Letters

Intranasal Fentanyl for Episodic Breathlessness

To the Editor:

Episodic breathlessness is a common and distressing symptom in advanced malignant and non-malignant disease. There is good evidence for the systemic use of opioids to relieve breathlessness[1,2] but not for the nebulized route.[1] The route of administration and the time to onset play an important role in selecting an ideal agent. Ideally, any drug used for episodic breathlessness should be easy to use both for patients, relatives, and health professionals, with rapid onset giving quick symptom relief in any setting.

Over recent years, nasal administration of drugs has attracted both clinicians and researchers. This route has various advantages, such as ease of administration, rapid onset and patient control.[3,4] The nasal cavity offers about 150 cm^2 surface area with highly vasculated mucosa[5] and direct connection to the circulation that bypasses the first-pass effect of the liver. Various studies have shown good absorption of opioids, such as oxycodone,[6] buprenorphine[7] or fentanyl.[8]

Fentanyl is a synthetic strong opioid agonist with lipophilic properties leading to rapid mucosal absorption. The bioavailability of intranasal fentanyl is about 70%.[8,9] Onset of action is rapid—from 12 to 22 minutes after administration.[3] Intranasal fentanyl is regularly used in patients with breakthrough pain, and provides effective analgesia in post-operative pain[10] and in palliative care.[4] Nebulized and transmucosal fentanyl have also been used for effective relief of breathlessness.[11,12]

We present three cases in which we treated severe dyspnea with intranasal fentanyl in patients receiving palliative home care.

Case 1

A 73-year-old man was diagnosed with metastatic carcinoma of the lung two weeks prior to death. When seen first at home, the patient was still mobile. His main symptoms were severe dyspnea and persistent cough for which he did not receive any treatment. We administered 50 μg of intranasal fentanyl followed by 100 μg within five minutes. Three minutes after the first puff, his condition improved, and he reported complete symptom control after four more minutes. His respiratory rate (RR) dropped from 30 to 12 breaths/min, and his oxygen saturation increased from 62% to 94%. The patient was then prescribed transdermal fentanyl 25 μ/h for baseline therapy and received 100 μg intranasal fentanyl as required, with good effect. He remained on this dose until he died three days later without having uncontrolled dyspnea recur. During this time, the patient needed intranasal fentanyl about seven times a day. Usually one puff was enough but occasionally he needed two puffs of 100 μg.

Case 2

An 88-year-old woman was treated in hospital for chronic heart failure stage NYHA IV, chronic pulmonary disease GOLD stage II, and pulmonary hypertension. Following her own wish, the patient was discharged from hospital to home for terminal care. Due to her deteriorating condition, the patient was unable to take oral drugs during the following week. After six days, she appeared to have distress due to dyspnea, was unconscious, and appeared to be dying. She was tachypneic, with an RR of 40–50 breaths/min and oxygen saturation of 65%. She received one puff of intranasal fentanyl 100 μg followed by one to three puffs four times over the next four minutes. In total, she received 1000 μg intranasal

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fentanyl. The patient was more settled after three minutes, her RR decreased to less than 20 breaths/min and the oxygen saturation rose to 75%. Ten minutes after the first puff, the patient became conscious again and was able to communicate clearly. She no longer seemed distressed and described her dyspnea as bearable. Her relatives were given written instructions as to how to administer the intranasal fentanyl. In the following hours, the patient received one more puff of 500 μg intranasal fentanyl and died peacefully eight hours later.

Case 3

A 72-year-old man with progressive interstitial lung disease, cardiac failure and chronic kidney failure was seen at home. Earlier pulmonary function test showed a reduction of lung diffusion to 33%; the partial oxygen pressure was 5.2 kPa. The patient complained of severe dyspnea on exertion and at rest. He was on continuous supplemental oxygen at 6–10 L/min. His RR was 20–35 breaths/min. Oxygen saturation was between 82% and 92%, but dropped considerably with the mildest exertion, such as standing up. Before going to the toilet, he needed preoxygenation at 12 L/min for a few minutes.

