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

Amy P Abernethy, David C Currow, Peter Frith, Belinda S Fazekas, Annie McHugh and Chuong Bui

BMJ 2003;327:523-528
doi:10.1136/bmj.327.7414.523

Updated information and services can be found at:
http://bmj.com/cgi/content/full/327/7414/523

These include:

References
This article cites 16 articles, 12 of which can be accessed free at:
http://bmj.com/cgi/content/full/327/7414/523#BIBL
8 online articles that cite this article can be accessed at:
http://bmj.com/cgi/content/full/327/7414/523#otherarticles

Rapid responses
7 rapid responses have been posted to this article, which you can access for free at:
http://bmj.com/cgi/content/full/327/7414/523#responses
You can respond to this article at:
http://bmj.com/cgi/eletter-submit/327/7414/523

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top left of the article

Topic collections
Articles on similar topics can be found in the following collections

Other Oncology (855 articles)
Other respiratory medicine (1067 articles)
Drugs: respiratory system (290 articles)

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

Amy P Abernethy, David C Currow, Peter Frith, Belinda S Fazekas, Annie McHugh, Chuong Bui

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 = 0.059).

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. A complex physio-logical and psychological sensation, its causes are often multifactorial, including the underlying disease, cachexia, and deconditioning. As disease progresses dyspnoea occurs more frequently and at rest. Depression, panic, anxiety, and insomnia can all result from the symptom and exacerbate it. Family and car-ers feel helpless as they face their distressed relative.

Despite optimal medical management many people are still breathless. Non-pharmacological approaches such as cognitive behaviour therapy, relaxation, breathing control, and cool air flowing from a fan directed at the face have provided some benefit. Respiratory rehabilitation is generally aimed at improving level of function rather than definitive symptomatic benefit.

Some clinicians acknowledge that opioids have a role in the management of intractable dyspnoea. In Australia, consensus guidelines from the Therapeutic Guidelines Group in Palliative Care conclude that opioids contribute to the management of refractory dyspnoea. 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. 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. Many of the studies thus far have focused on trying to establish whether opioids can improve function in the setting of dyspnoea. For patients, the relief of the sensation of dyspnoea is critical.

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 factors. Optimal treatment was considered to be in place if a specialist for respiratory, cardiac, or palliative care had reviewed the clinical case, examined the patient, and treated all identified reversible causes of the dyspnoea. 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.”

This was an eight day, randomised, double blind, crossover study. Participants received 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.

Since the active medication was a sustained release preparation we defined steady state as five times the period from administration to maximum concentration. For the product used the time to maximum concentration was nine to 12 hours. Steady state was defined as five times the period from administration to maximum concentration. We used Student's t test, and Fisher's exact test to evaluate sequence effects and the paired samples t test and McNemar's test to evaluate period effects. We approached analysis of the treatment effect in this two period, crossover trial by looking at the differences in the final result for each period. Since data on the visual analogue scale were acceptably normally distributed we used the paired samples t test to test relations for this continuous variable. We used McNemar's test for relations between categorical variables. We reported two tailed P values and assumed statistical significance if P < 0.05. We conducted sensitivity analysis by modelling worsening dyspnoea from baseline for patients who had withdrawn, by increasing end period morphine scores on the visual analogue scale by 5-30%.

Results

Flow of participants and follow up
Figure 1 shows the progress of participants through the study. Ten participants withdrew; five during the morphine period and five during the placebo period. Thirty eight participants completed the study, and compliance with the intervention and follow up were complete for all participants.
Participants were mainly elderly men with chronic obstructive pulmonary disease who were receiving supplemental oxygen (table 1). Functional status was generally poor, with 71% (34) unable to carry out any work activities (ECOG ≥ 2). Baseline characteristics were similar for both groups.

**Sequence and period analysis**

A sequence effect is noted when a difference occurs in response to treatment in period 1 compared with period 2, most commonly seen because an effect from active treatment is carried over into the outcome measurements of the next period. A period effect is noted when the underlying condition or ability to respond to treatment changes from one period to the next. In a crossover design, responses to treatment are suspect if any sequence or period effects are noted. In this study, we identified no notable sequence or period effects.

**Treatment analysis**

**Dyspnoea control**

At the end of the four day period, sustained release morphine was superior to placebo in diminishing dyspnoea (table 2). The respiratory rate was similar for patients receiving morphine compared with placebo (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 significantly more distressing vomiting, confusion, sedation, or suppression of appetite (data not presented).

As the occurrence of a side effect may have changed over the treatment period, the frequency of symptoms throughout the treatment period was reviewed. The morphine group consistently reported more constipation across the period. When morphine was administered first, the carry over of constipation into the placebo period was resolved by the end of the placebo period (figure 2). Other symptoms were relatively stable across both periods; the results are not shown here.

