Clinical Note

Opioids for Cancer Breakthrough Pain: A Pilot Study Reporting Patient Assessment of Time to Meaningful Pain Relief

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Abstract
Breakthrough pain is a common and distinct component of cancer pain that is usually managed with normal release opioids (also known as rescue medication) either before or soon after its onset. A prospective survey of hospice inpatients with breakthrough pain was undertaken to characterize their pain and then compare the time to onset of pain relief of their rescue medication. Patients presented with, on average, 1.7 different types of breakthrough pains (range, 1–4). The average number of breakthrough pains was four per day (range, 1–8), and the average duration of breakthrough pain was 35 minutes (range, 15–60); most occurred suddenly and unpredictably. Patients used morphine, oxycodone, hydromorphone, methadone, or oral transmucosal fentanyl citrate as rescue medication and the average time to meaningful pain relief following their administration was 31 minutes (range, 5–75). No difference was found between morphine, oxycodone, and hydromorphone. Methadone appeared to work faster than morphine ($P < 0.01$) but no faster than oxycodone or hydromorphone, whereas oral transmucosal fentanyl citrate worked faster than morphine, oxycodone, hydromorphone, and methadone ($P < 0.001$). J Pain Symptom Manage 2008;35:563–567. *© 2008 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Breakthrough pain, cancer, rescue medication, opioids

Introduction

Breakthrough pain is a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger despite relative stable and adequately controlled background pain. It is a heterogeneous pain state typically of fast onset and short duration. It typically feels much like background pain except that it is usually more severe. Breakthrough pain is common, often difficult to manage and its presence can have a negative impact on quality of life by imposing a significant physical, psychological, or economic burden on patients and their caregivers.[1–3]

Breakthrough pain is often managed with normal release opioids (also known as rescue medication) that are given in addition to regularly scheduled, around-the-clock (ATC) analgesics. The rapid onset and short duration of most breakthrough pain can make management

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difficult, as normal release oral opioids may take up to an hour to produce analgesia that then lasts for four hours after administration.[4] Recently, new formulations that deliver fentanyl directly through mucous membranes have been developed in an effort to provide a more rapid onset of effect.

There are few data describing patients' satisfaction with their rescue medication. The aim of this study was to describe the characteristics of breakthrough pain in a sample of hospice inpatients and then to compare patient assessment of time to relief among the various normal release opioids the patients had been prescribed for breakthrough pain.

Methods

A prospective survey of consecutive hospice admissions with breakthrough pain was undertaken. Consecutive patients newly admitted to hospice were evaluated. Eligible patients were already using oral formulations of morphine, oxycodone, hydromorphone, methadone, or oral transmucosal fentanyl citrate (OTFC), prescribed prior to admission for breakthrough pain; they were able to give consent, use a stopwatch, record their findings, had relatively well-controlled background pain and stable ATC analgesia throughout the assessment period. Patients were not included if they were confused, had uncontrolled background pain (including end-of-dose pain), were unable to complete the diary card, or had received radiotherapy or chemotherapy in the preceeding month.

Patients were first asked to characterize their breakthrough pain according to location, severity, temporal relations, relationship to fixed analgesic dose, precipitants, predictability, and palliative factors based on episodes of breakthrough pain experienced in the last 24 hours. If possible, they described episodes for which they had not used rescue medication. Patients were then asked to determine the speed of effectiveness of their respective rescue medication. The patient started a stopwatch when their rescue medication was administered and then stopped it when meaningful pain relief was first experienced; this time was then recorded by the patient on a diary card. Patients repeated this for five consecutive breakthrough pains; pains requiring repeat doses of rescue medication were not included.

Patients with multiple breakthrough pains were asked to assess the effect of rescue medication on the most severe pain. The time to effective pain relief for each breakthrough pain was then averaged for each rescue medication and the mean and standard deviation for rescue medication groups was then compared for statistical significance. Approval was obtained from the local Ethics and Research Committee.

