

Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea

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Abstract

Objective To determine the efficacy of oral morphine in relieving the sensation of breathlessness in patients in whom the underlying aetiology is maximally treated.

Design Randomised, double blind, placebo controlled crossover study.

Setting Four outpatient clinics at a hospital in South Australia.

Participants 48 participants who had not previously been treated with opioids (mean age 76, SD 5) with predominantly chronic obstructive pulmonary disease (42, 88%) were randomised to four days of 20 mg oral morphine with sustained release followed by four days of identically formulated placebo, or vice versa. Laxatives were provided as needed.

Main outcome measures Dyspnoea in the morning and evening as shown on a 100 mm visual analogue scale, quality of sleep, wellbeing, performance on physical exertion, and side effects as measured at the end of the four day treatment period.

Results 38 participants completed the study; three withdrew because of definite and two because of possible side effects of morphine (nausea, vomiting, and sedation). Participants reported significantly different dyspnoea scores when treated with morphine: an improvement of 6.6 mm (95% confidence interval 1.6 mm to 11.6 mm) in the morning and of 9.5 mm (3.0 mm to 16.1 mm) in the evening ($P = 0.011$ and $P = 0.006$, respectively). During the period in which they were taking morphine participants also reported better sleep ($P = 0.039$). More participants reported distressing constipation while taking morphine (9 v 1, $P = 0.021$) in spite of using laxatives. All other side effects were not significantly worse with morphine, although the study was not powered to address side effects.

Conclusions Sustained release, oral morphine at low dosage provides significant symptomatic improvement in refractory dyspnoea in the community setting.

Introduction

Breathlessness is a source of distress for 50-70% of patients requiring palliative care.¹ A complex physio-

logical and psychological sensation, its causes are often multifactorial, including the underlying disease, cachexia, and deconditioning.¹⁻² As disease progresses dyspnoea occurs more frequently and at rest.¹⁻³ Depression, panic, anxiety, and insomnia can all result from the symptom and exacerbate it.⁴⁻⁵ Family and carers feel helpless as they face their distressed relative.

Despite optimal medical management many people are still breathless.² Some clinicians acknowledge that opioids have a role in the management of intractable dyspnoea.⁶⁻⁸ In Australia, consensus guidelines from the Therapeutic Guidelines Group in Palliative Care conclude that opioids contribute to the management of refractory dyspnoea.⁸ By contrast, the consensus summary of the Global Initiative on Chronic Obstructive Lung Disease (GOLD) of the National Heart, Lung, and Blood Institute of the US National Institutes of Health and the World Health Organization states that opioids are contraindicated in the management of dyspnoea in chronic obstructive pulmonary disease.⁹ Concerns about respiratory depression and hypercapnia are cited.

The lack of consensus is understandable since high quality studies evaluating the role of opioids in the management of dyspnoea have been lacking. A meta-analysis of the double blind, randomised, placebo controlled studies to date indicates that oral or parenteral opioids are beneficial, but this conclusion is based on small trials using different opioids, methods, and outcomes.⁷

We evaluated the ability of opioids to relieve the sensation of breathlessness when the underlying aetiology has been maximally treated. We chose oral, sustained release morphine to reflect practical clinical care for outpatients. Our hypothesis was that morphine would be superior to placebo.

Methods

Participants

We recruited participants during April-November 2001, from the outpatient clinics for respiratory, cardiac, general, and palliative medicine at the Repatriation General Hospital in South Australia. Participants needed to be opioid naive (not formerly treated with long term opioids) adults with dyspnoea at rest in spite of receiving optimal treatment of reversible

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Table 1 Effect of morphine versus placebo on constipation at the end of the four day treatment period. Variable is measured on a categorical scale; response items are collapsed into dichotomous functional groupings. Values are numbers

Constipation on morphine	Constipation on placebo		Totals
	None or mild	Moderate or severe	
None or mild	26	1	27
Moderate or severe	9	1	10
Totals	35	2	37

P=0.021

factors. Other inclusion criteria were serum concentration of creatinine within twice the normal range, stable needs for oxygen and medication, and the ability to fill out diary cards. Exclusion criteria were recent use of opioids, confusion, obtundation, adverse reactions to opioids, and history of substance misuse.

