

Disabling dyspnoea in patients with advanced disease: lack of effect of nebulized morphine

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Disabling dyspnoea in patients with advanced disease: lack of effect of nebulized morphine. A. Nosedá, J.-P. Carpiaux, C. Markstein, A. Meyvaert, V. de Maertelaer. ©ERS Journals Ltd 1997.

ABSTRACT: The purpose of this placebo-controlled, double-blind, randomized study was to assess the effect of nebulized morphine on dyspnoea perceived at rest by patients with advanced disease.

Seventeen hospital in-patients with disabling dyspnoea received isotonic saline or morphine *via* nebulization for 10 min through a mouthpiece, combined with oxygen *via* nasal prongs. On four consecutive days, they were given one of the four following treatments in random order: saline with 2 L·min⁻¹ oxygen; 10 mg morphine with 2 L·min⁻¹ oxygen; 20 mg morphine with 2 L·min⁻¹ oxygen; and 10 mg morphine without oxygen (prongs fixed, no flow). Dyspnoea was assessed on a bipolar visual analogue scale (VAS) (-100% much more short of breath, +100% much less short of breath), and arterial oxygen saturation (Sa,O₂) and respiratory frequency (*f*R) were recorded at the end of nebulization and 10 min later.

In 14 subjects who completed the study, mean VAS ratings 10 min after the end of nebulization ranged +30 to +43%, with no significant difference between the four study days (VAS 20 mg morphine minus VAS saline, 95% confidence interval (95% CI) -6 to +8%). Sa,O₂ significantly increased on the 3 days with supplemental oxygen, and remained stable on the zero flow day. Respiratory frequency significantly decreased on the 4 days, with a trend to correlation between VAS rating and parallel change in respiratory frequency (Spearman's rank correlation coefficient (*r*_s)=-0.46; *p*=0.09).

We conclude that the subjects benefited from saline or morphine *via* a placebo effect and/or a nonspecific effect, and that nebulized morphine had no specific effect on dyspnoea.

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Disabling dyspnoea associated with severe lung or heart disease is often inadequately controlled, even with maximal treatment of the underlying condition. Systemic treatment with opioids has been reported to reduce dyspnoea in some patients groups [1, 2], but adverse effects are common and preclude their long-term use. Nebulized morphine is potentially attractive, since it is free of the adverse effects associated with systemic therapy and uncontrolled studies have suggested a beneficial effect on dyspnoea [3, 4].

The present study tested the hypothesis that opioid-sensitive receptors located in the respiratory tract [5] modulate dyspnoea perceived at rest by patients with advanced lung or heart disease. Hospital in-patients with disabling dyspnoea were, in a double-blind randomized protocol, given nebulized isotonic saline or nebulized morphine (10 or 20 mg) and the change in perceived shortness of breath was recorded on a bipolar visual analogue scale (VAS).

Subjects and methods

Study design

On four consecutive days, each subject received the four following treatments in random order: nebulized

isotonic saline with oxygen; 10 mg nebulized morphine with oxygen; 20 mg nebulized morphine with oxygen; and 10 mg nebulized morphine without oxygen. The primary outcome variable was dyspnoea, rated on a bipolar VAS; additional variables were arterial oxygen saturation (Sa,O₂) and respiratory frequency (*f*R). The protocol was approved by the Ethics Committee of the Hôpital Brugmann, and each subject gave informed consent.

Subjects

All subjects were hospital in-patients with severe lung or heart disease. Criteria for entry into the study were: 1) distressing dyspnoea not relieved by conventional medical therapy, (*i.e.* maximal treatment of underlying pulmonary and/or cardiac disease, including management of pleural effusion, when present); and 2) ability to rate dyspnoea on a VAS, as judged from normal cognitive function (Mini-Mental State Questionnaire Score of at least 24/30) [6], and specific understanding of the scale used in this study.

Seventeen patients (13 males and 4 females) were studied. Their anthropometric and clinical features are presented in table 1. The most frequent diagnosis (12 subjects) was chronic obstructive pulmonary disease (COPD);

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Table 1. – Anthropometric and clinical features of 17 patients with advanced disease and disabling dyspnoea

