The Use of Nebulized Opioids in the Management of Dyspnea: Evidence Synthesis

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Purpose/Objectives: To analyze the evidence about the use of nebulized opioids to treat dyspnea using the Priority Symptom Management (PRISM) level-of-evidence framework and to make a practice recommendation.

Data Sources: Computerized database and manual search for articles and abstracts that included experimental trials, chart reviews, and case studies.

Data Synthesis: 20 articles with evaluable evidence were identified. Analysis was complex because of heterogeneous variables and outcome measures. A major limitation is small sample sizes. The majority of PRISM level I and II studies indicated unfavorable evidence.

Conclusions: Scientific data supporting the use of nebulized opioids to treat dyspnea in patients with chronic pulmonary disease, including malignancy, are lacking.

Implications for Nursing: Insufficient data identify a need for further research with random crossover designs involving larger samples that are stratified according to prior opioid use. Consistency of study variables should be emphasized.

Dyspnea is a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity. The dyspnea experience derives from interactions among multiple physiologic, psychological, social, and environmental factors and may induce secondary physiologic and behavioral responses (American Thoracic Society [ATS], 1999). This definition stresses the subjective and multifactorial nature of the symptom.

Physiologic causes of dyspnea and alternative targets for treatment classified by ATS (1999) are (a) heightened ventilatory demands, (b) increased impedance or resistance to ventilation, (c) abnormalities of the respiratory muscles, and (d) abnormal central perception of dyspnea as a result of increased central respiratory drive. The sensation of dyspnea, like pain, has an affective dimension (Carrieri-Kohlman, Gormley, Douglas, Paul, & Stulbarg, 1996; Wilson & Jones, 1991). The same stimulus, such as walking up stairs, can make patients aware that their breathing has become labored, but patients' reaction to the breathlessness can vary greatly and make the symptom seem more or less severe. In other words, the affective component of a symptom, in this case dyspnea, can differ greatly and modulate the intensity of the

Key Points . . .

- ➤ Dyspnea is a subjective experience arising from interactions among multiple factors.
- ➤ Inhaled opioids may modify dyspnea through local action in the respiratory tract.
- ➤ Existing evidence fails to support the use of nebulized opioids to treat dyspnea.

Goal for CE Enrollees:

To enhance nurses' familiarity with the current evidence on the use of nebulized opioids in the treatment of dyspnea.

Objectives for CE Enrollees:

On completion of this CE, the participant will be able to

1. Describe the physiologic causes and cognitive variables that affect the experience of dyspnea.
2. Outline the current evidence supporting and disputing the use of nebulized opioids for the treatment of dyspnea.
3. Identify issues to consider when designing future research into the effectiveness of nebulized opioids for dyspnea.

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symptom (Carrieri-Kohlman et al.; Corfield et al., 1995). Therefore, the threshold for perception of dyspnea varies widely with different individuals and is related only moderately to the degree of pulmonary dysfunction or impairment.

Important cognitive variables that modify the perception of dyspnea are anxiety and depression (Dudley, Martin, & Holmes, 1964; Gift, 1991; Smith et al., 2001), personality (Chetta et al., 1998), and the meaning of the symptom for the person (Cioffi, 1991). Studies involving healthy subjects as well as those involving patients have suggested that perception of the intensity of breathlessness may be influenced by prior experience of the sensation (Belman, Brooks, Ross, & Mosenifar, 1991; Wilson, Oldfield, & Jones, 1993). The numbers of coping strategies (Kwiatkowski, Carrieri-Kohlman, Janson, & Stulbarg, 1995) and beliefs in coping strategy effectiveness (Janson-Bjerklie, Ferketich, Benner, & Becker, 1992) also affect the perception of dyspnea.

In patients with advanced cancer, the prevalence of dyspnea ranges from 15%–55% at referral to palliative care services to 18%–79% during the last week of life, with dyspnea reported as moderate to severe in 10%–63% of patients (Ripamonti & Fusco, 2002). Initial clinical management is dictated by the underlying pathophysiology. When malignancy is the underlying cause of dyspnea, treatment may include surgical resection, chemotherapy, radiotherapy, thoracentesis, or pleural sclerosing. Steroids may ameliorate pulmonary toxicity of radiotherapy or chemotherapy. Other interventions directed toward treatment of dyspnea are erythropoietin therapy or red-cell transfusion for anemia and antibiotics for pneumonia. Concurrent symptomatic management of dyspnea is needed with primary therapy or when primary therapy fails to resolve the underlying cause.

