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Nebulized Morphine as a Treatment for Dyspnea in a Child With Cystic Fibrosis

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ABSTRACT. *Objective.* To shed light on nebulized morphine, a new treatment for dyspnea in children with terminal lung disease.

Methods. A clinical case study was conducted on a patient in a tertiary care medical center.

Results. Nebulized morphine was administered in incremental doses ranging from 2.5 mg to 12.5 mg in a 10-year-old, 20-kg boy with end-stage cystic fibrosis. Before the nebulized morphine treatments were started, a dose of nebulized lidocaine failed to provide the patient with any relief. After each dose of morphine, the following parameters were recorded: visual analog "dyspnea" scores, vital signs, venous blood gases, and blood levels of morphine. The nebulized morphine was found to have a modest effect on the patient's dyspnea, with no significant differences found between the varying doses. Venous carbon dioxide tension levels increased <4 mm Hg for all doses except 12.5 mg, for which there was a 9-mm Hg increase. Systemic blood levels of morphine were <10 ng/mL at all doses. The nebulized morphine did not cause any significant changes in blood pressure or heart rate for doses <12.5 mg.

Conclusions. Inhaled morphine was associated with a mild, beneficial effect on dyspnea, with minimal differences found between the lowest and highest doses. This "ceiling" effect may be the result of saturation of opioid receptors in the lung, the variable bioavailability of inhaled morphine, or a placebo response. More studies are needed to determine what, if any, the optimum dose of nebulized morphine is for children. *Pediatrics* 2002;110(3). URL: <http://www.pediatrics.org/cgi/content/full/110/3/e38>; *cystic fibrosis, dyspnea, inhaled morphine, peripheral opioid receptors.*

ABBREVIATIONS. VAS, visual analog "dyspnea" scales; BP, blood pressure; HR, heart rate; RR, respiratory rate; PvCO₂, venous carbon dioxide tension; PCA, patient-controlled analgesia device.

Nebulized morphine has been shown in some studies to be an effective treatment for dyspnea.¹⁻³ Although most of the literature regarding this treatment involves terminal adult patients in a palliative care setting, 1 report described its use in a teenage boy with end-stage lung disease.⁴ When morphine is inhaled into the lung, the mechanism of action is believed to involve peripheral

opioid receptors of the μ , κ , and δ subtypes, as well as nonconventional opioid binding sites.^{5,6} Advantages of the inhaled route include a lack of adverse systemic effects, such as sedation, respiratory depression, and suppression of cough. We report a case of nebulized morphine used in various doses that was moderately effective in relieving dyspnea in a 10-year-old boy with severe, end-stage cystic fibrosis.

CASE REPORT

A 10-year-old, 20-kg boy with end-stage cystic fibrosis was admitted to the Walter Reed Army Medical Center with fever, increasing home oxygen requirements, pleuritic chest pain, and severe dyspnea. The patient's medical history was significant for liver failure necessitating a transplant at age 7. In addition, his respiratory tract was colonized with pan-resistant *Pseudomonas cepacia*. His medications included broad-spectrum antibiotics, pancreatic enzymes, metered-dose inhalers, and immunosuppressants.

Initially, the primary care team attempted to treat the boy with additional antibiotics, chest physical therapy, and adjustment of his inspired oxygen concentration on the basis of repeated venous blood gases drawn through a central catheter. Administration of lidocaine nebulizers resulted in no improvement in chest pain or dyspnea. At this point, after discussion with family members, palliative care was instituted and the pain service was consulted.

Treatment was initiated with 2.5-mg morphine nebulizers in 2 mL of saline and increased by 2.5 mg increments up to 12.5 mg to determine the optimum dose. At each dosing regimen, the following parameters were recorded to assess the patient's response: change in dyspnea symptoms 1 hour after nebulizer, as determined by 0 to 10 visual analog "dyspnea" scales (VAS); venous blood gases recorded before and 30 minutes after nebulizer treatment; blood pressure (BP), heart rate (HR), and respiratory rate (RR) before and 30 minutes after nebulizer treatment for the 2.5-mg, 7.5-mg, and 12.5-mg doses; and serum morphine levels drawn 30 minutes after treatment (Table 1). Aside from the changes in clinical parameters outlined, the patient experienced no significant side effects other than a strange, "metallic" taste in his mouth.

