Barriers to the Use of Buccal and Intranasal Fentanyl for Breakthrough Pain in Paediatric Palliative Care: an Exploratory Survey

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Dear Editor,

We recently administered a survey to investigate the prescribing of buccal and intranasal fentanyl for breakthrough pain in paediatric palliative care in the UK.

A Cochrane review did not find any evidence for how breakthrough pain should be managed in palliative care.¹ Meta-analyses of randomised controlled trials have demonstrated increased efficacy of fentanyl compared to oral morphine,² while pharmacokinetic studies highlight the onset and duration properties of fentanyl dosage forms that might be beneficial to certain patients experiencing breakthrough pain. Various dosage forms of fentanyl have been licensed for use in breakthrough cancer pain in adults, but UK NICE (2012) guidelines addressing strong opioid use in palliative care patients state that fentanyl should not be offered as first-line rescue medication. A lack of paediatric data for commercially available fentanyl transmucosal application systems means these products have traditionally not been recommended for first-line use in children.

The aim of this survey was to investigate current off-label prescribing of fentanyl for breakthrough pain relief in paediatric palliative care, and to ascertain any barriers to use. This is timely as one of the research recommendations in the NICE guidelines (2016) on end of life care for infants, children and young people with life-limiting conditions related to managing breakthrough pain.³

An anonymous online survey was delivered via Qualtrics to 124 members of the Association of Paediatric Palliative Medicine (APPM) in the UK. Participants were informed that their participation was voluntary and that they would not be identified. No incentives were provided. Two reminder emails were sent. Responses were analysed using Excel.

Respondents (36% response rate; n=44/121) were mainly consultants and associate specialist grade clinicians who had worked for over 5 years in paediatric palliative services. Less than half had prescribed buccal fentanyl and only 4 had prescribed intranasal fentanyl. These were prescribed less than once a month. Buccal fentanyl was mainly prescribed for breakthrough pain in paediatric oncology patients (13; n=16) with some additional prescribing to manage incident/movement related pain or for discomfort associated with neurological symptoms. Intranasal fentanyl was rarely prescribed.

The majority indicated that they would start fentanyl for breakthrough pain relief after other major opioids had been tried (12; n=16 for buccal and 3; n=4 for intranasal), in line with UK guidance (NICE and BNF). Most would prescribe not only alongside fentanyl transdermal patches as background pain relief, but also with other major opioids (n=11). Twenty seven percent indicated that they would not use buccal fentanyl for opioid naïve patients.

When initiating buccal fentanyl for breakthrough pain relief in opioid naïve patients one third of respondents referred to the dose in the APPM Master Formulary.⁴ The "notes" section states that fentanyl is only suitable for breakthrough pain relief in children already receiving a total daily dose equivalent of 180mg morphine or more, since the oral morphine equivalent (OME) of the smallest fentanyl lozenge available (200mcg) is 30mg. This suggests the need for the development of a fentanyl preparation with significantly smaller doses for the paediatric population.

According to BNF for Children (2016), the dose unit of buccal administration of fentanyl lozenges for breakthrough pain relief in children 16-17 years old who have been receiving opioid therapy for chronic cancer pain is initially 200 mcg, with no more than 2 dose units for each pain episode, in line with adult practice.⁵ The recommendation of the APPM formulary concurs with the BNF (i.e. the standard dose of a strong opioid for breakthrough pain is usually 1/10 to 1/6 of the regular 24-hour background opioid dose), although BNF...
does not provide a specific dose in relation to any fentanyl preparations for children aged 15 or below. The lack of a reliable scale for conversion of OME to transmucosal fentanyl may be one reason why respondents were not confident in prescribing transmucosal fentanyl.

Other medications, types of illness, and quality of mucosa were said to affect the initial dose of buccal fentanyl.

All three respondents answered differently regarding the initiating dose of intranasal spray for breakthrough pain. According to the APPM Master Formulary the starting dose of intranasal fentanyl for neonates-children <2 years who experience an episode of breakthrough pain is 1 mcg/kg as a single dose, while that for children 2-18 years is 1-2 mcg/kg as a single dose, with initial maximum dose of 50 mcg. The smallest intranasal dose available commercially is 50 mcgs/metered spray which is in excess of the dose usually required for neonates and small children. Using the parenteral solution transmucosally is difficult due to the potency of fentanyl and the concentration of the solution, whose dilution may affect its absorption.

In determining effectiveness of doses during titration, most of the 9 respondents to the question concerning the adjustment of transmucosal fentanyl, took into account previous analgesic requirements as well as perceived analgesic effect of individual doses, using pain scales or patient report.

When calculating the magnitude of fentanyl dose increments, respondents used standard titration practice, evaluating efficacy of initial dosing, judging the amount of breakthrough pain and background opioid (1/6 of background opioid in OME, or by 10% or 25% increment of dose).

Despite the kinetic advantages of fentanyl over morphine in terms of rapid onset of action, ease of use, side effect profile and shorter duration of action, barriers to the wider use of transmucosal fentanyl included lack of appropriate formulations for delivery of small dosages, lack of clear guidance, safety concerns and lack of local availability within hospital formularies. Lack of experience and clarity around dosing were frequently identified barriers to prescribing.

In conclusion, although some senior clinicians in paediatric palliative care are prescribing buccal fentanyl, and a few intranasal fentanyl, their use is low and there is uncertainty and inconsistency. Despite pharmacokinetic studies highlighting properties of fentanyl ideal for the relief of breakthrough pain, there is limited information relating to dosage and titration and a lack of reliable evidence-based conversion scales. More data is required to inform guidelines and new formulations are needed to permit the safe and reliable administration of very small doses.

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**Ethics** The survey was approved by UCL Ethics Committee.

**REFERENCES**