



Observational study

The use of rapid onset fentanyl in children and young people for breakthrough cancer pain[☆]Lucy Coombes^{*}, Kimberley Burke, Anna-Karenia Anderson*Children and Young People's Outreach and Symptom Care Team, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton, SM2 5PT, England, United Kingdom*

HIGHLIGHTS

- The first paper on the use of rapid onset fentanyl in children with cancer.
- Fentanyl lozenges appear to be safe and well tolerated in children as young as five.
- Children weighing as little as 13 kg were safely given fentanyl lozenges.
- Children should be started on the lowest available dose of rapid onset fentanyl.
- Dose should be titrated according to response.

ARTICLE INFO

Article history:

Received 17 March 2017

Received in revised form 19 June 2017

Accepted 5 July 2017

Available online 10 August 2017

Keywords:

Cancer

Fentanyl

Analgesics

Opioid

Breakthrough pain

Paediatric

ABSTRACT

Background and aims: No published studies have looked at the dosing and use of rapid onset fentanyl preparations in children. The primary aim of this study was to assess whether there is a correlation between effective dose of rapid onset fentanyl and background oral morphine equivalent analgesia in children less than 18 years old. Secondary objectives included establishing whether there is a correlation between effective dose of rapid onset fentanyl and age and weight. Reported side effects were also reviewed.

Methods: This study is a retrospective case note review of all children less than 18 years old who received rapid onset fentanyl products in a tertiary paediatric oncology centre in England between 2010 and 2015. Correlations were analysed using Spearman's correlation coefficient as data was non-parametric.

Results: Data on 26 children (5–17 yrs; 13–100 kg) was analysed. The most common diagnosis in children being given rapid onset fentanyl products was a solid tumour (84.6%). Eleven children used sublingual tablets, 17 used lozenges and one used a fentanyl nasal spray (three patients used two different preparations). The only significant correlation found was between dose of fentanyl lozenge and weight ($r_s = 0.81$, $p < 0.001$). Very few side effects were reported with the most frequent being nausea (8%) and sleepiness (8%).

Conclusions: Fentanyl lozenges seem to be safe and well tolerated in children as young as five years old, weighing as little as 13 kg. Results suggest that children should always be started on the lowest available dose of chosen preparation and that this dose should be titrated according to response.

This study demonstrates that there is no correlation between background opioid dose and effective dose of rapid onset fentanyl in children. This mirrors findings of similar studies in adults. There was a strong correlation between effective dose of fentanyl lozenge and weight. This may be in part due to clinicians being more inclined to increase fentanyl lozenge doses as the child is in control of when they have had enough medication. In contrast, buccal tablets are absorbed quickly and the child always receives the full dose, making clinicians more reluctant to titrate the dose.

Implications: This article presents initial evidence for feasibility and tolerability of fentanyl lozenges in children as young as five years old, who are on relatively low doses of background opioids. This could be of interest to clinicians who are looking for alternatives to oral opioids to manage breakthrough pain in children with cancer.

© 2017 Scandinavian Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

[☆] This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

^{*} Corresponding author.

E-mail address: lucycoombes@nhs.net (L. Coombes).

1. Introduction

Breakthrough pain (BTP) is a ‘transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain’ [1]. BTP is estimated to occur in 40–80% of adults with chronic cancer pain [2]. One small study in children with cancer who had severe pain showed that 57% experienced one or more episodes of BTP in a 24-h period [3]. Younger children had a significantly higher risk of experiencing breakthrough pain compared to teenagers [3].

