesia from anticancer therapies or anaesthetic or neurosurgical approaches.

These patterns have been described in various patient populations, including hospice programmes, home care and supportive care programmes, hospital settings and outpatient cancer pain clinics.[81–87] These clinical observations are in marked contrast to suggestions in the pharmacological textbooks and information from the medical literature suggesting that such patients would continue to escalate their requirement for opioid analgesics on the basis of tolerance alone. This is in concert with an extensive animal literature demonstrating the wide variability of tolerance development on the basis of behavioural, environmental and pharmacological factors. In the cancer patient with pain, in contrast to the animal paradigm, the pain stimulus is changing. Discerning the relative contributions of a change in pain state from that due directly to tolerance is confounding. From the clinical data, the overriding factor in dose escalation is progression of disease. Other factors which play a role include the patient's prior opioid exposure, the endpoint measured for opioid effect, and the type of pain. In a series of studies, Houde *et al.* demonstrated that pharmacological tolerance occurs in cancer patients and is characterised by a shift in the dose–response curve to the right.[88] These studies also demonstrated that cross-tolerance is incomplete and that dose escalation often requires a doubling of the dose because of the log dose–effect relationship.

There is no limit to tolerance. These aspects of tolerance have clinical implications. It is now well recognised that a wide range of opioid analgesics are used in cancer pain management, although numerous studies have demonstrated that the majority of patients may be managed in a dose range of 30–7,000 milliequivalents of morphine per 24 h.[78] There are, however, a series of patients who may require very large doses for adequate pain control and who require rapid dose escalation and doubling or tripling of their initial dose regimen. These high doses are often misinterpreted as inappropriate by inexperienced physicians who undermedicate patients because of their reliance on only standard doses rather than using the concept of opioid responsiveness as their endpoint.

Tolerance develops at different rates to the respiratory depressant, analgesic, emetic, pupillary constrictor, and slowly, if at all, to the constipatory effects of the opioids. This differential rate of development explains the safe use of large doses of opioids in cancer patients without compromising their respiratory status.

The fact that cross-tolerance is incomplete is reflected in part by the individual variability in response to opioid analgesics.[41] This concept is the basis for switching to alternative opioids. The mechanism of this phenomenon is that tolerance develops independently at each receptor subtype. For example, D-Ala2-D-Leu5-enkephalin, a delta selective opioid, produced significant analgesia following intrathecal administration in cancer patients tolerant to morphine.[84]

The mechanisms underlying tolerance are complex and include actions at the level of the receptor and effector systems as well as activation of antagonist systems and/or down-regulation of facilitary ones. Currently, at the molecular level, it is postulated that a functional decoupling of opioid receptors from G proteins may be the underlying explanation. Recent studies have demonstrated the role of NMDA receptors in the development of morphine tolerance.[89–91] MK801, an NMDA antagonist, not only reverses morphine tolerance, but prevents its development without reducing morphine analgesia. This dissociation of tolerance from pain inhibition suggests that different mechanisms account for these phenomena and, in part, help to explain why patients may continue to obtain analgesia even when tolerant to opioids. These studies also suggest that both non-opioid and opioid mechanisms are involved in tolerance development. Of particular clinical relevance is the fact that combinations of excitatory amino acid antagonists with opioid analgesics might facilitate the clinical usefulness of opioid drugs by limiting the development of tolerance.

At the current time there are multiple ways to provide analgesia to patients who are tolerant to opioid analgesics, such as the use of adjuvant analgesics, the use of oral, intravenous and epidural local anaesthetics, and the use of specific anaesthetic and neurosurgical approaches to interrupt pain pathways. The potential for drug combinations with excitatory amino acid antagonists offers important future approaches.

