Effect of Nebulized Morphine in Cancer Patients with Dyspnea: a Pilot Study

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Background: It is known that opioids may decrease subjective dyspnea. The recent finding that opioid binding sites are present in the peripheral bronchus supports the possibility of a local action of opioids. However, the clinical benefit of nebulized morphine is controversial. The purpose of this study was to confirm the feasibility of nebulized morphine and to evaluate its clinical benefits.

Patients and methods: Fifteen cancer patients with dyspnea in the Thoracic Oncology Division and Palliative Care Unit in the National Cancer Center Hospital East were given 20 mg of morphine hydrochloride dissolved in 5 ml of normal saline through an ultranebulizer. The subjective effects were evaluated using a visual analog scale (VAS) immediately before and 60 min after inhalation. Respiratory rate (RR), hemoglobin oxygen saturation (SpO₂) and blood pressure also were measured twice at these two time points. A questionnaire about adverse reactions was included.

Results: No major adverse reactions such as respiratory depression, sleepiness, nausea or vomiting were observed. VAS was significantly decreased after nebulization (p = 0.005) without any significant change in RR or SpO₂. In eight of 15 patients, dyspnea was improved as measured by a decrease in VAS of more than 10%. This correlated with the desire of the patients to continue its use.

Conclusion: Our preliminary data confirmed the feasibility of nebulized morphine and suggested its possible clinical benefit for dyspneic patients. A randomized controlled study is warranted to exclude a placebo effect and to compare the clinical benefits of nebulized morphine with those of other methods of treatment.

Key words: nebulized morphine – dyspnea – cancer – symptom control

INTRODUCTION

Dyspnea is defined as 'an uncomfortable sensation of breathing' (1) and this symptom is not always associated with respiratory failure defined as hypoxia and/or hypercapnea (2). It is one of the most frequent symptoms in cancer patients, occurring in 15–40% patients at the time of diagnosis of lung cancer (3) and in 29–74% patients with any kind of malignancy in the terminal stages (4,5). Despite this high prevalence, the pathogenesis of dyspnea is still not well understood (4) and it remains one of the most refractory symptoms (6).

Systemic administration of opioids can decrease dyspnea and increase exercise tolerance in patients with COPD (7) and cancer (8). Nebulized morphine has become one choice of treatment for dyspnea with anecdotal evidence especially in the hospice setting (9). Several retrospective studies have shown its practical benefits (10,11). A recent report that showed that opioid binding sites are present in the peripheral bronchus (12) supports the possibility of a clinical benefit from local action of opioids. One controlled trial in cancer patients has been reported. However, it failed to show a significant benefit of nebulized morphine over nebulized normal saline overall (13), perhaps owing to the small sample size, unsuitable patient selection, insufficient nebulization and/or inadequate evaluation.

We performed a clinical trial to administer morphine through a nebulizer to cancer patients whose dyspnea was not responsive to standard therapy. The purpose of this trial was to confirm the feasibility of nebulized morphine and to evaluate its clinical benefits.

PATIENTS AND METHODS

Between January and February 1998, 15 patients with thoracic cancer who were admitted to the Thoracic Oncology Division
and Palliative Care Unit in the National Cancer Center Hospital East entered this trial. Eligible patients were required (a) to have had a histological diagnosis of lung or thymic cancer and to be informed of the diagnosis, (b) to have dyspnea that was difficult to control with standard treatment, which included drainage for pleural or cardiac effusion, antibiotics for pneumonia and diuretics for cardiac failure, and (c) to have been informed of the purpose of this study. Patients who suffered from mental or cognitive disorders and whose medication for dyspnea had been changed in the past 24 h were excluded.

A 20 mg amount of morphine hydrochloride dissolved in 5 ml of normal saline was given through an ultranebulizer (9). Patients were asked to inhale deeply until the inhaler became empty.

Baseline dyspnea was assessed with the Hugh-Jones score (14) by patients themselves. The subjective effect of nebulization was evaluated with the Visual Analog Scale (VAS) of dyspnea, which is a 100-mm line anchored by the terms 'no dyspnea' and 'worst possible dyspnea', on which intensity of dyspnea is to be marked. It has been found to be reliable in the assessment of dyspnea (15) and be more sensitive and precise than Borg's scale and the Hugh-Jones score (16). The objective effect was measured after sitting at rest for five min; SpO₂ (hemoglobin oxygen saturated) and heart rate were measured with a pulse-oximeter at the digit. Respiratory rate (RR) was counted for 30 s and multiplied by two. Blood pressure was also measured. These subjective and objective evaluations were performed twice; immediately before and 60 min after completion of nebulization. The results were analyzed using the paired t-test (two-tailed Wilcoxon test). The decrease in the rate of dyspnea was defined as [1 - (VAS at 60 min after nebulization/VAS before nebulization)] × 100 (%).

Patients were asked to complete a questionnaire after completion of all evaluations: whether cough, nausea, sleepiness or other symptoms bothered them by using a four-point scale, grade 0 (not at all) to 3 (very much), whether the treatment provided any relief or not and whether they wanted to continue this treatment or not.

When a patient reported that the treatment did not relieve dyspnea and the adverse reactions were not remarkable, the dose of morphine hydrochloride was doubled to 40 mg (9) and tried again after a 4 h interval.