Opioid medications have been explored as a means of relieving dyspnea presumably because of their respiratory depressive effects. Opioids may blunt perceptual responses so that for a given stimulus, the intensity of respiratory sensation is decreased. Opioids are used in a variety of routes to manage dyspnea in palliative care. The inhalation of opioids is a novel approach to minimize systemic toxicity because they may modify respiratory sensation through a direct local binding action to sensory receptors in the respiratory tract.

Sources and Procedures to Establish Knowledge Base

As the first step in the synthesis of available evidence about the effectiveness of nebulized opioids to relieve dyspnea in patients with pulmonary disease including malignancy, a computerized bibliographic search of MEDLINE®, PREMEDLINE®, CINAHL®, CANCERLIT®, International Pharmaceutical Abstracts, *Dissertation Abstracts International,* and the Cochrane Database of Systematic Reviews was conducted in February 2002 by a professional librarian using the Boolean search words "dyspnea" and "drug therapy" combined with "cancer" or "neoplasm." A second search was conducted dropping the cancer diagnosis and allowing all diagnoses. This was done to include evidence of a drug therapy intervention in any patients experiencing dyspnea. The search was limited to adult populations and the English language and spanned from 1990 to February 2002. The search response to the first broad question on the "pharmacologic management of dyspnea" yielded more than 290 citations. Resource consideration prompted the authors to narrow the question to "the effectiveness of nebulized opioids to treat dyspnea." In addition to randomized controlled trials, the authors allowed nonrandomized trials, chart reviews, and case reports to incorporate all levels of evidence. From the original search, 20 citations, including one integrated review (Cochrane database), addressed nebulized therapy for dyspnea. Full manuscripts of those 20 citations were requested. Manual searches of the bibliographies of the retrieved articles uncovered 14 additional articles.

Fourteen of these 34 articles were eliminated because they were clinical reviews and summarized studies that already were included, commented on included studies, addressed administration of non-nebulized opioids, or reported a pediatric case study. Twenty published reports were found to contain evidence pertinent to the main question.

Each article was analyzed independently by at least two of the four authors. Using the critique process model from the Oncology Nursing Society (ONS, n.d.) Evidence-Based Practice (EBP) Resource Center, each author prepared a methodologic and utilization table to display critique findings. The merits and limitations of each study were discussed by at least three authors during phone conferences. Critical appraisal of each publication for scientific merit and clinical applicability was facilitated by the authors' team approach. The team consisted of two advanced practice nurses (APNs), one nurse educator, and one nurse researcher. This triad model, with different nursing perspectives and expertise, originated at the 2001 ONS APN Retreat by the EBP project team to develop a clinically relevant review.

The authors considered a number of published approaches to categorize the levels of evidence (e.g., Briss et al., 2000; Hadorn, Baker, Hodges, & Hicks, 1996; Ropka & Spencer-Cisek, 2001; Stetler et al., 1998). Ropka and Spencer-Cisek's adapted schema (see Table 1) was chosen because it is a relatively straightforward approach proposed by the ONS Priority Symptom Management (PRISM) project for symptom management evidence synthesis.

Overview of Relevant Literature

Literature reviewed in this article (see Table 2) is organized into two sections, one focusing on unfavorable evidence with respect to the effectiveness of nebulized morphine on dyspnea and the other on positive evidence. The seminal study by Young, Daviskas, and Keena (1989) is described initially because its findings are frequently the basis for comparison by subsequent researchers and it is the only study demonstrating positive effects of nebulized morphine in a controlled trial. Young et al. considered that low-dose nebulized morphine might relieve dyspnea through a direct effect on lung afferent nerves. The premise that nebulized opioids may exert a therapeutic effect via local opioid receptors in the lung underlies a number of studies. To determine whether inhaled morphine had an effect on exercise endurance limited by dyspnea, 11 patients with chronic lung disease completed a baseline progressive exercise test on a cycle ergometer to determine maximum workload. After rest or on a separate day, the patients were randomized to receive either 5 ml of inhaled morphine (1 mg/ml) or saline and then crossed over to the other arm. The exercise test was conducted 15 minutes after double-blinded inhalation. Oxygen was given during the exercise. Five patients increased their endurance time after placebo;

