Effect of Lorazepam Versus Morphine on Quality of Life in Hospice Patients with Dyspnea and Anxiety

Eliza S. Daubert, Pharm.D. Candidate, 2014[1], Scott Bolesta, Pharm.D., BCPS[1,2]

[1]Wilkes University Nesbitt College of Pharmacy and Nursing, Wilkes-Barre, PA and [2]Regional Hospital of Scranton, Scranton, PA

Introduction

Terminally ill patients usually suffer from numerous underlying disease processes and symptoms that decrease their quality of life. Literature suggests that among cancer patients, 25% experience severe depression and the incidence increases to 77% in those who are terminally ill[1]. Anxiety is another common psychiatric issue which must be considered when treating patients nearing the end of their lives. There is a lack of literature that specifically addresses how to best improve quality of life in palliative care settings by controlling the “symptom cluster” of anxiety and dyspnea[2]. At this time, morphine is considered the preferred pharmacologic treatment for refractory dyspnea, with adjunct anxiolytics provided as needed to control anxiety[3]. A 2010 study by Navigante and colleagues suggests that midazolam may be superior to morphine in treating idiopathic or disease-related breathlessness in patients with advanced cancer[4]. This finding brings into question whether terminally ill patients with dyspnea and anxiety might also benefit from therapy with benzodiazepines. By decreasing the severity of these symptoms, patient quality of life may be improved. The purpose of this study will be to determine whether treatment with benzodiazepine or opiate therapy has a greater impact on improving the quality of life in terminally ill patients who are enrolled in a hospice service. We hypothesize that treatment of hospice patients with benzodiazepines compared with opiates will result in an increased improvement in quality of life.

Materials & Methods

Study Design

This will be a prospective, randomized, double-blinded, clinical trial conducted through an outpatient hospice service in Scranton, PA. The study protocol will be approved by the institutional review board, and all participants, or legal guardians acting on their behalf, will be required to provide written informed consent.

Study Population

Participants will include all patients 18 years of age or older who are terminally ill, enrolled in a hospice service, diagnosed with the symptom cluster of anxiety and dyspnea, and able to take oral medications. Patients with a life expectancy of 14 days or less, severe respiratory depression, uncontrolled asthma, upper airway obstruction, uncontrolled bleeding, GI obstruction, hypercarbia, heart failure due to chronic lung disease, cardiac arrhythmias, increased intracranial pressure, head injuries, brain tumors, seizure disorders, or narrow angle glaucoma will be excluded. Those receiving concomitant therapy with azelastine, paraldehyde, olanzapine, or sodium oxybate will also be excluded.

Randomization and Treatment

This trial will enroll __ patients. Subject randomization will be performed by a computerized random number generator. Study subjects, investigators, and all those involved in the care of the subject during their hospice stay will be blinded to treatment. Treatment regimens were adapted from the trial by Navigante and colleagues and are shown in figure 1, below[3,4].

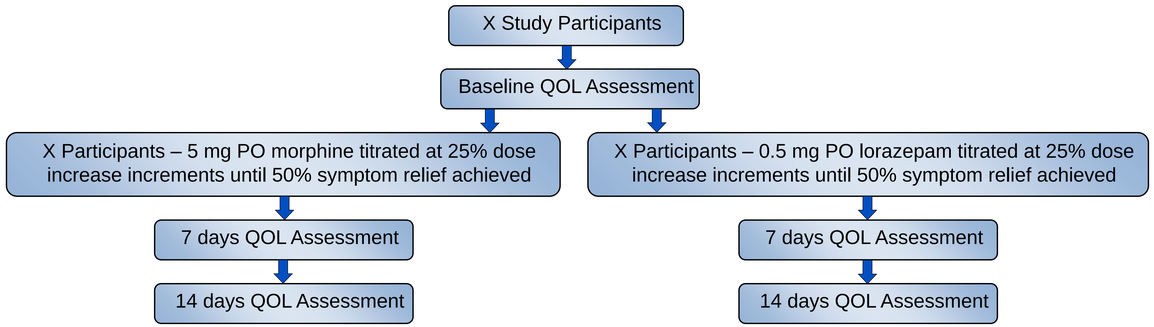

Figure 1: Basic Study Design

Symptom reduction will be evaluated using the Edmonton Symptom Scale, a validated assessment tool for determining the effectiveness of patients’ relief from physical and psychological distress[5].