Traditionally, children with BTP have been given a dose of immediate release oral morphine (or equivalent), in addition to their background dose, to manage these episodes. These oral opioids take 30–60 min to work and their effect can last for up to 4 h which is not ideal for a typical episode of breakthrough pain which is usually rapid in onset and of relatively short duration [3]. Newer rapid onset opioids in the form of buccal and transmucosal preparations of fentanyl have been available since the late 1990s for the treatment of BTP in adults with cancer who are already on >60 mg/day of oral morphine (or equivalent) [4]. These products are available as transmucosal lozenges, buccal or sublingual tablets, nasal sprays or oro-dispersible films and have a more rapid onset and shorter duration of action than oral morphine, which is better suited to the typical time course of BTP [5]. None of these preparations are licenced for use in children less than 16 years of age. The lozenges come in various dose sizes, the lowest being 200 µg. The lozenge is attached to a stick therefore the child can sweep it across their buccal mucosa and remove it when they have received adequate analgesia, thus not utilising the whole dose. The buccal and sublingual tablets and orodispersible films also come in various dose sizes, the lowest tablet size being 100 µg and film 200 µg, and the whole dose is absorbed fairly rapidly. These formulations may appear prohibitive for use in the paediatric population due to lack of smaller dose formulations. The lowest dose of nasal spray available is 50 µg per metered dose, although smaller doses can be given by using a mucosal atomiser device [6]. The Association of Paediatric Palliative Medicine suggests in their formulary that the lozenges can be used by children as young as two years old and that the intranasal spray can be used from the neonatal period [7].

Rapid onset fentanyl preparations generally seem to perform better than oral morphine and placebo in the management of BTP in adults but the absolute difference in outcomes is small [8–13]. Many of the earlier adult studies recommend starting with the lowest available dose and titrating the dose of rapid onset fentanyl until an effective dose is achieved and suggest that there is no

relationship between effective dose and the patient’s background opioid analgesic regime [9,11,14]. More recent studies have shown that dosing proportional to the background opioid dose is well tolerated, effective and safe in adults [15–18]. However, it is not clear from these studies whether patients would have received the same analgesic benefit with a lower starting dose of rapid onset fentanyl, as their starting dose was determined by their 24 h background morphine equivalent dose.

Although not licensed for use in children, rapid onset fentanyl preparations are sometimes used in the palliative care setting for children with BTP [7]. Clinicians tend to start at the smallest available dose and titrate as necessary to achieve control of BTP, giving younger children lozenges as they are able to use the medication as much as they need and discard the rest. However, there is no published literature on whether this is the most efficacious way of achieving optimum pain relief or whether dosing proportionate to background opioid dose is better. In fact, there is minimal, if any, published literature on the use of rapid onset fentanyl for BTP in children with cancer at all.

The primary aim of this study was to compare whether there is a relationship between the effective dose of rapid onset fentanyl and the 24 h background dose of oral morphine mg/kg (or equivalent) in children under the age of 18 years.

2. Methods

2.1. Design

This is a retrospective case note review.

2.2. Setting and population

All children under the age of 18 years under the care of the paediatric symptom and palliative care team at the Royal Marsden Hospital UK and who were prescribed rapid onset fentanyl for breakthrough cancer pain between 2010 and 2015.

Approval was obtained from the Trust’s Research and Development department to conduct this study as a service evaluation.

2.3. Data collection

Demographic data were collected along with information on the type of rapid onset fentanyl taken (lozenge, intranasal, buccal/sublingual tablet) and maximum effective dose reached. Dose in mg/kg/day of background opioid being taken converted to oral morphine equivalent (OME), side effects of rapid onset fentanyl reported and any other analgesic medication being taken were also recorded. OME dosages were calculated using conversion doses for opioids in the British National Formulary [19] except for methadone where a 2:1 conversion of oral methadone to oral morphine was used [20].

2.4. Data analysis

Demographic data is reported using descriptive statistics. The correlation between OME/kg/day and effective dose of fentanyl rapid onset analgesia was analysed using Spearman’s rank correlation coefficient as data was non-parametric. Data was analysed by type of rapid onset fentanyl analgesia taken (lozenge, intranasal spray, sublingual/buccal tablet). Correlation between body weight (kg) and maximum dose of rapid onset fentanyl analgesia was analysed in the same way, again as the data was non-parametric. Side effects experienced and other non-opioid analgesic medication being taken were analysed using descriptive statistics. All data was analysed using SPSS, version 23 (IBM/SPSS Inc., Armonk, NY).

Table 1
Demographic characteristics of patients.

Characteristics (n = 26)	Mean (SD, range)
Age (yrs)	13.0 (3.5, 5–17)
Weight (kg)	48.1 (19.4, 13–100)
Characteristics (n = 26)	n (%)
Gender	
Male	20 (76.9%)
Female	6 (23.1%)
Tumour type	
Solid	22 (84.6%)
Leukaemia/lymphoma	3 (11.5%)
Central nervous system	1 (3.8%)
Type of rapid onset fentanyl (µg) ^a	
Lozenge (200–1200)	17 (57.7%)
Sublingual tablet (100–1200)	11 (38.5%)
Intranasal (50)	1 (3.8%)

^a Three patients used two different preparations.