Results

Fifty patients were assessed in total (22 male); the average age was 68 years (range, 32–88) (Table 1). The commonest diagnoses were cancers of lung (23 patients), breast

Table 1
Characteristics of Patients Surveyed

	Morphine	Oxycodone	Hydromorphone	Methadone	OTFC
No. of patients	10	10	10	10	10
Males (%)	40	50	30	40	60
Average age (years)	67.9	67.6	68.1	69.6	64.5
Mean daily opioid dose (mg)	103	72	12.8	61	132
SD	69.3	54	10.6	38.1	103.3
Mean rescue medication (mg)	15	11	2.21	12	0.8
SD	7.5	6.2	1.6	8.6	0.5
% Episodes rescue taken	58.3	63.3	68	64	79.7
SD	23.1	29.8	27.4	22.2	17.3
Effectiveness of rescue medication[a]	6.2	6.6	6.3	6.7	8.1
SD	1.5	1.2	1.6	1.7	1.4

[a]Numerical Rating Scale 0–10.

(7), prostate (8), and unknown primary (4). The doses of ATC morphine, oxycodone, and hydromorphone were similar given their relative potencies, and the dose of methadone may be considered by some as higher given its equivalence to morphine at higher doses.[5] The ATC opioid was also used for breakthrough pain except for OTFC, where the ATC medication was morphine (6 patients), oxycodone (3), and hydromorphone (1).

Prior to admission, patients used rescue medication, on average, for 66.7% of breakthrough pains; there were no significant differences between the four opioid groups (Table 1). Reasons for not taking rescue medication included insufficiently effective (21 patients), adverse effects (19), anxiety about overdosing (10), concerns would affect daily routine (8), and no instructions (4); some patients gave more than one reason. Patients rated the effectiveness of rescue medication, using an 11-point numerical rating score (0 = no relief to 10 = complete relief), on average, as 6.7. No differences were observed among the oral opioids; OTFC was rated more effective than morphine, oxycodone, and hydromorphone ($P < 0.01$) and methadone ($P = 0.045$).

Although one target breakthrough pain was selected for the assessment, patients presented with an average of 1.7 different breakthrough pains (range, 1–4). The most common sites were lower limb (12 patients), back (11), chest (9), abdomen (5), and upper limb (5), and the average duration of breakthrough pains was 35.2 minutes (range, 15–60). There was no significant difference in duration among each of the five opioid groups (Table 2). The average number of daily episodes of individual pains was 4 (range, 1–8); 68% of pains occurred suddenly, 57% were either severe or excruciating, and 59% were unpredictable. Patients were asked what best relieved their breakthrough pain, and the commonest factors were analgesics (57%) and lying still (32%); in 61 pains these two factors were given together, and in 14% of pains, no palliative factors were identified.

In total, 250 breakthrough pains were assessed, 50 for each rescue medication. The dose of the oral rescue dose was, on average, 18% of the ATC dose, whereas for OTFC, the rescue dose was approximately 36% of the ATC dose. The average time to meaningful pain relief following the administration of rescue medication was 31 minutes (range, 5–75). No difference was found between morphine, oxycodone, and hydromorphone (Fig. 1). Methadone appeared to work faster than morphine ($P < 0.01$) but no faster than oxycodone or hydromorphone, whereas OTFC worked faster than morphine, oxycodone, hydromorphone, and methadone ($P < 0.001$).

Discussion

Successful management of breakthrough pain requires a comprehensive assessment, good communication, education and reassurance of the patient and family, and efforts to

Table 2
Breakthrough Pain Characteristics

Breakthrough Pain	Morphine	Oxycodone	Hydromorphone	Methadone	OTFC
Average duration	34.8	38.5	38	39.5	25
SD	11.7	13.3	11.8	15.2	8.5
Pain intensity (%)					
Mild	10	12	8	8	4
Moderate	36	34	36	36	30
Severe	44	44	42	48	48
Excruciating	10	10	14	8	18
Pathophysiology (%)					
Nociceptive	54	56	50	50	46
Neuropathic	12	11	11	14	21
Mixed	34	33	39	36	33
Etiology (%)					
Tumor related	69	65	60	66	75
Treatment related	13	13	16	14	9
Tumor/treatment unrelated	18	22	24	20	16