Confusion between the relationship of pain management to patient requests for physician-assisted suicide and euthanasia

In one survey, 69% of cancer patients reported that they would consider committing suicide if their pain was not treated adequately.[16] Uncontrolled pain is an important contributing factor in cancer patients assessed to be at risk for suicide.[92] Persistent pain interferes with patients' quality of life and this, in turn, influences a patient's choice about suicide or physician-assisted suicide.[93] Pain relief in oncology cannot be isolated from the overwhelming need to manage the multitude of physical as well as psychological symptoms that occur in this population of patients. It is the responsibility of the treating physician to manage pain in this patient population. The intent, goal, and conditions in which physicians and patients interact are directed toward the management of symptoms and should not be construed as euthanasia.

Aggressive treatment of pain with increasing doses of opioids to provide analgesia should not be referred to as 'hastening death'. Its intent and rationale are to manage uncontrollable or unendurable symptoms. The prevalence of and treatment for physical symptoms of pain, dyspnoea, delirium and psychological distress in the dying patient have become controversial issues. Their expert management, using opioids and sedative drugs, is misconstrued as active euthanasia. Poor understanding of the concept of tolerance, the lack of pharmacological data on drugs to provide terminal sedation, and the ambivalence on the part of patients, families and physicians because of ethical concerns, have thwarted the provision of appropriate medical care for this population of patients. At the present time, there are few highly trained physicians in cancer pain management, psycho-oncology or palliative care whose main interest is to place a high priority on pain management, symptom control and psychological support for patients with advanced disease. Any debate that focuses on the needs of the dying patient and their options for care at the end of life must recognise that the education and training of physicians, as well as patients and families, is the first step in providing patients with access to care that will facilitate their choice of options.[94–97]

References

1. World Health Organization. *Cancer Pain Relief.* Geneva: World Health Organization 1986.
2. World Health Organization. *Cancer Pain Relief and Palliative Care.* Geneva: World Health Organization 1990.
3. Bonica JJ. Cancer pain. In: Bonica JJ, ed. *The Management of Pain.* Philadelphia: Lea & Febiger 1990, 400–434.
4. Foley KM. The treatment of cancer pain. *N Engl J Med* 1985; **313**: 84–95.
5. Elliott K, Foley KM. Neurologic pain syndromes in patients with cancer. In: Portenoy RK, ed. *Neurologic Clinics. Pain: Mechanisms and Syndromes,* Vol. 7. Philadelphia: WB Saunders 1989, 333–360.
6. Portenoy RK. Cancer pain: pathophysiology and syndromes. *Lancet* 1992; **339**: 1026–1031.
7. Portenoy RK, Hagen N. Breakthrough pain: definition and management. *Oncology* 1989; **3** (Suppl): 25–29.
8. Ahles TA, Blanchard EB, Ruckdeschel JC. The multidimensional nature of cancer related pain. *Pain* 1983; **17** (3): 277–289.
9. Breitbart WS, Holland J. Psychiatric aspects of cancer pain. In: Foley KM, Bonica JJ, Ventafridda V, eds. *Advances in Pain Research and Therapy. Proceedings of the Second International Congress on Cancer Pain,* Vol. 16. New York: Raven Press 1990, 73–88.
10. Fishman B, Pasternak S, Wallenstein SL, *et al.* The Memorial Pain Assessment Card: a valid instrument for the assessment of cancer pain. *Cancer* 1986; **60**: 1151–1157.
11. Daut RL, Cleeland CS, Flanery RC. The development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain* 1983; **17**: 197–210.
12. Graham C, Bond SS, Gertrovitch MM, Cook MR. Use of the McGill Pain Questionnaire in the management of cancer pain – replicability and consistency. *Pain* 1980; **8**: 377–387.
13. Ventafridda V, Tamburini M, Caraceni A, DeConno F, Naldi F. A validation study of the WHO method for cancer pain relief. *Cancer* 1987; **59**: 850–856.
14. Stjernsward J, Teoh N. Current status of Global Cancer Control Program of the World Health Organization. *J Pain Symptom Man* 1993; **8**: 335–448.
15. Foley KM. Controversies in cancer pain – medical perspective. *Cancer* 1989; **63**: 2257–2266.
16. Cleeland CS. Pain control: public and physician attitudes. In: Hill CS, Fields WS, eds. *Advances in Pain Research and Therapy,* Vol. 11. New York: Raven Press 1989, 81–89.
17. Weissman DE, Dahl JL. Attitudes about cancer pain: a survey of Wisconsin's first year medical students. *J Pain Symptom Man* 1990; **5**: 345–349.
18. Van Roenn JH, Cleeland CS, Gonin R, Hatfield A, Pandya KJ. Physicians' attitudes toward cancer pain management survey: results of the Eastern Cooperative Oncology Group Survey. *Ann Int Med* 1993; **119**: 121–126.
19. Ferrell B, McGuire DB, Donovan MI. Knowledge and beliefs regarding pain in a sample of nursing faculty. *J Prof Nurs* 1993; **9** (2): 79–88.
20. Joranson DE, Cleeland CS, Weissman DE, Gilson AM. Opioids in chronic cancer and non cancer pain: a survey of state medical board members. *Fed Bull Med J Licensure Discipline* 1992; **79** (4): 15–49.
21. Peteet J, Tay V, Cohen G, Macintyre J. Pain characteristics and treatment in an outpatient cancer population. *Cancer* 1986; **57**: 1259–1265.
22. Grossman SA, Sheidler VR, Swedeen K, Mucenski J, Pianladosi S. Correlation of patient and care giver ratings of cancer pain. *J Pain Symptom Man* 1991; **6**: 53–57.
23. Landico AV. The Philippines: status of cancer pain and palliative care. *J Pain Symptom Man* 1993; **8**: 429–431.

