Recent and upcoming approaches in the management of cancer breakthrough pain

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SUMMARY POINTS

- The pharmacokinetics of the traditional oral opioids do not match the time course of breakthrough cancer pain, a common and distinct component of cancer pain which has a negative impact on quality of life for the patient.
- Fentanyl and alfentanil are potent, lipophilic, fast acting opioids with short durations of action and consequently more appropriate for the treatment of breakthrough cancer pain. These agents are ideal for oral transmucosal or nasal transmucosal administration.
- There are now four licensed preparations of fentanyl in the UK for the treatment of cancer breakthrough pain; lozenge, buccal tablet, sublingual tablet and nasal spray. They are not interchangeable and all require titration using the lowest dose.
- Alfentanil is available as a buccal or nasal spray. It is an unlicensed product and is available as a special order from Torbay Pharmacy Manufacturing Unit.
- There is a paucity of comparator studies for these new modes of administration.
- Further innovative delivery systems of fentanyl are on the horizon.

Introduction

The definition and appropriate management of cancer-related breakthrough pain has been the subject of much discussion within the palliative medicine fraternity in recent years. This distinct component of cancer pain negatively impacts on the quality of life for the patient and studies have found that up to 95% of patients with background pain experience breakthrough pain.¹

Definition, characteristics and current management

A recent task group from the Association of Palliative Medicine of Great Britain and Ireland defined breakthrough cancer pain (BTCP) as “a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, experienced by patients who have relatively stable and adequately controlled background pain”. Incident pain (precipitated by movement or activity and further divided into volitional, non-volitional and procedural) and spontaneous pain, falls within this definition.²

The results from the first phase of an ongoing international, multicentre observational study that surveyed 200 patients with

BTCP from the UK, Sweden and Denmark, found that patients experienced 3 episodes per day with a median duration per episode of 60 minutes. Patients described these as moderate to severe in 96% of episodes. Activities of daily living including ability to sleep, walk and get on with other people were affected in 90% of patients. Oral drugs were used as rescue medication in 95% of patients with a median time of 20 minutes to first noticing a reduction in pain and a median time to peak effect of 30 minutes.³

Current management uses supplemental analgesia (rescue medication) at a dose proportional to the total round the clock opioid dose. However, the pharmacokinetics of the oral opioids used to relieve BTCP e.g. morphine sulphate immediate release/oxycodone immediate release, do not match the time course of BTCP. These agents take 20 – 30 minutes to onset of action with a duration of approximately 4 hours. Multiple use of such analgesic agents results in ineffective treatment of BTCP episodes together with the additional problem of increased adverse effects, particularly sedation and confusion.

New approaches that better reflect the nature of BTCP are required. Potent agents with fast onset and short duration are preferable; fentanyl and alfentanil are two such agents.

Agents

Fentanyl is a synthetic opioid phenylpiperidone derivative with agonist activity at the mu-opioid receptor. It is sequestered into body fat and acts predominantly supraspinally in the thalamus with a minimal effect on the dorsal horn. It is highly lipophilic and crosses the blood brain barrier better than morphine. It has approximately 100 times the potency of morphine and causes less constipation, nausea and vomiting. Metabolism is by CYP3A4 to norfentanyl, an inactive metabolite. In renal impairment, fentanyl is relatively safe, although clearance may be reduced. It has a rapid onset and short duration of action with peak effects within 30 minutes. 100mcg given by intravenous injection produces analgesia for 10 to 20 minutes, while 1000mcg produces analgesia for 60 minutes.^{4,5}

The transdermal preparation of fentanyl is used in palliative care patients for background analgesia.

Alfentanil is a synthetic opioid with activity at the mu-opioid receptor. When given intravenously the peak analgesic effect occurs within 90 seconds and lasts for 5-10 minutes. When compared with fentanyl after single intravenous doses, it has a more rapid onset of action (0.75 minutes vs 1.5 minutes), a shorter duration of action (30 minutes vs 60 minutes)^{6,7,8} and an analgesic potency approximately one quarter that of fentanyl; it has approximately 20 times the potency of parenteral morphine.⁹ Elimination is mainly by metabolism in the liver with an elimination half-life of 90 minutes. It is licensed for intravenous (IV) injection or infusion.¹⁰ It is used as a step 3 analgesic in palliative care patients with renal impairment and is given by subcutaneous (SC) injection or continuous SC infusion both of which are off-licence routes of administration.