Outcomes

The primary outcome to be studied is the change in patients’ perception of their quality of life. This will be assessed using the FACIT-Pal, a validated quality of life questionnaire specially designed for use in patients receiving palliative care[6]. Patients will be assessed at baseline and after 7 and 14 days of treatment. Patients will receive treatment for 14 days, after which blinding will be removed and they will be allowed to either remain on the study medication or change to an alternate therapy.

Statistical Analysis

Enrollment of ___ patients will be necessary to detect an increase of ___ points in quality of life score on the FACIT-Pal questionnaire with a two-sided alpha of 0.05 and 80% power following treatment. The sample size will be increased to ____ to account for a 10% subject attrition rate. Baseline demographic information for the two treatment groups will be compared using descriptive statistics. Dichotomous variables will be analyzed using X^2 or Fischer’s exact test as appropriate. Continuous variables will be analyzed using Student’s *t*-test or Mann-Whitney’s rank test as appropriate. Continuous data will be reported as mean ± standard deviation. *P* values less than 0.05 will be considered statistically significant. A per-protocol analysis of the primary outcome will be performed and the change in quality of life observed in the benzodiazepine group will be compared to that observed in the opiate group using a multivariable logistic regression analyses to adjust for confounding variables.

Strengths & Limitations

To build upon the limited body of literature that addresses this clinical issue, this study has been designed to avoid the limitations of previous publications. By focusing on quality of life as the primary outcome, this study investigates a patient-oriented measure rather than the improvement of a singular symptom.

Strengths & Limitations

Quality of life is an understudied outcome in the hospice population and literature is lacking in this area. As Harding and colleagues note, "A primary reason for this dearth of evidence is the lack of appropriate and validated outcome tools, among other logistical and methodological challenges in....this population[7,8]." By using a validated tool, this study will decrease the literature deficit in this area[9].

This study avoids common limitations encountered in research by ensuring adequate power, blinding practitioners and patients to treatment, and using a robust randomization procedure. By examining the change in quality of life score, the results of this study will be able to compare the effects of lorazepam and morphine on the entire symptom cluster, rather than only dyspnea, as do prior publications.

Despite attempts to control confounding factors and outside influences, a potential limitation of this study is the geographic location from which the sample will be recruited. Most patients will likely be Caucasian which will limit the generalizability of the results to other ethnicities. Additionally, the findings of this study cannot be applied to patients in care settings other than hospice services or patients who have one or more of the exclusion factors.

Disclosure Statement

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with the commercial entities that may have direct or indirect interest in the subject matter of this presentation:

Eliza S. Daubert: Nothing to disclose

Scott Bolesta: Nothing to disclose

References

1. Breitbart W, Chocinov HM, Passik S. Psychiatric aspects of palliative care. In: Doyle D, Hanks GWC, MacDonald N, eds. Oxford Textbook of Palliative Medicine. 2nd ed. Oxford: Oxford University Press; 2001. 933-4.
2. Shuster JL. Delirium, confusion, and agitation at the end of life. *J Palliat Med.* 1998; 1(2):177-86.
3. Navigante AH, Cerchietti LC, Castro MA, et al. Midasolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. *J Pain Symptom Manage.* 2006 Jan.;31(1):38-47.
4. Navigante AH, Castro MS, Cerchietti LC. Morphine versus midazolam as upfront therapy to control dyspnea perception in cancer patients while its underlying cause is sought or treated. *J Pain Symptom Manage.* 2010 May;39(5):820-30.
5. Richardson LA, Jones GW. A review of the reliability and validity of the Edmonton Symptom Assessment System. *Curr Oncol.*2009;16(1):53-64.
6. Ventafridda V, Ripamonti C, de Conno F, Tamburini M, Cassileth B. Symptom prevalence and control during cancer patients’ last days of life. *J Palliat Care.* 1990;6:7-11.
7. Harding R, Higginson IJ. Palliative care in Sub-Saharan Africa. *Lancet* 2005;365:1971-7.
8. Harding R, Powell RA, Downing J, et al. Generating an African palliative care evidence base: the context, need, challenges, and strategy. *J Palliat Care.*2008;36:304-9.
9. Doyle Lyons K, Bakitas M, Hegel MT, et al. Reliability and validity of the Functional Assessment of Chronic Illness Therapy-Palliative Care (FACIT-Pal) scale. *J Pain Symptom Manage.*2009 Jan.;37(1);23-32.