Editorial

Fentanyl for episodic dyspnoea in cancer patients

Miguel Angel Benítez-Rosario

Palliative Care Unit, La Candelaria University Hospital, Tenerife, Spain

Corresponding to: Miguel Angel Benítez-Rosario, MD, PhD. PO Box 10521, SC Tenerife, Spain. Email: mabenros@gmail.com.

Abstract: Two different patterns of breathlessness have been identified: chronic or continuous breathlessness and breathlessness crisis (acute, incident, episodic, breakthrough breathlessness). Meta-analysis and systematic reviews prove that opioids are beneficial in either opioid-naïve or -tolerant patients. However, data from two recent randomised controlled trials were not able to show the effectiveness of fentanyl for the relief of exertion-induced dyspnoea.

Keywords: Fentanyl; opioids; dyspnoea; advanced cancer; palliative care

Submitted Jan 12, 2014. Accepted for publication Jan 13, 2014.

doi: 10.3978/j.issn.2224-5820.2014.01.02

Scan to your mobile device or view this article at: http://www.amepc.org/apm/article/view/3215/4128

Dyspnoea or breathlessness is defined by the American Thoracic Society as "*a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity*" (1). It is highly prevalent in patients with lung cancer, heart failure and chronic obstructive pulmonary disease, three of the most common illness worldwide. Patients with life-limiting cardio-respiratory illnesses have higher intensity of breathlessness for the last three months of life than patients with primary and secondary lung cancer, but breathlessness severity increases in both groups of patients on the last weeks of the life (2,3). Thus, prevalence and severity of dyspnoea escalate significantly as death approaches regardless of underlying life-limiting diseases.

Dyspnoea is mostly multifactorial, with the symptom resulting from the interaction of physiological, psychological, social, and environmental factors. Therefore, patients undergo a situation of total dyspnoea, concept that describes the patient's experience from multiple perspectives (physical, psychological, interpersonal, and existential) that, synergistically, combine to configure the symptom and to determine its impact (4).

Several studies and reviews have been carried on in the last years to characterize the dyspnoea phenomenon (5-12). Two different patterns of breathlessness have been identified: chronic or continuous breathlessness and breathlessness crisis (acute, incident, episodic, breakthrough breathlessness). These dyspnoea crises are defined as a "*clinically significant aggravation of dyspnoea in patients with continuous dyspnoea or occurring intermittently without constant breathlessness*". Episodic or breakthrough dyspnoea is characterized by a sudden increase of breathlessness intensity with a short duration (7-11).

The first principle of dyspnoea management is to optimize the therapy of any underlying conditions and reversible causes (such as cardio-respiratory diseases or complications, anaemia, primary or secondary lung cancer, muscle weakness, and psychological factors) that might cause or worsen the symptom. The symptomatic management of dyspnoea include pharmacological and non-pharmacological treatments (6,12-17).

Palliative pharmacological treatments of refractory dyspnoea include opioids, benzodiazepines, nebulised furosemide, selective serotonin reuptake inhibitors, and promethazine. Meta-analysis and systematic reviews prove that opioids, especially morphine and diamorphine, are beneficial in either opioid-naïve or -tolerant patients, providing the dose escalation a better response. However, there is no strong evidence on the efficacy of other opioids or other routes of opioid administration for the alleviation of dyspnoea (6,12-17).

Fentanyl is a potent μ-opioid with an evidence base for the treatment of pain. Its advantages against other opioids are its easy transdermal administration, the quick onset action of its transmucosal and intranasal formulations and its low toxicity on renal failure. An improved knowledge of

the efficacy of fentanyl may help to better manage dyspnea in patients with ingest limitations or with impaired renal function. On the other hand, the rapid-onset transmucosal and intranasal fentanyl could be selected as a more suitable treatment for breakthrough breathlessness than oral opioids.