The pathophysiological causes of dyspnea were evaluated by pulmonologists according to a previous classification (17). Other medical information was obtained from their medical records. Respiratory depression from nebulized morphine was defined as a decrease in RR of more than 10% and a reduction of the SpO₂ value of more than 5.

**RESULTS**

Patients' characteristics are given in Table 1. Two thirds of the patients described their baseline dyspnea as grade 4 on the Hugh-Jones score, which means dyspnea felt even during talking or changing clothes. Seven patients received oxygen therapy by nasal cannula continuously (median: 2 l/min), while three received it intermittently as required. Ten of the patients were already on systemic opioids for their pain and dyspnea, seven on morphine (median: 65 mg/day) and three on codeine (median: 90 mg/day).

No severe adverse reactions were observed. There was no respiratory depression. Other adverse reactions which are often observed during systemic administration of morphine, such as sleepiness, nausea and vomiting, did not occur, according to patients' reports. One patient reported, however, a grade 1 cough and two reported grade 1 bitter taste.

Subjective and objective changes between before and after nebulization are shown in Fig. 1. VAS was significantly decreased after nebulization (p = 0.005). Objective assessment of RR and SpO₂ showed no significant change. The rate of decrease of dyspnea for each patient is shown in Figure 2. Eight of 15 patients (53%) evaluated this treatment as effective and requested its continuation. The decrease in VAS in all these eight patients exceeded 10%, which was used as an arbitrary cut-off point. The other seven felt no subjective relief and in these patients a dose escalation to 40 mg morphine was also not effective, but no adverse reactions were seen with the double dose.
Neulized morphine for dyspnea

Figure 1. Subjective and objective effects of nebulized morphine. The VAS for dyspnea scored by patients decreased significantly 60 min after nebulization of morphine compared with before nebulization, while objective assessment of SpO2 and RR showed no significant change.

DISCUSSION

We found that dyspnea measured by a patient-scored VAS improved significantly after nebulization without any major adverse reactions or significant change in RR and SpO2. The findings suggested its possible clinical benefit.

According to our criteria, nebulized morphine was effective in nearly half of the cases, but ineffective in the remaining cases. It is difficult to draw some conclusions regarding differences in characteristics between the effective and ineffective groups because of the small sample size. However, we tried to show some tendencies in both groups. Regarding administration of opioids and oxygen, VAS of dyspnea, RR, SpO2, age and sex, no significant difference was detected between the two groups.Patients on systemic opioids had, however, a tendency to benefit from nebulized morphine compared with the non-opioid patients (p = 0.119, by Fisher r-test). This tendency, which has been reported before (12), may be explained by the prevalence and/or binding affinity of the pulmonary opioid receptor population being influenced by the presence of systemic opioids (12). Further work is necessary to confirm what might cause the difference in response to nebulized morphine.

No severe adverse reactions, including subjective ones, occurred in our study. There has been no report about subjective adverse reactions except nausea and drowsiness, according to Medline, between 1983 and 1999. One of the negative reactions in the present trial was a bitter taste, but it was tolerable.

Nebulized morphine did not cause any significant change in RR or SpO2 in our study. Systemic administration of opioids has also been reported to reduce subjective dyspnea without any significant change in RR, SpO2, or the concentration of CO2 (8,18). Its mechanism of action is still not well understood, but may include cerebral sedation, reduced sensitivity to hypercapnea, improved cardiac function, reduced O2 consumption, reduced cough and reduced anxiety (4).

The effect of nebulized morphine is unlikely to be caused by systemic absorption of the nebulized dose, because a nebulized dose of only 5–20 mg is reported to be effective. The systemic bioavailability of nebulized morphine is extremely poor, varying from 4 to 8% (19), whereas systemic doses required to affect dyspnea range from 5 to 50 mg. The mechanism of the likely local action is not well understood. It is expected that morphine binds to peripheral receptors to inhibit mucus secretion (10) and/or to induce peripheral analgesic effects (20) and/or something else unknown.

Nebulization has a number of advantages. First, the systemic side effects of opioids may be avoided or minimized, because its bioavailability is very small, as mentioned before. This is a great advantage of nebulization over systemic administration, since numerous patients on opioids suffer from its side effects.
such as constipation (21). Second, relief is likely to be more rapid than by oral intake. Relief of dyspnea has been reported to occur shortly after or within 10–15 min of application of nebulization treatment (8). Third, patients can manage their dyspnea by themselves easily on an 'as required' basis, when dyspnea occurs or worsens. These merits suggest the possibility of the use of nebulized morphine for patients at home as a rescue treatment during dyspnea attack or prophylactically before daily activities.

Its effective use in clinical practice needs further examination. How long its effectiveness sustains, how many times it can be used safely and what the limiting factor of this treatment is, are very important. From empirical data, it appears that its benefit lasts for a few hours and an increase in the dose up to 80 mg and in frequency up to every 2 h are tolerable (11). However, sound scientific evidence is required.

The limitations of this pilot study are as follows: (1) it was an uncontrolled open study with a small sample size; (2) the study population was not homogeneous; and (3) the assessment was made after administration of only a single dose. A randomized double-blinded controlled study which compares nebulized morphine with nebulized saline is now in progress to exclude a placebo effect and to compare the clinical benefits.

References