Original Article

Effects of Prophylactic Subcutaneous Fentanyl on Exercise-Induced Breakthrough Dyspnea in Cancer Patients: A Preliminary Double-Blind, Randomized, Controlled Trial

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Abstract

Context. Dyspnea is one of the most distressing symptoms in patients with cancer, and often worsens with breakthrough episodes on exertion. We hypothesized that fentanyl given prophylactically may alleviate breakthrough dyspnea.

Objectives. To determine the feasibility of conducting a randomized trial of subcutaneous fentanyl in patients with cancer, and examine the effects of fentanyl on dyspnea, walk distance, vital signs, and adverse events.

Methods. In this double-blind, randomized, controlled trial, we asked ambulatory patients with breakthrough dyspnea to perform a baseline six minute walk test (6MWT), and then assigned them to either subcutaneous fentanyl or placebo 15 minutes before a second 6MWT. We documented the change in dyspnea Numeric Rating Scale (NRS) score, walk distance, vital signs, and adverse events between the first and second 6MWT.

Results. A total of 20 patients were enrolled (1:1 ratio) without attrition. Comparison between baseline and second walk showed that fentanyl was associated with significant improvements in dyspnea NRS score at the end of the 6MWT (mean [95% CI] −1.8 [−3.2, −0.4]), dyspnea NRS score at rest of 15 minutes after drug administration (−0.9 [−1.8, −0.04]), Borg Scale fatigue score at the end of the 6MWT (−1.3 [−2.4, −0.2]), 6MWT distance (+37.2 m [5.8, 68.6]), and respiratory rate (−2.4 [−4.5, −0.3]). Nonstatistically significant improvements also were observed in the placebo arm, with no difference between the two study arms. No significant adverse effects were observed.

Conclusion. Prophylactic fentanyl was safe and improved dyspnea, fatigue, walk distance, and respiratory rate. We also observed a large placebo effect.

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Our results justify larger randomized controlled trials with higher fentanyl doses (clinicaltrials.gov registration: NCT01515566). J Pain Symptom Manage 2014;47:209–217.

Key Words
Dyspnea, exercise, opioids, fentanyl, neoplasms, randomized controlled trial, prophylaxis, subcutaneous

Introduction

Dyspnea is one of the most common and distressing symptoms among patients with cancer.[1] More than 80% of the patients who experience dyspnea report having breakthrough (or incidental) episodes, triggered by various factors such as exertion or emotional distress. Among these patients, one-third have five or more episodes per day, and most of these episodes last less than 10 minutes.[2] Breakthrough dyspnea is particularly challenging to treat because of its transient and episodic nature.

There have only been a handful of studies on therapeutic options for breakthrough dyspnea. Several small case series have documented the efficacy of oral transmucosal fentanyl citrate and intranasal fentanyl for breakthrough dyspnea episodes.[3–5] However, the only randomized controlled trial on breakthrough dyspnea comparing systemic hydromorphone, nebulized hydromorphone, and nebulized saline in patients with cancer found no significant difference in dyspnea relief.[6] Furthermore, all of these studies involved the use of opioids for treatment rather than primary prophylaxis of breakthrough dyspnea.

Fentanyl is a rapid-acting opioid that is highly lipophilic and is currently approved for the management of pain. When administered subcutaneously, fentanyl reaches a median peak concentration at 15 minutes (range 10–30 minutes),[7] making it a potentially attractive therapeutic agent for the management of breakthrough dyspnea. An improved understanding of the efficacy of subcutaneous fentanyl given prophylactically may allow us to better manage breakthrough dyspnea and to enhance patients' function and quality of life. In this study, we determined the feasibility of conducting a double-blind, parallel, randomized, placebo-controlled trial of subcutaneous fentanyl in cancer patients with breakthrough dyspnea. We also examined the effects of fentanyl and placebo on the intensity of dyspnea, six minute walk distance, physiologic parameters, and adverse events.

Methods

Patients

Inclusion criteria were diagnosis of cancer, outpatient at the Supportive Care Center at M. D. Anderson Cancer Center, aged 18 years or older, an average intensity of breakthrough dyspnea ≥3/10 on a Numeric Rating Scale (NRS), ability to communicate in English or Spanish, ambulatory with or without walking aid, Karnofsky Performance Status score of 50% or more, and a stable dose of strong opioids with a morphine equivalent daily dose (MEDD) of between 30 and 580 mg. Patients with dyspnea at rest with a score of ≥7/10, supplemental oxygen of more than 6 L/min, delirium (Memorial Delirium Assessment Scale >13/30), allergic reaction to fentanyl, history of substance abuse, recent history of coronary artery disease, uncontrolled tachycardia, or hypertension at the time of assessment were excluded. The Institutional Review Board at M. D. Anderson Cancer Center approved this study. All patients provided written informed consent.

Study Design

This double-blind, randomized, parallel, placebo-controlled trial was designed to examine study feasibility and the effect of subcutaneous fentanyl on dyspnea in a before-after comparison. We also included a placebo arm to examine the magnitude of placebo effect. Patients were screened and approached by our research staff for this trial at the Supportive Care Outpatient Clinic. Using a computer