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Original article

The effects of morphine on dyspnea and ventilatory function in elderly patients with advanced cancer: A randomized double-blind controlled trial

C. Mazzocato,[1] T. Buclin[2] & C.-H. Rapin[3]

Divisions of [1]Palliative Care, [2]Clinical Pharmacology, Departement of Internal Medecine, University Hospital, Lausanne; [3]Poliger, Departement of Geriatrics, HUG, Genève, Switzerland

Summary

Background: Dyspnea represents a very frequent and distressing symptom in patients with advanced cancer. This study was undertaken to assess the efficacy of morphine on dyspnea and its safety for ventilatory function in elderly advanced cancer patients.

Patients and methods: Nine elderly patients with dyspnea due to lung involvement were randomized to receive either morphine subcutaneously (5 mg in seven opioid-naïve patients and 3.75 mg in two patients on top of their regular oral dose of 7.5 mg q4h) or placebo on day 1. On day 2, they were crossed over to receive the alternate treatment. Dyspnea was assessed every fifteen minutes using a visual analogue scale (VAS: 0–100 mm) and the ordinal scale developed by Borg (0–10 points). Pain, somnolence and anxiety were assessed using VAS. Respiratory effort, respiratory rate and oxygen saturation were also measured repeatly.

Results: Mean changes in dyspnea 45 minutes after injection were -25 ± 10 mm and -1.2 ± 1.2 points for morphine, *versus* 0.6 ± 7.7 mm ($P < 0.01$) and -0.1 ± 0.3 points ($P = 0.03$) for placebo on VAS and Borg scale, respectively. No relevant changes were observed in somnolence, pain, anxiety, respiratory effort and rate, and oxygen saturation.

Conclusions: Morphine appears effective for cancer dyspnea, and it does not compromise respiratory function at the dose level used.

Key words: dyspnea, morphine, terminal cancer, ventilatory function

Introduction

Dyspnea represents a frequent and distressing symptom in patients with advanced cancer [1, 2]. The most frequent cause is the presence of lung involvement by primary or metastatic tumor [2]. In recent years, a number of drugs have been proposed for decreasing the sensation of dyspnea. Benzodiazepines have been found to exert contradictory effects on the dyspnea of both chronic pulmonary disease and cancer [3–6]. On the other hand, opioids have been suggested to be beneficial in decreasing the intensity of dyspnea without significantly altering the respiratory drive [7–9]. However, only one randomized double blind controlled trial has been published on the efficacy of morphine in patients with cancer dyspnea [8]. This study has been conducted in 10 patients with restrictive dyspnea due to progressive cancer.

Since dyspnea tends to vary dramatically from one moment to the other, and is frequently accompanied by other devastating symptoms like delirium, randomized control trials are extremely difficult to conduct in patients with severe cancer dyspnea at rest [9]. Hence the studies of pharmacological interventions and oxygen have only been able to recruit a limited number of patients [7–10, 13].

The purpose of this double blind, crossover study was to assess the efficacy of morphine, compared to placebo, on the intensity of dyspnea and its effect on respiratory function in elderly patients with advanced cancer.

Patients and methods

Population and treatment

Ten patients with dyspnea due to advanced cancer were considered for inclusion in this study. In all cases, patients scored within normal limits in the mini-mental state examination [11]. Other inclusion criteria were the absence of brain tumor and of acute incapacitating respiratory decompensation. Nine patients gave their informed consent. Seven opioid-naïve patients were randomized to 5 mg subcutaneous morphine or placebo on day 1. Two patients were already receiving oral morphine for analgesia. They were studied at their regular morphine dosing and received the regular oral dose with, in addition, half of the oral dose as a subcutaneous injection of morphine, or placebo (in summary these two patients received at that moment their usual 7.5 mg orally and either 3.75 mg morphine or placebo subcutaneously). This double dose was given to overcome the potential tolerance. Twenty-four hours later, the treatments were crossed over, and the patients who had received morphine were given placebo and vice versa.

