Fentanyl

What’s New, and What’s Not, But Might Be Interesting Anyway...

CAGPO
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Disclosure Statement

• I have no ongoing financial / business affiliation with any company

• Within the past 3 years, I have received speaker’s honoraria from Paladin Labs (Abstral) and Valeant (Onsolis)
Roundtable

New Opioids: Expensive Distractions or Important Additions to Practice?

Charles F. von Gunten, M.D., Ph.D.1 Eduardo Bruera, M.D.,2 Rosene D. Pirrello, R.Ph.,1,3 and Russell K. Portenoy, M.D.4-6
Fentanyl

- opioid agonist
- 80-100 x more potent than morphine
- lipophilic
- high volume of distribution
- short distribution $T_{1/2}$ (1-2 minutes)
- relatively long elimination $T_{1/2}$ (3.1-7.9h)
- blood-brain equilibration $T_{1/2} = 6$ min
  $(c/w 15-20$ min for morphine)
more fentanyl..

• metabolism hepatic, mostly CYP3A4
• one of our opioids of choice in renal failure
• bioavailability:
  – transdermal 92 %
  – intranasal  89 %
  – buccal     50 %
  – ingested  33 %

(all approximate and considerably variable)
“80-100 x more potent than morphine”

Meaning that

100 ug of fentanyl

is equivalent to

8 - 10 mg (8000 – 10 000 ug) of morphine

(via the same route)
Interesting fact # 1

2002 : Moscow Hostage Crisis

800 hostages held by Chechen rebels in Moscow theatre

‘gas’ used to quickly subdue everyone in the building later identified as 3-methylfentanyl, aerosolized with halothane

117 hostages died, ~ 50 rebels died/shot
Availabilities

• injectable (50 ug/mL)
• transdermal patch
• sublingual / buccal tablet
• transmucosal film
• intranasal
Implications of lipid solubility / high distribution volume

<table>
<thead>
<tr>
<th>Fentanyl given as:</th>
<th>T½ (‘context-sensitive’)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV bolus</td>
<td>2 minutes</td>
</tr>
<tr>
<td>20 minute infusion</td>
<td>8 minutes</td>
</tr>
<tr>
<td>30 minute infusion</td>
<td>12 minutes</td>
</tr>
<tr>
<td>60 minute infusion</td>
<td>19 minutes</td>
</tr>
<tr>
<td>4 hour infusion</td>
<td>2 hours</td>
</tr>
<tr>
<td>8 hour infusion</td>
<td>4 hours</td>
</tr>
<tr>
<td>12 hour infusion</td>
<td>5 hours</td>
</tr>
</tbody>
</table>
Transdermal (100ug patch) Fentanyl  (n=10)

Average time to Cmax from first patch = 36 hours, although essentially levels off by 12-24 hours
Some continued rise in serum levels over first few patch applications
Average time for levels to fall 50% after removal = 17 hours
Why Make a New Delivery System?

- can give bigger doses
- can give more accurate doses
- aid mucosal adherence
- attenuate peak plasma concentration
- can be patented
How do (some of) the new fentanyl products compare against one another?
<table>
<thead>
<tr>
<th>Product</th>
<th>FBSF</th>
<th>FBT</th>
<th>OTFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Bioavailability</td>
<td>71%</td>
<td>65% (±20%)</td>
<td>47%</td>
</tr>
<tr>
<td>Fraction Absorbed</td>
<td>51%</td>
<td>48% (±31.8%)</td>
<td>22%</td>
</tr>
<tr>
<td>Transmucosally</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; 800 µg (min)</td>
<td>60 (45-240)</td>
<td>40 (25-180)</td>
<td>25 (20-120)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; 800 µg (ng/mL)</td>
<td>1.67±0.75</td>
<td>1.59±0.90</td>
<td>1.26±0.41</td>
</tr>
<tr>
<td>AUC (hr·ng/mL)</td>
<td>14.46±5.4</td>
<td>9.05±3.72</td>
<td>4.79±1.96</td>
</tr>
</tbody>
</table>

fbsf = fentanyl buccal soluble film (onsolis)
fbt = fentanyl buccal tablet (abstral, fentora)
otfc = oral transmucosal fentanyl citrate (actiq)


