Original Article

Safety and Effectiveness of Intravenous Morphine for Episodic (Breakthrough) Pain Using a Fixed Ratio with the Oral Daily Morphine Dose

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Abstract

Breakthrough pain is normally severe in intensity and has a rapid onset. The availability of supplemental doses of opioids (rescue medication) in addition to the continuous analgesic medication is the main treatment suggested to manage these pain flares. The intravenous (IV) route may provide analgesia fast enough, but has never been assessed in clinical studies. The aim of this open-label study was to verify the safety and effectiveness of an IV dose equal to one-fifth the calculated equianalgesic total daily dose in advanced cancer patients with episodic pain. A consecutive sample of 48 cancer patients treated with oral morphine, who reported an acceptable basal analgesia and reported episodic pains, were selected for the study. The intravenous dose of morphine was one-fifth of the oral daily dose, converted into an IV dose using an equianalgesic ratio of 1/3 (IV/oral). Written orders were given and intravenous morphine (IV-M) was administered by nurses. For each episode, pain intensity and opioid-related symptoms were recorded at the start (T0), after achieving maximum pain relief (T1), and one hour after (T2). In five patients, blood samples were taken at the time intervals described for measuring plasma concentrations of morphine and related glucuronated metabolites. One hundred seventy-one breakthrough pains were recorded during admission. In 162 episodes, a reduction of pain intensity of more than 33% was obtained within a mean of 17.7 minutes, from a mean intensity of 7.9 (on a 0–10 numeric scale) to 3. One hundred thirty-six episodes had more than a 50% pain intensity decrease after the IV-M within a mean of 16.6 minutes, from a pain intensity of 7.9 to 2.6. No differences in age, sex, pain mechanism, and time of events were found. There was a trend but no statistically significant differences between the groups receiving different basal doses and time to reach the maximum effect. Twenty episodes in ten patients required an additional dose within 2 hours. Adverse effects were uncommon and were significantly related to the basal dose, and as a consequence, with the

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IV-M dose. Morphine concentration significantly increased at the time of pain intensity reduction, and then decreased. These observations suggest that IV-M at a dose equivalent to 20% of the basal oral dosage is safe and effective in the majority of patients experiencing pain exacerbation. This treatment is inexpensive and can be used at little risk to patients. J Pain Symptom Manage 2004;27:352–359. © *2004 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Intravenous morphine, breakthrough pain, cancer pain

Introduction

Patients with chronic cancer pain often report wide fluctuations in pain intensity. In the cancer population, breakthrough pain is a transitory flare of pain superimposed on an otherwise stable pain pattern in patients treated with opioids.[1] The definition of breakthrough pain varies among different researchers and covers widely different aspects. As large differences in the diagnosis of breakthrough pain by clinicians from different countries have been described,[2,3] it has recently been proposed that the term *episodic* or *transient pain*, which is easier to translate in the majority of languages (including English, French, German, Italian, and Spanish) be used.

Regardless of the definition, there are limited options for pharmacological treatment of fluctuations in pain intensity through the day for patients chronically treated with opioids.[4] The presence of breakthrough pain has been considered as a negative prognostic factor,[5,6] and interferes with the quality of life of these patients.[7]

Breakthrough pain is normally severe in intensity and has a rapid onset. It may or may not reflect an end-of-dose failure during dose titration.[4] The availability of supplemental doses of opioids (rescue medication) in addition to the continuous analgesic medication is the main treatment suggested to manage these pain flares, both in patients undergoing opioid titration and those with other patterns, such as movement-related pain. However, despite the growing interest in breakthrough or episodic pain during the last ten years, no prospective study has examined the safety and effectiveness of using standard extra doses of morphine, except as a control drug for studies of oral transmucosal fentanyl citrate (OTFC). In a randomized controlled trial with OTFC, only about 30% of patients receiving oral morphine had more than a 33% change in pain intensity score over 15 minutes.[8]

To control this kind of pain, the effect of any treatment should be rapid and without risks. Drugs and routes of administration with a fast onset should be chosen to meet the characteristics of a pain flare, specifically high pain intensity and a short duration. Oral administration of morphine yields a time-action profile that may not be optimal, as it may take more than 30 minutes to take effect and peak pharmacological effect may occur only after 40–60 minutes. This could explain the frequent failure of oral morphine. A short onset of effect is commonly obtainable only with parenteral or transmucosal administration of opioid analgesics.

