The Role of Inhaled Opioids and Furosemide for the Treatment of Dyspnea

Richard H Kallet MSc RRT FAARC

Numerous case reports, uncontrolled studies, and small randomized placebo-controlled trials have investigated the role of aerosolized opioids in the treatment of both dyspnea and pain. Recently, aerosolized furosemide was studied for the treatment of dyspnea. A direct effect on either pulmonary stretch receptors or irritant receptors has been proposed to explain the apparent effectiveness of these drugs. A review of the literature found 37 studies and reports: 23 on aerosolized opioids to treat dyspnea, 7 for analgesia, and 7 on aerosolized furosemide. In general, prospective double-blind randomized placebo-controlled trials have investigated the effects of aerosolized opioids on dyspnea and exercise tolerance in patients with stable chronic cardiopulmonary disease, and found no effect. In contrast, the vast majority of studies found that aerosolized opioids relieved dyspnea better than parenteral opioids and with less systemic adverse effects in patients with terminal lung cancer and cystic fibrosis. However, most of these findings come from uncontrolled studies and case reports. Aerosolized opioids also have been found to provide effective analgesia, again with less systemic adverse effect. Small, generally uncontrolled, studies suggest that aerosolized furosemide may relieve dyspnea both in patients with terminal cancer and those with chronic obstructive pulmonary disease. Routine clinical use of aerosolized opioids to treat dyspnea in terminal illness will require large randomized placebo-controlled trials. However, until these studies are done, the risk/benefit ratio favors use of aerosolized opioids and furosemide in selected patients, based on the principle of compassionate care. *Key words: dyspnea, breathlessness, aerosolized morphine, aerosolized furosemide, palliative care, chronic obstructive pulmonary disease.* [Respir Care 2007;52(7):900–910. © 2007 Daedalus Enterprises]

Richard H Kallet MSc RRT FAARC is affiliated with the Cardiovascular Research Institute, and with Respiratory Care Services, Department of Anesthesia, University of California, San Francisco at San Francisco General Hospital, San Francisco, California.

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Correspondence: Richard H Kallet MSc RRT FAARC, Respiratory Care Services, San Francisco General Hospital, NH:GA-2, 1001 Potrero Avenue, San Francisco CA 94110. E-mail: rkallet@sfghsom.ucsf.edu.

Introduction

Dyspnea is commonly encountered in patients with a variety of terminal diseases, such as metastatic cancer, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, congestive heart failure, and several neurological conditions. Between 33% and 47% of the general cancer population experience dyspnea,[1,2] and the incidence increases to 55–70% for those in the terminal stage.[3,4] In over 20% of these patients, dyspnea is reported to be the primary symptom.[5] In contrast to pain, which tends to be well-controlled in the final weeks of life, dyspnea progressively increases in frequency and intensity, particularly in those with primary lung cancer.[6] As breathing is *the* primal sensation of life, its disturbance evokes the most profound sense of dread. And in those grappling with terminal illness, dyspnea provokes psychological suffering, as it is invariably associated with impending death.

Often, reversing the underlying cause of dyspnea in the terminally ill is not feasible, so palliation of the symptom becomes the primary goal. Opioids have been used to treat dyspnea since the late 19th century, but their use fell from favor in the 1950s, once a clear relationship with respiratory depression was established.[7] In the 1980s, peripheral opioid receptors were discovered throughout the body,[8] thus raising the possibility that a direct pulmonary-targeted treatment for dyspnea with aerosolized opioids might be possible with less adverse effect.

This paper will review the scientific literature on the use of inhaled opioids for the treatment of dyspnea. This will be preceded by a brief review of the theoretical mechanisms of dyspnea, the pharmacology of opioids, and the causes of dyspnea in terminal illness. The paper will conclude with a description of new research that suggests aerosolized furosemide may be an effective alternative for the treatment of dyspnea.

Psychophysical Dimensions of Dyspnea

The perception of difficult breathing is a complex phenomenon, possessing diverse qualities best illustrated by the distinction between 2 words that are often used interchangeably: *dyspnea* and *breathlessness*. Whereas dyspnea refers to excessive exertion during the act of breathing, breathlessness is the unpleasant *urge* to breath that is closely associated with suffocation and breath-holding.[9] For simplicity, the term dyspnea will be retained in this paper.

