“It hurts when I move”: Managing Incident Pain in Palliative Care

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CancerCare Manitoba
Disclosure of Potential for Conflict of Interest

I have no financial arrangements/agreements to disclose

I am an employee of the University of Manitoba, CancerCare Manitoba, and the WRHA Palliative Care Program....

Does that make me conflicted?
Learning Objectives

After attending this session, participants will be able to:

briefly explain the pathophysiology of breakthrough and incident pain in relation to cancer patients

discuss methods of pain management for breakthrough/incident pain in cancer care

rationalize the use of specific analgesics for incident pain and routes of administration
Overview

Breakthrough and incident cancer pain
  Definitions and clinical features
  Epidemiology and impact

Diagnosis of BTP

Effective management of BTP
  Non-pharmacological and pharmacological strategies

Fentanyl citrate and BTP
  Evidence for efficacy and safety
Pain Definitions

Patients with cancer pain identify two separate components:

- persistent pain
- breakthrough cancer pain (BTP)
  - unpredictable
- related to movement (incidental)

Pain Definitions

Baseline persistent pain:

Constant or continuous pain that is experienced by the pt for more than 12 h/d

Breakthrough cancer pain:

A transitory exacerbation of pain that occurs on a background of stable (persistent) pain in pts receiving chronic opioid therapy

Pain Definitions

Incident Pain:

Caused by movement (voluntary or otherwise), cutaneous wounds, dressing changes, toileting, cough, etc.

Often predictable

Due to somatic, visceral, neuropathic pain

Related to baseline pain mechanism/cancer

Portenoy R *Sem Onc* 1997; 24(S16):7-12
Pain Definitions

Over the past 20 yrs, interest in BTP has grown:

- increased awareness of the condition
- increased research by medical community
- increase in pharmacological options available

Typical episode of BTP

- Excessive sedation
- Baseline opioid

Time

Incident

Pain

Bennett D et al P&T 2005;30:296–301
## Clinical Features of BTP

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to peak severity</td>
<td>3–5 minutes</td>
</tr>
<tr>
<td>Intensity</td>
<td>Severe or excruciating</td>
</tr>
<tr>
<td>Duration of episode</td>
<td>15–30 minutes</td>
</tr>
<tr>
<td>Number of episodes/day</td>
<td>1–5</td>
</tr>
<tr>
<td>Precipitated by an event†</td>
<td>55–60%</td>
</tr>
<tr>
<td>Predictable†</td>
<td>50–60%</td>
</tr>
</tbody>
</table>

Bennett D et al P&T 2005;30:296–301
## Features of uncontrolled baseline pain vs BTP

<table>
<thead>
<tr>
<th>Uncontrolled baseline pain</th>
<th>BTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Baseline pain is unacceptably high and is present for long periods of time (^1)</td>
<td>• A transient worsening of pain above the background pain level that lasts a few minutes (^2)</td>
</tr>
<tr>
<td>• Baseline pain is not well controlled (^1)</td>
<td>• Baseline pain is generally well controlled (^2)</td>
</tr>
<tr>
<td>• Arises due to the need for more aggressive treatment (^2)</td>
<td>• May be evoked by an activity or event (^2)</td>
</tr>
</tbody>
</table>

End-of-dose Pain

Sometimes classed as subtype of BTP

Not a true type of BTP; truly inadequately controlled baseline pain

Due to inadequate analgesic dose or declining analgesic levels at end of treatment period
characterized by gradual onset of intensity
is longer in duration
treated by adjusting background analgesic dose

Economic Burden of BTP

BTP is associated with high direct medical costs

US-based telephone survey of chronic pain pts:
those with BTP incurred approx 5x higher costs than those without d/t increased:
  hospitalizations
  emergency department visits
  physician office visits

Assessment of Pain

Comprehensive assessment of pain is optimal
Best treatments can be selected for baseline pain and BTP

Assessment focuses on patient self-assessment, pain history and physical examination to determine:
- Characteristics and location of the pain
- Frequency and duration of episodes
- Usual around-the-clock (ATC) medications and precipitating factors
- Effectiveness of existing pain medications
- Impact on the pt’s quality of life

Bennett D et al. P&T 2005;30:296–301
SIGN Guideline 106: Control of pain in adults with cancer. 2008
Assessment of Pain

Current Management of BTP

- Rule out treatable causes of pain
- Around-the-clock analgesia for baseline pain, as-needed analgesic for BTcP
- Use patient diary & non-pharmacological options
- Reassessment of pain and patient outcomes
- Effective analgesia increased patient function
- Baseline persistent pain controlled BTcP unchanged
- Refer to pain specialist
  1. Dose-limiting toxicities
  2. Aberrant drug behaviours

Modify treatment

- Successful
- Unsuccessful

Continue to reassess
1. Ongoing use of patient diary
2. Assess for the 4 As*

*The “four As” are analgesia, activities of daily living, adverse events, and aberrant drug-related behavior.

Reproduced from Bennett et al

Non-pharmacological Management

Cost-effective
Simple
No side effects or drug–drug interactions

Options include:
- Limitation of activities
- Ice or heat
- Corsets and bandages
- Counter-irritant creams
- Physical med techniques
- Patient education

Non-pharmacological interventions integrated with medical therapy to help relieve BTP

One approach to BTP therapy: increase dose of baseline analgesia or shorten dosing interval.¹


Adapted from Bennett¹, Simmonds³ and Coluzzi⁴
“You might at first experience a hint of drowsiness...”
# Morphine for treatment of BTP?

