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

Steven P. Cohen, MD, and Timothy C. Dawson, MD

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.

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 56 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...
opioid receptor types

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NA indicates not applicable.

tolic BP. In contrast, 30 minutes after his 12.5-mg dose, the pa-
tient'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 mini-
imum 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 nebu-
лизed morphine became inadequate. Four days before discharge,
the patient was placed on a morphine sulfate patient-controlled
algesia 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 consulta-
tion, the patient was discharged to hospice care on a combina-
tion 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, corticoste-
roids, 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 breath-
lessness 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 nonconven-
tional 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 li-
gands.9 This results in the activation of opioid recep-
tors 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 in-
clude the anti-inflammatory effects of μ and κ ago-
nists 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 nebu-
лизed morphine as a treatment for dyspnea,1–3 a re-
cent review of opioids for the palliation of dyspnea
by Jennings et al14 questioned its efficacy. There are,
however, several shortcomings to the studies ana-
lyzed. 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 can-
cer, 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 respi-
atory 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 cachec-
tic, opioid-naïve child. Supporting this hypothesis
are the disproportionately large reductions in RR,
HR, and BP that we observed after this treatment.

**TABLE 1. Nebulized Morphine (MSO4) Clinical Data**

<table>
<thead>
<tr>
<th>MSO4 Dose (mg)</th>
<th>VAS (0-10)</th>
<th>PvcO2 (mm Hg)</th>
<th>Systolic BP</th>
<th>HR</th>
<th>RR</th>
<th>Serum MSO4 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Post-</td>
<td>Pre-Post-</td>
<td>Pre-Post-</td>
<td>Pre-Post-</td>
<td>Pre-Post-</td>
<td>(30 Min Post-)</td>
</tr>
<tr>
<td>2.5</td>
<td>6/4</td>
<td>54/58</td>
<td>82/85</td>
<td>111/113</td>
<td>27/24</td>
<td>&lt;10</td>
</tr>
<tr>
<td>5.0</td>
<td>8/5</td>
<td>64.8/65</td>
<td>NA</td>
<td>NA</td>
<td>29/28</td>
<td>&lt;10</td>
</tr>
<tr>
<td>7.5</td>
<td>7/4</td>
<td>59.4/62.4</td>
<td>89/86</td>
<td>115/110</td>
<td>NA</td>
<td>&lt;10</td>
</tr>
<tr>
<td>10</td>
<td>7/4</td>
<td>59.7/60.5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>&lt;10</td>
</tr>
<tr>
<td>12.5</td>
<td>NA</td>
<td>45/54</td>
<td>94/81</td>
<td>109/95</td>
<td>28/22</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>
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 \( P_{\text{ACO}_2} \), 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.

REFERENCES

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Pediatrics 2002;110;e38
DOI: 10.1542/peds.110.3.e38

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