Original Article

Midazolam as Adjunct Therapy to Morphine in the Alleviation of Severe Dyspnea Perception in Patients with Advanced Cancer

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Abstract
The mainstay of dyspnea palliation remains altering its central perception. Morphine is the main drug and anxiolytics have a less established role. This trial assessed the role of midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in terminally ill cancer patients. One hundred and one patients with severe dyspnea were randomized to receive around-the-clock morphine (2.5 mg every 4 hours for opioid-naïve patients or a 25% increment over the daily dose for those receiving baseline opioids) with midazolam rescue doses (5 mg) in case of breakthrough dyspnea (BD) (Group Mo); around-the-clock midazolam (5 mg every 4 hours) with morphine rescues (2.5 mg) in case of BD (Group Mi); or around-the-clock morphine (2.5 mg every 4 hours for opioid-naïve patients or a 25% increment over the daily dose for those receiving baseline opioids) plus midazolam (5 mg every 4 hours) with morphine rescue doses (2.5 mg) in case of BD (Group MM). All drugs were given subcutaneously in a single-blinded way. Thirty-five patients were entered in Group Mo, 33 entered in Mi, and 33 entered in MM. At 24 hours, patients who experienced dyspnea relief were 69%, 46%, and 92% in the Mo, Mi, and MM groups, respectively (P = 0.0004 and P = 0.03 for MM vs. Mi and MM vs. Mo, respectively). At 48 hours, those with no dyspnea relief (no controlled dyspnea) were 12.5%, 26%, and 4% for the Mo, Mi, and MM groups, respectively (P = 0.04 for MM vs. Mi). During the first day, patients with BD for the groups Mo, Mi, and MM were 34.3%, 36.4%, and 21.2%, respectively (P = NS or not significant), whereas during the second day, these percentages were 38%, 38.5%, and 24%, respectively (P = NS). The data demonstrate that the beneficial effects of morphine in controlling baseline levels of dyspnea could be improved with the addition of midazolam to the treatment. J Pain Symptom Manage 2006;31:38–47. *© 2006 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Dyspnea, morphine, midazolam, cancer, anxiety, breathlessness, opioids, anxiolytic

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Introduction

Dyspnea remains one of the most challenging symptoms to manage in the setting of advanced malignancy[1] and it is one of the most common symptoms in advanced cancer patients.[2] The prevalence and severity of dyspnea increase in the last weeks of life,[3] and it is the main symptom in more than 20% of patients in the last 48 hours of life.[4] In a multinational study of terminal sedation, dyspnea was the most frequent symptom prompting sedation in 25–53% of patients.[5] Similarly, in an Italian palliative care unit, 28% of cancer patients had intractable dyspnea at the end of life, which required heavy sedation.[6] These studies suggest that in the last weeks of life, current management strategies, although helpful, are not adequate for symptom control, resulting in more frequent need for hospitalization and heavy sedation.[1,6]

Dyspnea should be distinguished from respiratory failure, which is defined as hypoxia and/or hypercapnia. The American Thoracic Society consensus statement defines dyspnea as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interaction among multiple physiologic, psychological, social, and environmental factors, and may induce secondary physiologic and behavioral responses."[7] This definition underlines the subjective and inherently multidimensional nature of dyspnea, and its impact on multiple domains of quality of life.[1] Like pain, dyspnea is a combination of sensation and perception, but in contrast to pain, the neural pathways underlying dyspnea are not well understood.[8] Anything that alters perception (pharmacological or nonpharmacological interventions) may improve the symptom. Clearly, opioids and anxiolytic agents work partially through this mechanism.[1] Currently, for terminally ill patients with advanced cancer, effective therapies targeting the sensation of dyspnea, for example reducing ventilatory demand or improving respiratory muscle strength, are lacking. Therefore, the mainstay of dyspnea palliation remains altering central perception, and morphine is still the first choice of pharmacological therapy.[8]

Many patients report anxiety concurrent with the feeling of breathlessness. Dyspnea can lead to anxiety, and anxiety can exacerbate dyspnea.[8] According to some authors,[8] although opioids may initially have anxiolytic properties, patients typically become tolerant to these effects, and for this reason, anxiolytics (such as benzodiazepines) may have a role in dyspnea management. Although some preclinical[9] and clinical trials[10,11] showed that under some conditions the concurrent use of opioids and benzodiazepines is safe, many physicians are still reluctant to use this combination because of their fear of respiratory depression.

A treatment for dyspnea should not only include measures to control baseline levels of the symptom, but also for controlling the breakthrough component. Particularly during the later episodes, patients experience intense anxiety (respiratory panic attacks), and in this setting, we speculated that a short-acting anxiolytic, such as midazolam, could be useful.

The present trial was designed to assess the role of midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception during the last week of life in patients with advanced cancer.

Methods

Study Design

The study protocol was reviewed and approved by the Research and Ethics Committees of the Angel H. Roffo Cancer Institute of the University of Buenos Aires, and was in accordance with the recommendations found in the Helsinki Declaration of 1975.

Patients were randomly assigned (using a random number generator in 1:1:1 ratio in blocks of nine) to one of the three treatment groups. The principal endpoints were dyspnea intensity (modified Borg scale)[12] and dyspnea relief (yes-no) after the intervention. Additional endpoints were episodes of breakthrough dyspnea (BD) requiring rescue medication (episodes/day), as well as frequency and severity of medication-related side effects. Patients who received morphine were systematically premedicated with laxatives.

Values are presented as mean with the 95% confidence interval (CI), or median with the interquartile range (IR). Unless otherwise noted, the Wilcoxon's signed rank test was used for intragroup comparisons, and the

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