Pt No.	Sex	Age yrs	Height cm	Weight kg	Main diagnosis [#]	Additional diagnosis [‡]	VC L	FEV ₁ L
1	M	70	163	63	COPD		1.91	0.73
2	M	86	160	53	COPD		2.56	1.15
3	F	53	152	40	COPD		1.70	0.74
4	M	74	174	57	COPD	Talc pleurodesis	1.69	1.07
5	F	67	153	65	COPD	Anaemia	1.23	0.70
6	M	78	160	50	COPD		2.37	0.71
7	F	68	146	67	COPD		1.94	0.74
8	F	74	146	50	IPF		1.57	1.13
9	M	59	170	86	COPD	Heart failure	3.08	1.08
10	M	74	175	85	COPD		2.92	1.64
11	M	76	167	48	Malignancy	Left pneumonectomy	0.89	0.70
12	M	58	169	53	COPD		2.50	0.73
13	M	84	169	60	Heart failure		NA	NA
14	M	44	178	68	Malignancy	Talc pleurodesis	NA	NA
15	M	62	177	70	Malignancy	Talc pleurodesis	NA	NA
16	M	73	165	70	COPD	Heart failure	1.63	0.70
17	M	67	168	40	COPD		2.93	1.02
Mean		69	164	60			2.07	0.92
SD		11	10	14			0.67	0.18

[#]: Main diagnosis responsible for dyspnoea; [‡]: additional diagnosis likely to contribute to dyspnoea. Pt: patient; M: male; F: female; VC: vital capacity; FEV₁: forced expiratory volume in one second; COPD: chronic obstructive pulmonary disease; IPF: idiopathic pulmonary fibrosis; NA: not available.

one of these patients had undergone talc pleurodesis for recurrent pneumothoraces. Of three subjects with malignancy as main diagnosis, one had recurrence of lung cancer on a stump of left pneumonectomy; one had lung cancer with pleural involvement; and one had metastatic pleurisy from unknown primary tumour. The latter two subjects had been managed by tube drainage and talc pleurodesis.

Spirometric data were available in 14 subjects and were consistent with severe airflow limitation. The treatments most often prescribed were: inhaled bronchodilators (n=14); oral or *i.v.* steroids (n=11); oral or *i.v.* theophylline (n=9), diuretics (n=8); nitrates (n=8); and oxygen (n=8). Steroids were given as a part of therapy for COPD, but also, although less frequently, for adrenal insufficiency (n=1), perimetastatic cerebral oedema (n=1), or hypercalcaemia (n=1). Other treatments included: anticoagulants (n=5); benzodiazepines (n=5); inhaled steroids (n=4); digoxine (n=4); antibiotics (n=4); antidepressants (n=2); analgesics (n=2); and angiotensin converting enzyme (ACE) inhibitor (n=1).

Treatment under investigation

At time zero, the subject was asked to rest in bed. Oxygen was stopped in those subjects receiving oxygen as a part of in-hospital treatment. At time 15 min, a 4 mL volume was nebulized, using an air-driven 5 L·min⁻¹ flow rate for 10 min, and administered to the subject *via* a mouthpiece. The solution contained either 10 mg morphine chlorhydrate (2 of the 4 days), 20 mg morphine chlorhydrate (1 day), or isotonic saline (1 day). Morphine solutions were stabilized using 1 mg Na₂S₂O₅. All solutions were sterile and conserved at 4°C, light-free. All morphine and saline solutions were prepared and coded independently in the hospital pharmacy. Oxygen was delivered at 2 L·min⁻¹ *via* nasal prongs on 3 of the 4 days, including the 20 mg morphine and

the saline day. On one of the two 10 mg days, prongs were fixed but no oxygen was given.

Outcome variables

Dyspnoea was rated on a 40 cm horizontal bipolar VAS labelled "much more short of breath" at the left end, "much less short of breath" at the right end and "no change" in the middle [7]. This scale allows the subject to report either an increase or a decrease in shortness of breath when moving off from the no change midpoint. It is particularly suited for evaluating the response to an acute intervention, and has been validated by our group in patients with chronic respiratory disease [7]. Dyspnoea ratings measured in this way are reported as percentages (range -100 to +100%).

Oxygen saturation was monitored using a Biox Ohmeda 3700 pulse oximeter (Madison, USA), with an ear probe. Respiratory rate was measured twice for 1 min, and the two results were averaged. SaO₂ and fR were measured at times 15 min (baseline), 25 min (end of nebulization), and 35 min. VAS ratings were recorded at times 25 min and 35 min.

Statistical analysis

Data were submitted to an analysis of variance (ANOVA) with two repeated measures: one for the treatments (four levels), and one for the time (two or three levels). In the case of significant difference between the treatments, mean contrasts between them were calculated. The study was designed to give a 90% chance of detecting a 25% change in dyspnoea at the 0.05 p-level. Assuming that dyspnoea could be assessed on the bi-polar VAS with a within-subject coefficient of variation of 15% [7], the sample size estimation indicated that at least 13 subjects were required. A p-value of less than 0.05 was considered statistically significant.