Table 1. Priority Symptom Management (PRISM) Levels of Evidence

PRISM Level	Level of Evidence[a]	Evidence Source
I	1	Qualitative systematic review (also called "integrative review") or quantitative systematic review (also called "meta-analysis") of multiple, well-designed, randomized, controlled trials of adequate quality
	2	At least one properly designed, randomized, controlled trial of appropriate size (record if multisite and over 100 subjects, but not required)
	3	Well-designed trial without randomization (e.g., single group pre/post, cohort, time series, meta-analysis of cohort studies)
II	4	Well-conducted, qualitative, systematic review of nonexperimental design studies
	5	Well-conducted case-control study
	6	Poorly controlled study (e.g., randomized controlled trial with major flaws) or uncontrolled studies (e.g., correlational descriptive study, case series)
	7	Conflicting evidence with the weight of evidence supporting the recommendation or meta-analysis showing a trend that did not reach statistical significance
		National Institutes of Health Consensus Reports
		Published practice guidelines, for example, from professional organizations (e.g., Oncology Nursing Society, American Society of Clinical Oncology), healthcare organizations (e.g., American Cancer Society), or federal agencies (e.g., National Cancer Institute, Centers for Disease Control and Prevention)
III	8	Qualitative designs
		Case studies; opinions from expert authorities, agencies, or committees

[a] Levels of evidence range from the strongest evidence at the top to the weakest level of evidence at the bottom.

Note. From "Rating the Quality of Evidence for Clinical Practice Guidelines" by D.C. Hadorn, D. Baker, J.S. Hodges, & N. Hicks, 1996, *Journal of Clinical Epidemiology, 49,* 750. Copyright 1996 by Elsevier Inc. Adapted with permission in "PRISM: Priority Symptom Management Project Phase I: Assessment" by M.E. Ropka & P. Spencer-Cisek, 2001, *Oncology Nursing Forum, 28,* 1589. Copyright 2001 by the Oncology Nursing Society. Reprinted with permission.

nine patients, however, showed a significantly longer ($p < 0.01$) mean endurance time after morphine. This benefit of nebulized morphine to increase endurance stimulated several randomized clinical trials to test similar and associated clinical questions.

Davis et al. (1994) showed one variation of positive evidence in a randomized double-blind crossover trial that compared the effect of equianalgesic single doses of nebulized morphine; morphine 6-glucuronide (M6-G), which is an active morphine metabolite; and placebo on exercise endurance in patients with chronic obstructive pulmonary disease (COPD). Measurements included six-minute walk tests and bicycle exercise endurance. A significant change in bicycle exercise endurance time was found with M6-G only. Davis et al. (1994) concluded that this may reflect a difference in potency between morphine and its metabolite.

Unfavorable Evidence

Jennings, Davies, Higgins, Gibbs, and Broadley (2002) conducted a systematic evaluation of the effectiveness of symptomatic treatments for breathlessness. Studies included in the review used opioid drugs given by any route and subsequently were divided into oral or parenteral and nebulized groups. These two groups were analyzed together and separately. Eighteen randomized, double-blind, placebo-controlled, crossover studies fulfilled the inclusion criteria for review. Nine of the 18 studies involved the use of nebulized opioids. The primary outcome measure was a subjective assessment of dyspnea. A secondary outcome measure was exercise tolerance. A meta-analysis was performed for the primary and secondary outcomes. Analysis specified a priori was carried out on the subgroup studies involving nebulized opioids. The overall review showed a strong effect of opioid treatment on breathlessness. A significantly stronger effect was found for the oral or parenteral opioid group. For the nebulized subgroup, the pooled result alone did not reach statistical significance. As a result of this integrated review, Jennings et al. concluded that no evidence supported the use of nebulized opioids for the treatment of breathlessness. All nine nebulized opioid studies included in the Jennings et al. analysis are reviewed individually and described in this synthesis.

Eight randomized, controlled trials and one nonrandomized study reviewed by the authors failed to demonstrate effect or benefit of a nebulized opioid. Harris-Eze et al. (1995) examined whether the administration of 2.5 mg and 5 mg of nebulized morphine would influence dyspnea during exercise in six patients with interstitial lung disease. As compared to nebulized saline (control), no significant difference was found in Borg dyspnea scores or maximal exercise performance in Harris-Eze et al.'s study. The modified Borg scale is a numerical rating scale of perceived breathlessness in which the patient rates words describing increasing degrees of breathlessness on a scale of 0–10. Extensive reports demonstrate the reliability and validity for Borg ratings of breathlessness (ATS, 1999). Similarly, in a small nonrandomized trial of eight terminally ill patients already receiving oral or subcutaneous opioids, Peterson, Young, Dunne, Galloway, and Parks (1996) demonstrated that nebulized 2.5 mg morphine, 5 mg morphine, or normal saline failed to improve subjective symptoms of dyspnea or respiratory function compared to

