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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.

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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.

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

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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 transmucousal 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 transmucousal 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.

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.

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).

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