Contemporary theories posit that dyspnea emanates from multiple sensory inputs that are integrated in the brain, which then evokes a response, both in terms of efferent discharge to the breathing muscles and to the sensory cortex (corollary discharge).[10] A shared characteristic between dyspnea and pain is the existence of a diverse vocabulary expressing sensational nuances related to underlying pathophysiologic derangements.[11] Moreover, dyspnea involves not only the generation of an unpleasant sensation, but a subjective *response* to it.[12] As with all perception, dyspnea is interpreted within the context of previous experience and learning, so that an individual's reaction to dyspnea frequently changes over time.[13] Therefore, the intensity of distress that accompanies dyspnea is highly individualized, and objective measures of lung function often bear little resemblance to how patients assess their quality of breathing.[12] Is important to emphasize that efferent discharge from the respiratory centers in the brain stem represents a complex processing and integration of multiple inputs, which include: afferent information regarding peripheral chemoreceptor stimulation; force-displacement in the chest wall; lung stretch; central chemoreceptor stimulation; and information from higher levels in the brain (Fig. 1).

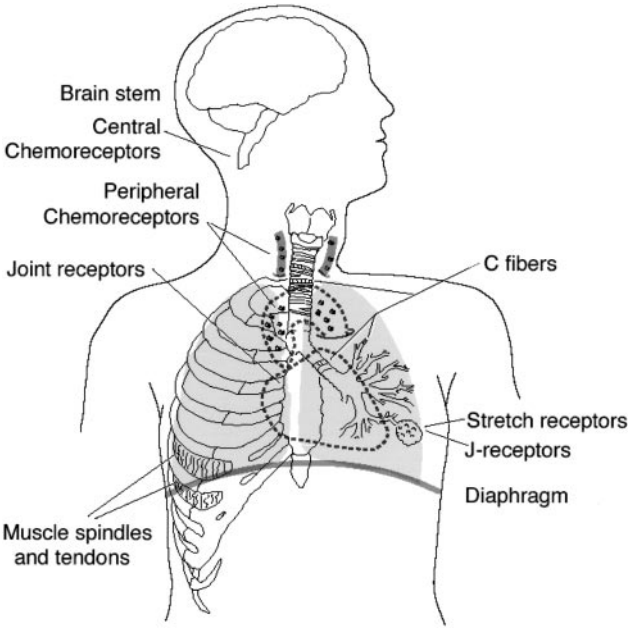

Fig. 1. A schematic representation of 3 categories of sensory inputs that, when integrated in the central nervous system, may contribute to the sensation of dyspnea. (1) Central chemoreceptors located in the brain stem are stimulated by carbon dioxide, whereas peripheral chemoreceptors are located in the aortic arch and the carotid arteries and are sensitive to both arterial carbon dioxide and oxygen tension. (2) Chest wall mechanoreceptors located in the muscle spindles and at the origins and insertions of the ribs provide information on displacement, whereas muscle tendons provide information regarding tension development. (3) Pulmonary receptors include irritant receptors in the central and peripheral airways (C-fibers), J-receptors, and stretch receptors located in the alveolar walls (see text).

A useful concept for understanding dyspnea is *length-tension inappropriateness*[14] or *neuromechanical dissociation*.[15] When efferent signals to the respiratory muscles cause contraction, mechanoreceptors in muscle fibers, ten-

dons and joints, and also in the airways and alveoli, evoke afferent information that conveys both the velocity and degree of displacement occurring in the chest wall and lungs. In this way, effort (efferent discharge from the respiratory centers in the brain stem), force developed in the inspiratory muscles, velocity, and displacement of the lungs and chest wall are integrated. Through habituation we come to experience a specific relationship between these elements as "normal breathing." Minor breath-to-breath imbalances that develop between force and displacement are used as a servo-mechanism, processed either at the spinal or medullary level, to adjust breathing effort and maintain minute ventilation. However, when tension in the ventilatory muscles is excessive, relative to both the shortening of the muscle fibers and the stretch of the lung tissue, dyspnea is evoked, as heightened efferent discharge to the respiratory muscles also causes stimulation of the reticular system, which evokes conscious awareness.[16] Likewise, dyspnea can occur in the presence of muscle weakness or fatigue, when length-tension appropriateness may be preserved but effort is disproportional to chest displacement. Of particular interest is the fact that breathlessness can be evoked independently of other stimuli, by elevated carbon dioxide.[17]

Furthermore, the *context* in which these signals occur impacts the interpretation of breathing sensations. For example, during heavy exercise the corresponding respiratory effort and work load are elevated, but this does not provoke distress because it is appropriate to the circumstances, and respiratory effort can be reduced simply by decreasing the activity level. However, if the same breathing pattern were to occur when sitting quietly in bed, it would elicit alarm, as the breathing pattern is inappropriate. More importantly, it implies that the subject *cannot do anything* to rectify the abnormality.[18]