Table 2
OME/kg/day of background medication.

	Mean (mg/kg/day)	SD	Range	Mean age (range; SD)
Sublingual (<i>n</i> = 11)	16.2	17.0	1.9–50.8	15.2 (11–17; 1.9)
Lozenge (<i>n</i> = 17)	18.5	29.5	1.1–93.3	12.0 (5–17; 3.5)
Nasal spray (<i>n</i> = 1)	3.5	–	–	6

Table 3
Spearman's correlation coefficients.

	Sublingual maximum dose	Lozenge maximum dose
Weight (kg)	.23	.81*
Age (years)	–.01	.47
Background OME/kg/day	.57	–.06

* $p < .001$ (2-tailed).**Table 4**
Reported side effects of rapid onset fentanyl.

Reported side effects (<i>n</i> = 26)	<i>n</i> (%)
Vomiting	1 (4)
Sleepiness	2 (8)
Nausea	2 (8)
Sore mouth	1 (4)
Did not like the taste	1 (4)
Sublingual tablet not dissolving	1 (4)

3. Results

Data on 26 patients was included in the study, demographic information is displayed in Table 1. 76.9% of children were males with a mean age of 13 years (SD = 3.5, range = 5–17) and a mean weight of 48.1 kg (SD = 19.4, range = 13–100). The most common diagnosis was a solid tumour (84.6%) and the most frequently used rapid onset fentanyl product was a lozenge (57.7%).

The mean OME/kg/day of background medication taken by children receiving each type of rapid onset fentanyl is shown in Table 2. The most frequently used background analgesic was a fentanyl patch (50%). Other background analgesics were morphine (25%), diamorphine (9%), oxycodone (7%) and methadone (9%). A significant correlation was found between fentanyl lozenge dose and body weight ($r_s = 0.81$; $p < 0.001$). No correlation was found between rapid onset fentanyl dose (μg) and background OME mg/kg/day or age (years) and effective dose of rapid onset fentanyl. No correlation was found between weight (kg) and buccal/sublingual fentanyl dose either (see Table 3).

Side effects were not often reported but the most frequent were sleepiness (8%) and nausea (8%) (Table 4). Three patients (12%) reported that their prescribed rapid onset fentanyl analgesia did not work. No serious adverse reactions or incidents were reported related to the use of rapid onset fentanyl.

Most of the participants were also on non-opioid analgesic medications including paracetamol (50%) and neuropathic pain agents (65%) such as ketamine, gabapentin, pregabalin and amitriptylline (Table 5).

4. Discussion

As far as the authors are aware this is the first paper to look at the effective dose of rapid onset fentanyl preparations in children with cancer in relation to age, weight and OME 24 h background analgesic dose. Our data shows that children as young as five years old and weighing as little as 13 kg were able to use the lowest available dose of fentanyl lozenges safely and with very few reported side effects. The children given these preparations predominantly had solid tumours. There is evidence that children with solid tumours are more likely than those with other types of cancer to require

Table 5
Concomitant non-opioid based medication prescribed.

Other non-opioid analgesics used (<i>n</i> = 26)	<i>n</i> (%)
Lidocaine patch	3 (12)
Dexamethasone	5 (19)
Gabapentin	8 (31)
Ketamine	8 (31)
Amitriptylline	4 (15)
Paracetamol	13 (50)
Ibuprofen	5 (19)
Carbamazepine	1 (4)
Entonox	1 (4)
Pregabalin	1 (4)

17 patients received one or more neuropathic agent (gabapentin, carbamazepine, amitriptylline, ketamine, pregabalin).

large doses of opioids to control their pain [21]. It is likely that in our cohort children were prescribed rapid onset fentanyl preparations in an attempt to control pain that was difficult to control with the usual background and breakthrough oral opioids available. This is indicated by five children in our cohort requiring more than one opioid based background medication (predominantly an iv/sc opioid infusion was added in whilst a fentanyl patch remained in situ) and 65% of the cohort required some form of neuropathic agent.

