Review: Oral or parenteral opioids alleviate dyspnea in palliative care

Jennings AL, Davies AN, Higgins JP, Gibbs JS, Broadley KE. **A systematic review of the use of opioids in the management of dyspnoea.** Thorax. 2002;57:939-44.

QUESTION

Are opioids effective in the treatment of dyspnea?

DATA SOURCES

Studies were identified by searching MEDLINE (1966 to 1999), EMBASE/Excerpta Medica (1980 to 1999), CANCERLIT (1988 to 1999), CINAHL (1982 to 1999), Cochrane Library, Dissertation Abstracts, and SIGLE; reviewing the reference lists of relevant studies, reviews, and book chapters; and contacting authors, other experts in the field, and palliative care organizations.

STUDY SELECTION

Studies were selected if they were randomized, double-blind, placebo-controlled trials of any opioid to alleviate breathlessness in patients with dyspnea.

DATA EXTRACTION

Data were extracted by 2 independent reviewers on study quality (concealment, blinding, withdrawals, and dropouts), disease that causes dyspnea, intervention (opioid used and dosage), study methods, and results. The main outcome measure was a subjective assessment of dyspnea. In studies of patients at rest, the breathlessness measurement nearest to 1 hour after opioid administration was used; in studies with exercise tests, the breathlessness measurement relating to the exercise test was used. Dyspnea measurements recorded at a fixed point during exercise or after a fixed length of exercise were used for meta-analysis.

MAIN RESULTS

18 crossover trials met the inclusion criteria. 9 trials involved oral (8 trials) or parenteral (1 trial) opioids (116 patients) and 9 involved nebulized opioids (177 patients). 9 trials of oral or parenteral opioids and 3 trials of nebulized opioids were included in a meta-analysis. Overall, opioids had a positive effect on the sensation of breathlessness (Table). When trials of oral or parenteral opioids and nebulized opioids were analyzed separately, only oral or parenteral opioids showed a positive effect (Table).

CONCLUSIONS

Oral and parenteral opioids are effective in the treatment of dyspnea. No beneficial effect is seen with nebulized opioids.

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Oral, parenteral, or nebulized opioids vs placebo for dyspnea*

Trials in meta-analysis	Number of trials	Standardized mean difference (95% CI)
All trials	12	–0.31 (–0.50 to –0.13)
Oral or parenteral opioids	9	–0.40 (–0.63 to –0.17)
Nebulized opioids	3	–0.11 (–0.32 to 0.10)†

*All trials were crossover trials. Follow-up not reported. CI defined in Glossary. A random-effects model was used.
†Not significant.

COMMENTARY

Opioids are commonly used to relieve dyspnea in palliative medicine, but their effectiveness is unclear. Jennings and colleagues did a systematic review that included a meta-analysis of the effectiveness of opioids in relieving dyspnea. Meta-analysis is necessary because of the small number of studies (only 18 were identified) and the small number of patients in each study (only 1 study had > 20 patients).

Overall, opioids showed a beneficial effect in relieving the sensation of breathlessness, but when the type of opioid was examined, only parental and oral opioids reduced breathlessness. Opioid receptors are abundant in the lung, and it has been suggested that nebulized opioids might relieve dyspnea or cough with minimal systemic effects (1). In this review, the nebulized opioids were ineffective compared with placebo in relieving the sensation of breathlessness. However, only 3 studies with 94 patients were combined in this analysis. It should be noted that the other 6 studies of nebulized opioids showed similar results but could not be included in the meta-analysis because of methodological or data insufficiencies.

Opioids were as effective in patients with chronic obstructive pulmonary disease (COPD) as in patients with cancer. Physicians have been reluctant to use opioids, especially in COPD, for fear of respiratory depression. However, 4 studies included in this review measured arterial blood gas tensions and reported no important changes during treatment. 9 studies that measured oxygen saturation also reported no important changes during treatment.

This review supports the use of oral and parenteral opioids to treat dyspnea in palliative care, but does not support the use of nebulized opioids. Furthermore, the review suggests that fear of respiratory depression may be exaggerated based on the data reported in the review. Nevertheless, the authors conclude that more studies are needed, which seems reasonable given the small numbers of studies and patients.

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Reference

1. **Zebraski SE, Kochenash SM, Raffa RB.** Lung opioid receptors: pharmacology and possible target for nebulized morphine in dyspnea. Life Sci. 2000; 66:2221-31.