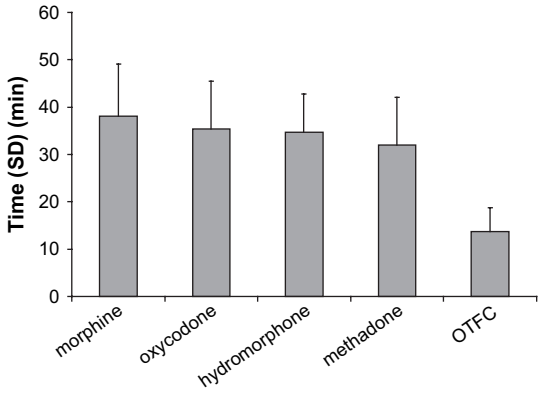

Fig. 1. Time to meaningful pain relief following rescue medication.

encourage the participation of patients and caregivers in the treatment plan. Integral to this is the appropriate use of rescue medication, which is not used for all breakthrough pain episodes. Reasons varied and appeared to be related either to the beneficial or adverse effects of the medication, the patient's fears or expectations, and information provided by the health care professional. It is possible that patient involvement and cooperation could be better achieved through an improved understanding of their rescue medication and the possible adverse effects. In some cases patient may choose to use nonpharmacological management options, either instead of, or alongside, pharmacotherapy.[6]

The relatively fast onset and short durations of most breakthrough pains can present a difficult clinical challenge given that oral opioids may lag behind the time course of the breakthrough pain.[4] In this survey, most breakthrough pains occurred suddenly, unpredictably and lasted an average of 35 minutes. Oral rescue medication appeared to produce an effect within 30–40 minutes. Therefore, when oral analgesics are deemed to be effective, the pain may in fact have spontaneously resolved.

The ideal rescue medication should be efficacious, have a rapid onset of action, a relatively short duration of effect, and minimal adverse effects. Fentanyl is a potent lipid-soluble opioid and when delivered transmucosally can produce a rapid onset of analgesia. In this survey, OTFC provided meaningful pain relief in a shorter period of time and was rated more effective than oral opioids. The physicochemical properties of fentanyl have led to the development of other transmucosal delivery systems using this opioid,[7] as its time-action profile appears to better match the time course of breakthrough pain. There has been a report suggesting that methadone may also have a faster onset of action than other oral opioids and patients surveyed using methadone appeared to achieve pain relief more quickly than those patients using morphine.[8] However, the long half-life of methadone and the potential for accumulation may make its use problematic.

The time to effective pain relief is a measure that has been used in pain research but may not have received adequate attention.[9] Unlike unidimensional pain measures, such as numerical rating scores or visual analog scales, meaningful pain relief better reflects the temporal aspects of pain and incorporates a subjective component to the measure. To increase the quality of the study, consideration should be given to other measures, including the use of multidimensional tools such as the McGill Pain Questionnaire.

Despite evidence that suggests OTFC is more effective than oral opioids in the management of breakthrough pain,[10] it is not routinely used as first-line rescue medication; thus, the patient population using OTFC may be a selected one, with more difficult pain syndromes. Although breakthrough pains in each rescue medication group were broadly similar in characteristics, a prospective study where patents are randomized to each of the rescue medications would have improved the quality of the study. In addition, although the dose of OTFC had been titrated to determine the effective dose, it appears that oral rescue medication was given in line with current recommendations,[11] which have not been evaluated in clinical studies and may therefore, not have been at the optimal dose.

There are other weaknesses to this report. The number of patients included is small, and thus the findings give only an indication of what patients' experience might be. The duration of breakthrough pain was collected retrospectively, whereas the time to effective relief was collected prospectively using stopwatches; this may lead to some inaccuracies including the observation that the time of onset of morphine analgesia appears longer than duration of breakthrough pain. Another

unknown quantity is that it is unclear how soon after the start of each breakthrough pain episode rescue medication was taken.

In conclusion, this small open pilot study confirms that breakthrough pain can present a challenge to the clinician and that patients may not always take rescue medication for all breakthrough pain episodes. Transmucosally administered fentanyl appeared to provide a faster onset to pain relief than orally administered opioids in patients with breakthrough pain, as assessed by the patient. Indeed, the time to effective relief for oral opioids may simply reflect the spontaneous resolution of breakthrough pain rather than any impact of the oral rescue medication. A randomized trial, preceded by a titration period for each opioid and using several unidimensional and multidimensional outcome measures, is being planned to confirm these findings.

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