## Pharmacology of Rapid Onset Opioids

<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

- 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

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1. Abstral, Product monograph Feb 2011
3. Onsolis, Product monograph May 2010
Interesting fact # 2

fentanyl: LD50 for monkeys = 0.03 mg/kg

(ie 600 ug of fentanyl will kill 50% of 20 kg monkeys)

LD50 for rats is 2.3 mg/kg iv, 1.0 mg/kg im
Breakthrough Pain - Definition

a transitory flare of pain that occurs on top of a background of otherwise controlled persistent pain.


Or, More Simply:

Does the patient have background pain?
(= pain present for >12 h/d during previous week, or would be present if not taking analgesic)

Yes

Is background pain adequately controlled?
(= pain rated as ‘none’ or ‘mild’, but not ‘moderate’ or ‘severe’ for >12 h/d during previous week)

Yes

Does the patient have transient exacerbations of pain?

Yes

Patient has breakthrough pain!

Portenoy et al, 1999
Breakthrough Pain - Classification

1. Incidental / Provoked
   (may or may not be predictable or under the patient’s control.)

2. Idiopathic / Spontaneous

   (3. End-of-Dose Failure)
Breakthrough Pain - Characteristics

*Episodes of BTP typically:*

Reach peak severity in 3 - 5 minutes

Severe or excruciating in severity

Last between 15 - 30 minutes

Occur 1 - 5 times per day

Pharmacological management of breakthrough cancer pain

Current approaches to the pharmacological management of BTcP include:

– increased dose of ATC analgesia for baseline pain
– addition of rescue analgesia:
  immediate-release opioids
– adjuvant therapies

Fentanyl: appropriate pharmacokinetics for treatment of breakthrough cancer pain

- OTFC has a time–action profile that closely matches the temporal characteristics of BTcP episodes:

<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 in (previous) Real Life

SC administration of 200ug fentanyl
• Tmax – median 15 minutes (range 10-30)
• Cmax – median 0.55 ng/mL (range 0.28-0.87)
• terminal ½ life = 10 hours (5.48 – 16.37h)

c/w: T½ 2.1 hours for morphine sc, 1.6 im
Tmax for im morphine = 20-21 min
Tmax for sc morphine = 15-16 min
Warning:

Many graphs coming up.
Efficacy of Abstral in patients with cancer:
Phase III Secondary endpoint

- Greater improvements in pain intensity difference were observed with Abstral versus placebo from 10 minutes post-dose
  - Significant differences were maintained throughout the 60-minute assessment period (Abstral versus placebo, p≤0.0055)

What the Terms Mean

• “Statistically significant difference”
  – between fentanyl product and placebo in mean pain intensity difference

• “Clinically Significant Difference”
  – variably defined, but takes longer
FBSF – serum concentrations with various doses

FBT Pharmacokinetics – single/multiple doses

( dose = 400 ug )
multiple = q6h x 8 days

Oral transmucosal administration

• Convenient and easy to use\(^1\)

• Takes advantage of characteristics of the oral mucosa that facilitate rapid absorption:\(^2\)
  – large surface area
  – high permeability
  – high vascularity
  – uniform temperature

• Associated with high bioavailability, due to avoidance of first-pass metabolism\(^3\)

Sublingual versus buccal administration

- The buccal mucosa is less permeable than the sublingual mucosa,\(^1\) therefore:
  - it may not provide the rapid absorption and good bioavailability associated with sublingual drug administration\(^1\)
  - a large proportion of fentanyl may be swallowed (49\%)\(^2\)
  - buccal administration may require prolonged contact between the treatment drug and the mucosa\(^2\)