Given the widespread use of rescue dosing, the lack of systematic clinical investigation of breakthrough pain and its therapies with older drugs, such as morphine, is remarkable. The intravenous (IV) route provides analgesia fast enough, as it allows an immediate and total availability of morphine, and makes rapid morphine titration possible. Because of these characteristics, IV morphine fits the temporal pattern of breakthrough pain.[9] In the controlled studies of OTFC, the only study published until now, no relationship with the basal doses of morphine or transdermal fentanyl was found.[8,10–12] The reasons for this observation have not been clearly explained. The aim of this open-label study was to verify the safety and effectiveness of a fixed dose proportional to the daily dose, 1:5, given by the IV route in

advanced cancer patients presenting with episodic pain.

Methods

The study sample included a consecutive sample of 48 cancer patients, who were admitted to a pain relief and palliative care unit, were treated with oral morphine and reported acceptable basal analgesia, and presented with episodic pain. All patients gave written consent for all the analgesic procedures, which were routine activities. According to department policy, an IV line was established for emergency treatment of symptoms. Patients were encouraged to call when their pain became severe (more than 7 on a 0–10 numerical pain scale, see below) and IV morphine (IV-M) was administered in about 5 minutes as a bolus. The IV-M dose was one-fifth of the oral daily dose, converted to the IV dose using an equianalgesic ratio of 1/3 (IV/oral).[13] For example, a daily oral morphine dose of 90 mg corresponds to an IV dose of 30 mg (1/3 ratio), and this yields a rescue dose of 6 mg (1/5 of the total daily dose). The IV-M dose was modified according to changes in the daily oral morphine dosage. Written orders were given and IV-M was administered by nurses. Patients were instructed to consider their daily maximum pain relief as the pain intensity before the episode of pain occurred.

For each episode, the time of onset (increase in pain intensity to a level that was unacceptable) was labeled T0. The time of a maximum pain relief, that is, the time of maximum reduction in pain, corresponding to a status similar to that experienced before the flare, was designated T1. One hour after this time was T2. At T0, T1, and T2, the following parameters were recorded: pain intensity, using a numerical scale from 0–10, and opioid-related symptoms, using a scale from 0–3 (absent, slight, moderate, severe). Data were collected by nurses trained in symptom measurement as part of their daily activity. The hours of the day during which the episodes occurred were recorded. Daily doses of oral morphine and basal pain intensity also were recorded.

Nineteen patients gave consent for blood sample analysis. However, it was possible to draw blood samples at the time intervals described in only five patients. Plasma concentrations of morphine and related glucuronated metabolites were measured by a high-performance liquid chromatography (HPLC) method after solid phase extraction (SPE). Briefly, a Millipore-Waters apparatus consisting of a model 590 pump equipped with a U6K injector, a solvent select valve, and a model LC 75 Perkin-Elmer ultraviolet detector was employed. The system was connected to a D-2000 Chromato-Integrator (Merck-Hitachi). A Symmetry C18-5 μm, 250 mm length and 4.6 mm i.d. column from Waters was operated at room temperature. The mobile phase was 5:95 CH_3CN: $Na_2HPO_4 \cdot 12H_2O$ 10 mM adjusted at pH 3.5 with H_3PO_4. The flow-rate was 1.2 mL/min and the column effluent was monitored at 214 nm. Plasma samples (0.5 mL), combined with nalorphine hydrobromide (200 ng) as the internal standard and 0.5 mL of NH_4HCO_3 10 mM (pH = 9), were extracted by solid phase extraction carried out on disposable columns (Isolute SPE C2 100 mg columns) primed with 2 mL of methanol and 2 mL of NH_4HCO_3 10 mM (pH = 9). After washing (2 mL) with the same bicarbonate buffer, columns were eluted with two fractions of methanol (0.5 mL). Eluate was evaporated to dryness under nitrogen flow and reconstituted with 100 μL of mobile phase; afterwards, 50 μL were injected into the chromatographic system. The detection limits for morphine, morphine-3-glucuronide and morphine-6-glucuronide were 5 ng/mL.