<table>
<thead>
<tr>
<th></th>
<th>Breakthrough cancer pain episode (typical)(^1)</th>
<th>Immediate-release morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Rapid and abrupt</td>
<td>Onset of analgesia after ≥30 minutes(^2)</td>
</tr>
<tr>
<td><strong>Peak</strong></td>
<td>Peak intensity reached within 3–5 minutes</td>
<td>Peak analgesic effect after 40–60 minutes(^3)</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>15–30 minutes</td>
<td>4 hours(^2)</td>
</tr>
</tbody>
</table>

Ideal analgesic for BTP

**Ideal agent:**
- Potent opioid, pure μ agonist
- Rapid onset, early peak effect
- Short duration
- Easily administered in all environments (hospital, home, LTC, PCH)
- Safely given to pts with advanced illness
Ideal analgesic for BTP

## Fentanyl

<table>
<thead>
<tr>
<th></th>
<th>Breakthrough cancer pain episode (typical)¹</th>
<th>Oral transmucosal fentanyl citrate²,³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Rapid and abrupt</td>
<td>Onset of analgesia after ∼5–10 minutes</td>
</tr>
<tr>
<td><strong>Peak</strong></td>
<td>Peak intensity reached within 3–5 minutes</td>
<td>Peak analgesic effect after ∼20 minutes</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>15–30 minutes</td>
<td>1–2 hours</td>
</tr>
</tbody>
</table>

Fentanyl Citrate

Lipophilic opioid analgesic
potency 100 times morphine

Well suited to oral transmucosal delivery
Quickly crosses cellular barriers, providing broad
tissue distribution and rapid onset of action

Oral transmucosal fentanyl citrate (OTFC)
First rapid-onset opioid approved for
treatment of BTP
Recommended by European Association of
Palliative Care

Abstral™ Product Monograph
Bennett D *et al.* P&T 2005;30:354–361

Actiq® Cephalon 2009
Hanks GW *et al.* Br J Cancer 2001;84:587–593
Oral Fentanyl Citrate vs Oral Morphine

Breakthrough cancer pain: a randomised trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR)

RCT in 134 adult cancer patients compared OTFC with MSIR

Key results:

- Mean pain intensity, pain intensity difference and pain relief scores all significantly better with OTFC vs MSIR at all time points

94% of patients chose to continue with OTFC in an open-label follow-on study vs 6% opting for MSIR

Oral Transmucosal Administration

Convenient and easy to use

Characteristics that facilitate rapid absorption:
- large surface area
- high permeability
- high vascularity
- uniform temperature

High bioavailability, due to avoidance of first-pass metabolism

Simmonds MA. Oncology 1999;13:1103–1108
## Incident Pain and Incident Dyspnea Protocol

<table>
<thead>
<tr>
<th>Step</th>
<th>Medication</th>
<th>Dose SL (50 µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fentanyl</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>Fentanyl</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>Sufentanil</td>
<td>12.5</td>
</tr>
<tr>
<td>4</td>
<td>Sufentanil</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>Sufentanil</td>
<td>50</td>
</tr>
</tbody>
</table>

WRHA Palliative Care Subprogram  
2000
New Fentanyl Products

Sublingual quick dissolving tablet-Abstral
Buccal quick dissolving film-withdrawn
“Lollipop”-Actiq
Pectin nasal spray-Fentora
“Actually, all the leading pain relievers act the same, though some may be quicker-acting than others.”
Dosage and Administration

To administer: tablet is placed under tongue and allowed to dissolve completely. Chewing, sucking or swallowing can result in reduced absorption and low plasma concentrations.
Oral Fentanyl in a Real-life Clinical Setting

92 yo woman with metastatic breast cancer, widespread bony disease
LA hydromorphone, fentanyl patch, methadone had some benefit, but still movement/BT pain
QoL affected-mobility, socialization
Trial in clinic: 100 mcg dose, easily tolerated, effective in 10 min
“My pain is gone!” Walking much easier
Continuing use at 100 mcg dose
Summary

Breakthrough/incident pain a problem for many cancer patients
Assessment important for proper therapy
Fentanyl, a potent opioid, shown to be effective therapy
Easily administered formulations available
Questions?

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Pharmacology of Rapid Onset Opioids

Different proportions of mucosal vs. oral absorption mean that patients can have different bioavailability between the ROOs. Patients therefore need to be titrated on each ROO, and not simply switched dose-for-dose between ROOs.

**ROO Pharmacology***

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Abstral</th>
<th>Actiq</th>
<th>Fentora</th>
<th>Onsolis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute bioavailability</td>
<td>54%</td>
<td>50%</td>
<td>65%</td>
<td>71%</td>
</tr>
<tr>
<td>Buccal absorption</td>
<td>mainly through the oral mucosa</td>
<td>25%</td>
<td>48%</td>
<td>51%</td>
</tr>
<tr>
<td>Tmax</td>
<td>30-60 min</td>
<td>20-40 min</td>
<td>35-45 min</td>
<td>60 min</td>
</tr>
</tbody>
</table>

*Clinical significance has not been established

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1. Abstral, Product monograph Feb 2011
3. Onsolis, Product monograph May 2010
# Opioids in Comparison

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Equiv/Lipid sol</th>
<th>Onset (min)</th>
<th>Peak effect (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10/ 1.4</td>
<td>7.5</td>
<td>25</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1-0.2/ 816</td>
<td>1.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.01-.04/ 1727</td>
<td>1.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>0.4-0.8/ 129</td>
<td>0.75</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**Elimination**

- Hepatic metabolism
  - fentanyl/sufentanil: oxaadative dealkylation
- Renal clearance
  - fentanyl <6%, sufentanil 0.6%

Single IV bolus dose studies