Table 2. – Outcome variables (VAS, S_{a,O_2} and f_R) for the 14 subjects who completed the study

	Saline + O ₂			10 mg morphine + O ₂			20 mg morphine + O ₂			10 mg morphine without O ₂		
	15 min	25 min	35 min	15 min	25 min	35 min	15 min	25 min	35 min	15 min	25 min	35 min
VAS rating %	-	+34 (25)	+42 (27)	-	+23 (24)	+33 (28)	-	+31 (26)	+43 (27)	-	+26 (30)	+30 (25)
S_{a,O_2} %	93 (5)	95 (5)	95 (4)	91 (7)	93 (7)	93 (6)	90 (4)	93 (4)	94 (4)	91 (5)	90 (8)	90 (8)
f_R breaths·min ⁻¹	20.1 (4.0)	17.0 (3.7)	19.1 (3.9)	19.8 (5.6)	18.7 (5.3)	17.9 (5.3)	20.3 (3.8)	18.4 (4.2)	19.1 (4.6)	19.9 (4.1)	17.5 (3.7)	19.0 (3.9)

Values are presented as mean, and SD in parenthesis. VAS: visual analogue scale; S_{a,O_2} : arterial oxygen saturation; f_R : respiratory frequency. 15 min: baseline; 25 min: at the end of nebulization; 35 min: 10 min after the end of nebulization.

Results

Fourteen of the 17 subjects completed the study. Subjects Nos. 6, 11 and 14 died (one with COPD, two with malignancy) on the third or fourth study day; all three deaths occurred during the night, none being related to the present experiment. The results that follow involve the 14 subjects who completed the study.

Of the 112 VAS ratings recorded throughout the study, 101 were positive (subject less short of breath), 7 zero (no change), and 4 negative (subject more short of breath). The 11 ratings $\leq 0\%$ were obtained after either 10 mg morphine with (n=4) or without (n=5) oxygen, or 20 mg morphine (n=2). No rating $\leq 0\%$ was recorded after saline. As shown in table 2, mean VAS ratings at time 25 min (at the end of nebulization) ranged from +23 to +34%. The additional improvement recorded at time 35 min (10 min after the end of nebulization) was significant (p=0.011). VAS ratings recorded at time 35 min are shown in figure 1. No significant difference in effectiveness was detected between the four treatments under investigation (p=0.362). The 95% confidence interval (95% CI) for the difference in VAS rating between the 20 mg morphine day and the saline day was -12 to +6% at time 25 min, and -6 to +8% at time 35 min.

Mean baseline S_{a,O_2} ranged 90–93% across the four study days (table 2). As expected, oxygen administration significantly increased S_{a,O_2} when combined either with saline (p<0.001), 10 mg (p=0.002), or 20 mg morphine (p<0.001). After 10 mg nebulized morphine without supplemental oxygen, S_{a,O_2} decreased slightly from 91 (5) to 90 (8) %, but the decrease did not reach significance (p=0.216). At baseline, the subjects were mildly tachypnoeic at rest (mean f_R 19.8–20.3 breaths·min⁻¹). Respiratory frequency significantly decreased over time (p=0.043), and no significant difference was detected between the four treatments (p=0.861). As illustrated in figure 2, there was a tendency for the largest improvements in shortness of breath (at time 35 min) to be associated with the largest decreases in f_R . The correlation between the two variables approached significance (Spearman's rank correlation coefficient (r_s) = -0.46; p=0.09).

None of the treatments caused any important adverse effect. Four of the 56 experiments were associated with minor manifestations: one subject felt the nebulized solution pricked his throat on the 20 mg morphine day and on the saline day; one subject complained about a bitter taste after 20 mg morphine; and a burst of cough was observed following 20 mg morphine in another subject.