**Participants’ withdrawals**

Ten participants withdrew from the study; three because of morphine side effects, two because of because of morphine side effects, two because of

**Table 2** Effect of morphine versus placebo on the sensation of dyspnoea at the end of the treatment period. End period values for morphine and placebo are means (SD). In this paired t test the differences in the same patient between morphine and placebo are presented as absolute values of the means (SD); 95% confidence intervals are also absolute values

<table>
<thead>
<tr>
<th>Time</th>
<th>Morphine (n=38)</th>
<th>Placebo (n=38)</th>
<th>Mean improvement in dyspnoea scores on morphine compared with placebo</th>
<th>95% CI of the mean improvement</th>
<th>P value (paired t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning</td>
<td>40.1 (24)</td>
<td>47.7 (26)</td>
<td>6.6 (15)</td>
<td>1.6 to 11.6</td>
<td>0.011</td>
</tr>
<tr>
<td>Evening</td>
<td>40.3 (23)</td>
<td>48.9 (24)</td>
<td>8.6 (19)</td>
<td>3.0 to 16.7</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Dyspnoea is measured on a 100 mm visual analogue scale (VAS), with zero as “no breathlessness” and 100 as “worst possible breathlessness.”
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. In this adequately powered, randomised controlled trial, morphine provided a 7-10 mm improvement in the visual analogue scale for dyspnoea—results with both clinical and statistical significance. These results were corroborated by participants’ reports of much better sleep during the morphine period. Sensitivity analysis showed that morphine still provided clinical benefit to the study population even if the modelled participants who withdrew experienced 25% worsening of their dyspnoea. Further, the results showed the same magnitude of improvement as seen in the pooled results of other trials (8 mm on the visual analogue scale).

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.

Oral, long acting morphine was chosen for its convenience and continuous action. The sustained release morphine product used can be given once daily; evidence for its efficacy as a 24 hour medication was provided by the dramatic improvements in the evening dyspnoea scores. A small background dose of opioid may be better tolerated than the peaks and troughs of immediate release formulations.

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.

<table>
<thead>
<tr>
<th>Sleep disturbed by breathlessness on morphine</th>
<th>Sleep disturbed by breathlessness on placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Totals</td>
<td>Totals</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Days</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 3 Effect of morphine versus placebo on sleep 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

<table>
<thead>
<tr>
<th>Constipation on morphine</th>
<th>None or mild</th>
<th>Moderate or severe</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or mild</td>
<td>26</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>9</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Totals</td>
<td>35</td>
<td>2</td>
<td>37</td>
</tr>
</tbody>
</table>

P=0.021

Table 4 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
**Table 5** Reasons for withdrawal of 10 patients from the study

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

**Limitations**

The study design has several limitations. Firstly, there was no washout (no treatment) period. Figure 2 shows the persistence of the side effects of morphine into the early part of the placebo period. We recognised these risks a priori. The challenge was to 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.11 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.

This study shows that rigorous randomised controlled trials can be performed in this population. Key factors were a short study period, simple bedside evaluation, collaboration across disciplines, one identified recruitment nurse, once daily dosing, and an evolving clinical culture that seeks evidence based approaches to care. 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.

We thank Greg Samsa of Duke University Medical Center, Durham, North Carolina, United States, and Adrian Esterman of Flinders Medical Centre, Bedford Park, South Australia, Australia, for reviewing the statistical analysis and providing critical feedback.

**Contributors:** APA was responsible for study design; obtaining funding; logistic, administrative, and technical support; recruitment of participants; collection, assembly, and analysis of data; statistical expertise; and data interpretation; drafting, critical revision, and final approval of the article. BSF was responsible for conception and design of the study; logistic, administrative, and technical support; analysis and interpretation of data; and drafting, critical revision, and final approval of the article. PF was responsible for study design; obtaining funding; logistic support; recruitment of participants; data interpretation; and drafting, critical revision, and final approval of the article. DCC was responsible for study design; obtaining funding; logistic support; recruitment of participants; data interpretation; and drafting, critical revision, and final approval of the article. BSF was responsible for study design; obtaining funding; logistic support; recruitment of participants; data interpretation; and drafting, critical revision, and final approval of the article. BSF was responsible for study design; obtaining funding; logistic support; recruitment of participants; data interpretation; and drafting, critical revision, and final approval of the article. BSF was responsible for study design; obtaining funding; logistic support; recruitment of participants; data interpretation; and drafting, critical revision, and final approval of the article. BSF was responsible for study design; obtaining funding; logistic support; recruitment of participants; data interpretation; and drafting, critical revision, and final approval of the article. BSF was responsible for study design; obtaining funding; logistic support; recruitment of participants; data interpretation; and drafting, critical revision, and final approval of the article. BSF was responsible for study design; obtaining funding; logistic support; recruitment of participants; data interpretation; and drafting, critical revision, and final approval of the article.
analysis of data; and drafting, critical revision, and final approval of the article. AM was responsible for logistic and technical support; recruitment of participants, collection, assembly, and interpretation of data; and drafting, critical revision, and final approval of the article. CB was responsible for conception and design of the study and critical revision and final approval of the article. APA is the guarantor.

Funding: Funds for the conduct of the study were provided by the Flinders Medical Centre Foundation of Bedford Park, South Australia, Australia ($A6000; €3500; £2400). APA’s salary was provided through a clinical scientist development award from the Doris Duke Charitable Foundation of New York, New York, United States.

Competing interests: Placebo capsules of identical appearance were provided by the company that manufactures sustained release morphine sulphate (Kapanol, GlaxoWellcome 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.