In our cohort younger children were more likely to be given fentanyl lozenge than sublingual tablet or nasal spray. This is likely to be because the child can be in control of the lozenge and remove it when they have had enough whereas with a nasal spray or buccal/sublingual tablet the whole dose has to be administered giving less control and leading to prescriber anxiety regarding overdose and unwanted side effects. Buccal/sublingual tablets were only prescribed for children aged 11 years and older. Three children (two receiving sublingual tablet and one receiving lozenge) reported that the rapid onset fentanyl preparation that they were prescribed did not provide any pain relief. Interestingly, the dose was not titrated in these children to see if a larger dose provided analgesia and all three remained on the lowest available dose. Again this may be due to prescriber anxiety of potential overdose and unwanted side effects.

There was a significant correlation found between fentanyl lozenge dose and body weight in our cohort ($p < 0.001$). This correlation was not found with buccal/sublingual tablets. The reason for this may again, be due to clinician reluctance to escalate doses of buccal/sublingual tablets as the child does not have the control they do with lozenges. No correlations were found between OME/kg/day and effective rapid onset fentanyl dose. This finding is similar to rapid onset fentanyl dose titration studies in adults where no meaningful relationship was found between background opioid regime and fentanyl lozenge [14].

Current guidance suggests that rapid onset fentanyl products should not be prescribed to patients who are on <60 mg/24 h of oral morphine or equivalent [5]. In our study children receiving as little as 27 mg OME/day were given fentanyl lozenges with minimal adverse effects. There is more control over lozenge use as it can be discarded when the child has had enough, thus our results suggest that lozenge can be given to those on smaller background OME doses than the manufacturers suggest. Manufacturer guidance should be followed for other preparations as there is minimal control over the actual dose taken.

In opioid tolerant adults with cancer pain intranasal fentanyl has been shown to be effective and generally well tolerated [22]. In paediatrics its use has mainly been confined to emergency medicine where it is administered predominantly to opioid naïve children with acute pain or fractures [6,23,24]. The use of intranasal fentanyl in children on background opioids with cancer pain is not common to our knowledge, and in our study only one patient received this type of rapid onset fentanyl. The smallest available metered spray administers 50 µg which may mean that clinicians are reluctant to prescribe this for younger children due to concern regarding over dose, adverse side effects and tolerability. Many accident and emergency units administer smaller doses by using the injection solution and an atomiser device [6] which may be something that paediatric palliative care physicians could consider in the future.

This study has several limitations. Firstly it was a single centred retrospective case note review and as such the sample size is small. Children took different rapid onset fentanyl preparations and results are not comparable across these preparations. The authors are aware that several of the children who took fentanyl lozenges did not utilise the whole dose. Participants were also on different background opioid analgesics and doses were converted to oral morphine equivalents. However, conversions between products are always approximate and vary between individuals [4].

In conclusion, our study suggests that fentanyl lozenges can be given safely to children as young as five years old weighing as little as 13 kg who are on less than the currently recommended 60 mg/day OME. Children should be commenced on the lowest available dose of their chosen rapid onset fentanyl preparation and this dose should be titrated according to response. More research is needed to establish whether dosing is safe in proportion to either weight or 24 h background OME in a larger multi-centred prospective study. More research is also needed to explore the use and dosing of intranasal fentanyl in children with breakthrough cancer pain.

Ethical issues

Approval was obtained from the Trust's Research and Development department to conduct this study as a service evaluation. Therefore, ethical approval was not required and the protocol was not registered.

Conflicts of interest

None.