*Limitations of buccal administration highlight the need for alternative oral transmucosal formulations of fentanyl*

2. Onsolis Product Monograph (May 2010)
Buccal or Sublingual?

ie Abstral / Fentora

Fentanyl buccal tablet 400 ug given to 90 randomized subjects (with naltrexone to minimize actual opioid effect)

<table>
<thead>
<tr>
<th></th>
<th>time to Cmax</th>
<th>AUC to Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buccal</td>
<td>0.75 (0.33-3.13) h</td>
<td>0.35 (0.16) ng</td>
</tr>
<tr>
<td>Sublingual</td>
<td>0.78 (0.17-3.00) h</td>
<td>0.35 (0.16) ng</td>
</tr>
</tbody>
</table>

*(Pooled other data: tablet 0.67 h, FBSF 1.0 hours)*

Darwish M et al, Clin Drug Investig. 2008;28(1)1-7
Relative Equivalence

(How does this translate to opioids I know already?)
## Typical Opioid Equivalence Table

<table>
<thead>
<tr>
<th>DRUG</th>
<th>PARENTERAL (IV/SC/IM)</th>
<th>ENTERAL (PO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>morphine</td>
<td>5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>hydromorphone</td>
<td>1 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>oxycodone</td>
<td>n/a</td>
<td>5 – 7 mg</td>
</tr>
<tr>
<td>fentanyl</td>
<td>50 ug (0.05 mg)</td>
<td>n/a</td>
</tr>
<tr>
<td>methadone</td>
<td>• consult / n/a</td>
<td>1 mg (* variable)</td>
</tr>
</tbody>
</table>
Conversion to Patch - “Guidelines”

* Approach with Caution *
(Manufacturer’s Table)

<table>
<thead>
<tr>
<th>TABLE C DOSE CONVERSION GUIDELINES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current Analgesic</strong></td>
</tr>
<tr>
<td>__________________</td>
</tr>
</tbody>
</table>

Alternatively, for adult and pediatric patients taking opioids or doses not listed in TABLE C, use the conversion methodology outlined above with TABLE D. TABLE C should not be used to convert from fentanyl transdermal system to other therapies because this conversion to fentanyl transdermal system is conservative. Use of TABLE C for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible (see DOSAGE AND ADMINISTRATION, Discontinuation of Fentanyl Transdermal System).

| Oral morphine | 60 to 134 | 135 to 224 | 225 to 314 | 315 to 404 |
| IM/IV morphine | 10 to 22 | 23 to 37 | 38 to 52 | 53 to 67 |
| Oral oxycodone | 30 to 67 | 67.5 to 112 | 112.5 to 157 | 157.5 to 202 |
| IM/IV oxycodone | 15 to 33 | 33.1 to 56 | 56.1 to 78 | 78.1 to 101 |
| Oral codeine | 150 to 447 | 448 to 747 | 748 to 1047 | 1048 to 1347 |
| Oral hydromorphone | 8 to 17 | 17.1 to 28 | 28.1 to 39 | 39.1 to 51 |
| IV hydromorphone | 1.5 to 3.4 | 3.5 to 5.6 | 5.7 to 7.9 | 8 to 10 |
| IM meperidene | 75 to 165 | 166 to 278 | 279 to 390 | 391 to 503 |
| Oral methadone | 20 to 44 | 45 to 74 | 75 to 104 | 105 to 134 |
| IM methadone | 10 to 22 | 23 to 37 | 38 to 52 | 53 to 67 |
| Recommended fentanyl transdermal system dose | 25 mcg/hr | 50 mcg/hr | 75 mcg/hr | 100 mcg/hr |

↓  ↓  ↓  ↓
Relative Equivalence # 1

In a 1999 study using OTFC (lozenge), relative potency of OTFC to IV morphine was about 10:1 (range 8 - 14)

** In contrast to IV fentanyl, which we would usually think of as about 80-100 times more potent.

Relative Equivalence Revisited

100ug fentanyl  ~  4.5mg IV morphine
(single-dose, hyperthermia/pupillary response)

• Saunders et al, J Clin Pharm 2012
Equivalence to what we’re used to?

