Original Article

Intravenous Morphine for Breakthrough (Episodic-) Pain in an Acute Palliative Care Unit: A Confirmatory Study

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Abstract
The aim of this prospective cohort study was to confirm the safety of intravenous morphine (IV-M) used in doses proportional to the basal opioid regimen for the management of breakthrough pain and to record the nurse compliance on regularly recording data regarding breakthrough pain treated by IV-M. Over a one-year period, 99 patients received IV-M for breakthrough pain during 116 admissions. The IV-M dose was 1/5 of the oral daily dose, converted using an equianalgesic ratio of 1/3 (IV/oral). For each episode, nurses were instructed to routinely collect changes in pain intensity and emerging problems when pain became severe (T0), and to reassess the patient 15 minutes after IV-M injection (T15). Nurses were unaware of the aim of the study and just followed department policy. In total, 945 breakthrough events treated by IV-M were recorded and the mean number of events per patient per admission was eight (95% confidence interval (CI) 6.9–9.5). The mean dose of IV-M was 12 mg (95% CI 9–14 mg). In the 469 events (49.6%) with a complete assessment, a decrease in pain of more than 33% and 50% was observed in 287 (61.2%) and 115 (24.5%) breakthrough events, respectively. The mean pain intensity decreased from 7.2 (T0) to 2.7 (T15). In eight episodes, no changes in pain intensity were observed and a further dose of IV-M was given. The remaining patients did not require further interventions. No clinical events requiring medical intervention were recorded. In this confirmatory study, IV-M was administered for the management of breakthrough pain in doses proportional to the basal opioid regimen to all patients, including older patients and those requiring relatively large doses. This did not result in life-threatening adverse effects in a large number of patients and was effective in most cases. The role of nurses is of paramount importance in monitoring and collecting data and gathering information for audit purposes on the unit. J Pain Symptom Manage 2008;35:307–313. © *2008 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Cancer pain, breakthrough-episodic pain, intravenous morphine

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Introduction

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] Breakthrough pain is normally severe in intensity and has a rapid onset. The presence of breakthrough pain has been considered as a negative prognostic factor for satisfactory pain control and can impair the quality of life of these patients.[2] The causes of breakthrough pain are diverse and may be related to end-of-dose failure during dose titration, the presence of unknown causes, or incident pain.[3]

The availability of supplemental doses of opioids (rescue medication) in addition to the continuous analgesic medication is the usual treatment for breakthrough pain. In some clinical settings, patients have an intravenous (IV) line, not only to provide hydration, but also to facilitate several therapeutic interventions, such as dose titration, administration of rescue doses, and treatment of emergencies. In some cases, an IV line is already present because an indwelling venous access device had previously been inserted, or is routinely established for these purposes, or to allow separate IV access for drug delivery. In a preliminary experience, intravenous morphine (IV-M) proved to be safe and effective for the management of breakthrough pain.[4] In our setting, this has been the preferred treatment during the past five years and specific changes in the clinical chart were designed for routinely monitoring the number of breakthrough events and the efficacy of this treatment during admission. The role of nurses is of paramount importance in a setting where continuous monitoring and immediate interventions are required.

The aim of this prospective cohort study was to confirm the safety of IV-M in a real clinical setting representing the routine activity of an acute palliative care unit. The secondary outcome was to record the compliance of a team composed of recently trained and experienced nurses in recording data regarding breakthrough pain treated by IV-M.

Methods

All the patients consecutively admitted to a pain relief and palliative care unit during a period of one year, from June 2005 to May 2006, were surveyed. From this sample, patients who were prescribed IV-M for breakthrough pain were included. Informed consent for recording data for the study was received from all patients at time of admission, and institutional approval was obtained.