New routes of administration

While there have been no new opioids introduced to the UK market since tramadol in 1994,¹¹ there has been a move in recent years by pharmaceutical companies to use different routes of administration for older established analgesic agents in combination with novel technology. The use of different transmucosal routes e.g. buccal, sublingual or nasal has specific advantages over the oral route; the large surface area which is well vascularised and highly permeable results in efficient drug absorption through the mucosal surface and rapid drug transport to the systemic circulation avoiding the gastrointestinal tract and first pass hepatic metabolism.¹²

Because of their high lipophilicity and consequent poor oral bioavailability, fentanyl and alfentanil are ideal for oral transmucosal or nasal transmucosal administration.

Products

Alfentanil has been available as a buccal/nasal spray for several years. This is an unlicensed product manufactured under a special licence by Torbay Pharmacy Manufacturing Unit (www.torbaypmu.nhs.uk).

It is formulated as a 5mg/5ml solution and comes with both buccal and nasal spray adaptors. Once opened it is stable for 28 days. Each 0.14ml actuation contains 140mcg alfentanil. Doses range from 2 to 12 sprays (280mcg to 1680mcg alfentanil). It is appropriate for BTCP but is of limited use due to the low concentration and resulting impracticality around the number of sprays required. It may have a place for short, planned procedural episodes eg dressing changes.

Several relevant formulations of Fentanyl for BTCP are now available (see Table 1):

- Lozenge (Actiq®) introduced in 2002; each oral transmucosal fentanyl citrate (OTFC) compressed lozenge has an integral oromucosal applicator and is intended for buccal administration.¹³
- Buccal tablet (Effentora®) introduced in April 2008; uses a delivery technology which produces an effervescent reaction that enhances the rate and extent of Fentanyl absorption through the buccal mucosa. Transient pH changes optimise dissolution and membrane permeation.¹⁴
- Sublingual tablet (Abstral®) introduced in September 2008; a quick dissolving sublingual tablet formulation. Within the tablet, ordered units of fine drug particles are attached to coarser carrier particles. Rapid disintegration of the tablet occurs; the ordered units adhere to the oral mucosa, the carrier particles dissolve and release the active compound which dissolves and is absorbed over the oral mucosa.^{15,16}
- Nasal spray (Instanyl®) introduced in October 2009, the first nasal preparation of Fentanyl and buffered with phosphate solution.¹⁷

All these products are licensed for breakthrough pain in patients using opioid therapy for chronic cancer pain taking at least 60mg oral morphine or its equivalent per day or at least 25mcg/hour of fentanyl transdermal for at least a week.

All apart from the lozenge (Actiq®) are intensively monitored medicines identified by the black triangle symbol (▼) in the BNF. Such drugs are monitored intensively by the Commission on Human Medicines (CHM) and the Medicines and Healthcare products Regulatory agency (MHRA). All suspected adverse reactions should be reported to the MHRA via the yellow card reporting scheme (<http://yellowcard.mhra.gov.uk>).¹⁸

Evidence

The evidence base supporting the efficacy and safety of these new formulations is generally poor with few published studies; the majority are comparisons against placebo. Currently there are minimal comparator studies and none with the standard treatment, morphine immediate release oral solution.

Intranasal fentanyl versus OTFC

A multinational, open label, cross-over study compared the efficacy of fentanyl intranasal, Instanyl® (INFS) with that of fentanyl lozenge, Actiq® (OTFC) for the relief of cancer related breakthrough pain. 196 patients were recruited from 44 study centres. Those enrolled were experiencing from 3 episodes of breakthrough pain per week to 4 episodes per day. 139 patients were randomised; 79 male and 60 female with a mean age of 62. 86 patients completed the study. 53 patients discontinued during the titration and efficacy phases; 17 due to adverse effects, 11 withdrew consent, 8 were not successfully titrated, 5 were not stable and 12 withdrew for other reasons.

