Nebulized Morphine
A Convenient and Safe Alternative to Dyspnea Relief?

Opioids have been used for many years to relieve breathlessness in patients with advanced COPD. They may possess several mechanisms by which they relieve dyspnea, both peripheral and central in origin. At the same time, their systemic use for this purpose gives rise to a concern about respiratory depression. Morphine also may be administered by the inhalational route to relieve breathlessness without inducing side effects that might be encountered if given systemically. In this issue of CHEST (see page 691), Foral and colleagues reviewed seven studies in patients with a variety of cardiorespiratory disorders who received nebulized morphine and whose dyspnea responses were subsequently assessed. Five of the studies were conducted in patients with COPD, while another study evaluated a mix of pulmonary and nonpulmonary patients, and the seventh studied a small cohort of patients with interstitial lung disease (ILD). All but one of the studies were prospective and double-blinded. Five studies were crossover in design, and only four studies (three in COPD patients) made use of placebos. In some studies, dyspnea was evaluated by means of a modified Borg scale or visual analog scale (VAS) during exercise. The authors’ conclusion was that the evidence did not support the use of nebulized morphine for the relief of dyspnea or in the improvement of exercise tolerance in patients with COPD or ILD. They recognized that differences in dose, differences in administration schedule, and inconsistent use of oxygen and bronchodilators could have contributed to the variability in results. In addition, all the prospective studies evaluated small numbers of patients (range, 6 to 16 patients). The retrospective investigation assessed 54 patients with different diagnoses. Most studies used morphine sulfate as the opiate, while another used glucuronide or chlorohydrate salt. In some studies, bronchodilators were administered before the morphine was nebulized. The doses and frequency of morphine use varied widely among the studies. Cumulatively, side effects were few and mild.

The depth and effectiveness of an inhaled drug depend on many factors, such as the size and physical characteristics of the aerosol particles, the amount of aerosol produced, the geometry of the airways, and the control of ventilation. Therapeutic aerosols are generally composed of a wide range of particle sizes and shapes. In those studies reviewed by Foral et al assessing mainly COPD patients, in which particle size was indicated to be 2.3 to 3 μm, a solution of morphine was more likely to deposit in the peripheral airways during tidal breathing than in those studies in which particle size was 4.9 μm, which tends to cause impaction in the central airways. Indeed, only in the study in which the particle size was 2.3 μm was there a statistically significant increase in exercise endurance time. This suggests that opioid receptors are present mainly in the peripheral airways, or that systemic absorption of the narcotic was enhanced. Furthermore, the underlying
disease for which the aerosol is delivered may influence the deposition of particles. Secretions, bronchoconstriction, or dynamic collapse may trap aerosolized drugs in the major airways. By contrast, the airways of patients with ILD may permit peripheral penetration of drugs since their caliber is large in relation to the lung volume because of increased elastic recoil and they are generally devoid of secretions. At the same time, this feature may be counteracted by an increased respiratory rate that promotes deposition of the aerosol in the upper airway. In the small study with ILD patients, the use of morphine in two different doses (ie, 2.5 and 5 mg) did not result in a significant relief of dyspnea, perhaps because of upper airway deposition, or because the dose of morphine was too small.

The dosing frequency of morphine also varied among the studies reviewed by Foral et al, which may have further clouded the issue. In four of the five prospective studies that primarily were of COPD patients, and in the one conducted in patients with ILD, dyspnea was evaluated after the subjects received single doses of inhaled opioids. In the fifth study, which consisted predominantly of COPD patients, relief of dyspnea was evaluated after 4 days of administering morphine with or without oxygen. In most of these studies, there were no significant effects on dyspnea. In the one uncontrolled retrospective study, which also assessed the most patients (54), 78% of the patients inhaled morphine every 4 h for >1 to >15 days. The majority of these patients reported some form of rapid dyspnea relief that lasted for >4 h. These findings may reflect the effect of cumulative dosing over time, something that was not achieved in the controlled, single-dose studies.

The manner in which dyspnea was evaluated also bears some thought. The sensitivity of the VAS has to do with its ability to detect changes in breathlessness. Most laboratories induce breathlessness by exercise to calibrate the VAS. Verbal descriptions of the sensation may differ between laboratories and thus may lead to variations in standardization, such as may have occurred in the studies described by Foral et al. The rating of perceived exertion (Borg scale) is now widely used. Wilson and Jones found greater reproducibility with the Borg scale, but suggested that the VAS might have greater precision and sensitivity. The specificity of the Borg scale depends on the instructions given to the subject. Finally, the studies described by Foral et al did not present data that plot breathlessness against ventilation or oxygen uptake, a more standardized way of quantifying the sensation for a given level of activity.

