Pharmacological management of breathlessness

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Session overview

• When should you use pharmacological intervention for the palliation of breathlessness?
• Drugs used for pharmacological management of breathlessness
• Consider the evidence for different drugs
• Balance of non pharm and pharm through the disease journey
Persistent or increasing dyspnea

Optimize bronchodilators, short and long-acting Oxygen

Non-pharmacological measures:
pursed-lip breathing, fan, relaxation, paced activities

Persistent or increasing dyspnea

Palliative pharmacological measures:
opioids, anxiolytics
Balance of Management Approaches

NonPh  NonPh  NonPh  Non-pharmacological
Pharm  Pharm  Pharm  Pharmacological

Dyspnoea on exercise  Dyspnoea at rest  Terminal dyspnoea

Wilcock, 1998
Optimize bronchodilators, short and long-acting Oxygen

Persistent or increasing dyspnea

Non-pharmacological measures: pursed-lip breathing, fan, relaxation, paced activities

Persistent or increasing dyspnea

Palliative pharmacological measures: opioids, anxiolytics

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Bronchodilators

• Bronchodilators are indicated for the palliation of breathlessness due to concurrent airflow obstruction

• The use of aerosol inhalers are preferred and should be tried before starting nebulisers unless patients are unable to manage this mode of delivery

(Hanks et al 2010)
Nebulised normal saline
Noseda 1997

• placebo-controlled, double-blind, randomized study

• 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 nebulisation

• Found greater effect in normal saline group on breathlessness
Steroids

- Steroids can result in a dramatic temporary improvement in the dyspnoea associated with lymphangitis carcinomatosis

- Use to alleviate breathlessness associated with bronchial compression by relieving peri tumour oedema

- Dexamethasone is usually the drug of choice because of its minimal salt retaining properties and relative potency compared to other steroids

(Hanks et al 2010)
Sildenafil

- For ILD patients with pulmonary hypertension secondary to respiratory disease

Others....

- Frusemide
- Beta-blockers
- Antibiotics
- Methylxanthines
- Oxygen
Persistent or increasing dyspnea → Optimize bronchodilators, short and long-acting oxygen

Persistent or increasing dyspnea → Non-pharmacological measures: pursed-lip breathing, fan, relaxation, paced activities

Persistent or increasing dyspnea → Palliative pharmacological measures: opioids, anxiolytics

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Drugs used

- Opioids
- Benzodiazepines eg lorazepam
- Antidepressants eg mirtazapine
- Nebulised furosemide
Opioids

- Fall in subjective feeling of breathlessness due to euphoria and anxiolytic properties of the drug
- Reduction in oxygen consumption and cardiac work load
- Reduction in the effect of carbon dioxide and oxygen levels on ventilation
- Direct reduction in respiratory drive with large doses
Opioids for the palliation of breathlessness in advanced disease and terminal illness. (Review)

Jennings AL, Davies AN, Higgins JPT, Anzueto-Cabeca J, Broadley KE

Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness (Review)

Barnes H, McDonald J, Smallwood N, Manser R
Opioids

- Use them first-line for palliative pharmacological management
- Use them for breathlessness at rest
- Consider them in anyone with severe SOB
- Always start laxatives and PRN antiemetic
Dosing and dose titration

- Marked improvement in 24hrs but benefit continued to increase over 6 days.
- Max 30mg/24hr
- Switch to sustained release ASAP.

Benzodiazepines

• Bind to a specific site on the GABA receptor

• Have hypnotic, sedative, anxiolytic and muscle relaxant actions

• Have also been shown to reduce hypoxic ventilatory drive
Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults (Review)

Simon ST, Higginson IJ, Booth S, Harding R, Bausewein C
Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study

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Abstract

Objective To evaluate the safety of benzodiazepines and opioids in patients with very severe chronic obstructive pulmonary disease (COPD).

Design Population based longitudinal consecutive cohort study.