The primary outcome measure was the time to 'meaningful' pain relief as determined by the patient using a stopwatch. This method was selected to ensure a patient-centred and clinically relevant endpoint. Secondary outcome measures were pain intensity at 60 minutes post-dose, patient's general impression of drug efficacy at 60 minutes, ease of drug administration and incidence and nature of adverse effects. An intention to treat analysis of all randomised patients was performed. 85.1% of patients reached an effective dose of INFS and 87.9% reached an effective dose of OTFC. The median time to onset of meaningful pain relief was 11 minutes for INFS and 16 minutes for OTFC. 65.7% experienced a faster onset of meaningful pain relief with INFS compared with OTFC.

The secondary outcome measures of pain intensity difference were significantly greater for INFS than OTFC from 5 minutes post-dose and clinically important pain relief ($\geq 33\%$ reduction in pain intensity) was seen 5 minutes after INFS in 25% of breakthrough pain episodes. A significant proportion of patients (77%) preferred INFS to OTFC. 90% of patients found INFS easy or very easy to use compared with 40% with OTFC. Both preparations were well tolerated. 56.8% patients experienced at least one adverse effect during the study. Nausea was the only adverse effect to occur in 5% or more in either treatment group. 15 patients discontinued due to adverse effects; the most common being nausea and vomiting.

This study is the first to compare two products specifically developed for the treatment of breakthrough pain. It does have design limitations. It was open label rather than double-blind due to practical difficulties with two completely different formulations. However the crossover design where patients acted as their own controls aimed to minimise potential confounding external factors. The comparator chosen (OTFC) was not the standard treatment for breakthrough pain (morphine immediate release oral liquid), but at the time of the study it was the only preparation with a specific marketing authorisation. It also, in terms of its pharmacokinetic profile, more closely matched the characteristics of breakthrough pain. The number of participants was relatively low and there was a high drop out rate; 38% of those randomised did not complete the study for a variety of reasons. However the sample size required to adequately power the study ($n=85$) was just achieved ($n=86$) and an intention to treat analysis was performed. It should be noted that studies in patients with advanced cancer as in this population are difficult logistically in terms of recruiting numbers because of strict exclusion criteria and in terms of the ability of the patients

to complete the study as their disease progresses. Nycomed, the manufacturer of Instanyl®, funded the study and also took responsibility for the study design and conduct.¹⁹

Practical issues

- The lozenge requires a degree of dexterity and patience by the user. It is unsatisfactory in about 25% of patients, who fail to obtain relief or have unacceptable side effects.⁴
- The buccal tablet takes up to 25 minutes to dissolve and leaves a distinct taste in the mouth.
- The buccal and sublingual tablets can be difficult to extract from their respective packaging. A specific technique is required. The nasal spray is packed in a child-resistant outer box. These packaging issues may be problematic for weak and frail patients.
- Any of the oral transmucosal preparations should be used with caution in patients with mouth wounds or mucositis as there is an increased risk of systemic opioid absorption from damaged mucosa.

Probably the most interesting difference with respect to dose titration with these new preparations is the lack of proportionality between regular background analgesic dose and breakthrough doses. All of these new products should be titrated from the lowest dose, irrespective of the level of background analgesia. It also is important to note that the lozenge, buccal, sublingual and intranasal preparations are not interchangeable. If transferring from one to another, then the new product must be re-titrated.

Forthcoming products

Nasalfent, marketed by Archimedes Pharma is a fentanyl nasal spray incorporating PecSys™ technology. Pectin, present in a low viscosity aqueous solution of fentanyl citrate, forms a thin gel layer on contact with the calcium ions present in nasal mucosal fluid. Absorption of fentanyl across the nasal mucosal membrane is modulated, allowing rapid but controlled absorption into the systemic circulation together with an increased duration of action. This technology avoids high levels of drug and dripping or swallowing of drug solution which are problems often associated with simple solutions used as nasal sprays.²² Phase 3 trial data has demonstrated pain relief within 5 minutes of dosing.²³

The manufacturer submitted a marketing authorisation application with the European Medicines Evaluation Agency in April 2009 and submitted a New Drug Application with the US Food and Drug Administration in September 2009. The product is targeted for launch from mid-2010.