Table 2. Studies Reviewed for Evidence Base

Study	Study Design	Subjects and Variables	Findings and Conclusions	PRISM Level
Unfavorable Evidence				
Jennings et al. (2002)	Integrated review	Systematic Cochrane review included 18 randomized, double-blind, placebo-controlled crossover trials of opioids for the treatment of dyspnea secondary to any cause. Meta-analyses were performed on all included studies and on various subgroups (e.g., nebulized opioids). Outcome measures were dyspnea and exercise tolerance.	Strong effect of non-nebulized opioids relative to placebo in reducing breathlessness was found. The subgroup analysis failed to show a positive effect of nebulized opioids on the sensation of breathlessness. Evidence supports the use of oral and parenteral opioids to treat dyspnea and argues against the use of nebulized opioids. Limitation: All but one study had a small sample (n = 6–18 subjects).	I
Harris-Eze et al. (1995)	Randomized clinical trial (RCT), double blind	6 opioid-naive subjects with interstitial lung disease on three separate days received nebulized saline (control) and 2.5 mg and 5 mg of morphine at 15 minutes before incremental exercise on a cycle. Performance and Borg dyspnea scores were measured.	No significant difference in Borg scores on the three test days was found. Compared to control, low-dose nebulized morphine did not significantly affect the relationship between dyspnea and ventilation during exercise.	II
Peterson et al. (1996)	Clinical trial, nonrandomized, not blinded	8 terminally ill opioid-tolerant patients (11 entered, 8 completed) received four daily doses of nebulized saline (control) and 2.5 mg and 5 mg morphine. Outcome measures were dyspnea visual analog scale (VAS) and respiratory function (forced expiratory volume in one second and forced vital capacity) at the start of each day (baseline) and one hour after the second dose of the day.	No changes were detected relative to baseline, and no differences were found among the three conditions. Value of adding nebulized morphine to oral or subcutaneous opioid therapy is limited.	II
Leung et al. (1996)	RCT, double blind	10 patients with chronic lung disease inhaled saline (control) or 5 mg morphine on separate days and performed a progressive exercise test 15 minutes after inhalation. Borg dyspnea scores were obtained before test, at end of each minute, and at maximum power output (end of test).	No significant difference in maximum power output or degree of breathlessness was found between placebo or morphine groups. Inhaled morphine at this dose does not relieve exercise-induced breathlessness or increase maximum output.	II
Beauford et al. (1993)	RCT, double blind, crossover	8 patients with chronic obstructive pulmonary disease (COPD) inhaled 0, 1, 4, or 10 mg morphine on four separate days. Borg dyspnea scores were obtained before and 45 minutes after treatment. Exercise tolerance, mental function, and psychological mood were measured.	No significant effect of any doses on dyspnea scores or exercise tolerance was found. None of the four doses significantly affected mental function; thus, testing with higher doses was recommended.	II
Jankelson et al. (1997)	RCT, double blind	16 opioid-naive patients with COPD inhaled saline (control) and 20 mg and 40 mg morphine. Patients performed six-minute walking distance tests immediately and 60 minutes after treatment. Modified dyspnea Borg scores were recorded with each walk.	No significant differences between placebo and doses of morphine on walk distance or dyspnea were found. Highest morphine plasma concentration was measured immediately after nebulization, but no correlation was found between changes in walk distance. Higher doses of morphine do not improve endurance or relieve dyspnea.	II
Masood, Subhan, et al. (1995)	RCT, double blind	In 12 healthy males, aged 18–25, the ventilatory effects of nebulized morphine (10 mg and 25 mg) were compared with IV morphine (1.0 mg and 2.5 mg) and placebo at 15 minutes after cycle ergometry. Occasions were separated by at least 48 hours. Physiologic data, dyspnea VAS, and plasma morphine levels were obtained.	Neither dose of inhaled morphine had a significant effect on pulmonary function or breathlessness at any level of exercise. IV morphine at 2.5 mg reduced breathlessness slightly at maximum workload. These data do not support the hypothesis that intrapulmonary opiate receptors modulate the sensation of breathlessness in healthy men.	II
Masood, Reed, et al. (1995)	RCT, double blind, crossover	In 12 men with severe COPD, the ventilatory effects of nebulized morphine (10 mg and 25 mg) were compared with IV morphine (1.0 mg and 2.5 mg) and placebo at 15 minutes after cycle ergometry. Tests were separated by 48 hours. Physiologic data, dyspnea VAS, and plasma morphine levels were obtained.	Neither IV nor inhaled morphine had a significant effect on pulmonary function of breathlessness. Findings do not support the hypothesis that intrapulmonary opiates modulate the sensation of breathlessness in patients with COPD.	II

