Review Article

Fentanyl for the Relief of Refractory Breathlessness: A Systematic Review

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Abstract

Context. Fentanyl is a potent opioid that has been proven to provide effective treatment for breakthrough cancer pain. Although opioids are the only drug group with evidence for the symptomatic treatment of breathlessness, evidence about the efficacy of fentanyl for the relief of breathlessness is unknown.

Objectives. We performed a systematic review to evaluate the current evidence for the use of fentanyl for the relief of breathlessness.

Methods. The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendation for systematic reviews. Four databases (MEDLINE, EMBASE, Cochrane Library, International Pharmaceutical Abstracts) were screened using "fentanyl" and "dyspnoea" (and synonyms) as search terms. Hand search and contact with relevant authors completed the search.

Results. A total of 622 references were retrieved, 13 of which met the inclusion criteria for this review. Two randomized controlled trials (RCTs) evaluated fentanyl for breathlessness, but one only included two patients. The other studies were before-after ($n = 2$) and case studies ($n = 9$). All studies reported successful relief of breathlessness after fentanyl application, but the only (pilot-) RCT failed to demonstrate a statistically significant difference compared with placebo. The nature and incidence of adverse events were comparable with other opioids, and no respiratory depression was observed.

Conclusion. Descriptive studies yielded promising results for the use of fentanyl for the relief of breathlessness; however, efficacy trials are lacking. Fully powered RCTs are warranted to determine the efficacy of fentanyl for breathlessness relief, but these require pilot studies to evaluate effective size, study procedures, and outcome measures. J Pain Symptom Manage 2013;46:874–886.

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Accepted for publication: February 18, 2013.

0885-3924/$ - see front matter
http://dx.doi.org/10.1016/j.jpainsymman.2013.02.019

Key Words
Dyspnea, fentanyl, systematic review, palliative

Introduction

Breathlessness (or dyspnea) is defined as a subjective experience of breathing discomfort.[1] It is one of the most common and distressing symptoms for patients with advanced diseases.[2,3] An observational study of 5320 patients in palliative care units (94.3% with cancer) in Germany reported a prevalence of breathlessness in 53.8% of the study population, which is supported by studies in other countries.[4–6] Refractory breathlessness is defined as a symptom that still persists after optimal treatment of the underlying condition.[7] The management of refractory breathlessness is complex and still insufficient because of a lack of effective treatments.[8] So-called "strong" opioids (e.g., morphine, diamorphine) are the only drug group with evidence for the symptomatic management of breathlessness. In most cases, morphine is administered orally or parenterally.[9,10]

Two different patterns of breathlessness have been identified: chronic or continuous breathlessness (breathlessness all the time) and episodes of breathlessness (acute, incident, breakthrough breathlessness).[8,11] Episodes of breathlessness are defined as a "clinically significant aggravation of dyspnoea in patients with continuous dyspnoea or occurring intermittently" and characterized by a sudden increase of breathlessness intensity with a short duration.[8] There are only two observational studies that explicitly assess episodes of breathlessness. The first study assessed episodic breathlessness in 70 cancer patients of whom 57 (81%) reported episodes of breathlessness.[8] The duration of the episodes was short (87% less than 10 minutes) with an average daily occurrence of 5–6 times in most patients. These results are supported by a descriptive study done by our study group, evaluating episodes in two countries (personal communication, Simon, 2013).

At the moment, immediate-release morphine is often used to manage episodes of breathlessness, but onset of action is around 20–30 minutes.[12] Unfortunately, this is longer than most episodes of breathlessness last.[11] Fentanyl is a potent highly lipophilic opioid with a broad evidence base for the treatment of pain and, in particular, breakthrough cancer pain, which shows similarities with episodic breathlessness.[13,14] For breakthrough cancer pain, fentanyl shows a quick onset of action (7–16 minutes) and a short period of drug action (approximately 60 minutes).[15] Fentanyl belongs to the group of strong opioids; opioids are the only drugs that have proven to be effective for the relief of breathlessness.[9,10] Therefore, fentanyl might be suitable for the relief of episodic breathlessness. However, the evidence for the efficacy or effectiveness of fentanyl for the relief of breathlessness is unknown.

To our knowledge, a systematic review assessing this question has not been performed to date. Therefore, this study aims to analyze and summarize the evidence about the use of fentanyl for the relief of breathlessness by systematically reviewing the available literature.

Methods

This systematic review follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[16]

Literature Search

Studies were identified from a search of the following four databases via OVID: The Cochrane Library (Wiley Interscience—June 2012), MEDLINE (1950 to June 2012), EMBASE (1980 to June 2012), and International Pharmaceutical Abstracts (1970 to June 2012).

The search strategy combined the following search terms (Medical Subject Heading and key words): "dyspnea," "dyspnoea," "breathlessness," "shortness of breath," "breathing difficulties" AND "fentanyl," "alfentanil," "sufentanil," "remifentanil."

Reference lists of all relevant studies related to fentanyl and the management of breathlessness were examined. Also, key textbooks (Goodman and Gilman's The Pharmacological Basis of Therapeutics, Oxford Textbook of