Analysis of outcome

The main *a priori* endpoint of this study was the subjective intensity of dyspnea according to the visual analog scale (VAS, modified by the

Table I. Difference in dyspnea (VAS and Borg scale) (mean ± SD).

Time	VAS		Borg	
	Placebo	Morphine	Placebo	Morphine
T_0	50.6 ± 18	57.8 ± 16	3.89 ± 1.8	3.66 ± 0 9
T_{45}	51.1 ± 15	32.8 ± 15	3.77 ± 1.85	2.44 ± 1.1
Mean difference	0.6 ± 7.7	−25.0 ± 10[a]	−0.10 ± 0.3	−1.20 ± 1.2[b]

[a] $P < 0.01$.
[b] $P = 0.03$.

addition of a numbered scale) and the Borg ordinal scale [12] determined forty five minutes after the injection of morphine or placebo. The scales were also applied at other time points between 0 and 4 hours after dosing. Other measurements included VAS for pain, somnolence and anxiety. The respiratory effort was determined using a six-point score based on respiratory frequency, presence of cyanosis, and utilization of accessory respiratory muscles (1: respiratory frequency < 20/min; 2: respiratory frequency between 20 and 25/min; 3: respiratory frequency between 26 and 30/min; 4: respiratory frequency > 30/min; +1: presence of cyanosis; +1: use of accessory respiratory muscles). These scores were developed for clinical trials evaluating the treatment of dyspnea [7] In addition, respiratory frequency and transcutaneous pulsoxymetry were recorded.

All assessments took place before the subcutaneous injection (T_0) and 45 minutes later (T_{45}) In addition, dyspnea, pain, anxiety and somnolence were assessed by VAS every 15 minutes for two hours and every hour up to four hours after injection. The mini-mental state examination was repeated two hours after injection.

Ethical considerations

The study was approved by the Ethics Committee of the University Hospital of Genève.

Statistical methods

The study endpoints were compared under each treatment using an analysis of variance for repeated measures, taking into account the baseline response level at T_0. When more than two measurements were performed, post-dosing results were compared to baseline using the least significant differences test Period and carry-over effects were explored using a similar approach.

Results

Sociodemographic and medical variables

During the nine-month study period, ten eligible patients were identified in a 120 beds geriatric hospital. Nine patients agreed to participate. Their mean age was 73 years (66–83 years), four patients were female. The main cause of dyspnea was primary or metastatic lung involvement as a consequence of lung cancer (seven cases), breast cancer (one case) and bladder cancer (one case). Additional complicating factors included a history of COPD (five cases), congestive heart failure (five cases), carcinomatous lymphangitis (two cases), bilateral pleural effusion (two cases), and pneumonia (one case). Seven patients were on no opioid medication, and two received oral morphine for analgesia at a dose of 7.5 mg every four hours. Mean survival after the study was 65 days (median 30 days, 6–362 days).

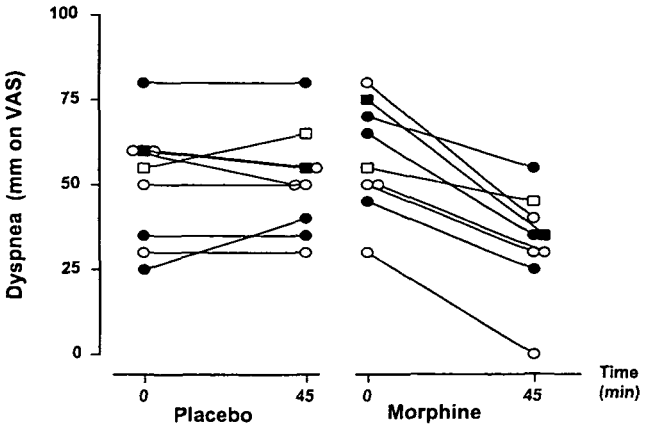

Figure 1. Dyspnea (VAS) at T_0 and T_{45} after placebo and morphine. Individual results. Closed symbols. placebo-morphine sequence. Open symbols: morphine-placebo sequence. Squares: patients previously on oral morphine.