24. McDonald N. Initiatives in China, WHO News. *Pall Med* 1992; **6**: 6–8.
25. Takeda F. Japan: status of cancer pain and palliative care. *J Pain Symptom Man* 1993; **8**: 425–427.
26. Wenk R. Argentina: status of cancer pain and palliative care. *J Pain Symptom Man* 1993; **8**: 385–388.
27. Brasseur L, Larue F. France: status of cancer pain and palliative care. *J Pain Symptom Man* 1993; **8**: 412–416.
28. Zenz M. Germany: status of cancer pain and palliative care. *J Pain Symptom Man* 1993; **8**: 416–419.
29. Joranson DE. Availability of opioids for cancer pain: recent trends, assessment of system barriers, new World Health Organization guidelines and the risk of diversions. *J Pain Symptom Man* 1993; **8**: 353–360.
30. Report of the International Narcotics Control Board for 1989. Demands for and supply of opiates for medical and scientific needs. New York: United Nations 1989.
31. Committee on Quality Assurance Standards. American Pain Society quality assurance standards for relief of acute pain and cancer pain. In: Bond MR, Charlton JE, Woolf CJ, eds. *Proceedings of the VIth World Congress on Pain.* Amsterdam: Elsevier 1991, 185–189.
32. Adhoc Committee on Cancer Pain of the American Society of Clinical Neurology. Cancer pain assessment and treatment guidelines. *J Clin Oncol* 1992; **10**: 1976–1982.
33. Spross JA, McGuire DB, Schmitt RM. Oncology Nursing Society position paper on cancer pain. *Oncol Nurse Forum* 1990; **17**: 595–614, 751–760, 943–955.
34. Dahl JL. State Cancer Pain Initiative. *J Pain Symptom Man* 1993; **8**: 372–375.
35. Arner S, Meyerson BA. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. *Pain* 1988; **33**: 11–23.
36. Hanks GW, Justins DM. Cancer pain management. *Lancet* 1992; **339**: 1031–1035.
37. Cherny NI, Thaler HT, Friedlander-Klar H, Lapin J, Portenoy RK. Opioid responsiveness of neuropathic cancer pain: combined analysis of single dose analgesic trials. *Neurology* 1994 (in press).
38. Portenoy RK, Foley KM, Inturrisi CE. The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusions. *Pain* 1990; **43**: 273–286.
39. Foley KM. The role of opioid analgesics in neuropathic pain. In: Besson JM, Guilbaud G, eds. *Lesions of the Primary Afferent Fibers as a Tool for the Study of Clinical Pain.* Amsterdam: Elsevier Science Publishers 1991, 277–292.
40. Rowbotham MC, Fields HL. Post-herpetic neuralgia: the relation of pain complaint, sensory disturbance, and skin temperature. *Pain* 1989; **39**: 129–144.
41. Galer BS, Coyle N, Pasternak GW, Portenoy RK. Individual variability in the response to different opioids: report of five cases. *Pain* 1992; **49**: 87–91.
42. Portenoy RK. Issues in the management of neuropathic pain. In: Basbaum A, Besson J-M, eds. *Towards a New Pharmacotherapy of Pain.* New York: John Wiley & Sons 1991, 393–416.
43. Portenoy RK. Adjuvant analgesics. In: Doyle D, Hanks GW, MacDonald RN, eds. *Oxford Textbook of Palliative Medicine.* Oxford: Oxford University Press 1993, 187–203.
44. Sawe J. Morphine and its 3- and 6-glucuronides in plasma and urine during chronic oral administration in cancer patients. In: Foley KM, Inturrisi CE, eds. *Advances in Pain Research and Therapy*, Vol. 8. New York: Raven Press 1986, 45–55.