In a 2008 study,

Patients receiving a mean oral morphine dose of 132 mg (daily) required 800 ug of oral transmucosal fentanyl citrate after dose titration for BTP episodes.

\[
\frac{c/w \text{ (expected)}}{10\% \text{ of daily dose of morphine}} = \text{about 15 mg po morphine, or about 7.5 mg iv morphine, equivalent to } \sim 75 \text{ ug iv fentanyl}\]

\[
\text{ie about four x different?}
\]

\[
\text{ie about ten x different?}
\]

Oxycodone IR & Buccal Fentanyl

Oxycodone IR & Buccal Fentanyl

dose-finding comparison study

Take-Home Message

• Equivalence is difficult to predict
• But these are **NOT IV fentanyl**, 
• And substituting IV fentanyl 400ug for a patient’s 400ug buccal fentanyl product runs a substantial risk of overdose
• Individual titration is necessary
Fentanyl Buccal Tablets for Breakthrough Pain in Highly Tolerant Cancer Patients: Preliminary Data on the Proportionality Between Breakthrough Pain Dose and Background Dose (Mercadante, JPSM, Sept 2012)

- All pts on >500mg/day morphine equivalent
- N= 12 patients, 79 ‘events’ (episodes of BTP)
- BT Fentanyl Tablet dose chosen based on amount of baseline opioid, proportionally:
  - 600 mg morphine / day - got 1000ug fent tab
  - 900 mg morphine / day - got 1500ug fent tab
- Range of fentanyl administered: 1200-4000 (mean 2233mg)
- Well tolerated
- Effective (15 minutes after FBT, 33% reduction in pain in 14 events, 50% reduction in 48 events).
- (data missing on 11 episodes, and 6 of 79 episodes not successfully treated with this regimen)

Take Home: for highly opioid tolerant cancer patients, you may want to start higher than 100ug buccal tabs.
(although this is not part of the official product monograph)
Fentanyl Products - Pharmacokinetics

Mel Davis’s Take:

Fentanyl Intranasal vs. Morphine IR tabs:

33.9% responders at 10 min with IN fentanyl versus

28.3% responders at 10 min with IR morphine

NNT = 18


Mel Davis’s Take:

Fentanyl Intranasal vs. Morphine IR tabs:

55.4% responders at 15 min with IN fentanyl versus
47.3% responders at 15 min with IR morphine

NNT = 12


<table>
<thead>
<tr>
<th>Abstral</th>
<th>Onsolis</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 ug $10.60</td>
<td>200 ug $12.00</td>
</tr>
<tr>
<td>200 ug $12.00</td>
<td></td>
</tr>
<tr>
<td>300 ug $14.39</td>
<td></td>
</tr>
<tr>
<td>400 ug $16.35</td>
<td>400 ug $16.35</td>
</tr>
<tr>
<td>600 ug $21.81</td>
<td>600 ug $21.81</td>
</tr>
<tr>
<td>800 ug $27.26</td>
<td>800 ug $27.26</td>
</tr>
<tr>
<td></td>
<td>1200 ug $30.00</td>
</tr>
</tbody>
</table>

Hospital formulary cost of 100ug injectable fentanyl: ~ $0.39
Hospital formulary cost of 10 mg injectable morphine: $0.55 (10 mg/mL) $0.21 (15 mg/mL)
Or 25 mg po morphine: $0.22
Interesting Fact # 3

Newish drug:

**prucalopride** (Resotran) – 5 HT4 receptor agonist

*(devoid of cardiac HERG-1 receptor activity)*

indication: stimulation of colonic motility (chronic constipation)

(and not at all related to fentanyl)
And what are the alternatives?
Fentanyl and Sufentanil