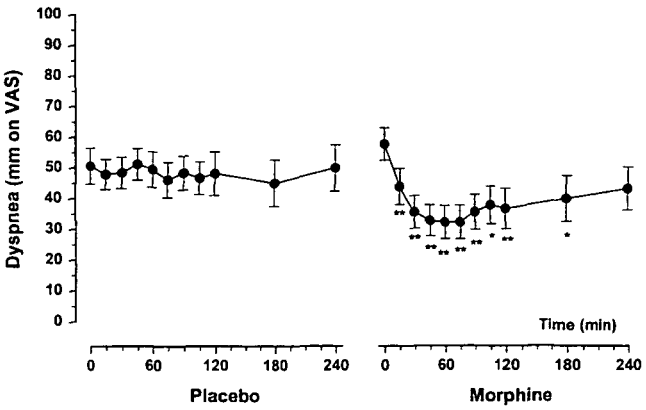

Figure 2. Intensity of dyspnea after morphine and placebo (VAS 0–100 mm) means ± SEM. Difference vs. baseline: * $P < 0.05$; ** $P < 0.01$.

Effects of morphine on dyspnea

Table 1 summarizes the difference in subjective dyspnea intensity between T_0 and T_{45}, measured both by VAS and the Borg ordinal scale. According to both measurements, morphine was significantly better than placebo for relieving dyspnea ($P < 0.01$, resp. $P = 0.03$). These results are summarized in Figure 1. Neither period nor carry-over effects were detected. Figure 2 shows that morphine decreased significantly the intensity of dyspnea from 15 minutes up to 180 minutes after dosing, while placebo had no significant effect during the whole observation period.

Effects of morphine on other variables

The Table 2 summarizes the results observed in the other variables between T_0 and T_{45}. A significant improvement was observed in both respiratory effort score ($P = 0.05$) and respiratory rate ($P = 0.02$) after morphine

Table 2. Difference in other variables.

Variables	Difference T_0–T_{45}		
	Placebo	Morphine	*P*-value
Pain (VAS: 0–100 mm)	−7.2 ± 22	−9.4 ± 14	0.82
Somnolence (VAS: 0–100 mm)	−10.6 ± 14	−7.8 ± 21	0.78
Anxiety (VAS: 0–100 mm)	−13.9 ± 21	−13.3 ± 17	0 95
Respiratory effort score (1–6)	0.1 ± 0.6	−0.4 ± 0.7	0.05
Respiratory rate (breath/min)	0 ± 1.7	−2 ± 2.2	0.02
Oxygen saturation (%)	−0 8 ± 1.3	0 ± 1.5	0.31

as compared to placebo. There were no other significant differences.

Side effects

Mini-mental state examinations were normal in all patients at T_0 and T_{120}. No patients reported any side effects after the administration of placebo. After the administration of morphine, one patient reported nausea and vomiting (T_{120}), one nausea (T_{120}), and one somnolence (T_{60}) and nausea (T_{105}). The symptoms were transient, and in only subject nausea and vomiting required treatment.

Discussion

In this double blind, cross over study, morphine worked significantly better than placebo in reducing the intensity of dyspnea in patients with advanced cancer.

Although a total of 20 patients were forseen for this study, only 9 patients were included in nine months. For logistic reasons the study needed to be closed at that point. Pharmacological studies of cancer patients with dyspnea are extremely difficult to conduct. Unlike patients with heart failure or COPD, cancer patients can rarely be submitted to standard exercise on a bicycle or treadmill, to produce a controlled level of dyspnea amenable to pharmacological modulation. In addition, cancer dyspnea tends to vary dramatically along time, is frequently accompanied by other devastating symptoms like pain or delirium, and is associated with a short survival. Patients with severe dyspnea may be excessively distressed or cognitively impaired and therefore unable to participate in clinical trials. These reasons explain that the recruitment of cancer patients with dyspnea in pharmacological studies has regulary been found extremely difficult [7–9, 13].

