In recent years, a growing interest in palliative care and in routes of administration other than oral have prompted more aggressive measures to improve the efficacy of analgesic interventions in patients with difficult pain conditions. This review provides an overview of the use of intravenous morphine to control pain in patients with cancer. Intravenous morphine has been increasingly used in different clinical situations—including breakthrough pain, poor pain control with escalating doses of oral opioids, retitrating patients with acute pain, treating patients with long-standing poor pain control and unpredictable needs, and optimising opioid therapy to prevent incident pain associated with bone metastases. Although intravenous administration requires supervision, it has considerable advantages, since direct administration into the circulation provides a rapid and predictable effect that is independent of absorption problems. IV morphine is advantageous in specific clinical situations and should be part of the armamentarium of all physicians treating pain in patients with cancer.

**Intravenous morphine for management of cancer pain**

Sebastiano Mercadante

In recent years, a growing interest in palliative care and in routes of administration other than oral have prompted more aggressive measures to improve the efficacy of analgesic interventions in patients with difficult pain conditions. This review provides an overview of the use of intravenous morphine to control pain in patients with cancer. Intravenous morphine has been increasingly used in different clinical situations—including breakthrough pain, poor pain control with escalating doses of oral opioids, retitrating patients with acute pain, treating patients with long-standing poor pain control and unpredictable needs, and optimising opioid therapy to prevent incident pain associated with bone metastases. Although intravenous administration requires supervision, it has considerable advantages, since direct administration into the circulation provides a rapid and predictable effect that is independent of absorption problems. IV morphine is advantageous in specific clinical situations and should be part of the armamentarium of all physicians treating pain in patients with cancer.

**Introduction**

Opioids are the cornerstone of cancer-pain management. Although oral administration of opioids is generally preferable, a parenteral route is often advisable in many circumstances during the progression of cancer. Intramuscular injections are inconvenient, so the choice is between an intravenous (IV) and subcutaneous route. The advantages of subcutaneous administration are that a smaller needle is required, the site of injection is not crucial, and close supervision is not necessary. However, an IV route may be advantageous in patients who already have an indwelling IV line, those with generalised oedema, patients who develop erythema, soreness, or abscesses, those with coagulative disorders, or patients with poor peripheral circulation. But the main advantage of IV route is pharmacokinetic; direct administration into the circulation provides a rapid and predictable effect, independent of absorption problems (panel).

Patients with poorly controlled pain with rapid escalation due to unstable disease may require aggressive pain treatment. IV morphine is mainly indicated for uncontrolled pain, and occasionally for vomiting, difficulties in swallowing, and respiratory distress. Brief hospital admission for the rapid titration of IV morphine is feasible, resulting in rapid, effective pain control for most patients.

**Panel: Intravenous morphine for management of cancer pain**

**Advantages**
- Total drug availability and predictable effects
- Short onset for opioid titration and breakthrough pain
- Flexible modalities: boluses, continuous infusion, patient-controlled analgesia
- Less initial metabolite formation
- Unlimited volumes
- Best for patients with oral tract precluded or poor gastrointestinal absorption

**Disadvantages**
- Need to maintain the intravenous route
- Increased cost
- More complex management for caregivers
- Close supervision needed
- Availability of sites (unless permanent access)

IV morphine can be titrated until symptom control is achieved, and then switched to oral or (less commonly) subcutaneous morphine before the patient is discharged. Most patients in acute units have an IV line to provide hydration and to facilitate therapeutic interventions, such as dose titration, administration of rescue doses, and treatment of emergencies. In some intensive-care settings, patients have an existing IV line where a port-cath was previously inserted, and to avoid the variability in drug availability characteristic of other routes of administration.

Physicians are often reluctant to use intensive procedures because of the possible risks and poor familiarity with the IV route. Moreover, there are no guidelines to help physicians in specific clinical situations in which IV morphine is a preferred intervention, from a pharmacokinetics point of view, for achieving rapid pain control. In recent years, a growing interest in palliative care and in routes of administration other than the traditional oral route have prompted more aggressive measures to improve the efficacy of analgesic interventions in patients with difficult pain scenarios. Despite its invasiveness, IV morphine may be useful in some clinical situations in a secondary-care setting, although there is little detailed information available regarding the optimum and flexible use. The aim of this review is to provide an overview of the use of IV morphine for management of cancer pain in a secondary-care setting.