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Table 2. Studies Reviewed for Evidence Base *(Continued)*

Study	Study Design	Subjects and Variables	Findings and Conclusions	PRISM Level
Noseda et al. (1997)	RCT, double blind	14 patients with severe lung or heart disease (17 entered, 3 died unrelated to study) received saline and 10 mg and 20 mg of morphine nebulized with 2 liters per minute of oxygen or 10 mg of nebulized morphine without oxygen. Bipolar dyspnea VAS that allows subject to indicate "more or less short of breath" was recorded at baseline, end of treatment, and 10 minutes later.	No significant difference between treatments was found. 101 of 112 VAS ratings were positive, indicating less shortness of breath. Because subjects benefited from saline or morphine, the results suggest a placebo or a nonspecific effect. Nebulized morphine had no specific effect on dyspnea at rest.	II
Davis et al. (1996)	RCT, double blind, crossover	79 patients with primary or secondary lung malignancy, stratified according to opioid naivete or tolerance, received a single predetermined dose of morphine compared to saline (control) administered through a nebulizer reservoir with mouthpiece. Borg dyspnea scores were measured prior to and at multiple intervals up to 24 hours post-treatment. Five patients withdrew on day one (4/5 received saline).	A significant change was documented with morphine from baseline, but no significant difference existed between morphine and saline. No significant difference was found in response between opioid-naive and opioid-tolerant groups. Data do not support the use of nebulized morphine for treatment of cancer-related breathlessness.	II
Favorable Evidence				
Young et al. (1989)	RCT, double blind, crossover	11 patients with advanced chronic lung disease whose exercise endurance was limited by dyspnea received 5 mg morphine and saline (control) on separate occasions. Cycle endurance was measured at 15 minutes after inhalation.	Mean increase in endurance time was significantly greater ($p < 0.01$) after the subjects inhaled morphine (64.6 seconds, SD = 115) than placebo (8.9 seconds, SD = 55). Small amounts of morphine delivered to lungs might act directly on lung afferent nerves to reduce dyspnea.	II
Davis et al. (1994)	RCT, double blind, crossover	18 patients with exercise-limiting COPD received equianalgesic single doses of morphine, morphine 6-glucuronide (M6-G), and saline (control). Outcome measurements were physiologic data, six-minute walk tests, and bicycle endurance.	Significant changes were found with M6-G in bicycle endurance but not in the walk test. This might reflect potency difference with M6-G or different actions of the compounds on ventilatory control.	II
Zeppetella (1997)	Open label, nonrandomized	17 patients with lung malignancy entered (3 did not complete all measurements) and received 20 mg morphine through a face-mask nebulizer every four hours for 48 hours. The Dyspnea Assessment Questionnaire (measuring quantity and quality of dyspnea for a combined score) was completed at baseline and 24 and 48 hours.	16 patients (94%) recorded significantly lower ($p < 0.0005$) questionnaire scores at 24 hours. Changes between 24 and 48 hours were not significant. A subgroup of opioid-naive patients (n = 4) showed no significant benefit from treatment. RCT is needed to formally assess the effect of regularly nebulized morphine.	II
Tanaka et al. (1999)	Open label, nonrandomized	15 patients with thoracic malignancy (10 already receiving systemic opioids) received 20 mg of nebulized morphine. In 7of the 15 patients, no relief was obtained and the dose was increased to 40 mg of morphine. Dyspnea VAS was measured before and 60 minutes after treatment.	Dyspnea VAS decreased significantly 60 minutes after nebulization ($p = 0.005$). Authors planned to conduct a double-blind RCT with normal saline to exclude a placebo effect.	II
Farncombe et al. (1994)	Chart review	An audit of records from a palliative care service (unknown total census) for 18 months revealed 54 patients who were treated with nebulized opioids to relieve dyspnea. Most were inpatients with moderate to severe breathlessness at rest.	12 of the 54 subjects received only one to two treatments. The majority (n = 34; 63% of study population or 81% of those who received more than three doses) documented "good" results with treatment modality. No adverse effects were reported. The study had no measurable outcomes.	III
Farncombe & Chater (1993)	Case report	Described the use of nebulized morphine in varying doses to manage dyspnea in four patients	Verbal, nonmeasured reports of relief after nebulized morphine were described. Nebulized morphine was well tolerated.	III
Quelch et al. (1997)	Case report	Anecdotal reports of the use of nebulized morphine (three patients) and hydromorphone (one patient) in a palliative care setting	Dyspnea improved in all four patients. Relief occurred only after escalation of dose to what appeared to be a threshold level, which varied with each patient.	III