Pinna *et al.* (18) evaluated fentanyl efficacy in exertion dyspnoea in patients with advanced cancer. They conducted a phase II randomized, double-blind, crossover, placebo controlled trial in 13 patients with an average intensity of exercise-induced dyspnoea ≥3/10 on a Numeric Rating Scale (NRS). Eleven males and two females, with a mean age of 65 years, were enrolled from an outpatient palliative care unit in Spain. Sample was designed for a two-tailed α of 0.05 and 80% statistical power. The six-minute walk test (6MWT) was used as trigger of exertion dyspnoea, and changes in breathlessness intensity, on a NRS, were assessed at 3 and 6 min walking, and 30 and 60 minutes after the end of the test. Other variables analysed were changes in oxygen saturation and distance walked during the test; side effects developed and treatment preference of the patients. Fifteen minutes before test, opioid naïve or tolerant-patients received 200 or 400 μg of oral transmucosal fentanyl citrate, respectively, or placebo. Comparison between fentanyl and placebo proved no statistically significant differences in any of the outcome measures.

Findings from Pinna *et al.* research (18) could be interpreted in different ways. First, fentanyl is not efficacious in breathlessness. Second, fentanyl does not relief exertion breathlessness or its efficacy depends on doses used. Third, opioids could not be beneficial to exercise-induced dyspnoea.

Simon *et al.* (17) performed a systematic review to evaluate the evidence of fentanyl efficacy for the amelioration of dyspnoea. They included in their review 13 studies: two randomized controlled trials (one only included two patients), two before-after studies and nine case studies. In total were evaluated 88 patients (14 suffering from COPD and 74 with cancer), from all the studies. The administration routes were nebulized fentanyl (70 patients), OTFC (nine patients) and intranasal fentanyl (n=5). Two case reports evaluated transdermal administration of fentanyl (n=3). None of the studies reported respiratory depression or decreases in oxygen saturation despite diverse doses were tested. Notwithstanding all studies described an improvement of breathlessness, the evidence for the fentanyl effectiveness is low because of methodological limitations of the studies. Moreover, the reviewers could not obtain information about the efficacy of fentanyl on the different types of dyspnoea, that is, continuous, induced or breakthrough breathlessness.

Recently, Hui *et al.* (19) reported, after Simon's systematic review, their findings on fentanyl effect on exercise-induced breathlessness. The study was designed to evaluate the practicability of conducting a randomized controlled trial of subcutaneous fentanyl for breakthrough dyspnoea in patients with cancer. Twenty two cancer patients with breakthrough breathlessness ≥3/10, Karnofsky Performance Status score of 50% or more, and a stable dose of strong opioids were enrolled in the trial. They also used the 6MWT as trigger of exertion induced dyspnoea, and evaluated changes in breathlessness intensity, on a NRS, Borg fatigue scale, respiratory rate and oxygen saturation, at the end of the test. Patients received subcutaneous fentanyl (between 15% and 25% of morphine equivalent daily dose) or subcutaneous 0.9% normal saline 15 minutes before 6MWT. Subcutaneous fentanyl was associated with significant improvements in outcome measures, but direct comparison between fentanyl and placebo revealed no statistical differences in any measures. Nevertheless, the study was underpowered to detect differences between active and placebo treatment.

As yet, findings of opioids efficacy for incident dyspnoea are insufficient. Only small case series have documented the improvement of dyspnoea episodes with intranasal and oral transmucosal fentanyl (17). On the other hand, the only randomized controlled trial on breakthrough dyspnoea published found no significant difference in dyspnoea relief between systemic hydromorphone, nebulized hydromorphone, and nebulized saline in cancer patients (20).

According to aforementioned studies, patients with chronic breathlessness must be treated with oral or parenteral morphine. Moreover, oral or parenteral morphine, or the rapid-onset formulations of fentanyl, should be used for dyspnoea crises in patients with constant breathlessness. Nevertheless, there are no data to support the routine use of opioids for exercise-induced dyspnoea in patients without chronic breathlessness. Four-registered randomised trials are underway (www.clinical trials.gov) to evaluate the efficacy of different fentanyl formulations for the relief of exercise dyspnoea. Their findings should help us to improve the knowledge of the exercise-induced dyspnoea treatment.

Acknowledgements

Disclosure: The author declares no conflict of interest.