Table 1: Licensed Fentanyl products for breakthrough pain

Product, formulation & cost	Dosing information	Administration method	Pharmacokinetics
Actiq® (Flynn Pharma)¹³ Fentanyl Oral transmucosal berry flavoured lozenge 200mcg, 400mcg, 600mcg, 800mcg, 1200mcg, 1600mcg £5.95 per lozenge	Initial 200mcg dose, titrating upwards until optimal dose established Repeat dose if adequate analgesia not achieved 15 minutes after dose consumed Maximum 2 units per episode Maximum of 4 doses per day once maintenance dose established	Place lozenge in mouth against the cheek and move around the mouth using the applicator to maximise the amount of mucosal exposure to the product Do not chew Consume over 15 minutes Use water to moisten the buccal mucosa in patients with dry mouth	25% dose absorbed from buccal mucosa 75% dose swallowed and absorbed from GI tract Bioavailability 50% Maximum plasma concentration 20 to 40 minutes after dose Pain relief seen within 15 minutes post dose ²⁰
Effentora® (Cephalon)¹⁴ Fentanyl buccal tablet 100mcg, 200mcg, 400mcg, 600mcg, 800mcg £5.14 per tablet	Initial 100mcg dose, titrating upwards until optimal dose established Maximum 2 tablets per episode Wait at least 4 hours before treating another episode	Place tablet in the buccal cavity, near a molar between cheek and gum. Retain long enough to allow disintegration of the tablet (approx 14 – 25 minutes) Do not suck, chew or swallow Do not consume any food or drink when tablet is in buccal cavity Any remaining tablet after 30 minutes may be swallowed with water	50% dose absorbed from buccal mucosa 50% dose swallowed and absorbed from GI tract Bioavailability 65% Maximum plasma concentration 20 – 240 minutes after dose Pain relief within 10 minutes of dose
Abstral® (Prostrakan)¹⁵ Fentanyl sublingual tablet 100mcg, 200mcg, 300mcg, 400mcg, 600mcg, 800mcg £4.99 per tablet	Initial 100mcg dose, titrating upwards until optimal dose established Repeat dose if adequate analgesia not achieved within 15 – 30 minutes Max 2 tablets per episode Maximum of 4 doses per day once maintenance dose established	Place directly under the tongue at the deepest part Allow to dissolve completely without chewing or sucking Do not eat or drink anything until the tablet is completely dissolved Use water to moisten the mucosa in patients with dry mouth	Quick dissolving formulation Rapid absorption of fentanyl over 30 minutes Estimated bioavailability 70% Mean maximal plasma concentration reached within 22.5 – 240 minutes Pain relief seen within 15 minutes post dose
Instanyl® (Nycomed)¹⁷ Fentanyl nasal spray 50mcg, 100mcg and 200mcg per dose £5.95 per dose	Initial 50mcg dose, titrating upwards until optimal analgesia established Maximum 2 doses per episode separated by 10 minutes Maximum 4 episodes per day Wait at least 4 hours before treating another episode	Sit or stand in an upright position 1 spray in 1 nostril 2nd dose if required in other nostril after at least 10 minutes Clean the nasal spray tip after each use	Rapid absorption of fentanyl through nasal mucosa Bioavailability approximately 89% Time to median maximum plasma concentrations 12 – 15 minutes Pain relief within 10 minutes of dose Pain relief maintained for up to 45 minutes ²¹ Concomitant use of the nasal constrictor Oxymetazoline should be avoided (decreases nasal absorption of fentanyl)

Fentanyl BEMA (bio-erodible muco-adhesive) discs developed by BioDelivery Sciences International introduces a novel drug delivery system; a buccal soluble film consisting of a small bio-erodible polymer film for application to the inner lining of the cheek. It is designed to adhere to oral mucosa in less than 5 seconds, to optimise delivery across the oral mucosa and to completely dissolve within 15 – 30 minutes.²⁴ The fentanyl buccal soluble film (Onsolis marketed by Meda Pharmaceuticals) was approved by the FDA in July 2009 and is available in the US under a restricted distribution programme. It is available in a range of strengths; 200mcg, 400mcg, 600mcg, 800mcg and 1200mcg.