**Breakthrough pain**

Patients with chronic cancer pain often report wide fluctuations in pain intensity. Breakthrough pain is a transitory flare of pain in an otherwise stable pain pattern in patients treated with opioids. Three categories of breakthrough pain have been identified: spontaneous pain with no evident precipitating event; incident pain, with a precipitating cause or event, such as activity; and end-of-dose failure, associated with a reduction in blood levels of analgesic medications provided at regular intervals. Although end-of-dose failure does not exactly fit the definition of breakthrough pain, it is a clinical scenario that requires rescue medications while adjusting the basal analgesic regimen. Another way to classify
breakthrough pain could be by the presence of volitional or precipitant factors, which have been identified in more than half of patients.7
Supplemental doses of opioids given in addition to the continuous analgesic medication are the main treatment used to manage breakthrough pain. Dosing recommendations are based on anecdotal experience only, and suggest a percentage of the patient’s total daily opioid dose as an effective dose for breakthrough pain. The European Association for Palliative Care (EAPC) recommends one-sixth (17%) of the daily dose as a starting point for morphine.1 However, oral opioids like morphine do not overlap the fast onset of most types of breakthrough pain. New delivery systems are more effective and faster than oral morphine. Trials of oral transmucosal fentanyl citrate (OTFC) suggest a lack of relationship between the effective OTFC dose and fixed-schedule opioid regimen, regardless of the opioid used,4 although this finding contradicts anecdotal assumptions from practical experience. Similar findings were reported in a study of buccal tablets of fentanyl.5 However, these trials were not designed to specifically address the relationship between continuous analgesia and breakthrough fentanyl dose (they aimed to show the superiority of OTFC over placebo, oral morphine, or usual oral opioids, or to assess the safety and efficacy of ascending doses of OTFC), so a better critical analysis may help to interpret the data. Some patients had dry mouth, mucositis, partial local metabolism, or used OTFC incorrectly, which may limit absorption through the buccal mucosa. Moreover, participants in many of the OTFC trials did not have adequately controlled background pain.7,10 Data pooled from these trials showed a relationship between the breakthrough-pain and around-the-clock opioid dose, despite large interindividual variability in dose requirements.21
IV morphine provides analgesia fast enough to overlap breakthrough pain. In a preliminary study of 48 cancer patients treated with oral morphine, who reported an acceptable basal analgesia and episodic pains, IV morphine was given at one-fifth of the oral daily dose, converted into an IV dose using an equianalgesic ratio of 1 to 3 (IV to oral). In 162 of 171 breakthrough episodes of severe intensity, a reduction of pain intensity of more than 33% was observed within a mean of 17 min, and in 136 episodes there was a decrease of more than 50% in pain intensity after IV morphine. Adverse effects were uncommon and were related to the basal dose, and consequently the IV-morphine dose. These findings suggest that IV morphine at 20% of the basal oral dose is safe and effective in most patients experiencing pain exacerbation.22 This was confirmed in a subsequent study; IV morphine administered for the management of 945 episodes of breakthrough pain, in doses proportional to the basal opioid regimen, was effective and did not result in life-threatening adverse effects, even in older patients or those given large doses. A decrease in pain of more than 33% was observed in 61–2% of breakthrough events, and a decrease of more than 50% was observed in 24–5% of events. The mean pain intensity decreased from 7.2 to 2.7, on a numerical scale from 0 to 10 after 15 min.10
In doses proportional to the scheduled daily dose of opioids, both IV morphine and OTFC were safe and effective, but IV morphine had a shorter onset than OTFC, which is considered the drug with the fastest onset.9 Therefore, in patients with an IV line in situ, or in specific intensive settings, IV morphine offers a rapid, effective, and safe way to manage breakthrough pain. A fixed dose of about one-fifth of the oral daily dose was feasible, probably because the availability was not modifiable, compared with OTFC. Intranasal opioid kinetics are similar to IV opioids and may be an alternative fast and effective analgesia for breakthrough pain.15–17
Opioid titration
Oral opioids or continuous infusion of morphine without titration will have a slow onset to effective analgesia. Given parenterally, opioids can produce fast and effective plasma concentrations compared with oral or transdermal routes, therefore an analgesic effect can be achieved in a shorter time (figure). The basic principle of effective and safe dosing is dose titration to the onset of analgesia, followed by maintenance infusions based on the titrated dose, or (when possible) by a conversion to oral route.18–20
IV morphine has been used for rapid opioid titration in various clinical situations, including poor pain control with escalating doses of oral opioids, to titrate patients with acute pain, in patients with long-standing poor pain control and unpredictable needs, and to optimise opioid therapy for preventing incident pain associated with bone metastases.
In a comparative study of IV and oral morphine, oral morphine was titrated with 5–10 mg every 4 h (according to EAPC recommendations) and the same dose was provided as needed, whereas the IV group received boluses of 1–5 mg every 10 min. Subsequently, after finding the effective dose by titration, the total daily dose was converted to oral morphine.20 As expected, satisfactory pain relief at 1 h was achieved by 31 patients in the IV group, compared with 31 patients in the oral group, while no differences in
pain intensity and adverse effects were found 24 h later. IV dosing has a short lag-time between injection and effect (initial 3 min, peak 30 min) compared with oral dosing (initial 15–30 min, peak 45–60 min). This advantage is evident in the first hours after administration, when more IV boluses were allowed, rather than 24 h after, when repeated dosing of oral morphine in both groups provides similar effects.