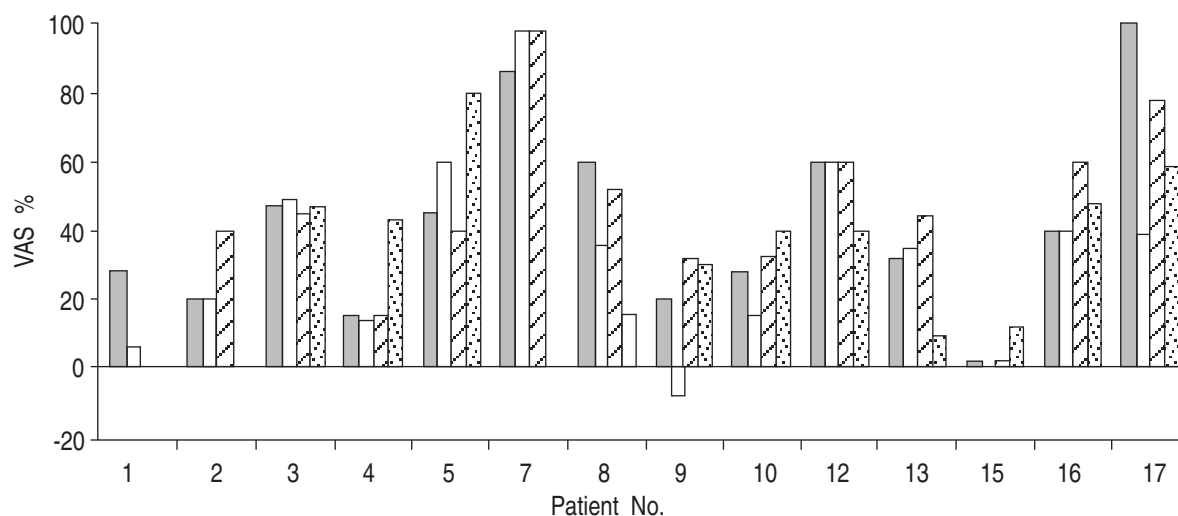


Fig. 1. – Visual analogue scale (VAS) ratings, expressed as a percentage, recorded, at time 35 min, on four consecutive days in 14 patients with disabling dyspnoea, 10 min after the end of: nebulized saline with 2 L·min⁻¹ oxygen (—); 10 mg morphine with 2 L·min⁻¹ oxygen (—); 20 mg morphine with 2 L·min⁻¹ oxygen (·); or 10 mg morphine without oxygen (□).

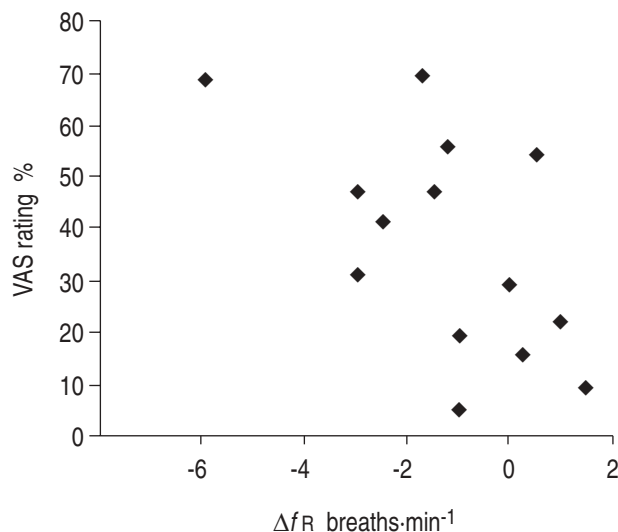


Fig. 2. — Visual analogue scale (VAS) ratings recorded at time 35 min, 10 min after the end of nebulized treatment plotted against the parallel changes in respiratory frequency (ΔfR). The values taken into account were the averages of the four treatments, since no treatment difference was detected either for VAS or fR . A nonparametric correlation analysis was performed (Spearman's rank correlation coefficient (r_s) = -0.46; $p=0.09$).

Discussion

In this controlled study, we assessed the effect of nebulized morphine on the sensation of dyspnoea experienced by hospital in-patients with advanced disease, and found no difference in efficacy between saline, and 10 mg or 20 mg morphine. The study was originally designed because of recent claims that inhaled opioids are able to relieve severe dyspnoea from malignant or nonmalignant lung disease [3, 4]. Our results do not support the hypothesis that nebulized morphine may decrease dyspnoea through a local action on the airways.

In two studies published in the 1980s, a decrease in exercise-induced dyspnoea was obtained in COPD subjects following oral administration of either 15 mg dihydrocodeine [1], or 0.8 mg·kg⁻¹ of a morphine solution [2]. However, serious side-effects occurred in the latter study. Since the existence of opioid-sensitive receptors in the respiratory tract has been demonstrated [5], it is not surprising that the potential of inhaled morphine for reducing dyspnoea has elicited several trials. In 1989, YOUNG *et al.* [8] reported an increase in exercise endurance in COPD patients after a low 5 mg dose of nebulized morphine [8]. However, these authors did not assess dyspnoea, and their results were strongly influenced by a spectacular improvement in one individual. A first claim of a beneficial effect on dyspnoea at rest from a small 5 mg dose of nebulized morphine involved a single patient with mesothelioma, whose dyspnoea was unresponsive to a large 160 mg·day⁻¹ oral dose of morphine [3]. In 1994, FARNCOMBE *et al.* [4] reported a beneficial effect in a group of 54 patients with disabling dyspnoea from either malignant ($n=40$) or nonmalignant ($n=14$) disease. Thirty four patients received morphine (5–30 mg), the remainder various other opioids, and 34 of the 54 subjects claimed a decrease in shortness of breath. Although the study was uncontrolled and dyspnoea not quantitated, other groups com-