Etiology of Dyspnea in Terminal Illness

Because multiple physiologic inputs are responsible for generating dyspnea, numerous pathophysiologic disturbances can impact the intensity and quality of the sensation. When examining factors that contribute to dyspnea in advanced diseases, it is apparent that some factors can be treated readily, whereas others are not amenable to rapid reversal (Table 1). Thus, treatment should focus initially on salient causes of dyspnea, such as correction of hypoxemia with supplemental oxygen, acute hypercapnia with noninvasive positive-pressure ventilation, reversal of bronchospasm with β agonist and steroids, relief of chest wall restriction by drainage of pleural effusions or ascites, and reduction of pulmonary edema with diuretics. Palliative therapy with aerosolized opioids should be considered *only* when conventional approaches do not produce satisfactory results or corrective treatment is not plausible. In particular, muscle weakness, anxiety, and panic appear to be common features of advanced disease that greatly impact dyspnea but may not be amenable to standard therapies, and thus may form a strong rationale for using aerosolized opioids.

Pharmacology

In the 1970s it was discovered that the central nervous system produces endogenous opioids (endorphins) that are important in regulating not only the perception of pain, but also sleep, learning, memory, and appetite.[19] In particular, endorphins are up-regulated in response to both stress and chronic pain.[19,20] In brief, endorphins modulate afferent impulses, so that the perception of pain (nocioception) is either altered or inhibited. That the medulla was discovered to be rich in opiate receptors[21] provided the first anatomic evidence for the long-recognized effects of exogenous opiates on respiratory drive.[7]

Although they do not play a regulatory role in the control of breathing in normal subjects, endorphins blunt the ability of patients with COPD to compensate for increased resistive work load (but not carbon dioxide sensitivity).[22] Similar to the body's response to chronic pain, the brain up-regulates endorphins as an adaptive response to the chronic stress associated with increased work of breathing. A similar effect is achieved with oral dihydrocodeine, which improves mobility and dyspnea in ambulatory patients with COPD,[23] and with subcutaneous morphine sulfate to ameliorate dyspnea in patients with terminal cancer.[24]

By the early 1980s, opioid receptors were discovered on peripheral sensory nerves throughout the body. These receptors, which are found at multiple locations, are up-regulated during inflammation, as a result of interactions with the immune system.[8] In brief, opioids decrease calcium currents within the cell bodies, which inhibits neuronal firing and transmitter release. In addition, opioids depress the release of pro-inflammatory "Substance P," which may help to decrease local inflammation.[25] It is postulated that during inflammation the normally impermeable perineurium sheath that protects nerve fibers is disrupted, allowing access to opioid agonists and possibly the activation and peripheral migration of opioid receptors within the nerve.[6]

Three main opioid receptors have been identified in the respiratory tract: μ (MOR), δ (DOR), and κ (KOR), which mediate the effects of the 3 primary families of endogenous opioids (endorphins, enkephalins, and dynorphins, respectively) as well as exogenous opioids such as morphine and codeine.[25] In addition, the lungs also may contain a novel opioid receptor.[26] Animal studies have revealed the presence of opioid receptors in the trachea, bronchi, and pulmonary arteries, but these receptors are

Table 1. Pathophysiology of Dyspnea in Terminal Illness

Disease State	Physiologic Factors	Mechanisms That Contribute to Dyspnea
Advanced cancer	Muscle weakness: ↓ muscle bulk, deconditioning, electrolyte imbalance, malnutrition, anemia, tumor infiltration	Imbalance: effort vs displacement
	↓ lung compliance: pneumonia, pulmonary abscess	Imbalance: force vs displacement
	↓ chest wall compliance: pleural effusion, tumor infiltration	Imbalance: force vs displacement
	↑ airways resistance: compressive tumors	Imbalance: force vs displacement
	↑ V_D/V_T: pulmonary embolism → hypercapnia, pulmonary hypertension, stimulation of pulmonary C-fibers	↑ respiratory drive
	Superior vena cava syndrome: vascular wall obstruction	Unknown
	Anxiety, depression, panic	↑ respiratory drive, ↑ perceptual focus on breathing
Heart failure	Muscle weakness: ↓ muscle bulk, deconditioning, ↓ perfusion	Imbalance: effort vs displacement
	↓ lung compliance: engorgement/pulmonary edema.	Imbalance: force vs displacement
	↓ chest wall compliance: ascites	Imbalance: force vs displacement
	Diffusion defect: hypoxemia	↑ respiratory drive
	↑ airways resistance and bronchial sensitivity	Imbalance: force vs displacement
	↑ V_D/V_T: ↓ V_T and ↓ lung perfusion → hypercapnia	↑ respiratory drive
	Anxiety, depression	↑ respiratory drive, ↑ perceptual focus on breathing
Idiopathic pulmonary fibrosis	↓ lung compliance: lung scarring	Imbalance: force vs displacement
	Diffusion defect: hypoxemia	↑ respiratory drive
	Muscle weakness: ↓ muscle bulk, deconditioning	Imbalance: effort vs displacement
	Anxiety, depression, panic	↑ respiratory drive, ↑ perceptual focus on breathing
COPD	Muscle weakness: deconditioning, altered geometry from hyperinflation	Imbalance: force vs displacement
	↓ lung compliance from hyperinflation	Imbalance: force vs displacement
	↑ airways resistance	Imbalance: force vs displacement
	↑ V_D/V_T → hypercapnia	↑ respiratory drive
	↑ $\dot{V}/\dot{Q}$ mismatching → hypoxemia	↑ respiratory drive
	Anxiety, depression, panic	↑ respiratory drive, ↑ perceptual focus on breathing
Neurologic diseases	Muscle weakness	Imbalance: effort vs displacement
	Loss of airway control: choking	↑ respiratory drive
	↑ airways resistance: retained secretions	Imbalance: force vs displacement
	↓ lung compliance: pneumonia	Imbalance: force vs displacement
	Anxiety, depression, panic	↑ respiratory drive, ↑ perceptual focus on breathing

