CMRO
Current Medical Research & Opinion Vol. 29, No. 1, 2013, 93–97
0300-7995
doi:10.1185/03007995.2012.755120
Article ST-0266.R1/755120

Brief report

Meaningful cut-off pain intensity for breakthrough pain changes in advanced cancer patients

Sebastiano Mercadante
Anesthesia and Intensive Care Unit and Pain Relief and Palliative Care Unit, La Maddalena Cancer Center, Palermo, Italy

Claudio Adile
Pain Relief and Palliative Care Unit, La Maddalena Cancer Center, Palermo, Italy

Riccardo Torta
Antonella Varetto
Department of Psycho-Oncology, University of Turin, Turin, Italy

Fabio Fulfaro
Department of Oncology, University of Palermo, Palermo, Italy

Antonino Giarratano
Department of Anesthesia, Intensive Care & Emergencies, University of Palermo, Palermo, Italy

Alessandra Casuccio
Department of Experimental Biomedicine and Clinical Neuroscience, University of Palermo, Palermo, Italy

Address for correspondence:
Prof. Sebastiano Mercadante, Anesthesia and Intensive Care Unit & Pain Relief and Palliative Care Unit, La Maddalena Cancer Center, Via san Lorenzo 312, 90145 Palermo, Italy.
Tel.: +39 091 6806521; Fax: +39 0916806110;
terapiadeldolore@lamaddalenanet.it;
03sebelle@gmail.com

Keywords:
Breakthrough pain – Cancer pain – Meaningful pain intensity – Palliative care

Accepted: 29 November 2012; published online: 13 December 2012
Citation: Curr Med Res Opin 2013; 29:93–97

Abstract

Objectives:
To assess the level of pain intensity at which patients feel the impetus to ask for a breakthrough cancer pain (BTcP) medication, and level of pain intensity at which patients consider they have achieved acceptable pain control after receiving a BTcP medication.

Methods:
A consecutive sample of patients who were receiving oral morphine equivalents equal to or more than 60 mg daily, and were prescribed rapid onset opioids for the management of episodes of BTcP, were included in the study. Focused educational activities regarding BTcP and numerical scales were established during hospital admission. At discharge patients were interviewed to find out what was the pain intensity level which gave the impetus to take the BTcP medication, what was the pain intensity for acceptable pain control after a BTcP medication had been given, and which factors prevented the patient calling for BTcP medication. A brief COPE (coping orientation to problems experienced) questionnaire was also administered.

Results:
Fifty-two patients were recruited for this study. The meaningful pain intensity for asking for a BTcP medication was 7.1; 77% of patients had a pain intensity of 7–8 on a numerical scale of 0–10. The meaningful pain intensity for adequate analgesia after a BTcP medication was 3.5. Similarly, 77% of patients had a pain intensity of 3–4. There was no relationship with the variables examined. Concerns by patients about the use of BTcP medications were minimal.

Conclusion:
The meaningful BTcP intensity and pain intensity expected after BTcP medication can be useful in selecting patients in studies of BTcP. The principal limitation of this study was the specific setting of an acute unit with specific features and the relatively low number of patients. This observation should be followed up by further surveys with a larger number of patients and different settings.

Introduction

Breakthrough cancer pain (BTcP) has been defined as "a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific trigger, despite relatively stable and adequately controlled background pain"[1,2]. BTcP is often managed with opioids that are given in addition to regularly scheduled, around-the-clock analgesics.

To evaluate the effects of an analgesic drug, pain intensity is commonly measured at intervals after the administration. The time to effective pain relief is a measure that has been recently used to better reflect the temporal

aspects of pain incorporating a subjective component to the measure[3]. This is a very important aspect as treatment is dependent on the clinical judgment of patients[4,5]. This parameter has been also used for controlled studies to compare the rapidity of the analgesic effects of different fentanyl formulations. This is obviously dependent on the characteristics of the drug administered. For example the median time to onset of meaningful pain relief was significantly shorter in patients receiving oral transmucosal fentanyl citrate (about 15 minutes) than in patients receiving oral opioids (more than 30 minutes)[3], and was 11 minutes for intranasal fentanyl[6].

However, the pain intensity at time of meaningful pain relief has never been assessed. In the measurement of cancer pain exacerbations, patients commonly use numerical rating scales more appropriately than verbal scales[7]. Numerical scales have been commonly used as a single entity, percentage pain intensity difference, the sum of pain intensity differences, pain relief, and percentage of maximum total pain relief. In the last decade scientists tried to define a clinically important difference in pain outcome measure and found that the best cut-off points to define clinical difference in pain intensity was a pain intensity difference of 2 points, a pain relief difference of 2 points, and a sum of the pain difference of 2 points. The best cut-off point for both the percentage of maximum pain relief and percentage pain intensity difference was 33%[8]. These measures have been invariably used in many clinical trials to evaluate the effects of BTcP medications. However, levels of pain do not always fit these figures. For example changes in pain intensity may differ from 9 to 6, or from 6 to 4.