The patient's venous carbon dioxide tension (PvCO₂) levels did not increase significantly above baseline until he reached a nebulized morphine dose of 12.5 mg. With the 2.5-mg nebulizer dose, the patient's PvCO₂ increased from 54 mm Hg to 58 mm Hg. At the 5- to 10-mg doses, the patient's PvCO₂ either remained unchanged or increased slightly. However, at the 12.5-mg dose, there was a significant jump from 45 mm Hg to 54 mm Hg. Given that no previous PvCO₂ had been as low as 45 mm Hg during this hospitalization, the possibility of an air bubble or laboratory error was considered.

The patient completed VAS for only the first 4 doses. At these doses, there was a modest decrease in VAS that showed little variance with the amount of morphine given. For example, at 2.5 mg, the patient recorded a drop in dyspnea from 6 to 4; with 10 mg, the decrease was from 7 to 4. Nevertheless, both the primary team and the patient's family reported that the patient seemed more relaxed after the nebulizers.

Pre- and postnebulizer vital signs were recorded for only 3 doses. Here, the patient exhibited a slight dose-response. After the 2.5-mg nebulizer, the patient's RR dropped from 27/min to 24/min, which was accompanied by slight increases in HR and sys-

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TABLE 1. Nebulized Morphine (MSO₄) Clinical Data

MSO ₄ Dose (mg)	VAS (0-10)		Pvco ₂ (mm Hg)		Systolic BP		HR		RR		Serum MSO ₄ (ng/mL) (30 Min Post-)
	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-	
2.5	6	4	54	58	82	85	111	113	27	24	<10
5.0	8	5	64.8	64.5		NA		NA		NA	<10
7.5	7	4	59.4	62.4	89	86	115	110	29	28	<10
10	7	4	59.7	60.5		NA		NA		NA	<10
12.5		NA	45	54	94	81	109	95	28	22	<10

NA indicates not applicable.

tolic BP. In contrast, 30 minutes after his 12.5-mg dose, the patient's RR dropped from 28 to 22, his HR dropped from 109 to 95, and his systolic BP dropped from 94 to 81.

Serum morphine levels were attained for all morphine doses from 2.5 mg to 10 mg, with all revealing a concentration of <10 ng/mL (therapeutic serum level: 50–100 ng/mL). This is the minimum concentration that our laboratory is able to detect. On the basis of the mild cardiorespiratory depression experienced after the 12.5-mg dose coupled with the absence of any additional benefit, the patient's optimum nebulized morphine dose was set at 10 mg every 4 to 6 hours as needed for the remainder of his hospital course.

As palliative care was administered and antibiotic therapy was discontinued, the patient's dyspnea level increased and the nebulized morphine became inadequate. Four days before discharge, the patient was placed on a morphine sulfate patient-controlled analgesia device (PCA) to supplement his nebulizer, set at a 0.5 mg demand dose with an 8-minute lockout period. This resulted in a dramatic increase in his Pvco₂ (the Pvco₂ values on the last day of admission ranged from 96.2 mm Hg to 97.9 mm Hg). According to the patient's parents, the intravenous morphine did seem to help in alleviating his dyspnea (no VAS were obtained), but only at sedative doses. Two weeks after our initial consultation, the patient was discharged to hospice care on a combination of morphine nebulizer therapy and morphine PCA. Six weeks later, he died of respiratory failure.

DISCUSSION

Dyspnea is defined as the relentless awareness of shortness of breath. Reported in up to 70% of patients with terminal lung disease, dyspnea has a debilitating effect on function and quality of life.⁷ Perhaps in part because the cause of dyspnea has yet to be fully elucidated, its presence in the setting of terminal lung disease can be extremely difficult to treat. In the past, a variety of pharmacologic and nonpharmacologic methods have been advocated, including bronchodilators, anxiolytics, corticosteroids, nebulized lidocaine, and position changes.⁷ However, most of these therapies have been ineffective. In a study that evaluated pain treatment in children with cystic fibrosis, Ravilly et al⁸ found that more than half of the children ended up requiring opioids.