45. Osborne RJ, Joel SP, Slevin ML. Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *Br Med J* 1986; **292**: 1548–1549.
46. Osborne RJ, Joel SP, Trew D, Slevin ML. The analgesic activity of mM6G. *Lancet* 1988; **i**: 828.
47. Osborne RJ, Joel SP, Trew D, Slevin ML. Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite M6G. *Clin Pharmacol Ther* 1990; **47**: 12–19.
48. Paul D, Standifer KM, Inturrisi CE, Pasternak GW. Pharmacological characterization of M6G, a very potent morphine metabolite. *J Pharmacol Exp Ther* 1989; **251**: 477–483.
49. Poulain P, Moran-Ribon A, Hanks GW, Hoskin PJ, Aherne GW, Chapman DP. CSF concentrations of M6G after oral administration of morphine. *Pain* 1990; **5** (Suppl): S194.
50. Hand CW, Blunnie WP, Claffey LP, McShane AJ, McQuay HJ, Moore RA. Potential analgesic contribution from morphine-6-glucuronide in CSF. *Lancet* 1987; **ii**: 1207–1208.
51. Portenoy RK, Thaler HT, Inturrisi CE, Friedlander-Klar H, Foley KM. The metabolite, M6G, contributes to the analgesia produced by morphine infusion in pain patients with normal renal function. *Clin Pharm Ther* 1992; **51**: 422–431.
52. Portenoy RK, Khan E, Layman M, *et al.* Chronic morphine therapy for cancer pain: plasma and cerebrospinal fluid morphine and morphine-6-glucuronide concentrations. *Neurology* 1991; **41**: 1457–1461.
53. Portenoy RK, Foley KM, Stulman J, *et al.* Plasma morphine and M6G during chronic morphine therapy for cancer pain: plasma profiles, steady-state concentrations and the consequences of renal failure. *Pain* 1991; **47**: 13–19.
54. Petreson GM, Randall CTC, Paterson J. Plasma levels of morphine and morphine glucuronides in the treatment of cancer pain: relationship to renal function and route of administration. *Eur J Clin Pharmacol* 1990; **38**: 121–124.
55. Hagen N, Foley KM, Cebrone DJ, Portenoy RK, Inturrisi CE. Chronic nausea and M6G. *J Pain Symptom Man* 1991; **6**: 125–128.
56. McQuay HJ, Caroll D, Faura CC, Gavaghan DJ, Hand CW, Moore RA. Oral morphine in cancer pain: influences on morphine and metabolite concentration. *Clin Pharmacol Ther* 1990; **48**: 236–244.
57. Breda M, Bianchi M, Ripamonti C, Zecca E, Ventafridda V, Panerai AE. Plasma morphine and M6G patterns in cancer patients after oral, subcutaneous, sublingual, and rectal short-term administration. *Int J Clin Pharmacol Res* 1991; **11** (2): 93–97.
58. Fainsinger R, Schoellrs T, Bruera E. Methadone in the management of cancer pain: a review. *Pain* 1993; **52**: 137–147.
59. Inturrisi CE, Colburn WA, Kaiko RF, Houde RW, Foley KM. Pharmacokinetics and pharmacodynamics of methadone in chronic pain patients. *Clin Pharm Ther* 1987; **41**: 392–401.
60. Ettinger DS, Vitale PJ, Trump DL. Important clinical pharmacological considerations in the use of methadone in cancer patients. *Cancer Treat Rep* 1979; **63**: 457–459.
61. Grochow L, Sheidler V, Grossman S, *et al.* Does intravenous methadone provide long lasting analgesia than intravenous morphine? A randomized double-blind study. *Pain* 1989; **38** (2): 151–157.