Statistical Analysis

Frequency analysis was performed using chi-square tests. The paired Wilcoxon signed-rank test and paired samples Student's *t*-test were used to compare the scores or the means of non-parametric and parametric variables, respectively, at the different time intervals. A one-way analysis of variance (ANOVA) and Kruskal-Wallis statistic test were used to compare the different parametric or non-parametric variables. All *P* values were two-sided and *P* values less than 0.05 were considered statistically significant.

Results

Patients had their basal pain under control (mean 3.1, 95% CI 2.7–3.6). Forty-eight patients

Table 1
Patient Characteristics

Number of patients	48
Age	62.2 (95% CI 58–65)
Sex (M/F)	23/25
Basal morphine dose	199 mg (95% CI 167–231)
Number of events	171 (3.5 events per patient, range 1–17; 1.6 events a day, range 1–7)
Primary tumor	
Gastrointestinal	13
Lung	11
Urogenital	7
Breast	6
Other	11
Pain mechanism	
Somatic	25
Visceral	9
Somatic-neuropathic	8
Neuropathic	3
Visceral-neuropathic	1
Somatic-visceral-neuropathic	2

had at least one episode of pain flare during their hospital admission (the mean admission period was 4.1 days, range 2–7). Patient characteristics are described in Table 1. One hundred seventy-one breakthrough pains were recorded during admission. Most patients presented two or more events during their hospital stay, for a mean of 3.5 events per patient, with 1.6 events per day on average. Fifteen, six, twelve, four, three, two and one patients had one, two, three, four, five, six, and seven episodes, respectively, during their admission. Nineteen, fourteen, eight, two, four, and one patients had pain episodes in one, two, three, four, five, and seven days, respectively.

Changes in pain intensity and time to reach an adequate pain intensity are presented in Table 2. In 162 episodes, a reduction of pain intensity of more than 33% was obtained within a mean of 17.7 minutes (95% CI 16–19), from a mean intensity of 7.9 (95% CI 7.7–8.1) to 3 (95% CI 2.7–3.2). One hundred thirty-six episodes had more than a 50% pain intensity decrease after IV-M within a mean of 16.6 minutes (95% CI 15–18), from a pain intensity of 7.9 (95% CI 7.7–8.1) to 2.6 (95% CI 2.4–2.9). No differences in age, sex, pain mechanism, and time of events were found.

Time to Reach the Maximum Reduction in Pain

Patients were divided according to the time needed to reach their target pain intensity (within 15 minutes, between 15 and 30 minutes, and more than 30 minutes, respectively). Sixty-seven episodes were effectively controlled within 15 minutes, with a mean of 9.7 minutes (95% CI 9.4–10) and a mean percentage pain intensity reduction of 70% (95% CI 65–75). The mean basal dose for this group was 171 mg (95% CI 139–204). Ninety-six episodes were effectively controlled between 15 and 30 minutes, with a mean of 22.3 minutes (95% CI 20.9–23.6) and a mean percentage pain intensity reduction of 54% (95% CI 51–57). The basal dose in this group was 209 mg (IC 95% 163–255). Eight episodes were controlled 30 minutes after IV-M (mean 47.5 minutes, 95% CI 43.0–51.9), with a percentage pain intensity reduction of 35% (95% CI 18–52). The basal dose was 346 mg (95% CI 103–796). Thus, there was a trend in the relationship between basal doses and time to reach the maximum effect, but no statistical difference ($P = 0.130$).