Protocol

Baseline assessment on day 0 included recording the participant's demographic characteristics, medical history, physical examination, vital signs, medications, and oxygen requirements. We measured performance status by using the categorical scale of the Eastern Cooperative Oncology Group (ECOG), where 0 is "fully active" and 4 is "completely disabled."¹⁰

This was an eight day, randomised, double blind, crossover study. Participants were randomised to 20 mg oral morphine sulphate with sustained release (Kapanol, Glaxo Wellcome Australia) in the morning for four days, followed by four days of identically formulated placebo, or vice versa. They also received open label docusate sodium (50 mg) plus senna (8 mg) capsules (Coloxyl with Senna, Sigma) and were advised to take up to four daily as needed.

Outcome measures on days 4 and 8 provided steady state data. The primary outcome variable was the sensation of dyspnoea as measured on a visual analogue scale in the evening on the final day of the period.¹¹ Anchors were "no breathlessness" at 0 mm and "worst possible breathlessness" at 100 mm. Other variables included morning dyspnoea on the scale, exercise tolerance measured on the modified scale of the Medical Research Council of Great Britain, respiratory rate, blood pressure, heart rate, oxygen saturation, disturbance of sleep by breathlessness, and four or five point categorical scales for nausea and vomiting, constipation, confusion, somnolence, appetite, and overall wellbeing.¹² Study nurses used a categorical scale to evaluate any sedation.

We prespecified all analyses on an intention to treat basis. We reported two tailed P values and assumed statistical significance if $P < 0.05$.

Results

Ten participants withdrew, five during the morphine period and five during the placebo period. Thirty eight participants completed the study.

Participants were mainly elderly men with chronic obstructive pulmonary disease who were receiving supplemental oxygen. Functional status was generally poor, with 71% (34) unable to carry out any work activities (ECOG ≥ 2). Baseline characteristics were similar for both groups.

Dyspnoea control

At the end of the four day period, sustained release morphine was superior to placebo in diminishing dyspnoea. In the evening morphine resulted in an improvement of 9.5 mm (SD 19, 95% confidence interval 3.0 mm to 16.1 mm, $P = 0.006$) in the reported dyspnoea score on the visual analogue scale. In the morning morphine resulted in an improvement of 6.6 mm (SD 15, 1.6 mm to 11.6 mm, $P = 0.011$). Significantly fewer participants receiving morphine reported that their sleep was disturbed by breathlessness (1 v 8, $P = 0.039$; see bmj.com). Exertional performance and overall sense of wellbeing were not significantly different.

Side effects

The respiratory rate was similar for patients receiving morphine (mean 20, SD 5) and placebo (mean 21, SD 4; $P = 0.143$). No episodes of severe sedation or obtundation were recorded. Side effects potentially attributable to morphine were quantified. Categorical responses were collapsed into categories for "no" or "mild" distress and "moderate" or "severe" distress. Morphine caused more distressing constipation than placebo (table 1). Neither treatment caused significantly more distressing vomiting, confusion, sedation, or suppression of appetite.

