Original Article

Once-Daily Opioids for Chronic Dyspnea: A Dose Increment and Pharmacovigilance Study

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Abstract

Context. Randomized controlled trials can answer questions of efficacy, but long-term pharmacovigilance studies generate complementary safety data.

Objectives. Level I evidence supports short-term efficacy of opioids in reducing chronic refractory dyspnea. This study aimed to determine the minimum effective once-daily dose of sustained-release morphine, and whether net clinical benefits are sustained safely.

Methods. In a Phase II dose increment study, 10 mg daily of sustained-release morphine was administered, and increased in nonresponders by 10 mg daily each week to a maximum of 30 mg daily. The participant was withdrawn if there were unacceptable side effects or no response to maximum dose. If participants had a 10% improvement in dyspnea over their own baseline, they joined a long-term Phase IV effectiveness/safety study at that dose. Complying with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, response and side effects are described, with demographic and clinical characteristics of responders.

Results. Eighty-three participants (53 males, mean age 75 years, 54% with chronic obstructive pulmonary disease) provided more than 30 patient-years of data. Fifty-two participants derived ≥10% benefit (on average 35% improvement over baseline), giving a response rate of 62% (number needed to treat of 1.6: number needed to harm 4.6); for 70%, this dose was 10 mg/24 h. Benefit was maintained at three months for 28 (33%) people. Ranking of breathlessness was

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reduced significantly ($P < 0.001$), but constipation increased ($P < 0.001$) despite laxatives. There were no episodes of respiratory depression or hospitalizations as a result of the sustained-release morphine. Overall, one in three people continued to derive benefit at three months.

Conclusion. Ten milligrams of sustained-release oral morphine once daily is safe and effective for most people who respond. J Pain Symptom Manage 2011;42:388–399.

Key Words
Palliative care, dyspnea, opioids, clinical effectiveness, respiratory

Introduction

Randomized controlled trials can answer questions of efficacy, and although toxicities are reported, these studies are usually of the briefest duration to see a clinical benefit and rarely designed with power to detect significantly different levels of toxicities, especially if they are rare. The optimal way to answer questions of safety, sustained benefits, and long-term toxicities is through ongoing pharmacovigilance studies to understand the net clinical benefit in everyday practice. Pharmacovigilance studies are, by definition, uncontrolled studies.

Dyspnea is more than a sentinel clinical sign; dyspnea, experienced acutely or chronically, threatens a person's very existence, psychological well-being, and social functioning. Once reversible causes of dyspnea have been addressed, residual symptomatology is "refractory dyspnea."[1]

At a population level, refractory dyspnea is a significant chronic burden for a sizeable number of individuals.[2,3] Moreover, with many respiratory, cardiac, hematological, oncological, and neuromuscular disorders, breathlessness is likely to worsen over time.[4] There are no symptom-specific medications to treat refractory dyspnea registered with pharmaceutical regulatory bodies such as the U.S. Food and Drug Administration, the European Medicines Evaluation Agency, or the Australian Therapeutic Goods Administration.

Evidence, including an adequately powered randomized study and a meta-analysis, demonstrates that opioids reduce the intensity of refractory breathlessness.[1,5] The effect of opioids on the subjective sensation of breathlessness is further supported by recent evidence demonstrating that blockade of endogenous opioids during exercise worsens the perception of breathlessness without changing the ability to exercise in people with chronic obstructive pulmonary disease (COPD).[6]

The American College of Chest Physicians has recently released a position paper endorsing the use of opioids for people who have breathlessness "that persists at rest or with minimal activity."[7] Although data supporting opioids for the treatment of refractory dyspnea are clear, studies to date have not yet defined the minimum effective once-daily dose.[1,8,9] Furthermore, since the study by Abernethy et al., which evaluated the efficacy of 20 mg oral morphine daily, a 10 mg/24 h preparation has become available.

Prospective data about long-term safety of opioids for refractory dyspnea are lacking. Many clinicians continue to extrapolate from the acute toxicity witnessed when frail or infirm patients who were opioid-naïve were administered opioids in the emergency room or postoperatively, with severe side effects including confusion, drowsiness, and respiratory depression.[10,11] These observations, first made more than six decades ago, still largely underpin the poor uptake of an entirely different way of prescribing opioids for refractory breathlessness—regular low doses orally. International guidelines for opioids in refractory breathlessness continue to reflect concerns generated by the way opioids are used for acute pain.[12,13] Lack of dosing and safety data continue to be one barrier in the registration of a dyspnea-related indication for morphine.

Given the chronic nature of breathlessness for many people, there are justifiable concerns that benefits of opioids may diminish over time. There have been no longitudinal prospective data describing the net clinical benefits of