62. Rogers AG. The use of methadone in opioid tolerant patients. *J Pain Symptom Man* 1988; **3**: 45.
63. Kalso E, Poyhia R, Onnela P, Lanko K, Tigersledt I, Tammusto T. Intravenous morphine and oxycodone for pain after abdominal surgery. *Acta Anesthesiol Scand* 1991; **35**: 642–646.
64. Poyhia R, Olkkola KT, Seppala T, Kalso E. The pharmacokinetics of oxycodone after intravenous injection in adults. *Br J Clin Pharmacol* 1991; **32**: 516–518.
65. Poyhia R, Seppala T, Olkkola KT, Kalso E. The pharmacokinetics and metabolism of oxycodone after intramuscular and oral administration to healthy subjects. *Br J Clin Pharmacol* 1992; **33**: 617–621.
66. Dayer P, Desmeules J, Leeman T, Stribeni R. Bioactivation of the narcotic drug codeine in human liver immediate by the polymorphic monooxygenase catalyzing debrisoquin four hydroxylation (cytochrome P450 DB1-BUF). *Biochem Biophys Res Commun* 1988; **152**: 411–416.
67. Rogers A. The under utilization of oxycodone. *J Pain Symptom Man* 1991; **6**: 452.
68. Houde RW. Clinical analgesic studies of hydromorphone. In: Foley KM, Inturrisi CE, eds. *Advances in Pain Research and Therapy. Opioid Analgesics in the Management of Clinical Pain*, Vol. 8. New York: Raven Press 1986, 129–136.
69. Moulin DE, Kreeft JH, Murray-Parsons N, Bouquillon AL. Comparison of continuous subcutaneous and intravenous hydromorphone infusions for management of cancer pain. *Lancet* 1991; **337**: 465–468.
70. Babul N, Darke AC. Putative role of hydromorphone metabolites in myoclonus. *Pain* 1992; **51**: 260–261.
71. Moulin DE, Ling GSF, Pasternak GW. Unidirectional analgesic cross-tolerance between morphine and levorphanol in the rat. *Pain* 1988; **33**: 233–239.
72. Dixon R, Crews T, Inturrisi CE, Foley KM. Levorphanol: pharmacokinetics and steady state plasma concentrations in patients with pain. *Res Commun Chem Pathol Pharmacol* 1983; **41**: 3–17.
73. Wallenstein SL, Rogers AG, Kaiko RF, Houde RW. Clinical analgesic studies of levorphanol in acute and chronic cancer pain: assay methodology. In: Foley KM, Inturrisi CE, eds. *Advances in Pain Research and Therapy.* New York: Raven Press 1986, 211–215.
74. Kaiko RF, Foley KM, Grabinski PY, *et al.* Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol* 1985; **131**: 180–185.
75. Foley KM. Opioid analgesics in clinical pain management. In: Herz A, Akil H, Simon EJ, eds. *Handbook of Experimental Pharmacology*, Vol. 104-II. New York: Springer Verlag 1993, 697–762.
76. Portenoy RK, Southam MA, Gupta SK, *et al.* Transdermal fentanyl for cancer pain: repeated dose pharmacokinetics. *Anesthesiology* 1993; **78**: 36–43.
77. Cherny NI, Chang V, Ingham J, *et al.* The course of cancer pain pharmacotherapy: a longitudinal survey of strategies used by pain service physicians. *J Clin Oncol* 1994 (submitted).
78. Coyle N, Adelhardt J, Foley KM, Portenoy RK. Character of terminal illness in the advanced cancer patient: pain and other symptoms in the last 4 weeks of life. *J Pain Symptom Man* 1990; **5**: 83–93.