Patients requiring a further IV-M dose within two hours were considered unresponsive. The dose chosen was unable to appropriately cover the possible tail of the episode. Twenty episodes in ten patients required a further dose within 2 hours. This group of patients was receiving basal doses of 261 mg, and reported a high level of pain intensity (9 ± 1.1 SD). With the dose of IV-M, they had temporary relief to a mean pain

Table 2
Changes in Pain Intensity and Time to Reach Maximum Pain Relief

	Pain Intensity				
	T0	T1	Time	*P*	Change %
All patients	7.9 (7.7–8.1)	3.2 (2.9–3.4)	18.5 (17–20)	< 0.0005	−60 (56–62)
Morphine basal dose <60 mg	7.1 (6.5–7.6)	3.0 (2.7–3.2)	22.0 (17–27)	0.002	−57 (54–60)
Morphine basal dose 60 to <120 mg	7.9 (7.6–8.2)	3.4 (3.1–3.7)	18.1 (15–20)	< 0.0005	−56 (53–60)
Morphine basal dose 120–240 mg	8.2 (7.8–8.6)	2.9 (2.4–3.4)	15.8 (13–18)	< 0.0005	−64 (58–69)
Morphine basal dose >240 mg	7.9 (7.6–8.3)	3 (2.4–3.6)	19.6 (16–22)	< 0.0005	−61 (54–69)

Data are expressed as mean (95% CI).

intensity of 3.7 (± 1.4 SD), which was achieved in a mean of 16 minutes (±9.1 SD) and represented a percentage reduction of 58% (±14 SD). No relationship between basal doses and occurrence of new episodes occurring within the two hours after IV-M were found.

Basal Opioid Regimen and Effects of IV-M

Patients were also divided according to their basal doses (<60 mg = group 1, 60 to <120 mg = group 2, 120–240 mg = group 3, and >240 mg = group 4). Twelve, sixty-four, forty-one, and forty-eight events were recorded in the four groups, respectively. Pain intensity was significantly reduced after IV-M at all the doses used. However, patients receiving the lowest daily doses of morphine (less than 60 mg) showed a less intense analgesic effect, but less nausea/vomiting, with IV-M compared to patients receiving higher doses ($P < 0.020$, and $P < 0.017$, respectively). No differences were found for drowsiness and confusion. As mentioned above, the different doses did not influence the need for further rescue doses within two hours.

Adverse Effects

Acute adverse effects occurring after IV-M were those commonly observed with opioid therapy. A minority of episodes were followed by adverse effects at an intensity of 2 or 3 on the scale used. Patients developed moderate-severe nausea/vomiting during 12 episodes, drowsiness during 25 episodes, and confusion during one episode. The occurrence of such adverse effects was not significantly related to the basal dose and, as a consequence, with the IV-M dose.

Plasma Concentration Changes

In five patients, it was possible to obtain sequential blood samples for analysis at the time of the event (T0), at the maximum pain relief (T1), and one hour after. Data are presented in Table 3. Significant changes were observed with morphine only. Morphine concentration increased at the time of pain intensity reduction, and then decreased.

Discussion

Current dosing recommendations for breakthrough pain generally suggest that the effective dose of breakthrough pain medication must be a percentage of a patient's total daily opioid dose.[13,14] One recommendation is that the rescue dose should correspond to the dose given every four hours, about 16% of the total daily dose, administered as often as required.[13] These recommendations, which are based entirely on anecdotal experience, favor the selection of a short-acting opioid at a dose proportionate to the total daily dose. However, no prospective study has ever confirmed the efficacy and safety of this approach.