Patients were treated according to the department policy: An IV line is routinely established for emergency treatment of symptoms. Patients are encouraged to call when their pain gets severe either during the initial medication titration phase, or when basal pain is controlled (considered when the mean pain intensity is equal to or less than 4/10) and superimposed episodes of breakthrough pain occur. The IV-M dose is 1/5 of the oral daily dose, converted using an equianalgesic ratio of 1/3 (IV/oral).[4] For example, a daily oral morphine dose of 90 mg corresponds to an IV dose of 30 mg (1/3 ratio), and then is converted to 6 mg, or one-fifth the daily dose; the 6 mg IV dose is used for each episode of breakthrough pain. The calculated dose of IV-M is administered by nurses over about 5 minutes. The IV-M dose is modified according to eventual changes of the daily oral morphine dosage. In patients receiving other opioids, conversion ratios approved at our institution and used for many years were used.[5]

Written orders for breakthrough pain are routinely given in the therapy chart. For each episode, nurses are instructed to routinely collect changes in pain intensity (numerical scale 0–10) and emerging problems when called for pain increases considered to be severe in intensity by patients (T0), and 15 minutes after IV-M injection (T15). As a routine, a physician on duty is present in the department, and the palliative care team is available on call for any emergency or consultation.

Nurses were unaware of the aim of the study and followed department policy, after being instructed in preliminary meetings about the protocols established in the unit during the past five years, including the monitoring and treatment of breakthrough pain. The daily hours in which episodes occur, daily doses of oral morphine, and basal pain intensity were also recorded. From the nurse diary and meetings, relevant or life-threatening problems requiring medical consultation were extrapolated by the Chief Nurse, acting as a research

nurse (GI) participating into the study. In these meetings, further explanations about the need to monitor breakthrough pain events were readdressed, as a part of a continuous educational program.

The principal outcome was the evaluation of the number of patients who could benefit from IV-M within 15 minutes, a clinically meaningful time to evaluate a dose administered as needed, the number of patients who required a further treatment, and the occurrence of any adverse effect severe enough in intensity to require medical intervention. The secondary outcome was to evaluate the compliance of a team, composed by recently trained and experienced nurses, in routinely collecting data on breakthrough pain management with IV-M.

Statistical Analysis

For analysis, patients were divided according to age: ≤ 65 years and > 65 years. Analysis of proportions was performed using the Chi-square test. The one-way analysis of variance was used to compare mean doses, mean admission times, and mean daily breaks among different groups of samples. The Kruskal–Wallis statistic test was used to compare the different nonparametric variables. All *P*-values were two-sided, and *P*-values less than 0.05 were considered statistically significant. Data were analyzed by SPSS Release 14.0 and Systat Software 11.

Results

Ninety-nine patients underwent 116 admissions and received IV-M for treating breakthrough pain. Fifty-three patients were males. The mean age was 62 years (95% CI 60–65), and 42% of patients were over 65 years. The mean admission time was 6.5 days (95% CI 5.9–7.2). In total, 945 breakthrough events were treated by IV-M. The mean number of events during admission was 8 (95% CI 6.9–9.5). The mean dose of IV-M was 12 mg (95% CI 9–14 mg). Doses of more than 10 mg of IV-M were given for 432 events (45.7%). Dose ranges of IV-M for breakthrough pain according to age and gender for all patients included in the study are presented in Table 1.

Table 1
Dose Ranges of IV-M for Breakthrough Pain According to Age and Gender for All Patients Included in the Study

Doses of IV-M (mg)	Number of Patients				
	≤65 years	>65 years	Males	Females	Total
<10	260	253	245	268	513
10–30	189	132	169	152	321
>30	72	39	80	31	111
Total	521	424	494	451	

In 476 episodes (50.4%), changes in pain intensity were not reported by nurses in the record sheet. Of interest, the number of patients with incomplete documentation on changes in pain intensity decreased during the year of observation, being 68%, 58%, and 24% in the first, second and third quarter, respectively.

In 469 events (49.6%), the assessment, including changes in pain intensity 15 minutes after IV-M injection, was complete. In 287 (61.2%) and 115 (24.5%) events, respectively, pain intensity declined by more than 33% and 50%. The number of patients with a reduction in pain intensity of >33%, according to the dose range, age, and gender, are presented in Table 2. The mean pain intensity decreased from 7.2 (T0) to 2.7 (T15). In eight episodes, no changes in pain intensity were observed and a further dose of IV-M was given. During the remaining episodes, despite having less than a 33% decrease of pain intensity 15 minutes after IV-M, the patients did not require further interventions.