Participants' withdrawals

Ten participants withdrew from the study; three because of morphine side effects, two because of potential morphine effects, and five for reasons unlikely to be related to morphine (table 2). All of those who withdrew because of side effects of morphine

Table 2 Reasons for withdrawal of 10 patients from the study

Patient	Treatment on day of withdrawal	Day (of 8)	Reason for withdrawal	Comment
1	Morphine	1	Nausea and vomiting	Likely to be caused by morphine
2	Morphine	2	Sedation	Likely to be caused by morphine
3	Morphine	3	Nausea and vomiting	Likely to be caused by morphine
4	Morphine	4	Chest pain and nausea	Nausea may be caused by morphine
5	Morphine	6	Rapid atrial fibrillation, admitted to intensive care unit	Unlikely to be caused by morphine
6	Placebo	2	Chest infection	Not caused by morphine
7	Placebo	2	Fall with fracture	Not caused by morphine
8	Placebo	4	Wanted to take opioids for shoulder pain	Not caused by morphine
9	Placebo	5	Increased dyspnoea with treatment change	Likely to be caused by change from morphine to placebo; refused to continue with crossover
10	Placebo	6	Constipation and sedation	Likely carryover effects of morphine

reported that the symptom was causing them “moderate” or “severe” distress. Notably, one participant’s dyspnoea was so improved with the first treatment (morphine) that the participant withdrew at crossover.

Sensitivity analysis

A conservative sensitivity analysis model assumed that all participants who withdrew did so because of problems with morphine. We included baseline scores on the visual analogue scale for the 10 withdrawn participants in the study dataset and then increased the scores for the end period on morphine systematically to model worsening dyspnoea. All participants who withdrew could have had at least a 10% worsening of their morning scores for dyspnoea or a 25% worsening of their evening scores, and the results of this study would still show a statistically significant improvement with morphine.

Discussion

Oral, sustained release morphine can provide added relief to patients who have intractable breathlessness despite maximal treatment of the underlying causes of dyspnoea.

The results of this study are applicable to many outpatient settings in general practice, palliative care, and respiratory care. The study population of elderly, poorly functioning people predominantly with chronic obstructive pulmonary disease represents patients we encounter often, for whom few symptomatic options are available. The criteria used to identify participants were simple and as broad as possible. Patients needed only to be suffering from the symptom of refractory breathlessness. We specifically avoided invasive procedures such as measuring arterial blood gases or pulmonary function to identify eligible candidates as this would not be generalisable or ethical for many outpatient and palliative care settings.

Although the results are significant and generalisable, clinicians should prescribe morphine for the control of dyspnoea with care. This was not a safety study, and it was not powered to detect significant side effects. The data imply that side effects were minimal. Neither respiratory depression nor severe sedation was identified. All participants who withdrew because of morphine encountered vomiting or sedation, which may be transient or treatable. Constipation was the only notable and common side effect. Review of the daily constipation scores showed that the constipation started to improve by the fourth day of the morphine period; early intervention could have an impact. An important consideration is that most patients who would be considering this treatment do not have any other options and are otherwise severely distressed and limited by their breathlessness. Hence, although the risk of constipation and other side effects is real, this may be an appropriate treatment for many patients, provided that the patient and doctor monitor for clinical benefit and side effects together.

Limitations

The study design has several limitations. Firstly, there was no washout (no treatment) period. A persistence of the side effects of morphine into the early part of the placebo period can be seen (see bmj.com). We recognised these risks a priori. The challenge was to

What is already known on this topic

Pooled data in a meta-analysis of eight small underpowered randomised trials support the clinical use of oral or parenteral opioids including morphine to manage refractory breathlessness

Clinical guidelines for the management of intractable dyspnoea in the palliative care and respiratory settings are contradictory owing to inadequate primary evidence supporting the efficacy and safety of morphine in this setting

What this study adds

This is the first adequately powered randomised controlled trial that showed the superiority of oral morphine for relief of the sensation of breathlessness.

This study was completed before the meta-analysis was published; it confirms the main findings of the meta-analysis with results of the same magnitude

The morphine administered in this study was an oral, once daily, sustained release formulation.