During recent years, continuous venous access has become more frequently used in cancer patients, particularly those having a subcutaneous port or an intravenous central catheter. Even in the palliative care unit setting, this practice is growing.[15,16] IV-M recently has been reported to be effective in rapid titration, and the same dose was considered useful for pain episodes during the titration phase. Such an approach was effective and safe, and was employed similarly in this study. Specifically, a 20% dose of the basal regimen, administered by IV injection, was evaluated according to previous pilot experience.[9]

In the current study, IV-M was safe and effective for almost all episodes of pain flares. IV-M provided rapid analgesic effects in patients with a severe pain flare, whose basal pain was responsive to the opioid regimen. The effect was maintained for a time that would include the duration of most pain episodes. Only twenty episodes in ten patients required a further IV-M dose within two hours. This group of patients would probably be considered as patients requiring higher doses of morphine for a possibly

Table 3
Plasma changes of Morphine and Its Metabolites at Times Determined in Five Patients

	T0	T1	T2
Morphine (ng/mL)	39 (5–130)	121 (33–375)[a]	73 (5–258)[b]
M3G (ng/mL)	590 (125–1134)	777 (251–2117)	868 (139–2744)
M6G (ng/mL)	35 (5–59)	62 (5–130)	70 (16–176)

Data are expressed as mean (range).
[a] $P < 0.05$ (T0 vs. T1).
[b] $P < 0.05$ (T1 vs. T2).

better control of basal pain. Increasing basal doses of morphine, despite adequate pain control, challenging the therapeutic window in terms of risks of adverse effects, should be explored in further studies with appropriate design. Alternatively, the need for a second dose also may be due to a second, unrelated episode.

The percentage of the daily morphine dose to use as IV-M was chosen according to local policy deriving from previous experience in several patients. To evaluate the effectiveness, a 50% cut-off point for the percentage of maximum pain relief has been considered a simple clinical endpoint that is easily understood by professionals and patients. Recent studies show that a value of 33% should be clinically important to measure the real benefit for the patients.[17] This level was achieved in about 17 minutes in about 94% of patients receiving IV-M. OTFC produced a >33% change in about 42% of patients within 15 minutes after administration when compared to oral morphine (about 32%).[8] In the current study, despite selection criteria that were stricter and included episodes with a high pain intensity (more than 7/10 on a numerical scale), most patients obtained a clinically important benefit. The outcome was neither influenced by the pain mechanism or timing of the event.

Curiously, new drugs and devices have been studied, rather than morphine, for the treatment of breakthrough pain. In recent studies, OTFC has been shown to be an effective treatment for breakthrough pain episodes. OTFC produced a faster onset of relief and a greater degree of pain relief than the usual medication[9] at 15, 30, and 60 min.[11]

The OTFC trials contradicted the anecdotal assumption that the effective dose for breakthrough pain is a percentage of the daily dose; there was no relationship between the effective OTFC dose and fixed schedule opioid regimen, regardless of the opioid used.[9–11] Although patients on higher doses of original medication generally required larger doses of OTFC, no reliable equivalency ratio was observed, perhaps because rapid absorption changes the pharmacodynamics of treatment. However, in successfully treated patients, the regular rescue dose was a moderate predictor of the effective OTFC dose.[9] Of interest, 66% of the episodes treated with placebo did not require an additional dose of medication. This can be explained by the normal course of episodes, which are often relatively short-lived and improve spontaneously, or a true placebo response.[10] Alternatively, such episodes resolved because of a low pain intensity of the flare (see below).

Concerns arise from these studies.[8–11] Eligible patients were defined as having their basal pain no more than moderate, but presenting on average four pain episodes per day. Doses equivalent to about 20 mg of oral morphine were effective in patients taking a mean dose of 100 μg per hour of fentanyl, decreasing pain scores from a mean intensity of 6 to 2.8 by 60 minutes. Therefore, the pain intensity was presumably not severe in some patients, or the pain spontaneously subsided. This is confirmed by the large number of episodes that resolved with placebo. A mean intensity of 4.7–4.8 of basal pain (with some patients at the highest extremes), cannot be universally considered as a well-controlled pain, especially if matched with a pain intensity of breakthrough events of 6.8 on average (with some patients at the lowest extremes). Moreover, almost no adverse effects were reported with usual breakthrough medication in comparison with OTFC, the doses of which were titrated in patients apparently responsive to their usual medication. These data mean that probably most patients were undertreated either with basal or "as needed" medication. Moreover, the type of randomization may not have produced well-matched groups, as pointed out by authors. For example, patients with high intensity baseline pain were receiving higher doses of usual medication (28 mg of morphine equivalents) and received higher doses of OTFC (400 μg). Irrespective of the total daily doses, 200 or 400 μg of OTFC were effective in most patients, the higher dose producing a significantly greater mean pain intensity difference and pain relief than the lower dose. However, it could be also argued that patients receiving 400 μg would have responded equally to lower doses. On the other hand, using different units of OTFC for each episode may be time-consuming, exceeding the spontaneous duration for breakthrough pain, which can spontaneously subside (as evidenced by placebo patients).