V_D/V_T = ratio of dead space to tidal volume
COPD = chronic obstructive pulmonary disease
$\dot{V}/\dot{Q}$ = ventilation-perfusion

particularly prominent in the bronchioles and the alveolar walls near the pulmonary capillaries.[26]

Pulmonary opioid receptors are associated primarily with vagal afferent C-fibers (irritant or rapidly-adapting fibers) and the juxta-pulmonary capillary receptors (J-receptors), which are located in the alveolar wall.[27] Stimulation of C-fibers in the small airways and J-receptors in the alveoli by acute pulmonary congestion and edema, multiple pulmonary embolisms, and inflammation may be responsible, in part, for triggering the sensation of dyspnea, as well as tachypnea, bronchoconstriction, and increased airway secretions.[27,28] In a manner analogous to pain, opioids may alter the perception of dyspnea by modifying signals from pulmonary afferent C-fibers. A third type of vagal afferent fiber is the pulmonary stretch receptors that, when stimulated, typically by large tidal volumes, reduce the sensation of air hunger. Inhaled opioids also may act on these fibers.

Pharmacokinetics

Despite the anatomic evidence cited above, it remains unclear whether the effects of aerosolized opioids on dyspnea are due to modifications in peripheral afferent signaling that alters proprioception, or that opioids absorbed into the systemic circulation act on central nervous system control of breathing. Most studies that have examined inhaled opioids did not observe signs of sedation or respiratory depression.[29–34] However, hypercapnia[35] and profound respiratory depression[36] occasionally have been

reported. Inhaled opioids also provide effective analgesia,[37–41] which suggests the possibility that dyspnea is modified, at least in part, through a central mechanism. Systemic absorption of opioids may occur from the pulmonary circulation. But a more likely source is absorption from the gastrointestinal tract, due to aerosol impaction in the oropharynx and subsequent swallowing of opioid-containing secretions. Yet in cancer patients who suffer from intractable dyspnea, relatively small amounts of inhaled opioids appear to improve breathing comfort, despite the fact that these patients already are receiving high levels of parenteral opioids for pain management.[29,30,42–44]

Six studies have assessed absorption and bioavailability of morphine, morphine-6-glucuronide (a potent metabolite of morphine), and fentanyl, administered via jet nebulizer with mask, during spontaneous breathing,[39,45–47] via endotracheal tube during passive mechanical ventilation,[48] or with a prototype breath-actuated unit-dose nebulizer during spontaneous breathing.[49] All of these studies were carried out on healthy volunteers with normal pulmonary function. In the most widely cited study, Chrubasik et al[48] reported that serum morphine levels following inhalation varied widely among individuals, with a relative systemic bioavailability of 17% (range 9–35%). The maximum serum morphine concentration was achieved by 45 min and was approximately 6 times lower than with intramuscular administration.

Penson et al[45] found that plasma concentration of morphine-6-glucuronide rose slowly, reaching a peak at 1.2 h, with a significantly prolonged elimination half-life. This was attributed to continued prolonged absorption from the lungs, buccal cavity, or stomach after nebulization. The relative bioavailability was only 6% (range 4–11%). Similarly, Quigley et al[47] reported that peak plasma concentration of morphine-6-glucuronide occurred between 2 h and 3 h and was dose-dependent. Although Masood and Thomas[46] reported that peak plasma concentration was achieved within 10 min with aerosolized morphine, systemic bioavailability was only 5%, compared to 24% with oral administration. In contrast, Ward et al[49] reported similar time course and bioavailability profiles for the inhaled and intravenous administration routes. This may be explained by the use of a highly efficient, nonconventional nebulizer, and measurement of arterial plasma rather than venous plasma concentration. With nebulized fentanyl, which is highly lipid soluble, peak serum levels were achieved by 15 min, but with low systemic bioavailability.[39]