References

1. Dyspnea. Mechanisms, assessment, and management: a consensus statement. American Thoracic Society. Am J Respir Crit Care Med 1999;159:321-40.
2. Currow DC, Smith J, Davidson PM, et al. Do the trajectories of dyspnea differ in prevalence and intensity by diagnosis at the end of life? A consecutive cohort study. J Pain Symptom Manage 2010;39:680-90.
3. Bausewein C, Booth S, Gysels M, et al. Individual breathlessness trajectories do not match summary trajectories in advanced cancer and chronic obstructive pulmonary disease: results from a longitudinal study. Palliat Med 2010;24:777-86.
4. Abernethy AP, Wheeler JL. Total dyspnoea. Curr Opin Support Palliat Care 2008;2:110-3.
5. Reddy SK, Parsons HA, Elsayem A, et al. Characteristics and correlates of dyspnea in patients with advanced cancer. J Palliat Med 2009;12:29-36.
6. Wiseman R, Rowett D, Allcroft P, et al. Chronic refractory dyspnoea--evidence based management. Aust Fam Physician 2013;42:137-40.
7. Simon ST, Higginson IJ, Benalia H, et al. Episodic and continuous breathlessness: a new categorization of breathlessness. J Pain Symptom Manage 2013;45:1019-29.
8. Simon ST, Weingärtner V, Higginson IJ, et al. Definition, Categorization, and Terminology of Episodic Breathlessness: Consensus by an International Delphi Survey. J Pain Symptom Manage 2013. [Epub ahead of print].
9. Weingärtner V, Bausewein C, Higginson IJ, et al. Characterizing episodic breathlessness in patients with advanced disease. J Palliat Med 2013;16:1275-9.
10. Simon ST, Bausewein C, Schildmann E, et al. Episodic breathlessness in patients with advanced disease: a systematic review. J Pain Symptom Manage 2013;45:561-78.
11. Simon ST, Higginson IJ, Benalia H, et al. Episodes of breathlessness: types and patterns - a qualitative study exploring experiences of patients with advanced diseases. Palliat Med 2013;27:524-32.
12. Currow DC, Higginson IJ, Johnson MJ. Breathlessness--current and emerging mechanisms, measurement and management: a discussion from an European Association of Palliative Care workshop. Palliat Med 2013;27:932-8.
13. Jennings AL, Davies AN, Higgins JP, et al. A systematic review of the use of opioids in the management of dyspnoea. Thorax 2002;57:939-44.
14. Booth S, Moosavi SH, Higginson IJ. The etiology and management of intractable breathlessness in patients with advanced cancer: a systematic review of pharmacological therapy. Nat Clin Pract Oncol 2008;5:90-100.
15. Viola R, Kiteley C, Lloyd NS, et al. The management of dyspnea in cancer patients: a systematic review. Support Care Cancer 2008;16:329-37.
16. Ben-Aharon I, Gafter-Gvili A, Leibovici L, et al. Interventions for alleviating cancer-related dyspnea: a systematic review and meta-analysis. Acta Oncol 2012;51:996-1008.
17. Simon ST, Köskeroglu P, Gaertner J, et al. Fentanyl for the relief of refractory breathlessness: a systematic review. J Pain Symptom Manage 2013;46:874-86.
18. Pinna MA, Bruera E, Moralo MJ, et al. A Randomized Crossover Clinical Trial to Evaluate the Efficacy of Oral Transmucosal Fentanyl Citrate in the Treatment of Dyspnea on Exertion in Patients With Advanced Cancer. Am J Hosp Palliat Care 2013. [Epub ahead of print].
19. Hui D, Xu A, Frisbee-Hume S, et al. Effects of Prophylactic Subcutaneous Fentanyl on Exercise-Induced Breakthrough Dyspnea in Cancer Patients: A Preliminary Double-Blind, Randomized, Controlled Trial. J Pain Symptom Manage 2013. [Epub ahead of print].
20. Charles MA, Reymond L, Israel F. Relief of incident dyspnea in palliative cancer patients: a pilot, randomized, controlled trial comparing nebulized hydromorphone, systemic hydromorphone, and nebulized saline. J Pain Symptom Manage 2008;36:29-38.

Cite this article as: Benítez-Rosario MA. Fentanyl for episodic dyspnoea in cancer patients. Ann Palliat Med 2014;3(1):4-6. doi: 10.3978/j.issn.2224-5820.2014.01.02