Moreover, many controlled studies often included patients with mild to moderate pain having BTcP episodes of moderate to severe pain, where there are more probabilities of overlapping pain intensities which conversely may influence the results obtained with the study drug[9], providing misleading data regarding the drug efficacy (for example increasing the placebo effect) or even the need of dose titration consequent to a lack of relationship between the dose of background opioid regimen and the successful dose for BTcP[1]. Thus, the level of pain intensity which is considered acceptable for patients at time of meaningful pain relief could be important to provide a common parameter as it expresses a relevant individual measure.

Of interest, the pain intensity of a BTcP event has been largely reported with pain intensity ranging from mild to excruciating pain. This variability in selecting patients has been reported as a confounding factor in many clinical trials where fluctuations of pain of moderate intensity, which could potentially disappear spontaneously, may be treated as they would BTcP episodes[1]. This level of pain intensity is the indicator to decide whether and when to administer a BTcP medication. The severity of pain considered to be deserving an intervention from individuals has never been explored. Patients' impetus for taking BTcP medication is variable as well as patients' reasons for not always taking BTcP medication, including lack of intensity of pain, adverse effects and concerns about adverse effects[2]. For most studies of BTcP a pain of moderate to severe intensity (≥5–10/10 on a numerical scale from 0 to 10) has been considered as an inclusion criteria[10]. In other studies more stringent criteria were adopted, patients being invited to call for administration of study medication when pain is considered severe (≥7–10/10)[1,9].

The aim of this study was to assess the individual level of pain intensity at which patients feel the impetus to seek for BTcP medication, and level of pain intensity at which patients achieve acceptable pain control after receiving BTcP medication.

Patients and methods

All the patients admitted to a Pain Relief and Palliative Care unit in a period of 10 months, from March 2011 to December 2011, were surveyed. From this sample, patients who were receiving opioids in doses of oral morphine equivalents equal to or more than 60 mg daily, and were prescribed rapid onset opioids (ROOs) for the management of BTcP, were included into the study. Informed consent and institutional approval were obtained. Patients with cognitive disturbances or who died during admission were excluded.

Patients were treated according to the department policy. After achieving adequate analgesia, patients were encouraged to call when they felt that their pain increased in a significant way compared to their basal pain.

Written orders for BTcP, including drugs and doses to be administered, are routinely given in the therapy chart. As a routine, for each episode, trained nurses recorded pain intensity and adverse effects severe enough in intensity to require medical intervention, when called for pain increases considered to be severe in intensity by patients and 15 minutes after administering the rescue dose of opioids. A physician on duty is present in the department, and the palliative care team is available on call for any emergency or consultation in case of development of severe adverse effects. Educational activities regarding BTcP and numerical scales were established during hospital admission, particularly focusing on their experience and the changes in pain intensity observed after administering the BTcP medication.

At discharge patients who had their background pain controlled (pain intensity of ≤4/10 on a numerical scale from 0 to 10) were interviewed to answer the following questions:

(a) After your experience with BTcP and medications given for that, what is the pain intensity level (on a

numerical scale from 0–10) which gives impetus to take the BTcP medication?
(b) What is the pain intensity level (on a numerical scale from 0–10) which provides acceptable pain control after a BTcP medication is given?
(c) What prevents you from calling for BTcP medication: concerns about adverse effects, low level of pain intensity, BTcP medication considered ineffective, episode of pain too short, other reasons.

Level of education was also collected (primary school, secondary school, degree). A brief COPE (coping orientation to problems experienced) questionnaire was also administered[11]. Psycho-oncologists, expert in interpreting the items from the questionnaire, provided three general coping profiles: problem focused, emotion focused, avoidance.

Statistical analysis

Statistical analysis of quantitative and qualitative data, including descriptive statistics, was performed for all the items. Frequency analysis was performed with the chi-square test. Continuous data were expressed as mean ± standard deviation, unless otherwise specified. One-way analysis of variance (ANOVA) was conducted to analyze the possible relationship between clinical variables and meaningful pain intensity for BTcP.

Data were analyzed by Epi Info software (version 6.0, CDC, Atlanta, GA, USA) and SPSS Software 14.0 version (SPSS Inc., Chicago, IL, USA). All *P* values were two-sided and *P* values less than 0.05 were considered to indicate statistical significance.

