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Case report

Fentanyl nasal spray in a patient with end-stage COPD and severe chronic breathlessness

Cite as: Janssen DJA, van den Beuken-van Everdingen MHJ, Verberkt CA, *et al*. Fentanyl nasal spray in a patient with end-stage COPD and severe chronic breathlessness. *Breathe* 2019; 15: e122–e125.

Chronic breathlessness syndrome, defined as breathlessness that persists despite optimal treatment of the underlying pathophysiology, resulting in disability, is a major problem for patients with advanced chronic lung disease, and can be difficult to manage [1, 2]. Opioids should be considered for treatment of these patients [3]. Episodic breathlessness is severe worsening of breathlessness intensity, which can be predictable or unpredictable [4]. Episodic breathlessness can have a major impact on activities of daily life, but ~90% of episodes last for 20 min or less [5]. Therefore, the selection of appropriate palliative pharmacological therapy is a complex issue. Indeed, the onset of action of short-acting oral opioids is between 15 and 30 min [6]. The rapid onset of action (between 1 and 4 min [7]) is the major advantage of fentanyl nasal spray. This case report relates the experience and insight gained when fentanyl nasal spray was prescribed to a patient with end-stage chronic obstructive pulmonary disease (COPD) and the lessons we have learned. Written informed consent for publication of the clinical details was obtained from the deceased patient's spouse.

Case report

A 59-year-old woman was admitted to the palliative and supportive care unit for patients with end-stage chronic lung disease for end-stage COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade 4D). Before transfer to our unit, she was admitted to the hospital for exacerbation of COPD.

She had completed an in-patient pulmonary rehabilitation programme, 3 years prior to admission. She experienced severe breathlessness even then, mainly due to very severe hyperinflation. During this pulmonary rehabilitation programme, she was prescribed morphine sustained release (SR) 10 mg tablets, twice daily. She was prescribed fentanyl 50 µg nasal spray, for episodes of acute breathlessness, as needed, with a maximum of four doses per day. She had been prescribed morphine immediate release (IR) 5 mg oral solution for acute breathlessness earlier. However, this did not control the episodes of acute breathlessness fast enough. She was discharged after the programme. She continued to receive prescriptions from both her chest physician and her general practitioner.

Task 1
What is the evidence for using fentanyl nasal spray for breathlessness?

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Insufficient control of chronic breathlessness may induce excessive use of fentanyl nasal spray in COPD patients. Prescription of fentanyl nasal spray for breathlessness should only be done as part of palliative treatment and requires close follow-up. http://bit.ly/2YdOjJ1

Answer 1

In 2013, Simon *et al.* [8] published a systematic review concerning fentanyl for the relief of refractory breathlessness. They found two before–after studies, nine case studies and two randomised controlled trials (RCTs) (one including two patients). All descriptive studies reported relief of breathlessness after the use of fentanyl, but the pilot RCT (n=12) didn't find a statistically significant improvement in breathlessness compared with placebo. In total, five patients were described using intranasal fentanyl, while the other studies concerned nebulised fentanyl (n=70), oral transmucosal fentanyl (n=9), transdermal fentanyl (n=3) and intravenous remifentanil (n=1) [8]. Since then, a few other studies have been published using intranasal fentanyl for breathlessness. Harlos *et al.* [9] reported the use of intranasal fentanyl in 11 dying newborns and infants, and reported that in eight cases a decrease in laboured breathing and restlessness was observed. A more recent case series (n=16) described successful use in children with life-limiting conditions and acute respiratory distress (after the first dosage laboured breathing improved in 89%; tachypnoea improved in 73% and, if reported, dyspnoea improved in 59%) [10]. A pilot RCT in 23 patients with cancer did not show a difference in exercise-induced dyspnoea between the nasal fentanyl and control group, although the study was not powered to detect between-group differences [11]. Finally, a pilot RCT in six patients with chronic heart failure suggested lower breathlessness scores after a 6-min walk test with than without intranasal fentanyl (p=0.048), but did not include a placebo arm [12]. To conclude, several case series show the benefits of fentanyl nasal spray for treatment of breathlessness, but scientific evidence is scarce.

At the time of the current admission, the hospital discharge letter of our patient, mentioned the prescription of fentanyl 50 µg nasal spray. She told us that she used one bottle with 10 doses, every day, for chronic breathlessness. She did not have the nasal spray with her at the time of admission. Fentanyl nasal spray was ordered and delivered to our unit the next day. She did not use other opioids. On the day of admission, we decided to administer a fentanyl 12 $\mu g \cdot h^{-1}$ patch, one patch to be administered every 72 h. We also prescribed 5 mg morphine IR oral solution, as needed, with a maximum of six doses per day, for episodic breathlessness. She tried morphine IR 5 mg oral solution once, after which she felt drowsy and uncomfortable for several hours. The next day, she took 10 doses of fentanyl nasal spray within a few hours. She continuously asked for more fentanyl nasal spray. She experienced anxiety, restlessness, sweating and shaking. At this point, she told us that before admission she had used at least 40 doses of fentanyl nasal spray, every day, instead of 10. Only then did we realise the overdose of fentanyl nasal spray, due to uncontrolled chronic breathlessness.

Task 2

How often does fentanyl dependence occur in patients taking rapid-onset fentanyl for nonmalignant diseases?