These pharmacokinetics studies suggest that systemic absorption and a central action of aerosolized opioids cannot fully explain the apparent effects on dyspnea, particularly in patients already receiving systemic opioids for analgesia. The wide range in systemic bioavailability found in mechanically ventilated subjects with normal lungs may reflect variability in jet nebulizer performance, coupled with the limitations of drug delivery imposed by the artificial airway and a passive breathing pattern. These studies also have limited relevance to patients with advanced pulmonary disease, because pathologic alterations in airway geometry and pulmonary perfusion, along with abnormal breathing patterns, would probably alter drug deposition.

Aerosolized Opioids in the Management of Dyspnea

A PubMed title word search from 1965 through 2006 was done, using various combinations of the terms dyspnea, breathlessness, aerosolized, nebulized, opioids, morphine, fentanyl, and hydromorphine. The references for each found paper also were searched to cull additional publications. A total of 30 studies were found (Table 2). Seven of these were small prospective randomized placebo-controlled trials that examined the effects aerosolized morphine sulfate on exercise endurance in patients with stable COPD[50–54] or idiopathic pulmonary fibrosis,[55] or in healthy volunteers.[56] There also have been 13 (mostly uncontrolled) studies and case reports on the effects of aerosolized opioids in end-stage cardiopulmonary disease (COPD, idiopathic pulmonary fibrosis, and congestive heart failure),[43] advanced cancer,[29–33,36,42,57,58] and cystic fibrosis.[35,59,60] In an unusual case report,[61] a patient with severely debilitating paroxysmal coughing was successfully treated with aerosolized morphine.

Five of the 6 double-blinded randomized placebo-controlled studies that examined the effects of aerosolized opioids in patients with COPD or idiopathic pulmonary fibrosis reported no improvement either in exercise tolerance or dyspnea, compared to placebo.[51–55] In the one positive study,[50] the improvement in exercise endurance was minor. In contrast, all the uncontrolled trials[29–31,43,47,58] and case studies[35,36,42,44,57,59,60,62] that examined the effects of aerosolized opioids in patients with end-stage disease (usually metastatic cancer) reported subjective improvements in dyspnea, paroxysmal coughing, and breathing pattern following aerosolized opioids. Characteristically, in these studies patients appeared to have intractable dyspnea despite receiving generous amounts of intravenous or oral opioids for pain management. Yet supplementation with 5–10 mg of aerosolized morphine sulfate, repeated either as-necessary or every 4 h, almost uniformly improved dyspnea, breathing pattern, and the general appearance of these patients. In patients with opioid tolerance the dose often needed to be increased to approximately 20 mg,[7] and in the final days of life, doses as high as 45–70 mg sometimes were required.[33,63]

As morphine sulfate can cause bronchospasm from histamine release, some have added a 2–4-mg dose of dexamethasone as prophylaxis.[36,59] Others have used an initial test dose of only 2.5 mg morphine sulfate to evaluate any

Table 2. Summary of Studies That Evaluated Aerosolized Opioids for the Treatment of Dyspnea or Pain