mented with some enthusiasm about the results on the basis of a similar favourable experience with inhaled morphine [9, 10]. The present study was specifically designed to evaluate the contribution of morphine-sensitive receptors located in the respiratory tract to the sensation of dyspnoea. Isotonic saline was used as placebo, and it was found that dyspnoea, quantitated on a bipolar VAS particularly well-suited to assess the response to an acute intervention, was not reduced to a greater extent following morphine than following saline.

The significance of this negative study needs to be discussed. That the dose of nebulized morphine was too small seems an unlikely explanation for the lack of specific effect on dyspnoea, since the 10 and 20 mg doses used compare well with the 5–30 mg claimed to be beneficial in about two thirds of the subjects in the study by FARNCOMBE *et al.* [4]. That the delay to assess the response was not sufficiently long is no more convincing. Indeed, the mean delay to obtain a peak serum concentration following nebulized morphine is 45 min [11], so that we deliberately chose to record the response on the bipolar VAS after 10 and 20 min, as the study aimed to specifically evaluate the intrapulmonary action of nebulized morphine. That the scale used to assess a change in shortness of breath was not sufficiently sensitive also seems unlikely, since this scale was shown to be sensitive to either bronchodilation [12] or to bronchoconstriction [13] in patients with asthma or COPD. Finally, the small number of patients (estimated for a size effect of 25%) could be incriminated, but the difficulty of recruiting patients for this kind of study is obvious. Other groups have reported negative results with inhaled morphine. BEAUFORD *et al.* [14] found no effect of 1 to 10 mg nebulized morphine on dyspnoea assessed during an incremental exercise test in COPD patients. Similarly, MASOOD and co-workers [15, 16] reported that the dyspnoea/ventilation relationship during submaximal exercise is unaffected by nebulized morphine (10 or 25 mg) either in healthy subjects [15] or in patients with COPD [16]. HARRIS-EZE *et al.* [17] reached the same conclusion in patients with interstitial lung disease, for smaller 2.5 and 5 mg doses.

Whilst we were unable to demonstrate any specific effect from nebulized morphine on dyspnoea, the present study showed a beneficial effect on dyspnoea from the four regimens being evaluated. Indeed, 101 of the 112 VAS ratings recorded during the study were positive, meaning the subjects felt less short of breath than at baseline, and the increase in rating over time was statistically significant. Oxygen *via* nasal prongs was included in the study protocol, as there is a theoretical potential for inhaled morphine to lower oxygen saturation. Although the effect of supplemental oxygen on dyspnoea at rest has been disputed [18], at least two studies have shown that oxygen reduces dyspnoea at rest to a greater extent than air (delivered in similar fashion) in hypoxaemic patients with COPD [19], or with terminal cancer [20]. In the present study, the beneficial effect on dyspnoea cannot be ascribed to oxygen, since an equal efficacy was obtained with 10 mg nebulized morphine, without the addition of oxygen. Our results suggest rather a placebo effect and/or a nonspecific effect, possibly mediated through a decrease in respiratory frequency. A placebo effect of similar magnitude on dyspnoea

at rest has been demonstrated previously following nebulized saline in patients with severe asthma or COPD [7]. Other studies have provided arguments in favour of a nonspecific reduction in dyspnoea related to the use of either nasal prongs [18], or a face mask [21].

In conclusion, we have shown that 10 or 20 mg nebulized morphine, administered *via* a mouthpiece, combined with oxygen *via* nasal prongs, is not more effective than isotonic saline in relieving disabling dyspnoea in patients with advanced disease. This result is not unexpected, in view of several studies that have reported a lack of effect of nebulized morphine on exercise-induced dyspnoea in various populations [14–17], but is at variance with the description of a beneficial effect from inhaled opioids on dyspnoea at rest in a recent uncontrolled study [4]. Our patients benefited symptomatically from either saline or morphine, as a result of a placebo effect and/or a nonspecific effect from treatment. Our findings do not support the hypothesis that nebulized morphine, at a dose of 10 or 20 mg, has an intrapulmonary action of clinical relevance.

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