Patient-controlled analgesia relies on individual titration of the analgesic dose and can provide rapid pain relief for a wide range of requirements. Patients with severe cancer pain and insufficient analgesia with step-two drugs were titrated with morphine delivered intravenously by a patient-controlled analgesia pump; the pump was set with a bolus dose of 1 mg, lock-out time of 5 min, and hourly maximum dose of 12 mg.\(^5\) Substantial pain relief was achieved within 24 h with mean doses of 32 mg per day of IV morphine, which were then converted to a mean of 139 mg oral morphine. In 15 of 28 patients who were assessed with this aim, the mean time to achieve sufficient analgesia was 6 h. Adverse effects were mild and were mostly present before the start of the study.

Enting and colleagues\(^{22}\) prospectively assessed the efficacy of the start of parenteral opioids in patients who failed with oral or transdermal opioids. An infusion of various opioids was started at 50–70% of the equianalgesic dose (a median of 80 mg per day [5–640 mg] of IV morphine equivalents) and rescue doses were offered as needed.\(^{22}\) Doses were titrated up to 135 mg of IV morphine equivalents, obtaining good pain control in 52 of 100 of patients within 48 h. Compared with the oral or transdermal opioids, no major changes in adverse effects were noted. Follow-up data are difficult to assess, because of the variability in the second evaluation time (1–27 days), when an improvement was seen in 71 of 100 patients.

In patients with breakthrough pain on movement caused by bone metastases, a titration with IV morphine was effective in preventing or reducing the intensity of pain and allowing better mobility, with doses higher than those effective to control basal pain.\(^{21}\) As expected, a minority of patients (8 of 25 patients) developed adverse effects of moderate to severe intensity, requiring symptomatic treatment or a decrease in opioid dose. Data from this study suggest that the intensity of incident pain may be reduced by increasing the opioid dose above the dose effective for controlling pain at rest. This approach was based on animal models of bone metastases showing hypersensibility to some innocuous stimuli, such as movement, requiring pre-emptive higher doses of basal opioid medication to reduce the increased pain input.\(^{21}\)

**Rapid titration and parenteral routes**

Severe or crescendo pain requires aggressive dosing that is not feasible with oral dosing or standard methods of opioid titration. This type of pain can result from rapid loss of efficacy of a regular treatment, or because of changes in the causes of pain. Additionally, patients may present with uncontrolled pain for weeks or months because of undertreatment and consequent psychological distress. Most patients with cancer have moderate pain intensities and require simple and soft titration schedules, but acute severe pain requires rapid application of powerful analgesic strategies and aggressive treatment. Optimum opioid dose is unpredictable, so a traditional titration can take several days and will result in unwanted suffering for the patient.

From a pharmacokinetic point of view, the IV route provides the best total drug availability and rapid effective plasma concentrations for timely intervention. Elsner and colleagues\(^{24}\) found that IV titration is more rapid than oral and subcutaneous titration. Boluses of IV and subcutaneous morphine were given every 5 min and 30 min, respectively. The doses were proportional to the previous daily opioid consumption—2 mg for patients receiving less than 120 mg of oral morphine and 10 mg for those receiving more than 120 mg. The investigators likely assumed that, after 30 min, IV morphine allowed in five boluses of 2 mg would be equivalent to the dose administered subcutaneously (10 mg), reaching a peak at the same time as that expected for the subcutaneous route. Titration stopped after patients in both groups achieved similar pain intensity, within a mean of 53 min for the IV group and 77 min for the subcutaneous group. The proportion of patients with 30% and 50% pain relief was higher in the IV group, despite this group having higher initial scores of pain intensity. In the IV group, a ratio of 1:6.6 for the IV titration dose to the daily requirement of oral opioids was found four days after titration, whereas this ratio was only 1:3.7 in the subcutaneous group. This calculation was based on data for a small number of patients, so no conclusion can be drawn. As expected, pain relief and adverse effects 24 h and longer after titration were comparable between groups. As reported in other studies, some symptoms, such as nausea, improved rather than worsened after pain control was achieved.