First Author	Year	Subjects	*n*	Design	Intervention	Evaluation	Results	Overall Finding (+ or −)
Chrubasik[38]	1987	Postoperative abdominal Surgery	20	Randomized	Supplemental morphine sulfate via intravenous or aerosol. Dosing strategy unclear, mean doses not different (23 mg vs 21 mg, respectively)	Vital signs, P_{CO_2}, subjective report, adverse effects	No difference in vital signs, P_{CO_2} ↓ adverse effects with aerosolized morphine sulfate	+
Young[50]	1989	Advanced COPD	11	Double-blinded randomized placebo-controlled crossover	5 mg morphine sulfate	Endurance at 80% maximum workload	Mean increase of 35%	+
Worsley[39]	1990	Post-surgery	20	Randomized placebo-controlled	100 and 300 μg fentanyl citrate	Visual analog scale, time to alternative analgesia to treat pain	↓ visual analog scale, ↑ time to alternative analgesia	+
Higgins[40]	1991	Post-surgery	30	Double-blinded randomized	64, 159, and 318 μg fentanyl citrate	Visual analog scale, time to "escape analgesia" to treat pain	↓ visual analog scale at all doses, larger ↓ in visual analog scale and ↑ time to additional analgesia at higher doses.	+
Farncombe[43]	1993	End-stage COPD, CHF, IPF	4	Uncontrolled	5 mg morphine sulfate every 4 h, ↑ to 18–25 mg	Subjective report	↓ dyspnea, ↑ relaxation	+
Beauford[51]	1993	Stable COPD	8	Double-blinded randomized placebo-controlled crossover	1, 4, and 10 mg morphine sulfate	Maximum exercise, dyspnea (Modified Borg Scale), $\dot{V}_E$, $\dot{V}_{O_2}$	No difference	−
Tooms[42]	1993	End-stage mesothelioma	1	Case report	5 mg morphine sulfate every day	Subjective report	↓ distress	+
Farncombe[58]	1994	Advanced cancer	3	Uncontrolled	5–15 mg morphine sulfate every 4 h 8 mg hydromorphine every 4 h 25–50 mg anileridine every 4 h	Subjective report, breathing pattern	↓ dyspnea, ↓ respiratory rate, ↑ relaxation	+
Masood[52]	1995	Stable COPD	12	Double-blinded randomized placebo-controlled crossover	10 and 25 mg morphine sulfate	Exercise endurance, dyspnea (visual analog scale)	No difference	−
Harris-Eze[55]	1995	IPF	6	Double-blinded randomized placebo-controlled crossover	2.5 and 5 mg morphine sulfate	Exercise endurance, dyspnea (Modified Borg Scale), $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$	No difference	−
Masood[56]	1995	Healthy males	12	Double-blinded randomized placebo-controlled crossover	10 and 25 mg morphine sulfate, compared to both placebo and intravenous 1 and 2.5 mg	Exercise endurance, dyspnea (visual analog scale)	No difference	−
Leung[53]	1996	Stable COPD	10	Double-blinded randomized placebo-controlled crossover	5 mg morphine sulfate	Exercise endurance, dyspnea (Modified Borg Scale), $\dot{V}_E$	No difference	−
Noseda[32]	1997	Severe COPD (14 of the 17 patients had severe airflow limitation), CHF, IPF	17	Double-blinded randomized placebo-controlled crossover	10 and 20 mg morphine chlorhydrate, compared to both placebo and oxygen therapy	Dyspnea (visual analog scale)	No difference	−
Jankelson[54]	1997	Stable COPD	16	Double-blinded, randomized placebo-controlled crossover	20 and 40 mg morphine sulfate	6-min walk distance, dyspnea (subjective report)	No difference	−

(Continued)

Table 2. (Continued)

First Author	Year	Subjects	*n*	Design	Intervention	Evaluation	Results	Overall Finding (+ or −)
Stein[57]	1997	Advanced cancer	1	Case report	2.5 mg morphine sulfate every 4 h ↓ to every day at bedtime	Effect on severe, paroxysmal coughing	Cessation of paroxysmal coughing	+
Zeppetella[29]	1997	Advanced career	17	Uncontrolled	20 mg morphine sulfate every 4 h over 48 h	Dyspnea (Dyspnea Assessment Questionnaire)	↓ Dyspnea Assessment Questionnaire score at 24 h	+
Lang[36]	1998	Advanced cancer	1	Case report	4 mg morphine sulfate + 4 mg dexamethasone	Dyspnea	Severe respiratory and cardiovascular depression	
Tanaka[30]	1999	Advanced cancer	15	Uncontrolled	20 mg morphine chlorhydrate	Dyspnea (visual analog scale)	↓ visual analog scale	+
Sarhill[44]	2000	Advanced cancer	1	Case report	4 mg hydromorphine every 4 h	Dyspnea (subjective report)	↓ dyspnea and anxiety, ↑ relaxation and exercise tolerance	+
Janahi[59]	2000	Cystic fibrosis	1	Case report	2 mg morphine sulfate every 4 h + 2 mg dexamethasone	Dyspnea (Modified Borg Scale), blood gases	↓ Modified Borg Scale and P_{CO_2}	+
Cohen[35]	2002	Cystic fibrosis	1	Case report	2.5–12.5 mg morphine sulfate	Dyspnea (visual analog scale)	↓ visual analog scale	+
Graff[60]	2004	Cystic fibrosis	1	Case report	25–50 μg fentanyl citrate every 4 h	Dyspnea (Modified Borg Scale), S_{pO_2}, activity level	↓ Modified Borg Scale, ↑ S_{pO_2}, ↑ activity level	+
Coyne[31]	2002	Advanced cancer	35	Uncontrolled	25 μg fentanyl citrate	Dyspnea (subjective report)	↓ dyspnea in 81%	+
Quigley[47]	2002	Advanced cancer	9	Uncontrolled	5, 10, or 20 mg morphine-6-glucuronide	Dyspnea (visual analog scale)	↓ visual analog scale	+
Rutherford[61]	2002	Asthma	1	Case report	Morphine sulfate (dose not reported) × 2.5 years	Total disability, severe paroxysmal coughing	Marked ↓ coughing, ↑ quality of life	+
Bartfield[41]	2003	Abdominal pain in emergency department	50	Double-blinded randomized placebo-controlled	1.5 μg/kg fentanyl citrate vs intravenous fentanyl citrate	Pain (visual analog scale)	Decrease in visual analog scale not different at 30 min for intravenous vs inhaled	+
Ballas[62]	2004	Acute sickle-cell crisis	2	Case report	20 mg morphine sulfate every 6 h	Chest-wall pain (verbal report on a 1–10 scale)	Pain ↓ 50–90%	+
Bruera[33]	2005	Advanced cancer	11	Double-blind randomized placebo-controlled crossover	Aerosolized morphine sulfate vs subcutaneous 45 mg morphine sulfate	Dyspnea Intensity Score	↓ Dyspnea Intensity Score, compared to placebo. No efficacy difference between inhaled and subcutaneous	+
Fulda[34]	2005	Post-traumatic chest injury	44	Double-blinded randomized placebo-controlled	Aerosolized morphine sulfate vs patient-controlled analgesia via intravenous pump: 12 mg aerosolized 6.2 mg patient-controlled every 4 h	Chest-wall pain (visual analog scale), Sedation Score	↓ visual analog scale, compared to placebo. No efficacy difference between inhaled and patient-controlled. ↓ sedation with inhaled	+
Lefevre[37]	2006	Musculoskeletal pain in emergency department	102	Uncontrolled	Morphine sulfate: 0.2 mg/kg Fentanyl citrate: 3 μg/kg Alfentanil: 15 μg/kg	Pain (verbal report on a 1–10 scale)	Approximately 50% ↓ in pain	+