The findings by Ravilly et al⁸ are not surprising. Opioids have been administered through a variety of routes to relieve dyspnea since the late 19th century. They are believed to reduce the sensation of breathlessness primarily through a central effect on the brain but may possess a peripheral effect as well, as evidenced by the fact that low doses of morphine administered directly to the lung via nebulizer are effective in some patients. In fact, all 3 conventional opioid receptor types (μ , δ , and κ) have been isolated in lung tissue, and it is believed that nonconventional opioid receptors are present as well.^{5,6} Although peripheral opioid receptors are involved in pain modulation just as central receptors are, there

are differences. Tissue damage, as occurs in the lung with respiratory ailments, results in the migration of immune cells that release endogenous opioid ligands.⁹ This results in the activation of opioid receptors previously dormant on peripheral sensory nerve terminals.¹⁰ Although there is a ceiling effect on the degree of analgesia attainable with the peripheral administration of opioids, benefits of this route include the anti-inflammatory effects of μ and κ agonists and a lack of tolerance under conditions of inflammation.¹¹ One study suggested the κ receptor to be the predominant opioid receptor found in the lung.¹² An additional mechanism for the therapeutic effects of inhaled morphine might be the inhibition of pulmonary-irritant receptors.¹³

Although there is evidence that points to nebulized morphine as a treatment for dyspnea,^{1–3} a recent review of opioids for the palliation of dyspnea by Jennings et al¹⁴ questioned its efficacy. There are, however, several shortcomings to the studies analyzed. First, most of the studies were small, with only 1 containing >18 patients. Second, virtually all of the studies evaluated inhaled opioids in patients with either chronic obstructive pulmonary disease or cancer, which lead to different anatomic and physiologic changes than cystic fibrosis. Third, in only 1 study were the subjects acutely ill, palliative care patients, and none involved children. Fourth, most of the studies analyzed measured some type of exercise function, not dyspnea at rest. Last, results of both the non-nebulized and nebulized opioid studies were actually mixed, so it is possible that a certain subset of patients may be candidates for inhaled narcotics. This last point is supported by numerous studies showing that peripherally administered opioids may be effective in other contexts.^{15,16}

In people with cystic fibrosis, pulmonary injury leads to the activation of opioid receptors in the respiratory tract, which might form the basis for the therapeutic effects of nebulized morphine. Ironically, this tissue damage may provide a portal for the systemic absorption of drugs. Although there are other explanations for the increased Pvco₂ seen after the 12.5-mg morphine dose, such as laboratory error or a small air bubble in the sample, we believe respiratory depression from high central nervous system opioid levels to be the most likely cause. Although a subtherapeutic adult blood level was recorded after the 12.5-mg dose of nebulized morphine, this may have been sufficient to cause side effects in a cachectic, opioid-naïve child. Supporting this hypothesis are the disproportionately large reductions in RR, HR, and BP that we observed after this treatment.

Nebulized morphine is simple to administer and less likely than systemic opioids to cause the adverse side effects that result from activation of central nervous system opioid receptors. These include nausea, vomiting, pruritus, and, in patients with end-stage lung disease, the potentially catastrophic effects of respiratory depression and suppression of cough. As seen in our patient, the administration of a relatively large dose of morphine into the lungs via nebulizer resulted in only small increases in $PvCO_2$, whereas a much lower dose given by PCA resulted in significant respiratory depression.

The assessment of pain (and probably dyspnea) levels can be difficult in pediatric patients. However, our patient reported decreases in his dyspnea level with nebulized morphine, whereas nebulized lidocaine failed to provide any benefit. It is interesting that he did not experience a graded dose-response to the treatment, as no significant difference in dyspnea reduction was observed between the 2.5-mg and 10-mg doses. This may have been attributable to a ceiling effect from receptor saturation, the wide bioavailability of nebulized drugs, or a placebo effect. The bioavailability of nebulized morphine has been reported to range from 5% to 35%, given that much of the drug is deposited in the delivery apparatus.^{17,18}

CONCLUSION

We report a young boy with terminal cystic fibrosis who obtained moderate relief of dyspnea with nebulized morphine. This case demonstrates a need for additional study to determine the best candidates for this treatment, to assess optimal dosing regimens, and to confirm its efficacy.

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