Side effects were minimal and no evidence of respiratory depression was found. Constipation was treated expectantly

develop a short protocol that would be acceptable and ethical for a group of very ill patients who did not have any other medical options. Although a parallel trial would have addressed this concern, it would have doubled numbers in a clinical population for which others have had difficulty recruiting. Instead we elected a crossover trial with an analysis plan that concentrated on the end of the treatment period only.¹³ We planned that sequence and period analyses would precede any analysis of treatment; fortunately, neither sequence nor period effects were identified.

Secondly, there was no blinding for constipation. To accommodate this, the only investigator aware of the constipation was the study nurse (AM), who was not involved in the analysis. Thirdly, the morphine dose chosen was 20 mg daily. Some clinicians may regard this as a relatively high dose in patients who had not been treated with opioids before. As the study was being designed it was the lowest once daily, sustained release formulation available. Subsequent dose ranging studies are needed.

Fourthly, the reduced evening dyspnoea scores and improved sleep may have been related to changes made by the participant, such as increased use of oxygen during the day or continuous positive airway pressure at night. Such potential confounders should have been equally distributed between the groups through randomisation. Finally, the clinical significance of a 7-10 mm change in the visual analogue scale may be questioned. We are not aware of any studies that correlate direct clinical meaning with specific changes of distance in the dyspnoea scale. None the less, in a population of patients in whom pharmacological treatment is not an option, the opportunity for a 5-10% improvement in a disabling symptom is welcome.

Future directions include an effectiveness study that is adequately powered to evaluate safety. Such a study may well show that, with close monitoring, patients could continue taking opioids while tolerance develops to the nausea and sedation. Dose ranging studies in opioid tolerant and naive participants are also planned.

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Competing interests: Placebo capsules of identical appearance were provided by the company that manufactures sustained release morphine sulphate (Kapanol, Glaxo Wellcome Australia); no direct funds were provided by the drug company.

Ethical approval: The study was approved by the local institutional research and ethics committee, and the trial was registered with the Australian therapeutic goods administration.

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Prognosis for South Asian and white patients newly admitted to hospital with heart failure in the United Kingdom: historical cohort study

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Abstract

Objectives To compare patterns of admission to hospital and prognosis in white and South Asian patients newly admitted with heart failure, and to evaluate the effect of personal characteristics and comorbidity on outcome.

Design Historical cohort study.

Setting UK district health authority (population 960 000).

Participants 5789 consecutive patients newly admitted with heart failure.

Main outcome measures Population admission rates, incidence rates for first admission with heart failure, survival, and readmission rates.

Results When compared with the white population, South Asian patients had significantly higher age adjusted admission rates (rate ratio 3.8 for men and 5.2 for women) and hospital incidence rates (2.2 and 2.9). Among 5789 incident cases of heart failure, South Asian patients were younger and more often male than white patients (70 (SD 0.6) v 78 (SD 0.1) years and 56.5% (190/336) v 49.3% (2494/5057)). South Asian patients were also more likely to have previous myocardial infarction (10.1% (n = 34) v 5.5% (n = 278)) or concomitant myocardial infarction

(18.8% (n = 63) v 10.7% (n = 539)) or diabetes (45.8% (n = 154) v 16.2% (n = 817), all P < 0.001). A trend was shown to longer unadjusted survival for both sexes among South Asian patients. After adjustment for covariables, South Asian patients had a significantly lower risk of death (hazard ratio 0.82, 95% confidence interval 0.68 to 0.99) and a similar probability of death or readmission (0.96, 0.81 to 1.09) compared with white patients.

Conclusions Population admission rates for heart failure are higher among South Asian patients than white patients in Leicestershire. At first admission South Asian patients were younger and more often had concomitant diabetes or acute ischaemic heart disease than white patients. Despite major differences in personal characteristics and risk factors between white and South Asian patients, outcome was similar, if not better, in South Asian patients.

Introduction

People of South Asian origin (Indian (subcontinent) origin) comprise the largest ethnic minority group in the United Kingdom—4.1% of the population in 2001. The incidence of coronary heart disease is around 40% higher among this group than among the indigenous

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