



INHALED AEROSOLIZED OPIOIDS

Michael McPeck BS RRT FAARC

In this issue we are going to take a superficial look at administration of opioid medications by the aerosol route for the relief of pain and dyspnea. There is more to this topic than we can cover in a single installment so we will introduce the subject here and dive deeper into practical details in a subsequent column. I will qualify this topic right off the bat as being an area of very little hard science and considerable controversy for a variety of reasons that will be discussed at the appropriate time later in this piece. But for now, the underlying premise is that morphine sulfate and other opioids administered in aerosol form may be effective at relieving debilitating dyspnea and breathlessness in patients with end-stage COPD and severe bronchogenic pain in patients with lung cancer. Dyspnea becomes quite prevalent with advancing lung cancer and is a major factor in the gradual deterioration in quality of life as the disease progresses. It has been noted that 50 to 70% of lung cancer patients experience distressing respiratory symptoms at some time during the last 6 weeks of life. And one of the causes of hospital admission late in the course of

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lung cancer is the patient's inability to cope at home with the level of dyspnea they experience. Palliative efforts with inhaled opioids are not new; some of the earliest reports of relevance are around 25 years old. The more recent reports through the 1990s make for interesting reading although, as will be described, they are almost entirely anecdotal. But they do comprise the early accounts of compassionate and intuitive attempts to relieve pain and breathlessness with this technique. Frank and overt pain management had sort of been swept under the rug until the year 2000 when the Joint Commission officially recognized that pain is a major health problem and "patients have the right to appropriate assessment and management of pain" (JCAHO, 2000). Since then, as the medical profession has refocused its approach to pain management, it seems there has also developed a renewed interest in inhaled opioids on a presumptive basis, despite lack of concrete evidence of its benefits.

Although morphine sulfate is regarded as the prototypical opioid pain medication, other analgesics include the opium derivatives: hydromorphone, codeine and oxycodone plus the synthetics: fentanyl, meperidine, propoxyphene and methadone. Systemic opioids act at different levels of the central

nervous system to induce analgesia by mimicking the actions of endogenous neurotransmitters at opioid receptor binding sites. Five different opioid receptors have been identified: Mu (effects include analgesia, vomiting, constipation and pruritis), Kappa (mediates sedation and spinal analgesia), Delta (also mediates analgesia and may potentiate morphine analgesia), plus Sigma and Epsilon. Morphine is a strong Mu activator with an appreciable affinity also for Kappa and Delta. Oral morphine has been reported to result in a marked improvement in the exercise capacity of patients with COPD. Opioid receptors have been found on sensory nerves arising from all areas of the respiratory tract. Further, locally applied opioids have been shown to inhibit both cough and bronchoconstrictive reflexes, and the antitussive activity of systemically administered opioids has also been inhibited by opioid antagonists that act only at peripheral sites. The effective management of pain recognizes three major approaches based upon the type of pain: acute, temporary; chronic; and palliative care (intractable pain of terminal disease). Opioid drugs have the flexibility to be given by any route of administration including oral, intravenous, intramuscular, subcutaneous, intrathecal, sublingual, rectal or inhalation. So it is an attractive hypothesis that direct topical deposition of an opioid via the aerosol route may be helpful in the palliative management of dyspnea and pain in end-stage COPD and terminal lung cancer.

The major areas of concern with inhaled morphine are efficacy and outcomes, addiction, safety, cost and, of course, technical considerations such as how to do it. Although there is a sizable literature on this subject it suffers, frankly, from being highly anecdotal and grossly absent in those features that resemble any degree of scientific control. Nevertheless, reported outcomes of inhaled morphine include reduction in shortness-of-breath, increased exercise tolerance and subjective improvement in well-being. Fortunately, attitudes toward potential for addiction in palliative medicine are changing. Addiction is no longer recognized as a valid consideration in the palliative care of terminally ill patients. Similarly, clinician acceptance is changing as well. A clinical practice guideline referring to management of cancer pain published as early as 1994 stated thusly: "The obligation to alleviate suffering is an essential component of the clinician's broader ethical duties to benefit and not harm; it dictates that health professionals maintain clinical expertise and knowledge in the management of pain even where present educational programs do not pro-