Titration with IV morphine can provide fast and effective pain relief, and can also provide information about the amount of opioids necessary for a subsequent treatment.\(^4\) In these circumstances, it may be advisable to expedite opioid titration using the fastest methods. In a pilot study of patients receiving high doses of oral morphine equivalents, 10–20 mg of IV morphine was administered over 15 min and the dose doubled every half an hour until pain was controlled.\(^{20}\) Satisfactory relief of excruciating pain was achieved within a mean of 90 min, then maintenance analgesia was initiated according to the number of morphine boluses administered.

Controversies exist regarding the modalities of rapid dose titration. A large single bolus of morphine without titration to pain relief can lead to alternating pain and toxic effects and does not allow an estimation of patients’ needs; however, titration with small doses at long intervals may limit the advantage of a rapid titration. Familiarity with opioid pharmacokinetics and pharmacodynamics, and clinical experience, are helpful in selecting the most...
Conversion between IV and oral route

The subsequent opioid doses to be given after successful titration is a matter of controversy. The hourly dose is suggested to be one-third or one-fourth of the parenteral loading dose, given by continuous infusion with a rescue dose being equivalent to the hourly dose. 26–29 This small dose often results in frequent demands. When converting oral morphine to IV or subcutaneous administration, a relative potency ratio of 1:2 to 1:3 has been recommended, whereas a ratio of 1:6 is indicated for acute administration. These ratios are based on clinical experience. 1 The increase in relative potency with chronic oral morphine has been attributed to the extensive first-pass metabolism of oral morphine and the analgesic activities of morphine-6-glucuronide (M6G). Large variability within and between individuals, both in the pharmacodynamics and pharmacokinetics of morphine, can complicate the calculation of conversion ratios when changing the route of administration. Moreover, disease-related conditions, such as liver and kidney dysfunction or states of dehydration, can compromise the linearity of the dose–concentration relationships of morphine and its metabolites.

A 2003 study 30 supported the commonly used oral-to-IV relative potency ratio of 1:2 to 1:3 in patients with cancer pain receiving chronic morphine treatment. The oral-to-IV relative ratio of the regression coefficients was 1:2·9. Plasma concentrations of morphine and M6G in patients treated intravenously were about twice as high as those in the oral treatment group. Although a summation of effect is not appropriate because the contribution of M6G to morphine analgesia is unclear, the calculated equi-concentration ratios of the morphine dose range from 1:1·8 (morphine and M6G) to 1:2·9 (morphine alone), and are consistent with the oral ratios that have been used in clinical practice. A substantial first pass glucuronidation was confirmed by glucuronide–morphine ratios, which were about three times higher in patients treated orally than in those treated intravenously. No correlations were found between morphine-related variables and blood urea nitrogen, creatinine values, or hepatic biochemical markers. In a retrospective study of patients switched to the oral route after continuous IV morphine infusion, the steady doses for stable analgesia showed little variation from the initial IV-to-oral conversion ratio of 1:3, with no differences when analysed by age and gender. 1 Nelson and colleagues 31 calculated oral morphine dose by multiplying the daily parenteral dose by three; an approach based on clinical observations in the postoperative setting that the loading dose predicts analgesic needs. The dose administered as a bolus was assumed to last about 4 h and was calculated for 24 h. For example, an effective bolus of 10 mg corresponded to an expected daily dose of 60 mg (10 mg every 4 h). The dose was converted to oral morphine using a ratio of 1:3 for patients with a low test dose, and a more prudent ratio of 1:2 in patients requiring higher doses of IV morphine. The oral morphine dose of 180 mg per day (or 120 mg per day) was divided into two or three administrations of a sustained-release formulation, maintaining the same IV dose for breakthrough episodes. This approach was safe; no decreases in dose were required, only further small dose increments until the achievement of dose stabilisation, which typically happened within 2–3 days. Patients were discharged within a mean of 4–5 days, with a mean dose of oral morphine of 131 mg per day and acceptable pain control. 1 Thus, the total amount of morphine required during IV titration can be a basis to determine an adequate dose of an oral sustained-release formulation to facilitate discharge.