The patient was on steroids, diuretics and antiarrhythmic medication but did not receive any specific medication for breathlessness. Without changing his medications, intransasal fentanyl 100 μg one to four puffs was prescribed as needed for dyspnea, with notable symptom relief. Over the next two weeks, he was stable, needing about two to five puffs of 100 μg intranasal fentanyl daily. Three days before he died, he accidentally smoked a cigarette when on supplemental oxygen. Due to a fire, he burned his beard and face and developed facial edema, especially around the nose, leading to more breathing problems. However, he was still able to use intranasal fentanyl, with good symptom relief. Three days later, the patient deteriorated and refused to continue his supplemental oxygen. Upon losing consciousness, he became restless and appeared to have more severe dyspnea. After receiving two to four puffs of 100 μg intranasal fentanyl seven times within 20 minutes, his restlessness subsided and he died peacefully 30 minutes later.

Comment

Episodic breathlessness is common in patients with advanced lung pathologies. It is similar to breakthrough pain in its quick onset, distress for patients, and difficulty to control sufficiently. These three cases demonstrate that intranasal fentanyl can offer rapid symptom control to patients who suffer from severe dyspnea due to malignant and nonmalignant disease. To our knowledge, this is the first report describing the use of intranasal fentanyl for the relief of dyspnea.

Since 2003, the first author has had wide experience using intranasal fentanyl in the home care setting for dyspnea. Because we use it in appropriate doses, none of the patients had to be admitted to hospital because of dyspnea at the end of life. Overall, intranasal application of fentanyl is well tolerated and accepted by patients and carers, especially as it can be used in any setting and without the presence of a health care professional.

Fentanyl spray is prepared by the pharmacy using fentanyl citrate in various concentrations, with one puff of the spray containing 50 μL. Concentrations vary from 25 to 500 μg in 50 μL; occasionally higher concentrations are used. Depending on the concentration, the time of onset is within a minute, with good symptom relief between one and four minutes. The four-hour dose in one puff has a faster onset than the one-hour dose.

When we first began using intranasal fentanyl for the treatment of dyspnea, we started with the one-hour dose of the mean equivalent daily dose (MEDD) of the basic opioid. However, this regularly failed to result in sufficient symptom relief. After further careful titration, we used the four-hour dose of the MEDD, leading to satisfactory relief of dyspnea. For example, if a patient is on a fentanyl patch 100 μg/h, we would administer a total of 400 μg fentanyl intranasally. As the onset of action is comparable to the intravenous administration of fentanyl, we allow repetition of the same dose after five minutes until sufficient symptom relief. The doses in our cases extend to higher levels compared to the reported doses in pain studies,[4,10] but doses up to 200 μg have been tested with intervals of five minutes.[13] None of the studies related the administered dose to the MEDD, which, in our experience, is

helpful in titrating the right dose. We used intranasal fentanyl successfully in opioid-naïve patients without side effects such as respiratory depression, but we think that dose titration should be started at lower doses in these patients (with doses around 50 μg).

All the patients reported here died either shortly after we started intranasal fentanyl or weeks later. Despite higher doses, we could not see any relationship between the first application and the patients' deaths, as there was always a considerable time lag.

Side effects related to the use of the nasal spray include light injury to the nasal mucosa in about 1% of patients or mild burning of the mucosa due to the preservative in about 10% of patients. It is possible to produce the spray without preservative, but stability of the spray is then limited to three weeks. Underdosing of the patient might be a consequence of repeating the puffs too quickly as the reservoir may not be filled up again.

For episodic breathlessness in over 200 patients, we have found no evidence of excess use by patients self-administering their doses. We would suggest that it is, therefore, likely to be safe, although more research is necessary to determine optimum doses and effectiveness of the intranasal application.

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