COPD = chronic obstructive pulmonary disease
CHF = congestive heart failure
IPF = idiopathic pulmonary fibrosis
S_{PO_2} = oxygen saturation measured via pulse oximetry
$\dot{V}_{CO_2}$ = carbon dioxide production
$\dot{V}_E$ = minute ventilation
$\dot{V}_{O_2}$ = oxygen consumption, V_D/V_T = ratio of dead space to tidal volume.

tendency for bronchospasm prior to administering a higher dose.[7] Fentanyl does not cause histamine release and therefore is an attractive alternative in severely dyspneic patients with reactive airways disease. Doses of 20–100 μg of fentanyl have been used to treat dyspnea.[7,31,60] With hydromorphone an initial aerosolized dose of 1–2 mg every 4 h has been recommended,[7] but doses as high as 4–8 mg every 4 h have been used.[44,58,63]

Only 2 prospective, randomized, double-blinded, placebo-controlled trials have examined the efficacy of aerosolized opioids on dyspnea in patients with advanced disease. Noseda et al[32] found no benefit from 10 mg or 20 mg of aerosolized morphine citrate on dyspnea in 17 patients with severe chronic lung disease or metastatic cancer. In contrast, Bruera et al[33] found that aerosolized morphine sulfate given to patients with metastatic cancer was as effective as subcutaneous administration in reducing dyspnea. These discrepant results may be explained by the fact that 12 of the 17 patients in the study by Noseda et al[32] had COPD, whereas only 3 had metastatic cancer. Two of the patients with cancer died before completing the protocol, and their data were not included in the analysis. In addition, Noseda et al[32] measured dyspnea only 10 min after completion of nebulization, which based on the results of aerosolized opioid studies for pain management,[34,38,41] may have been an insufficient amount of time to accurately judge efficacy.

Aerosolized Opioids in the Management of Pain

Seven studies have evaluated aerosolized opioids for analgesia in postoperative management following general surgery,[38–40] chest trauma,[34] sickle cell crisis,[62] and management of pain in the emergency department setting.[37,41] All the studies found that aerosolized opioids provide adequate analgesia, and several reported a lower incidence of adverse effects, including sedation.[34,37,38] Average doses that provide adequate analgesia appear to be 12–20 mg morphine sulfate every 4–6 h,[34,38,62] and 150–300 μg fentanyl citrate.[37,40,41] Only one of the studies with fentanyl allowed repeated supplemental administration, which was at half the initial dose.[37]

When compared to intravenous administration, aerosolized opioids tend to have a slower onset of action, but the quality of analgesia is not different by 30 min.[34,38,41] Some studies reported onset of pain relief in 3–5 min.[37,40,62] Although routinely administering aerosolized opioids for analgesia has been criticized as awkward and inefficient,[40] it may be useful as a temporizing measure in patients in whom either intravenous access is difficult or the adverse effects of sedation must be avoided.