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Table 2. Studies Reviewed for Evidence Base *(Continued)*

Study	Study Design	Subjects and Variables	Findings and Conclusions	PRISM Level
Ahmedzai (1988)	Case report	Described the use of nebulized lignocaine and diamorphine to manage respiratory distress in one terminally ill patient	Rapid relief of dyspnea was reported in this single case without clear outcome measures.	III
Tooms et al. (1993)	Case report (letter to the editor)	Anecdotal report of use of 5 mg of nebulized morphine in a patient with mesothelioma on high doses of systemic opioid	Positive results of treatment were found in this specific patient until three days before the patient's death.	III
Lang & Jedeiken (1998)	Case report	Described adverse effect in one patient with the inhalation of 4 mg morphine and 4 mg dexamethasone	Severe respiratory depression that reversed over time with ventilatory support was noted in one patient after nebulized treatment. Patients should be monitored closely during first dose of inhaled opioid.	III

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baseline, and no differences were found among the three treatments.

Leung, Hill, and Burdon (1996) extended the hypothesis of Young et al. (1989) to determine whether inhaled morphine at the 5 mg dose would not only increase endurance but also reduce the sensation of exercise breathlessness in the same population. Their results showed that inhaled morphine did not reduce breathlessness and contradicted Young et al.'s findings by revealing that inhaled morphine did not increase the maximum power output achieved during progressive exercise. Leung et al. concluded that further studies using nebulized morphine in higher doses were needed to determine whether a dose-dependent response exists.

Beauford, Saylor, Stansbury, Avalos, and Light (1993) tested a 10 mg morphine dose in similar conditions of incremental exercise. Eight patients with COPD were tested on a cycle ergometer on four separate days 45 minutes after receiving placebo, 1 mg, 4 mg, and 10 mg dose of nebulized morphine. A focus of this study was to measure mental function or psychological mood with the nebulized intervention. No statistically significant difference in Borg dyspnea scores or exercise performance was found among the different doses, although a trend of improved exercise tolerance was noted at the highest morphine dose. Because mental function was not altered, Beauford et al. recommended additional studies with higher doses of morphine.

Jankelson, Hosseini, Mather, Seale, and Young (1997) also addressed the question of higher doses. They studied 20 mg and 40 mg doses of inhaled morphine and measured systemic absorption to determine whether beneficial actions, if any, were local or systemic. Sixteen patients with COPD completed six-minute walk tests immediately after receiving the nebulized test solution and again 60 minutes later. No difference was found in arterial oxygen saturation, modified Borg score, or heart rate between placebo and either dose of morphine. The higher dose of inhaled morphine achieved the highest plasma concentration that was measured immediately after inhalation and decreased steadily in the hour thereafter. These authors concluded that useful clinical benefit likely would not be found in testing higher doses.

Masood, Subhan, Reed, and Thomas (1995) tested the hypothesis that intrapulmonary opiate receptors modulate the sensation of breathlessness in healthy subjects by comparing nebulized and IV morphine. No significant effect on breathlessness during exercise was found with 10 mg and 25 mg inhaled morphine or 1 mg IV morphine. IV 2.5 mg morphine reduced breathlessness at the highest workload. Masood, Reed, and Thomas (1995) replicated the study in a patient population of 12 men with COPD, postulating that breathlessness caused by other factors such as disease may be relieved by inhaled morphine. In this study, using the same nebulized and IV doses of morphine as in the healthy subject study, none of the treatments significantly altered breathlessness or ventilation.

All of the previously mentioned studies measured exertional dyspnea or exercise endurance. Noseda, Carpiaux, Markstein, Meyvaert, and de Maertelaer (1997) assessed the effect of nebulized morphine on dyspnea perceived at rest by 17 patients with advanced lung or cardiac disease, including three with a malignant diagnosis. Ten mg and 20 mg of nebulized morphine combined with 2 liters of oxygen, 10 mg of nebulized morphine without oxygen, and a saline placebo were compared. Dyspnea was measured using a visual analog scale (VAS) at the end of nebulized treatment and again 10 minutes later. No significant difference in effectiveness was detected among the four interventions. Of the 112 VAS ratings recorded throughout the study, 101 were positive (i.e., subject was less short of breath), suggesting a placebo or a nonspecific effect that led Noseda et al. to conclude that nebulized morphine had no effect on dyspnea.