Results

All the screened patients were available for the study, and data from fifty-two patients were available. Patient characteristics are presented in Table 1. Twenty-eight patients were males, and the mean age was 58.6 years (SD 10.8). The mean Karnofsky performance status was 50.3 (SD 10.4). The median admission time was 5 days and a median of nine breakthrough pain events for each patient were treated during that time. At time of discharge the background pain intensity was 2.6 (SD 1.4). Opioids and doses prescribed for background analgesia are shown in Table 2. Drugs and doses prescribed for BTcP are shown in Table 3. The meaningful pain intensity for asking for a BTcP medication was 7.11 (SD 0.8). The majority of patients (77%) had a pain intensity of 7/10 (n. 21) or 8/10 (n.19). The meaningful pain intensity for adequate analgesia after a BTcP medication was 3.5 (SD 1.04). The majority of patients (77%) had a pain intensity of 4/10 (n. 27) or 3/10 (n.13).

There was no relationship with the variables examined (Table 4). Only 12 patients were concerned about seeking BTcP medication, for the following reasons: low pain intensity (2 patients), the short duration of effect (2 patients), inefficacy (1 patient), fear of adverse effects (3 patients), other reasons (4 patients).

Table 1. Patient characteristics.

Age, mean (SD)	58.6 (10.8)
Gender (F/M)	24/28
Primary tumor:	
lung	10
urogenital	10
pancreas	8
gastrointestinal	8
breast	8
head & neck	2
others	6

Discussion

Many controlled studies of ROOs for the management of BTcP have reported significant differences in pain intensity and onset in comparison with placebo or oral opioids. Populations included in these trials, however, were quite non-homogeneous in terms of levels of pain intensity, as patients were often included without a clear distinction between the BTcP intensity and background pain.

Table 2. Opioids and doses prescribed for background analgesia.

	Frequency	Mean dose, mg/day (SD)
SR oral morphine	6	257 (331)
Oral methadone	5	64 (56)
SR oral hydromorphone	17	73 (74)
SR oral oxycodone/naloxone	3	37 (6)
Transdermal fentanyl	10	1.9 (1.6)
Transdermal buprenorphine	3	0.9 (0.6)
SR oral oxycodone	3	60 (35)
Multiple opioids or combination with non-opioid	5	

SR = sustained release.

Table 3. Drugs and doses prescribed for BTcP.

	Frequency	Mean dose (SD)
Oral morphine	9	28 mg (48)
Fentanyl buccal tablets	19	616 μg (602)
Pectyn–fentanyl nasal spray	3	433 μg (351)
Intranasal fentanyl	5	220 μg (110)
Sublingual fentanyl tablets	5	420 μg (110)
Intravenous morphine	1	5.0 mg
Oxycodone–paracetamol	4	7.5 mg (2.9)
Oral transmucosal fentanyl	3	1133 μg (1137)
NSAIDs	2	
Tramadol	1	

BTcP = breakthrough cancer pain, NSAIDs = non-steriodal anti-inflammatory drugs.

Table 4. The relationship between clinical variables and meaningful pain intensity for Breakthrough cancer pain (BTcP).

	Meaningful pain intensity for BTcP *P**	Meaningful pain intensity after BTcP medication *P**
Gender	0.794	0.699
Age group (≤65/>65)	0.597	0.330
Primary tumor	0.692	0.943
Education	0.690	0.341
Opioid for background analgesia	0.811	0.146
Opioid for BTcP	0.825	0.516
Brief coping profiles	0.674	0.495

*Univariate analysis of variance (ANOVA).

Some patients had relatively high levels of background pain and some others had low level of BTcP[1,9,10]. This bias has often amplified the effects of the comparison substances, either placebo or oral opioids. Daily fluctuations of pain intensity may induce patients to treat them as they would episodes of BTcP, for example with ROOs, and the spontaneous course of pain fluctuations may render the interpretation more difficult.