This product has an absolute bioavailability of 71%. Approximately 51% is absorbed from the buccal mucosa with the remainder swallowed and absorbed from the GI tract. Of the swallowed fentanyl approximately 20% of the dose escapes hepatic and intestinal first pass elimination and becomes systemically available.²⁵

In a study that compared the relative bioavailability of Onsolis and Actiq® in 12 adult normal volunteers, the rate and extent of fentanyl absorption were considerably greater with Onsolis (62% greater maximum plasma concentration and 40% greater systemic exposure).²⁶ Efficacy and safety in treating BTCP has been demonstrated in placebo-controlled studies.²⁷ It is currently under review in the EU with approval expected sometime in 2010. It is likely to be marketed as Breakyl.

Fentanyl multidose dry powder inhalers

At least three preparations are in development using different technologies to deliver fentanyl via the inhaled route; Fentanyl Taifun, a multi-dose dry powder inhaler,²⁸ Stacatto Fentanyl AZ-003, a breath actuated inhaler²⁹ and AeroLEF, a breath-actuated jet nebuliser.³⁰ Early reports demonstrate good efficacy in treating breakthrough pain.

Conclusion

After years of suboptimal symptomatic management of BTCP we now have access to several relevant and more appropriate licensed products, with the promise of others to follow. These utilise the pharmacokinetic properties of fentanyl and allow wider patient choice. As with any new drug delivery system there are cost implications. However in patients for whom BTCP dramatically affects their quality of life, the use of these agents may be of real benefit. More robust comparator studies are required to help guide product choice.

REFERENCES

- 1 Zepettella G, Riberio MDC Opioids for the management of breakthrough (episodic) pain in cancer patients *CDSR* 2006 Jan 25; (1) CD004311
- 2 Davies AN, Dickman A, Reid C, Stevens AM, Zepettella G. The management of cancer-related breakthrough pain: recommendations of the task group of the science committee of the association of palliative medicine of Great Britain and Ireland. *European Journal of Pain* 2009; 13: 331-8
- 3 Davies et al European survey of oncology patient's experience of breakthrough cancer pain: UK, Sweden and Denmark results. Poster presented at EFIC September 2009
- 4 Twycross R, Wilcock A Palliative Care Formulary third edition, May 2007 www.palliativedrugs.com updated June 2008 [Accessed 1 May 2010]
- 5 *Summary of Product Characteristics Sublimaze* Date of revision of text 9 September 2009 Electronic Medicines Compendium Available from <http://emc.medicines.org.uk/medicine/939/SPC/Sublimaze/> [Accessed 1 May 2010]
- 6 Willens JS, Myslinski NR Pharmacodynamics, pharmacokinetics and clinical uses of Fentanyl, Sufentanil and Alfentanil *Heart and Lung* 1993; 22: 239-251
- 7 Scholz J, Steinfath M, Schultz M Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update. *Clinical Pharmacokinetics* 1996; 31 (4) 275 – 292
- 8 Hall T, Hardy J The lipophilic opioids: Fentanyl, Alfentanil, Sufentanil and Remifentanil In: Davis M et al (eds) *Opioids in cancer pain* 2005. Oxford University Press, Oxford
- 9 Larijani G, Goldberg M. Alfentanil hydrochloride: a new short acting narcotic analgesic for surgical procedures *Clinical Pharmacy* 1987; 6: 275 – 282
- 10 *Summary of Product Characteristics Rapifen* Date of revision of the text 10th July 2009 Electronic Medicines Compendium Available from: <http://emc.medicines.org.uk/medicine/930/SPC/Rapifen/> [Accessed 1 May 2010]
- 11 Public assessment report Tramadol 50mg PL 17907/0110 MHRA 2006 <http://www.mhra.gov.uk/home/groups/lunit1/documents/websitesresources/con2025320.pdf> [Accessed 1 May 2010]
- 12 American Academy of Pediatrics, Alternative routes of drug administration-advantages and disadvantages *Pediatrics* July 1997; 100 (1) 143 – 52