OTFC doses should not exceed 20% of patients' around-the-clock medication.[9] Doses of

200 μg of OTFC (about 20% of a fentanyl daily dose of 960 μg, obtained by using a patch of 40 μg/h of transdermal fentanyl) are not equivalent to 20 mg of oral morphine. In a postoperative study, it has been calculated that OTFC: intravenous morphine ratio is 1:10, that is, about 1:30 with oral morphine.[18] Using the previous example, according to these calculations, a dose of 200 μg of OTFC fentanyl should correspond to 2 mg of IV-M, that is, 6 mg of oral morphine. This calculated morphine dose may be relatively more potent in patients taking fentanyl than those taking morphine because of the occurrence of asymmetric tolerance between different opioids.

This complexity suggests that the finding of no proportionality between the effective rescue dose and the basal dose observed in the OTFC studies should not be generalized. More research is needed.

No other studies using morphine as rescue drug have been reported so far. The only study dealing with oral morphine showed that the mean ratio of the rescue:total daily dose was 0.15 (range 4–50%).[8] Prior to the rescue dose the mean pain intensity was approximately 6, and 60 minutes after the selected oral dose of morphine equivalents, the mean pain intensity was 2.5, with a progressive decline of about 30% for each subsequent period of 15 minutes.[8] This information is expected considering that the peak pharmacological effect with morphine may occur only after 40–60 minutes.[19] The maximum pain relief was achieved 60 minutes after, and this could coincide with a spontaneous recovery of the event.

IV-M was safe, as only a low intensity of opioid-induced adverse effects was observed, even when administering large intravenous doses. As expected, the most frequent symptom occurring after IV-M was drowsiness. This may reflect the predisposition of opioid-tolerant patients. The frequency of significantly important adverse effects was limited and accepted by most patients. Of interest, the occurrence of such adverse effects was not related to the dose of IV-M. Intravenous morphine has been found to improve the balance between analgesia and adverse effects,[20] was quite tolerated during acute titration,[9] and resulted as a versatile method of continuous administration.[15] In previous trials of OTFC, the incidence of adverse effects was reported and suggested a dose-response relationship. However, intensity of these adverse effects was never reported. Of interest, 10 patients (about 14%) withdrew from the study due to adverse effects.[11]

Due to the lack of blinding, the results of this study should be interpreted with caution. Probably some episodes would have spontaneously disappeared. Although the use of placebo probably would have improved the meaning of such a practice, a double-blind approach was not taken into consideration due to ethical reasons in such patients. However, the high intensity of pain during episodes, which was a selection criterion, should have limited bias. Nurses were involved and recorded the data, recommending patients to consider as maximum pain relief when the pain intensity would be similar to the basal pain, considered to be controlled. To collect such acute data in real time, it was preferred to use very simple tools, avoiding other instruments, such as pain relief intensity, which would have confused the monitoring and introduced further burden for patients.

In conclusion, IV-M at a dose equivalent to 20% of the basal oral dosage is safe and effective in the majority of patients experiencing pain exacerbation. The dose chosen also prevented the occurrence of other episodes within two hours in almost patients. This treatment is inexpensive and can be used without relevant risks for patients. Should data regarding the risks be confirmed in a larger number of patients, this treatment could be feasible even at home.

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