No age differences were found in mean doses ($P = 0.469$), number of events ($P = 0.544$), and admission time ($P = 0.781$). Similarly, no gender differences were found in mean doses ($P = 0.556$), number of events ($P = 0.935$), and admission time ($P = 0.238$).

Table 2
Number of Patients Assessed Presenting a Decrease in Pain Intensity >33%, According to Dose Range, Age, and Gender

Doses of IV-M (mg)	Number of Patients			
	≤65 years	>65 years	Males	Females
<10	78	75	65	88
10–30	64	32	47	49
>30	29	9	25	13
Total	171	116	137	150

Of the 469 events completely assessed, 167 (35.6%), 124 (26.4%), and 178 (38%) episodes were recorded between 7 AM and 2 PM, between 2 PM and 9 PM, and between 9 PM and 7 AM, respectively.

Discussion

The optimal opioid dose to be administered for breakthrough pain is controversial. Due to the variability in presentation of pain flares, it is difficult to provide clear guidelines. To date, dosing recommendations are based on anecdotal experience only; they suggest that the effective dose of breakthrough pain medication is a percentage of the patient's total daily opioid dose. In the case of morphine, the European Association for Palliative Care recommends one-sixth (17%) of the daily dose as a starting point.[6]

In contrast to this recommendation, all the trials with transmucosal fentanyl (OTFC) have found no relationship between the effective OTFC dose and a fixed schedule opioid regimen, regardless of the baseline opioid used. The latter findings can have different explanations. Sixty-six percent of the episodes treated with placebo did not require an additional dose of medication. This is likely to be attributed to the normal course of episodes, which are often relatively short-lived and improve spontaneously, or a true placebo response. Alternatively, episodes resolved because of a low pain intensity of the flare. Although no reliable equivalency ratio with the baseline regimen was observed, patients on higher doses of original medication generally required larger doses of OTFC, and in successfully treated patients, the regular rescue medication, such as oral morphine, was a moderate predictor of the effective OTFC dose.[7–10] Observations from data pooled from trials of OTFC showed a statistically significant relationship between the breakthrough dose and around-the-clock dose, despite enormous interindividual variability in patients' dose requirements for breakthrough pain.[11]

According to these studies, effective OTFC doses are independent of the basal opioid regimen and should be titrated. However, in patients who require multiple titrations, as often occurs in the setting of a palliative care unit, the practical use of OTFC is difficult. The potential need to use different lozenges of OTFC for treating each episode may be time-consuming and may exceed the duration of the breakthrough pain.

Given the short duration of many breakthrough pains, and their variable pain intensities, it could be argued that, to cover the majority of episodes, a rapid and intense treatment should be provided, although this could expose patients to adverse effects. We have shown in a preliminary study 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.[4] However, physicians are often reluctant in using intensive procedures because of the possible risks and poor familiarity with the IV route. In recent years, a growing interest in palliative care and skills in other routes of administration prompted physicians to develop more aggressive measures to improve the efficacy of analgesic interventions in some difficult conditions.[12–17]

This confirmatory study in a large number of episodes of breakthrough pain showed that IV-M at doses proportional to the basal opioid regimen provided prompt analgesia and was effective in most cases. The breakthrough pain was equally distributed during the daily hours, and age and gender did not influence the outcome. Of interest, a relatively large number of patients received doses of IV-M of more than 10 mg without evident risks, independent of age. Most patients in this study did not require further IV-M doses, and in more than 60% of patients, the decrease in pain intensity was more than 33%. To evaluate the effectiveness of a treatment, a 33% cut-off point for the percentage of maximum pain relief is considered as a consistent and relevant clinical endpoint. This level of change in pain intensity has been best associated with clinically important differences by patients.[18] Some patients had relatively small decreases in pain intensity, but only a minority of patients required a further intervention.