- 13 *Summary of Product Characteristics Actiq* Date of revision of the text December 2009 Electronic Medicines Compendium available from:
<http://emc.medicines.org.uk/medicine/11145/SPC/Actiq/>
[Accessed 1 May 2010]
- 14 *Summary of Product Characteristics Effentora buccal tablets* Date of revision of the text 10th December 2009 Electronic Medicines Compendium available from:<http://emc.medicines.org.uk/medicine/21401/SPC/Effentora+100%2c+200%2c+400%2c+600+and+800+micrograms+buccal+tablets/> [Accessed 1 May 2010]
- 15 *Summary of Product Characteristics Abstral sublingual tablets* Date of revision of the text 19th September 2008 Electronic Medicines Compendium available from <http://emc.medicines.org.uk/medicine/21371/SPC/Abstral+Sublingual+Tablets/>
Accessed 1 May 2010
- 16 Bredenberg S, Duberg M, Lennernas B, et al In vitro and in vivo evaluation of a new sublingual tablet system for rapid oromucosal absorption using fentanyl citrate as the active substance *European Journal of Pharmaceutical Sciences* 2003; 20(3) 327-334
- 17 *Summary of Product Characteristics Instanyl* nasal spray Date of first authorisation of the text 20th July 2009 Electronic Medicines Compendium available from:
<http://emc.medicines.org.uk/medicine/22242/SPC/Instanyl+50%2c+100+and+200+mcg+dose+nasal+spray/>
Accessed 1 May 2010
- 18 British National Formulary 58, September 2009
- 19 Mercandante S, Radbruch 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, randomised, crossover trial *Current Medical Research and Opinion* 2009; 25: 11: 2805 – 15
- 20 Farrar JT, Cleary J, Rauck R et al Oral transmucosal fentanyl citrate: randomised, double-blinded, placebo-controlled trial for breakthrough pain in cancer patients *Journal of the National Cancer Institute* 1998; 90: (8) 611-616
- 21 Stam WB, Lenre M, Nolte T et al Efficacy of intranasal fentanyl spray versus oral transmucosal fentanyl citrate, fentanyl buccal tablet and oral morphine for breakthrough pain in cancer: a meta-analysis of randomised controlled trials. Poster presentation. Presented at ISPOR 11th Annual European Congress. Athens, Greece. 8-11 November 2008
- 22 www.drugs.com/nda/nasalfent_090907.html
Accessed 1 May 2010
- 23 Wallace M, Taylor D, Rauck R, Galan V, Burton A, Portenoy R Fentanyl pectin nasal spray (FPNS) with PecSys®: Efficacy, tolerability, and onset of action in the treatment of breakthrough cancer pain (BTCP) *The Journal of Pain*, 2009; 10: 4: S36
- 24 <http://www.biodeliverysciences.com/BEMA.php>
accessed 8 Jan 2010
- 25 http://www.onsolis.com/pdf/onsolis_pi.pdf accessed 1 May 2010
- 26 <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=11655#nmlm34090-1> accessed 1 May 2010
- 27 Rauck R, North J, Gever LN, Tagarro L, Finn AL Fentanyl buccal soluble film for breakthrough pain in patients with cancer: a randomised, double-blind, placebo-controlled study *Annals of Oncology*, published online 25 November 2009
<http://annonc.oxfordjournals.org/cgi/reprint/mdp541v1>
Accessed 1 May 2010
- 28 <http://www.medicalnewstoday.com/articles/47122.php>
Accessed 1 May 2010
- 29 A. Clark, M. Rossiter-Rooney, F. Valle-Leutri Aerosolized liposome-encapsulated fentanyl (AeroLEF) via pulmonary administration allows patients with moderate to severe post-surgical acute pain to self-titrate to effective analgesia *The Journal of Pain*, 2008, 9, (4) 42-42
- 30 <http://www.ymbiosciences.com/products/aerolef/index.php>
accessed 10 Jan 2010