vide this." One of the advantages of topical pulmonary delivery is a high local bioavailability along with a relatively low systemic bioavailability, when compared to more direct routes of administration such as intravenous. This would explain the high degree of safety claimed by those who have used inhaled morphine extensively. The potential for respiratory depression, usually associated with parenteral morphine administration, seems to be absent or unreported. Because systemic absorption of nebulized opioids is low, proponents regard them as relatively safe, even at "high" doses. But they point out that respiratory depression is much less likely to occur when the dose is titrated. However, a review of the literature reveals a great deal of dose variability while noting that some patients exhibit a "threshold" dosage level at which they begin to perceive relief of symptoms. One paper states dose escalation steps of 1, 4 and 10 mg, another 2.2, 4.4 and 8.8 mg, another 2.5 and 10 mg and yet another 10 and 25 mg. Still others used doses of 20 and 50 mg in the nebulizer. If dosages are not titrated upwards, or if therapy is discontinued at lower dosages, the effective threshold may not be discovered leading some to believe that some treatment failures may be due to failure to deliver a dose just above the threshold. So clearly it would appear that any palliative protocol involving an aerosolized opioid should include the provision for dose escalation in search of the effective threshold for any specific patient.

In reading many of the earlier papers on inhaled opioids I was struck by a high degree of what I would refer to as "nebulizer naïveté." Statements to the effect that "the patient was given 10 mg of morphine sulfate by nebulizer every 4 hours" were quite common. The type or brand of nebulizer was not mentioned in many of the papers. The type of patient interface (mask or mouth-piece) was rarely specified. Also, nebulizer fill volumes or treatment times were not specified or taken into consideration. Despite indicating the "dose" placed into the nebulizer, the actual nebulizer concentration of opioid in mg per mL was not routinely stated. In fact, the concept of a "delivered dose" or "inhaled dose" was notably absent. One factor that seemed to be very consistent throughout the various published studies I read was that the usual treatment frequency was every 4 hours. This is most likely due to the known pharmacokinetics of morphine and is beyond the scope of this article.

One paper I encountered in a hospice and palliative care journal summarized the advantages of inhaled morphine thusly: ease of administration, preservation of patient independence, limited systemic absorption and toxicity, increased acceptance by patients and families, speed of onset and action, non-invasive, relatively inexpensive and efficacious on an "as needed" basis. Patient complaints include "whooziness," although this is reportedly rare, a claustrophobic feeling from wearing an aerosol mask, the treatments are fatiguing and some terminal patients are too weak to tolerate it, a bitter taste left in the mouth and mixing the medication and preparing the nebulizer at home was too difficult for some patients or families. On balance, most of the reported experience with inhaled opioids to date has been anecdotal; there are no large scale randomized controlled clinical trials from which to learn or emulate. And there probably won't be. Nevertheless, with a renewed emphasis on pain identification and management in our healthcare system, this is an area that may continue to develop based upon clinical intuition plus trial

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and error. That's not necessarily a bad thing but the lack of certainty does make it difficult to develop appropriate departmental procedures and clarify the role of RT in this type of therapy. I suspect that most RT departments have, understandably, not proactively created a P&P for inhaled morphine. Over the past few years, the AARC Helpline and RC_WORLD Listserv on the Internet periodically field questions on this topic from practitioners who are scrambling at the last minute to come up with a suitable protocol with which to fulfill their first order for inhaled morphine. Accordingly, now that we have brushed the surface of this topic in this issue of Focus Journal, and now that we have touched on nasal aerosol drug delivery in the previous issue, we will tie these two topics together in the next installment of this column as we explore techniques and procedures for pulmonary delivery of inhaled opioids and further discuss transporting drugs that target the CNS across the blood-brain barrier through nasal delivery methods.

Mike McPeck, RRT FAARC is President of Healthline Medical, Inc. Baldwin Park, CA. He is a veteran therapist and author and is Assistant Professor for the RC Program at SUNY in Stony Brook, NY.