In a randomized, double-blind study, Davis, Penn, A'Hern, Daniels, and Slevin (1996) compared a single predetermined dose (range = 5–50 mg) of nebulized morphine on one occasion and 5 ml nebulized normal saline on another, administered through a nebulizer with a mouthpiece driven by air at a rate of 8 liters per minute. The study included 79 patients with breathlessness at rest caused by primary or secondary malignancy. Subjects were stratified so that patients receiving oral opioids regularly were randomized separately from those naive to opioids. The benefit of therapy was measured with 10 cm VAS and a modified Borg score prior to each nebulized solution and at 5, 30, 60, and 90 minutes and 2, 3, 4, 6, 8, 12, and 24 hours post-treatment. The greatest improvement in post-treatment score that expressed as a percentage of pretreatment score was seen at one hour. Crossover data of 66 patients showed no significant difference in response to nebulized morphine and normal saline. Davis et al. (1996) concluded that the study did not support the use of nebulized morphine for cancer-related breathlessness and that longitudinal evaluation was warranted. A strong treatment effect was noted

in some patients regardless of whether they were opioid tolerant or naive. This study is reported in abstract form only; complete published data could not be located. An attempt to contact the lead researcher was unsuccessful.

Favorable Evidence

A striking point of this synthesis is that the stronger evidence against benefit of nebulized opioids comes from the randomized clinical trials and primarily includes patients with chronic lung disease. One exception is Davis et al. (1996), who studied the use of nebulized morphine in patients with cancer. The evidence in favor of nebulized opioids, although weaker, is found primarily in patients with malignant causes of breathlessness. The positive weaker evidence is from uncontrolled trials or case reports.

Zeppetella (1997) assessed the effectiveness of 20 mg of morphine administered through a face-mask nebulizer every four hours for 48 hours to 17 breathless patients with thoracic malignancies. In this open-label, noncontrolled study, measurements using the Dyspnea Assessment Questionnaire and a VAS score one hour before the first dose of nebulized morphine and at 24 and 48 hours were compared. Sixteen patients (94%) recorded significantly lower scores ($p < 0.0005$) at 24 hours. The change between 24 and 48 hours was not significant. However, only 14 patients completed the trial. Three patients stopped after 24 hours: Two disliked the face-mask nebulizer; one was too weak to continue. Zeppetella indicated that the subgroup of patients on oral opioids found the nebulized morphine beneficial, but opioid-naive patients seemed to experience little benefit.

In another open-label, noncontrolled, single-group study, Tanaka et al. (1999) treated 15 patients with cancer who were experiencing dyspnea and were unresponsive to standard therapy with 20 mg morphine through an ultranebulizer. Subjective effects were evaluated with a VAS immediately before and 60 minutes after treatment. Dyspnea ratings were significantly decreased ($p = 0.005$) after the nebulizer treatment. In 8 of 15 patients, the decrease in VAS scores measured more than 10%. The other seven patients felt no subjective relief, and in these patients, a dose escalation to 40 mg also was not effective. Although attempting to draw conclusions regarding characteristic differences between two groups is difficult because of the small sample size, Tanaka et al. proposed that the patients on systemic opioids had a tendency to benefit from the nebulized morphine compared to the nonopioid patients ($p = 0.119$). The authors postulated that this benefit tendency might be explained by the prevalence or binding affinity of the pulmonary opioid receptors influenced by the presence of systemic opioids.

In a large retrospective chart review of palliative care patients spanning 18 months, Farncombe, Chater, and Gillin (1994) found 54 patients (40 with a malignant and 14 with a nonmalignant diagnosis) who received nebulized opioids. The majority ($n = 34$) received morphine; other nebulized opioids administered were hydromorphone, codeine, and anileridine ($n = 1$). Twelve of the 54 subjects discontinued treatment after one or two doses for reasons such as claustrophobia, perceived ineffectiveness, and increasing severity of illness. In the 42 continuing patients, Farncombe et al. noted symptom relief and no adverse effects in 34 patients. Outcome measures such as being less short of breath, decreased concern about respiratory condition, being more relaxed, or increased exercise tolerance were observations documented in the charts from patients, staff, or visitors. Seventeen patients received nebulized opioids for more than 15 days. Although this is a large sample, the evidence, particularly because of the lack of standardized measurement, is insufficient to assess outcomes.