Our results confirm those of the only controlled study using morphine injections for cancer dyspnea [8]. However, Bruera et al. found in a previous uncontrolled report that the duration of dyspnea relief after morphine injection was much shorter than the duration of analgesia in a group of patients with cancer pain and dyspnea [7]. Our study focused on a population in which the majority of patients had no pain. In addition, the assessment in our study was done under double-blind conditions, while the observation from Bruera and al. was conducted on a open basis. Our results and those of a recent randomized continuous sequential clinical trial [9] suggest that the duration of dyspnea relief after morphine injection may be longer than initially reported and perhaps as long as the duration of analgesia induced by this drug. This has important implications for the prescription of morphine for cancer dyspnea. Another possible explanation for this finding is that our patients were on average ten years older than those of Bruera et al., and morphine elimination may have been slower. This point needs to be further investigated in future studies.

Several questions remain open with regard to the mode of action of opioids on dyspnea. Our results (Table 2) indicate that the beneficial symptomatic effect of morphine is not related to anxiolytic or sedative actions. This is consistent with the previously reported lack of correlation between intensity of anxiety and dyspnea [14]. Accordingly, other studies showed limited or no benefit of benzodiazepines in the management of dyspnea associated with cancer and COPD [4–6]. Our results are in agreement with those of Bruera et al. [8], showing that the relief of dyspnea in elderly cancer patients is not associated with a marked respiratory depression, as indicated by the lack of differences in oxygen saturation. Although the changes in both respiratory rate and respiratory effort score are limited, these findings suggest that the the symptomatic efficacy of morphine could be explained in part by a decrease in respiratory rate and effort (Table 2). Future studies should attempt to better characterize the action of morphine on these objective variables. Another mode of action may rely on a decrease in cardiac pre-load in patients with congestive heart failure [15, 16]. However, this action cannot account on its own for all the effects of morphine, since different studies have demonstrated a beneficial effect on dyspnea in patients without cardiac failure [17–20]. Morphine could also modify the central perception of dyspnea, as it alters the perception of pain [19]. Some authors report a decreased oxygen consumption [17, 20], but these results have not been confirmed by others [19]. Finally, the hypothesis of an ameliorated pulmonary function has not been confirmed [17, 19].

Our results suggest that intermittent injections of morphine (5 mg subcutaneously) can be used safely for the symptomatic relief of cancer dyspnea, even in severely affected patients, without significantly increasing somnolence, at least on the start term. However, numerous questions remain open with regard to the practical utilization of opioids, in particular the optimal drug dose, frequency and modalities of administration (e.g., regular *versus* as needed administration? place of slow release opioids? suitability of other opioids than morphine?). Only one trial has compared the efficacy of two different doses of morphine on dyspnea. This study, conducted in dyspneic patients already receiving morphine for analgesia, suggest that supplemental doses of morphine reaching of only one-quarter of the regular four-hourly dose may suffice to reduce dyspnea [9].

While our findings as well as other controlled and uncontrolled reports suggest that opioids are effective in the relief of dyspnea in both cancer and COPD patients [7–9, 13, 17–20], benzodiazepines continue to be the most widely recommended and used drugs in these conditions, in spite of limited evidence of efficacy [4, 5]. Our results, though limited, could contribute to a wider use of morphine to alleviate cancer-related dyspnea.

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Correspondence to:
Dr C. Mazzocato, MD
Division de soins palliatifs
Hôpital de Beaumont
Centre Hospitalier Universitaire Vaudois
1011 Lausanne
Switzerland
E-mail: Claudia.Mazzocato@ chuv.hospvd.ch