Some clinicians add the opioid doses taken before rapid titration to the maintenance infusion. 24 This test dose, however, provides the individualised correct dose, regardless of the previous analgesic regimen. 27
In conclusion, a conversion ratio between IV route and oral route of 1:2-5 seems to be feasible in most patients with cancer pain.

Comparison with the subcutaneous route
The advantage of a subcutaneous route is the simplicity of use, which allows administration of parenteral morphine or other opioids in settings with low-level facilities, such as hospices, nursing homes, or home care. Simple devices have been used for single-bolus injections, with results similar to those achieved with continuous administration. Other than the movement involved in breathing.

In a small study, an IV-to-subcutaneous-oral conversion ratio of 1:2 was started by continuous infusion with a simple drip. Both IV and subcutaneous routes provided similar analgesic effects, although investigators judged the IV route to be more potent. In a randomised clinical trial, subcutaneous morphine titration required more time and higher doses than IV titration in patients with exacerbation of cancer pain. Pain control was achieved in the two groups, within a mean of 53 and 77 min, respectively. In the IV group there was better pain control despite the initial higher scores of pain intensity. 24 h later, pain relief and adverse effects were comparable.

Risk of respiratory depression with parenteral opioids
Respiratory depression with an increase in arterial carbon dioxide and a decrease in respiratory rate is still a feared adverse effect of the therapeutic use of morphine and other opioids, particularly in opioid-naive patients. Comorbidities, including pulmonary metastases, pleural effusions, chronic obstructive lung disease, and pulmonary embolism, may complicate or potentiate opioid-induced respiratory depression. Studies done at steady state and in opioid-naive patients undergoing symptomatic therapy for dyspnoea with oral morphine did not show significant respiratory changes. Patients who are given IV morphine for emergency pain situations could be at higher risk of respiratory depression. In non-oxygen-dependent patients, parental titration of opioids by continuous infusion, with increases of equivalent doses of oral morphine from a mean of 73 mg at baseline to 169 mg at completion of titration, did not significantly change end-tidal carbon dioxide when pain control was achieved, in a median time of 3 days. No patient had clinically significant respiratory depression necessitating opioid discontinuation or dose reduction. No life-threatening adverse effects were recorded in patients receiving IV morphine for breakthrough pain, even in older patients or when high doses were administered. Respiratory depression never occurred, and no emergency calls were needed. These findings confirm that, in patients receiving opioids, administering consistent doses of morphine with rapid modalities has a low risk, if careful titration is done by skilled professionals in an adequate environment. This risk can be explained by the protective effect offered by opioid tolerance in patients who chronically receive relevant opioid doses for the management of cancer pain. Moreover, pain is a natural antagonist to opioid respiratory depression. Although in some cases, pain relief may allow better ventilation by reducing the pain associated with the movement involved in breathing.

Potential interactions of morphine
Interactions of morphine with antineoplastic agents have never been described, apart from opioids sharing CYP3A4 or CYP2D6 metabolism. Insufficient effectiveness of serotonin-antagonists has been reported in patients with cisplatin-induced emesis who were receiving morphine, possibly due to the reinforcement of emetic mechanisms of the two drugs.

Conclusion
The use of IV morphine has advantages in specific clinical situations and should be part of the armamentarium of physicians who treat patients with cancer pain. Other than providing obvious benefits for patients with life-threatening conditions, IV morphine may have other advantages. Although no study has assessed the cost-effectiveness of IV morphine, it is likely that an oral titration would require many days or even weeks to reach...
an effective dose in patients with relevant needs, while prolonging suffering for patients with high levels of pain intensity. Escalation regimens with dose increments of 30–50% every 24–48 h are commonly suggested, and the effects of each increment should be judged after the steady-state level is reached, that is, 4–5 half-lives later. This approach results in an increase in the cost of hospital stay. The mean time for hospital discharge after dose titration with IV morphine was 4–6 days, decreasing the cost for hospital stay and allowing bed availability for other patients. The economic aspect of the use of IV morphine is a worthwhile topic for further exploration.

Conflicts of interest
The author declared no conflicts of interest.

References