In a separate article, Farncombe and Chater (1993) described the use of nebulized morphine to manage dyspnea in four patients with end-stage chronic lung and cardiac disease. The case discussions reported decreased dyspnea in all four patients. One patient with idiopathic pulmonary fibrosis demonstrated improved arterial oxygenation after nebulization, and in two of the four patients, respiratory rates decreased. One patient experienced a smothering feeling with the nebulized route and the morphine was switched to a subcutaneous route.

Quelch, Faulkner, and Yun (1997) presented anecdotal reports to document the benefit of nebulized opioids to control dyspnea in four terminally ill patients. Relief occurred only after escalation of dose to what appeared to be a threshold level, which varied in each patient. Ahmedzai (1988) and Tooms, McKenzie, and Grey (1993) both described the effective use of nebulized morphine in two separate case reports. Relief of symptoms was noted in both reports without clear measures of outcome.

Discussion

Analysis Complexity

Analysis of this literature was difficult because of a lack of homogeneity of several variables: dosage, type of nebulizer administration, timing of doses and measurement of dyspnea, populations studied, dyspnea measured at rest or with exercise, and outcome measures.

Within most studies and the examined literature, the populations range from healthy volunteers to patients with various diagnoses (i.e., malignant versus nonmalignant lung disease). Often in the same study, some subjects were opioid tolerant and others were opioid naive. Exertional dyspnea and dyspnea at rest were measured. The nebulized interventions also varied with respect to medication and dosage. Although morphine was used most consistently, a wide range of dosage for the medications was represented in the studies. In the reviewed literature, nebulized opioids were administered as a single treatment or repeated measures, with or without oxygen, and sometimes through a mask or a mouthpiece. Most significant is the variability of outcome measurements. Common outcome measures in the reviewed studies were a dyspnea VAS or a modified Borg score (range = 0–10). However, other outcome measures included exercise tests that measured endurance, power output, or distance walked (e.g., six-minute walk test).

Quality of Evidence

The level of evidence identified in terms of PRISM category (see Table 2) is dramatically different for studies that did not find evidence of the effectiveness of nebulized morphine on dyspnea (9 of 9 or 100% PRISM level II) versus those that found favorable evidence of the effectiveness of nebulized morphine (2 of 9 or 22% PRISM level II; 7 of 9 or 78% PRISM level III). The studies at PRISM level II typically were well controlled but had small sample sizes. With a single exception, all of the PRISM level II studies that did not find evidence for the effectiveness of morphine had 6–16 subjects each (median = 12 subjects). The single study with a larger

sample size (Davis et al., 1996) found no overall effectiveness in a crossover design with 66 patients with cancer but demonstrated strong effects for some patients in a sample that mixed opioid-naive and opioid-tolerant patients. Consequently, because of restricted sample size or patient variability with prior opioid experience, many of the studies may be inadequately powered to find real, albeit small, differences in the effectiveness of nebulized morphine versus normal saline.

Conclusion

The scientific evidence that supports the use of nebulized opioids to treat dyspnea is lacking. The higher-level evidence indicates no effect of nebulized opioids on dyspnea and exercise tolerance. Lower-level evidence notes a positive effect from the intervention in individual clinical settings and patients such as those already receiving systemic opioids or experiencing dyspnea at rest versus exercise-induced dyspnea. A placebo (e.g., nebulized normal saline) may have a therapeutic effect. In addition, a nebulized intervention may influence the affective component of dyspnea, providing one more coping strategy for patients who are severely short of breath.

Most often, no or only minor complications such as lightheadedness or nausea occurred as a result of the nebulized opioids, indicating a relatively good safety profile. A major exception (Lang & Jedeikin, 1998) is a case of severe respiratory depression following first administration of nebulized morphine that highlights the need to monitor the initial dose.

Further research involving randomized crossover designs with larger samples of patients who have been stratified by prior opioid experience is needed. This research should include more emphasis on maintaining consistency in dosages of opioid and mode of their administration by nebulizer. The sparseness of side effects from the administration of nebulized opioids suggests that higher doses may be used, and dosing with nebulized opioids over several days might be warranted. If the effects of nebulized opioids still are indistinguishable from those of nebulized normal saline as a placebo for patients overall and separately for patients who are opioid tolerant and opioid naive, then the evidence of the lack of effectiveness of nebulized opioids for the control of dyspnea will be far more definitive.

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