Occupational Exposure Risks to Health Care Providers

Health care professionals have a propensity for developing chemical dependencies.[64] Anesthesiologists appear to be at particular risk, and this has been attributed to a combination of high job stress and extraordinary access to controlled substances.[65] Yet others postulate that inadvertent aerosolization of intravenously administered opiates in the exhaled gas may sensitize health care workers through "second-hand" exposure.[64] Over time this sensitization may enhance the probability of addiction.

Aerosolized fentanyl and propofol have been detected in the operating theater and in the expiratory limb of anesthesia ventilator circuits.[66] This raises concern regarding occupational risk. However, the potential for aerosolized opioid exposure is much greater in the critical care environment, given the tremendous frequency of intravenous infusions of high-dose opioids and the elevated minute ventilation demands of patients. Yet there is no evidence of widespread opiate addiction among critical care practitioners, which suggests that access to these drugs without stringent accountability is a more likely explanation. At this juncture, theoretical concerns over health care worker exposure should not preclude consideration of aerosolized opioid therapy in patients with terminal illness. Nevertheless, future prospective studies of aerosolized opioid therapy should evaluate environmental pollution to assess potential risks to health care providers.

Aerosolized Furosemide in the Treatment of Dyspnea

The potential effectiveness of aerosolized furosemide to treat dyspnea was first reported in a patient with end-stage Kaposi's sarcoma.[67] Recent uncontrolled studies[68,69] examined the potential of aerosolized furosemide to reduce dyspnea in patients with terminal cancer. Shimoyama and Shimoyama[68] reported 3 patients with dyspnea that was refractory to treatment, including parenteral morphine sulfate. Aerosolized delivery of 20 mg furosemide reduced dyspnea and respiratory rate, with the onset of effect occurring within 20–30 min and lasting for more than 4 h. In some patients, both respiratory rate and use of accessory muscles also diminished. In each case, diuresis could not explain the improvement in dyspnea, as urine output did not increase during the study period.

Kohara et al[69] reported that dyspnea was significantly reduced in 12 of 15 patients who received 20 mg of aerosolized furosemide. No change was observed in arterial blood gases, respiratory rate, or heart rate. However, a small double-blinded randomized placebo-controlled study[70] with 7 patients with advanced cancer found that dyspnea tended to worsen after aerosolized furosemide, but the difference was not significant.

Aerosolized furosemide prevents bronchospasm[71,72] and may ameliorate dyspnea because of its bronchodilatory effects.[73–75] Moreover, in experimental models of dyspnea induced by breath-holding,[76] resistive-loading with and without hypercapnia,[76] and hypercapnia with constrained ventilation,[77] 40 mg of aerosolized furosemide increased breath-holding time and reduced dyspnea.

In theory, aerosolized furosemide may reduce dyspnea by suppressing pulmonary C-fibers in bronchial epithelium.[76] Inhaled furosemide inhibits cough and prevents bronchospasm when the lungs are exposed to aerosolized low-chloride solutions.[78] This suggests that ionic changes in the cellular environment are circumvented, which prevents stimulation of irritant receptors.

On the other hand, dyspnea can be relieved by deep lung inflation through the stimulation of pulmonary stretch receptors.[79] Furosemide also stimulates pulmonary stretch receptors[80] and may relieve dyspnea by mimicking the effects of large tidal volumes.[77] Aerosolized furosemide is believed to stimulate pulmonary stretch receptors by inhibiting cellular ionic transport mechanisms and thus increasing local sodium concentrations.[76] Although most studies have not observed renal effects from aerosolized furosemide,[68,76] Moosavi et al[77] reported brisk diuresis among normal study subjects. Therefore, another potential effect of inhaled furosemide on dyspnea in patients with cardiopulmonary disease may emanate simply from a reduction in pulmonary edema that decreases either respiratory effort or J-receptor stimulation.

Reported adverse effects from aerosolized furosemide were generally mild and included transient nausea, and sleeplessness in some patients.[69] Among normal research subjects the most frequent adverse effects were pharyngeal and substernal irritation, intermittent cough, and a strong urge to urinate.[77]

Summary

In conclusion, higher-level clinical evidence consistently shows that aerosolized opioids are not effective in improving dyspnea or exercise tolerance in patients with chronic cardiopulmonary diseases, including COPD and idiopathic pulmonary fibrosis. Predominantly low-level clinical evidence supports aerosolized opioids for palliation of dyspnea in patients with advanced cancer and cystic fibrosis. There is some higher level clinical evidence that aerosolized opioids can be utilized for systemic analgesia. However, this should be restricted to circumstances where effective parenteral administration is delayed because of difficulty in achieving intravenous access. Alternatively, lower-level clinical evidence suggests that aerosolized furosemide may reduce dyspnea both in patients with advanced cancer and in those with COPD.

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