79. McQuay HJ. The logic of alternative routes. *J Pain Symptom Man* 1991; **5**: 73–136.
80. Mather LE. Novel methods of analgesic drug delivery. In: Bond MR, Charlton JEO, Woolf CJ, eds. *Proceedings of the VIth World Congress on Pain.* Amsterdam: Elsevier 1990, 159–174.
81. Twycross RG. Clinical experience with diamorphine in advanced malignant disease. *Int J Clin Pharm Ther Toxicol* 1974; **9**: 184–198.
82. Portenoy RK, Moulin DE, Rogers AG, Inturrisi CE, Foley KM. Continuous intravenous infusion of opioids in cancer pain: review of 46 cases and guidelines for use. *Cancer Treat Rep* 1986; **7**: 575–581.
83. Kanner RM, Foley KM. Patterns of narcotic drug use in a cancer pain clinic. Research developments in drug and alcohol use. *Ann N Y Acad Sci* 1981; **362**: 161–172.
84. Moulin DE, Max MB, Kaiko RF, *et al.* The analgesic efficacy of intrathecal D-Ala2-D-Leu5-enkephalin in cancer patients with chronic pain. *Pain* 1985; **23**: 213–221.
85. Gourlay GK, Cherry DA, Cousins MJ. A comparative study of the efficacy and pharmacokinetics of oral methadone and morphine in the treatment of severe pain in patients with cancer. *Pain* 1986; **25**: 297–312.
86. Foley KM. Clinical tolerance to opioids. In: Basbaum AI, Besson JM, eds. *Toward a New Pharmacotherapy of Pain.* Chichester: John Wiley & Sons 1991, 181–204.
87. Foley KM. Changing concepts of tolerance to opioids. What the cancer patient has taught us. In: Chapman CR, Foley KM, eds. *Current and Emerging Issues in Cancer Pain: Research and Practice.* New York: Raven Press 1993, 331–349.
88. Houde RW, Wallenstein SL, Beaver WT. Evaluation of analgesics in patients with cancer pain. In: Lasagna L, ed. *Clinical Pharmacology. International Encyclopedia of Pharmacology and Therapeutics*, Vol. 1. Oxford: Pergamon 1966, 59–97.
89. Trujillo KA, Akil H. Opiate tolerance and dependence: recent findings and synthesis. *New Biol* 1991; **3**: 915–923.
90. Trujillo KA, Akil H. MK801 prevents the development of opioid tolerance. *Science* 1991; **251**: 85–88.
91. Tiseo PJ, Chen J, Pasternak GW, Inturrisi CE. Modulation of morphine tolerance by the competitive N-Methyl-d-Aspartate receptor antagonist LY274614: assessment of opioid receptor changes. *J Pharmacol Exp Ther* 1994; **268** (1): 195–201.
92. Breitbart W. Cancer pain and suicide. In: Foley KM, Ventafridda V, Bonica J, eds. *Advances in Pain Research and Therapy, Second International Congress on Cancer Pain,* Vol. 16. New York: Raven Press 1990, 399–412.
93. Foley KM. The relationship of pain and symptom management to patient requests for physician-assisted suicide. *J Pain Symptom Man* 1991; **6**: 289–297.
94. Ventafridda V, Ripamonti C, DeConno F, Tamburini M. Symptom prevalence and control during cancer patients' last days of life. *J Palliat Care* 1990; **6**: 7–11.
95. Roy DJ. Need they sleep before they die? *J Palliat Care* 1990; **6**: 3–4.
96. Mount B. A final crescendo of pain? *J Palliat Care* 1990; **6**: 5–6.
97. Foley KM. Pain, physician-assisted suicide and euthanasia. *Am Pain Soc J* 1994 (in press).