Unless the opioids were absorbed systemically in adequate quantities (thereby affecting central pain receptors), it is understandable why most studies failed to show a significant effect. It is not even known whether there are opiate receptors in the human chest wall or lung. There are experimental data in animals demonstrating the presence of opiate receptors in the lung involved in the control of breathing, but afferent pulmonary receptors in humans have not been described.4 In any case, if they are present, they are not affected by the doses of morphine used in the studies reviewed by Foral et al. Furthermore, most studies demonstrating the systemic absorption of morphine fail to result in improvement in the dyspnea score during exercise testing. Jankelson et al found that plasma concentrations of 40 mg nebulized morphine were similar to those resulting 15 min after IV doses of 1 to 2.5 mg, indicating efficient absorption across the lung. Yet, their study did not provide evidence for or against the presence of opiate receptors in the lung. Conversely, if there were an opiate that relieved dyspnea through central mechanisms, then the inhalational route could provide rapid drug delivery. Higher doses than those used in the studies reviewed by Foral et al, however, would have to be used for adequate dyspnea relief.

Ultimately, if aerosolized opiates are found to be effective in relieving dyspnea, appropriate studies would need to be conducted to compare this form of drug administration with systemic use. Nebulized opiates may also be better tolerated at higher doses than systemic administration, although, as Foral et al point out, rare cases of respiratory depression and bronchoconstriction have been described. On the other hand, the use of morphine, whether or not used in combination with other drugs, such as phenothiazines or benzodiazepines, is probably more convenient when orally administered, and may be devoid of serious side effects.5 It may be that patients with different illnesses need different drugs and routes of administration for achieving optimum relief of breathlessness. Such a goal is desirable, and indeed imperative, in order to improve the chronic impairment of quality of life in patients with advanced respiratory or cardiac illness.

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Integrated System for Chronic Disease Management

Can We Apply Lessons Learned From France?

Can we study the experiences of one nation and adapt them to another? Can a solution for one population be expanded to meet needs of others? Are there universal principles that may be applied? What kind of understanding is required to do so?

In the current issue of CHEST (see page 695), Stuart and Weinrich challenge readers to reflect on these questions and compare France and America. The authors describe the long-term care crisis we face in America and argue why we have an opportunity now to “fix it” due to the US Supreme Court Olmstead decision (judicial mandate) and the President’s “New Freedom Initiative” (political support).

The authors have sought international best practices as models for development of integrated community health systems for high-cost patients in the United States. They have described the background, evolution, and successes in the French regional approach to chronic respiratory insufficiency, and suggest France may provide lessons for a more global chronic care model for America.

A historical tradition exists for comparing France and the United States to answer these questions. In 1830, Alexis de Tocqueville officially visited America to learn about our new evolving democracy. He sought lessons that might apply to France where the 1789 revolution had created the possibility for “liberty, equality, and fraternity.” Democracy in America1 sought to determine if the American experience could be translated into models for France and other evolving European democracies. His footsteps have since been retraced and observations re-evaluated.2

Like de Tocqueville, I traveled abroad to learn from another nation. Since 1967, I have visited France on several occasions to observe patients who need long-term mechanical ventilation and get community-based support not available in America. I interviewed many people representing a diversity of perspectives: government officials, professionals, patients/families, health-care and social service providers, and health industry representatives. I gained insights about social, economic, political, and cultural factors that must be understood. I learned why their system works and how it evolved over 40 years.3–12

The long-term care crisis in America is severe and will only get worse unless addressed by long-term care policy. The 2001 Fred Friendly Seminar, “Chronic Care in America...Who Cares?” dramatized situations of victims who related personal stories describing the impact of chronic care on their lives.13 Web site data put the crisis in global perspective: three of every four US health-care dollars are spent on chronic diseases; 125 million Americans have some chronic health problem (60 million have multiple conditions); this will increase to 157 million in 2020 at an estimated annual cost of $1 trillion; 26% of American adults (mainly working women) currently serve as informal personal caregivers; many also making significant out-of-pocket financial contributions to the well-being of loved family members or friends; and 89% of Americans find it difficult to get insurance for chronic health needs.13 Situations and statistics like these should outrage all Americans.

The need to address population-based chronic care is not limited just to the United States. A health-care crisis challenges many other nations due to growing demands for long-term care. Existing health and social service delivery systems are not prepared for these new demands. A 1990 Max-Plank-Institut health-care summit of social scientists and experts in health-care policy was convened to address the growing need for chronic care due to demographic, social, and political changes in a unified Germany.14 Participants analyzed alternative delivery models suitable for the elderly and persons with chronic health needs. They reviewed the evolution of different community-based models in countries with national health systems, national health insurance, and evolving market/regulatory approaches. In addition to the analysis of finance systems, transnational analysis was undertaken to evaluate differences between nations’ health-care delivery models based on the same financial approach (France/Germany). German authorities wanted to know the following: (1) What are suitable models for persons with long-term requirements for health care and medical technology? (2) What can

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