This treatment was uneventful, and no life-threatening adverse effects were recorded, even in older patients. Respiratory depression, which is the most feared adverse effect, never occurred, and no emergency call was needed. This finding confirms that patients receiving

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VALUTAZIONE DEI SINTOMI

SINTOMI	GIORNI	20/3	21/3	22/3	24/3					
Dolore	M	6	3	2	2					
	P	5	3	2-3	0					
Episodi Break (Incidente?)	M									
	P-N									
Dispnea	M	0	1	0	0					
	P	0	1	1	0					
Nausea		1	1	1	0					
Vomito		1	0	0	0					
Sonnolenza	M	0	1	1	0					
	P	1	0	0	0					
Confusione	M	0	1	0	0					
	P	1	1	0	1					
Astenia		2	1	2	1					
Transito	M	2gg	E+	E+	1g					
Intestinale	P-N									
Xerostomia		1	1	1	1					
Disfagia		0	1	0	0					
Pirosi		0	0	0	0					
Compliance		BUONA	BUONA	BUONA	BUONA					
Mini-Mental Score										
Di stress Psicologico										
KARNOFSKY		50	50	50	50					
ENTRATE										
Nutrizione		1	1	0	0					
Idratazione		2	1	1	1					
Idratazione Parenterale										

REVISIONE

DATA	20/3			21/3											
Analgesico	ora	VAS	min	ora	VAS	min	ora	VAS	min	ora	VAS	min	ora	VAS	min
MORFINA	10	10-2		12	8-2										
	18'15	8-2		21	9-2										
	23'20	7-2													
Via EV															

DIDASCALIA:
Dolore ***0-10*** su scala numerica: dove **2-3 dolore lieve o accettabile, 4-6 dolore moderato, 7-8 dolore forte, 9-10 dolore insopportabile .**
Transito Intestinale: Stipsi = S indicare l'eventuale numero di giorni. **Diarrea=D** utilizzare il segno + in base al numero di scariche (es. due scariche D++). **Evacuazione= E** utilizzare il segno + in base al numero di evacuazioni.
Nutrizione/Idratazione scala 0123: **0=(buone); 1 (ridotta); 2 (fortemente ridotta); 3 (assente).**
Tutti gli altri sintomi scala numerica 0123: **0 (assente); 1 (lieve); 2 (media); 3 (forte)**

KARNOFSKY

100 Normale	**50 Autonomo, richiesta frequente di assistenza**
90 Segni minori di malattia	**40 Non autonomo, assistenza particolare**
80 segni di malattia	**30 Severamente compromesso**
70 Incapacità al lavoro attivo	**20 Stato Avanzato**
60 Autonomo, richiesta occasionale assistenza	**10 Moribondo**

Emesso da: DS Verificato da: AQ File: DRTER02.doc Revisione del: 22/10/2001 Archiviato da: AQ

Fig. 1. Symptom monitoring sheet used at the Pain Relief and Palliative Care Unit. See under "REVISIONE" the changes in pain intensity after IV-M administration.

opioids incur little risk even when receiving IV bolus doses of morphine. This can be explained by the protective effect offered by opioid tolerance in patients chronically receiving an opioid for the management of cancer pain.

The second outcome was to observe how a newly established nurse team, composed of a mixture of old and new professionals (about 50% experienced and 50% new), reports the treatment of breakthrough pain on the monitoring and clinical sheets (Fig. 1). Documentation of changes in pain intensity was often incomplete, as in about 50% of episodes some data were missed. This was expected, given that the nature of the study focused on the monitoring of nurse activity and intervention in a team comprising both experienced and recently trained staff, who were unaware of the study's second outcome, and recorded data as they would for any routine activity. However, positive changes occurred during the year and data were collected more appropriately in the last four months, when 75% of events were correctly reported in the chart, confirming the improved attitudes of nurses to routinely collect data on breakthrough pain management.

For an appropriate evaluation of the data presented, it should be taken into account that the setting of this observational study typically reflects the real clinical situation occurring in an acute palliative care unit, rather than that of a controlled study. Of course, IV-M is not for routine use, particularly at home or for patients without IV lines followed in hospices with low-level facilities. After achieving stabilization in an acute palliative care unit, patients can be transferred to other therapies, including the oral or transmucosal route of opioid administration, without any risk. The chances of developing relevant toxicity are minimized after patients already have been tested with the IV route, which should have the highest potential of producing toxicity.

In conclusion, IV-M administered for the management of breakthrough pain in doses proportional to the basal opioid regimen did not result in life-threatening adverse effects in a large number of patients and was considered effective by patients in most cases. Education in breakthrough pain is essential, as nurses have a prominent role in assessing, treating, monitoring, and collecting data regarding breakthrough pain.

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