- both synthetic μ agonist opioids
- highly lipid soluble
  - transmucosal absorption; effect in approx 10 min
  - rapid redistribution, including in / out of CSF; lasts approx 1 hr.
- fentanyl » 100x stronger than morphine
- sufentanil » 1000x stronger than morphine

10 mg morphine

\[ \approx 10 \ \mu g \text{ sufentanil} \]
\[ \approx 100 \ \mu g \text{ fentanyl} \]
**INCIDENT PAIN PROTOCOL** (winnipeg)

<table>
<thead>
<tr>
<th>Step #</th>
<th>Medication (50 μg/ml)</th>
<th># Micrograms Sublingually</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fentanyl</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>Sufentanil</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>Sufentanil</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>Sufentanil</td>
<td>100</td>
</tr>
</tbody>
</table>

(see also http://palliative.info)
fentanyl or sufentanil is administered SL 10 min. prior to anticipated activity
repeat q 10min x 2 additional doses if needed
increase to next step if 3 total doses not effective
physician order required to increase to next step if within an hour of last dose
the Incident Pain Protocol may be used up to q 1h prn
Effervescent Morphine Results in Faster Relief of Breakthrough Pain in Patients Compared to Immediate Release Morphine Sulfate Tablet

Enno Freye, MD, PhD*; Joseph Victor Levy, MS, PhD†; Dagmar Braun, MD‡

*Department of Vascular Surgery and Renal Transplantation, University Clinics, Düsseldorf, Germany; †Department of Research and Development, Riemser Pharmaceutical, Greifswald-Riems, Germany; ‡Department of Physiology and Pharmacology, University of the Pacific School of Dentistry, San Francisco, California, U.S.A.

Abstract: Morphine tablets have been formulated to produce an easily ingested effervescent solution when placed in water. It was hypothesized that an aqueous solution would result in fast gastrointestinal transit with a more rapid onset of action compared to immediate release morphine sulfate (IRMS), which would be especially beneficial in treating breakthrough pain (BTP). In an open-label safety and efficacy study, effervescent morphine was given to 76 chronic cancer pain patients for treatment of BTP evaluating time until pain relief, global satisfaction and side effects. Results were compared to those obtained using an IRMS formulation in a preceding run-in period. For BTP, a mean dose of 28 mg of effervescent morphine (range 10–80 mg) resulted in a highly significant reduction of pain score (mean 7.8 to mean 3.2; P < 0.001). Efficacy was not different from that observed with IRMS. However, mean time until sufficient pain relief was significantly shorter than with IRMS (13 ± 5.6 vs. 27 ± 4.4 minutes; P < 0.01). The incidence of side effects was similar with the new morphine formulation and with IRMS. There was no relationship between the previous dose of the daily opioid and the effective dose of effervescent morphine. The dose for treatment of BTP was determined by individual titration and not predicted by the dose taken with the basic pain medication. Compared to IRMS, overall satisfaction for effervescent morphine was rated “superior” by 16.7%, and “better” by 63.2% of patients. Effervescent morphine offers an alternative for management of breakthrough cancer pain compared with the commonly used IRMS. ■

Key Words: breakthrough pain, effervescent morphine, morphine immediate release, cancer pain

INTRODUCTION

Although it has been estimated that cancer pain can be effectively managed in 70–90% of patients by the use of medications listed in the WHO analgesic protocol,

13 minutes (effervescent) vs 27 (IR tab) to ‘sufficient pain relief’

Intranasal Fentanyl / Sufentanil injectable solutions?

[50ug/mL]
some thoughts on “off-label” use
some thoughts on formulary issues
Summary Points

• substantial variability from product to product
• fentanyl buccal tablet is the only formulation currently available in Canada
• main (only, at present) on-label indication is for cancer-related breakthrough pain
• individual dose titration necessary
• * NOT equivalent to IV fentanyl dose *
• cost concerns limit formulary approval & availability at present, although many third-party plans do cover
Questions?

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