For this reason, it is of paramount importance to assess at what pain intensity patients have the impetus to take medication for BTcP. Regardless of data extrapolated by controlled studies where the driving force is imputable to different factors, including the design and inclusion criteria, to objectify the level of pain currently experienced at which patients seek medication, it is necessary to gather this information from patients who are educated and trained in distinguishing the changes of pain intensity. We can estimate that an admission time of 5 days, during which patients experience 8–10 episodes, mainly successfully treated, may be reliable to recognize the individual threshold to ask for BTcP medication and the level of pain intensity corresponding to acceptable pain control with the drug and dose prescribed. In this paper, the mean pain intensity at which patients feel the need for BTcP medication was about 7/10 on a numerical scale. A reduction of approximately two points or a reduction of approximately 30% of pain intensity has been reported to be a clinically important difference[8,12,13]. It has been reported that percentage change in pain ratings correlates better with patient perception of benefit[14]. However, an important clinical difference does not always correspond to what a patient feels or expects. On the other hand the higher baseline scores (for example the typical pain intensity of a BTcP event) require larger raw changes to represent a clinical important difference[13]. In this paper patients presenting an episode of severe intensity (on average 7 on a numerical scale of 0–10) were satisfied with about a 50% pain decrease. These cut-off points should be taken into account for future studies of drugs used for BTcP.

Coping strategies may potentially influence the outcome. However, no specific coping profile was associated with the two levels of pain intensities chosen by patients. The reason may relate to the poor capacity of the brief COPE, which is disease-oriented, in this study setting. Alternately, the training and education of patients, as well as the friendly environment and positive communication may have flattened this aspect. This is also confirmed by the fact that concerns about the use of BTcP medications were minimal, different from what was observed in patients who did not receive adequate training[2]. This can reflect the positive experience of patients about safety and effectiveness in the unit.

Conclusion

On the basis of the present observation, patients needing a BTcP medication are likely to have a pain intensity of ≥7 on a numerical scale of 0–10, and patients who are satisfied after receiving a BTcP medication are likely to have a pain intensity of ≤4/10. This occurs in both cases in 77% of patients. These cut-off points could help in selecting patients in studies of BTcP, avoiding the inclusion of patients with intermediate situations, which often contribute to misinterpretation of data reported in the literature. Other studies performed in different settings, at home or in outpatient clinics, and with a larger sample of patients, should confirm this preliminary observation. Cultural differences should be also explored.

Transparency

Declaration of funding

The authors received no payment in preparation of this manuscript.

Declaration of financial/other relationships

S.M. has served on the Speakers Bureaus for Grunenthal, Janssen, Teva, Molteni and ProStrakan. C.A., R.T., A.V., F.F., A.G., and A.C. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

CMRO peer reviewers may have received honoraria for their review work. The peer reviewers on this manuscript have disclosed that they have no relevant financial relationships.

Acknowledgments

The authors are indebted to the nurses of the unit of La Maddalena cancer center, and the staff of psycho-oncologists of the University of Turin.

References

1. Mercadante S. Rapid onset opioids for breakthrough pain. Titrating or not titrating, this is the question? Eur J Pain 2011;5(Suppl 2):443-8
2. Davies A, Vriens J, Kennett A, et al. An observational study of oncology patients' utilization of breakthrough pain medication. J Pain Symptom Manage 2008;35:406-11
3. Zeppetella GB. Opioids for cancer breakthrough pain: a pilot study reporting patient assessment of time to meaningful pain relief. J Pain Symptom Manage 2008;35:563-7
4. Davies A, Dickman A, Reid C, et al. The management of cancer-related breakthrough pain: recommendations of a task group of the Association of Palliative Medicine of Great Britain and Ireland. Eur J Pain 2009;13:331-8
5. Webber K, Davies A, Cowie M. Breakthrough pain: a qualitative study involving patients with advanced cancer. Support Care Cancer 2011;19:2041-6
6. Mercadante S, Radbruck L, Davies A, et al. A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: an open-label, randomized, crossover trial. Curr Med Res Opin 2009;25:2805-15
7. Brunelli C, Zecca E, Martini C, et al. Comparison of numerical and verbal rating scale to measure pain exacerbations in patients with chronic cancer pain. Health Qual Life Out 2010;8:42
8. Farrar J, Portenoy RK, Berlin J, et al. Defining the clinically important difference in pain outcome measure. Pain 2000;88:287-94
9. Mercadante S. The use of rapid onset opioids for breakthrough cancer pain: the challenge of its dosing. Crit Rev Oncol Hematol 2011;80:460-5
10. Davies A, Zeppetella G, Andersen S, et al. Multicentre European study of breakthrough cancer pain: characteristics and patient perceptions of current and potential management strategies. Eur J Pain 2011;15:756-63
11. Carver C. You want to measure coping but your protocol's too long: consider the brief COPE. Int J Behav Med 1997;4:92-100
12. Farrar J, Young J, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149-58
13. Farrar J, Polomano R, Berlin J, et al. A comparison of change in the 0–10 numeric rating scale to a pain relief scale and global medication performance scale in a short-term clinical trial of breakthrough pain intensity. Anesthesiology 2010;11:1464-72