Answer 2
Data concerning fentanyl dependence in patients with nonmalignant diseases taking rapid-onset fentanyl are scarce. A study in 105 patients using oral transmucosal fentanyl for nonmalignant pain did not show a difference in the Leeds Dependence Questionnaire between baseline and the end of the study (follow-up was limited to 30 days) [13]. Fine *et al.* [14] reported <1% dependency in an 18-month study exploring long-term safety and tolerability of oral transmucosal fentanyl in 646 patients with chronic nonmalignant pain. Sitte and Bausewein [7] reported no evidence of excess use in over 200 patients self-administrating their dosages of intranasal fentanyl for episodic breathlessness.

We discussed the excessive use of fentanyl with the patient and her husband. Together, we decided to discontinue fentanyl nasal spray. Instead, we increased the fentanyl patch dose to 50 $\mu g \cdot h^{-1}$, one patch every 72 h. Until the fentanyl patch achieved the optimal effect, 2.5 mg morphine was administered subcutaneously, six times daily, at fixed times, to treat chronic breathlessness, to prevent breathlessness episodes and to decrease her withdrawal symptoms. Meanwhile, our psychosocial team started treating her for anxiety. They also advised the interdisciplinary team on the management of her complex behaviour. The interdisciplinary team started the treatment programme, with a focus on breathlessness management. A few days later (1 week after admission), the withdrawal symptoms disappeared. Both her chronic breathlessness as well as acute episodes of breathlessness and anxiety were within control. We found a highly motivated patient, who participated in all treatment activities. Every week we decreased the dosage of the fentanyl patch, stepwise from 50 $\mu g \cdot h^{-1}$ to 37 $\mu g \cdot h^{-1}$, then 25 $\mu g \cdot h^{-1}$, and 12 $\mu g \cdot h^{-1}$, until it could be discontinued. We discussed alternatives to the morphine injections, such as morphine SR tablets, but she strongly preferred morphine injections, with a butterfly cannula. She continued with 2.5 mg subcutaneous morphine administration, five to six times daily, until she was admitted to the hospital 10 months later. She died after a few weeks in the hospital.

Lessons learned

We have learned several important lessons from this case. First, previous authors found no evidence of excessive use of fentanyl nasal spray for episodic breathlessness [7]. However, we discovered excessive use of fentanyl nasal spray in a patient with advanced lung disease and chronic severe breathlessness. Secondly, treatment of chronic severe breathlessness is complex, and close follow-up of opioid treatment is needed. There was no follow-up for this case after discharge from the pulmonary rehabilitation centre in 2014. Her chronic breathlessness was very severe and uncontrolled. She stopped using morphine SR tablets when she experienced discomfort with the medication and tried to control her severe chronic breathlessness with the medication prescribed for episodic breathlessness. The frequent use of fentanyl spray by patients to relieve uncontrolled chronic breathlessness is explained by the short duration of action of fentanyl nasal spray [15]. Thus, the prescription of fentanyl nasal spray for acute episodes of breathlessness needs to be part of a comprehensive palliative breathlessness treatment programme, for both chronic breathlessness as well as acute episodes of breathlessness. In this case, we chose morphine subcutaneous injections, with a butterfly cannula, to treat breathlessness. This was not our first choice, obviously. We preferred to prescribe morphine SR tablets, with a maximum dose of 30 mg per day. Indeed, most patients respond to a relatively low dose of morphine SR tablets [16], and oral morphine ≤30 mg a day is not associated with increased hospital admission or mortality in patients with COPD [17]. Nevertheless, our patient, who had a poor prognosis of survival, had a strong preference for morphine injections, because she had previously experienced discomfort with morphine SR tablets. It is not known if short-acting injections have a higher risk for overdose than SR tablets in patients with end-stage lung disease and breathlessness. In fact, a study on long-term use of opioids showed that patients with initiation with long-acting opioids were more likely to become long-term users than those initiated with short-acting drugs [18]. While she stayed in our specialised unit, we were able to closely monitor and control the use of morphine injections. Thirdly, continuity of care for these patients with very severe breathlessness is of paramount importance. At admission, the excessive use of fentanyl nasal spray was not communicated to our team. Hence, we were unaware of the doses used by the patient and were unprepared for the challenges faced. It took us several days to discover the actual dose of fentanyl taken by the patient, and to start a fentanyl patch with an appropriate dosage to treat the withdrawal symptoms. Finally, excessive use of fentanyl nasal spray in a patient with severe breathlessness can be managed by providing an interdisciplinary palliative treatment programme, including pharmacological and non-pharmacological treatment of breathlessness. This improved the quality of life of our patient in the last year of her life.

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Conflict of interest

D.J.A. Janssen reports personal fees for lectures from Boehringer Ingelheim, Novartis, AstraZeneca and GlaxoSmithKline, outside the submitted work. M.H.J. van den Beuken-van Everdingen reports personal fees for lectures from Takeda and Mundipharma, outside the submitted work. C.A. Verberkt has nothing to disclose. J.P.H.M. Creemers has nothing to disclose. E.F.M. Wouters reports personal fees for board membership from Nycomed and Boehringer Ingelheim, personal fees for lectures from AstraZeneca, GlaxoSmithKline, Novartis and Chiesi, and grants from AstraZeneca and GlaxoSmithKline, outside the submitted work.

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