References

- [1] Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain* 2009;13:331–8.
- [2] Deandrea S, Corli O, Consonni D, Villiani W, Greco MT, Apolone G. Prevalence of breakthrough cancer pain: a systematic review and a pooled analysis of published literature. *J Pain Symptom Manage* 2014;47:57–76.
- [3] Friedrichsdorf SJ, Finney D, Bergin M, Stevens M, Collins JJ. Breakthrough pain in children with cancer. *J Pain Symptom Manage* 2007;34:209–16.
- [4] Twycross R, Wilcock A, Howard P. *Palliative Care Formulary*. 5th ed. Amersham: Halstan Printing Group; 2014.
- [5] Wilcock A, Twycross R. Therapeutic reviews. *J Pain Symptom Manage* 2012;44:131–49.
- [6] Borland M, Jacobs I, King B, O'Brien D. A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. *Ann Emerg Med* 2007;49:335–40.
- [7] The Association of Paediatric Palliative Medicine. Master formulary, 3rd ed. Available from: <http://appm.org.uk/resources/APPm+Master++Formulary+2015+protected.pdf> [accessed 29.06.16].
- [8] Jandhyala R, Fullarton JR, Bennett MI. Efficacy of rapid-onset oral fentanyl formulations vs. oral morphine for cancer-related breakthrough pain: a meta-analysis of comparative trials. *J Pain Symptom Manage* 2013;46:573–80.
- [9] Coluzzi PH, Schwartzberg L, Conroy JE, Charapata S, Gay M, Busch MA, Chavez J, Ashley J, Lebo D, McCracken M, Portenoy RK. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Pain* 2001;91:123–30.
- [10] Slatkin N, Xie F, Messina J, Segal TJ. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. *J Support Oncol* 2007;7:327–34.
- [11] Portenoy RK, Taylor D, Messina J, Tremmel L. A randomised, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. *Clin J Pain* 2006;22:805–11.
- [12] Rauck RL, Tark M, Reyes E, Hayes TG, Bartkowiak AJ, Hassman D, Nalamachu S, Derrick R, Howell J. Efficacy and long-term tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain. *Curr Med Res Opin* 2009;25:2877–85.
- [13] Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. *J Natl Cancer Inst* 1998;90:611–6.
- [14] Christie JM, Simmonds M, Patt R, Coluzzi P, Busch MA, Nordbrock E, Portenoy RK. Dose-titration, multicentre study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. *J Clin Oncol* 1998;16:3238–45.
- [15] Mercadante S, Villari P, Ferrera P, Casuccio A, Mangione S, Intravai G. Transmucosal fentanyl vs intravenous morphine in doses proportional to basal opioid regime for episodic breakthrough pain. *Br J Cancer* 2007;96:1828–33.
- [16] Mercadante S, Adile C, Cuomo A, Aielli F, Cortegiani A, Casuccio A, Porzio G. Fentanyl buccal tablet vs. oral morphine in doses proportional to the basal opioid regimen for the management of breakthrough cancer pain: a randomized, crossover, comparison study. *J Pain Symptom Manage* 2015;50:579–86.
- [17] Mercadante S, Ferrera P, Adile C, Casuccio A. Fentanyl buccal tablets for breakthrough pain in highly tolerant cancer patients: preliminary data on the proportionality between breakthrough pain dose and background dose. *J Pain Symptom Manage* 2011;42:464–9.
- [18] Mercadante S, Porzio G, Aielli F, Averna L, Ficocceralla C, Casuccio A. The use of fentanyl buccal tablets for breakthrough pain by using doses proportional to opioid basal regimen in a home care setting. *Support Care Cancer* 2013;21:2335–9.
- [19] Joint Formulary Committee. *British National Formulary*. 70th ed. London: BMJ Group and Pharmaceutical Press; 2015.
- [20] Quill T, Kuderer N. Methadone dose conversion guidelines. University of Rochester Medical Center; 2014. Available from: https://www.compassionandsupport.org/pdfs/professionals/pain/methadone_dose_conversion_guideline.pdf [accessed 14.09.16].
- [21] Collins JJ, Grier HE, Kinney HC, Berde CB. Control of severe pain in children with terminal malignancy. *J Pediatr* 1995;126:653–7.
- [22] Kress HG, Orońska A, Zaczmarek Z, Kaasa S, Colberg T, Nolte T. Efficacy and tolerability of intranasal fentanyl spray 50 to 200 µg for breakthrough pain in patients with cancer: a phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open label extension treatment period. *Clin Therapeut* 2009;31:1177–91.
- [23] Borland ML, Jacobs I, Geelhoed G. Intranasal fentanyl reduces acute pain in children in the emergency department: a safety and efficacy study. *Emerg Med (Fremantle)* 2002;14:275–80.
- [24] Holdgate A, Cao A, Lo KM. The implementation of intranasal fentanyl for children in a mixed adult and pediatric emergency department reduces time to analgesic administration. *Acad Emerg Med* 2010;17:214–7.