Setting Centres prescribing long term oxygen therapy in Sweden.

Patients 2249 patients starting long term oxygen therapy for COPD in Sweden between 2005 and 2009 in the national Swedishox Register.

Main outcome measures Effects of benzodiazepines and opioids on rates of admission to hospital and mortality, adjusted for age, sex, arterial blood gases, body mass index (BMI), performance status, previous admissions, comorbidities, and concurrent drugs.

Results 1681 (76%) patients were admitted to hospital, and 1129 (50%) died under observation. No patient was lost to follow-up.

Benzodiazepines and opioids were not associated with increased admission hazard ratio 0.98 (95% confidence interval 0.97 to 1.0) and 0.98 (0.96 to 1.0), respectively. Benzodiazepines were associated with increased mortality (1.21, 1.06 to 1.30) with a dose response trend. Opioids also had a dose response relation with mortality: lower dose opioids (≤30 mg oral morphine equivalents a day) were not associated with increased mortality (1.03, 0.84 to 1.26) in contrast with higher dose opioids (1.21, 1.02 to 1.44). Concurrent benzodiazepines and opioids in lower doses were not associated with increased admissions (0.86, 0.53 to 1.42) or mortality (1.25, 0.78 to 1.99). Associations were not modified by being naive to the drugs or by hypercapnia.

Conclusions Lower dose opioids are not associated with increased admissions or deaths in patients with COPD and might be safe for symptom reduction in severe respiratory disease.

Introduction

Breathlessness is a major cause of impaired activity and quality of life, affecting as many as a fifth of people aged over 65.1, 2 Chronic obstructive pulmonary disease (COPD) is a major cause of breathlessness, morbidity, and mortality. Worldwide, more than 300 million people have COPD, many of whom have breathlessness that affects their daily life for many years.2, 3 Breathlessness predicts mortality in COPD, to a stronger degree than impairment of lung function.3 The burden of breathlessness increases with increasing age and severity of the respiratory disease; 98% of patients with end stage respiratory disease experience breathlessness, which persists at rest or on minimal exertion, despite optimal treatment of the underlying disease (chronic refractory breathlessness).3 Patients with severe COPD are more breathless than patients with advanced lung cancer and are breathless for longer periods of time.4 Randomised trials have shown that oral sustained release morphine can relieve chronic refractory breathlessness.7, 8 Whether benzodiazepines reduce breathlessness is not clear, and their safety in this setting is unknown. Benzodiazepines are also used to treat anxiety and opioids to treat pain, conditions that are highly prevalent in patients with severe COPD.9 A concern among clinicians is that benzodiazepines and opioids alone or in combination could cause adverse events, including respiratory depression, confusion, falls, and even premature death in patients with respiratory compromise. Risks might be higher in frail patients, especially if they have not previously been treated with either or both drugs, and in people with severe COPD and hypercapnia. These concerns are cited by clinicians as an obstacle to prescribing these drugs and might contribute to less than optimal management of breathlessness.10, 11
Benzodiazepines

- Lorazepam 0.5-1mg sl/po prn
- Diazepam 2-5mg nocte
- Diazepam 2-5mg tds
- Midazolam 2-5-5mg sc stat
- CSCI
Antidepressants

- Antidepressants, such as selective serotonin re-uptake inhibitors and tricyclic antidepressants have been investigated.
- Serotonin affects the modulation of central respiratory control and sensitivity to carbon dioxide.
- Reduction in breathlessness in healthy volunteers using SSRIs.
Antidepressants

• Sertraline
  Phase 3 RCT of sertraline vs placebo
  Currow et al 2017

• Mirtazepine
  BETTER-B
  Feasibility double blind multi-site RCT
  Higginson et al
Nebulised frusemide

- Depressant effect on C-fibres and vagal irritant receptors such as pulmonary stretch receptors
- Prolongs breath holding time and alleviates experimentally induced dyspnoea in normal volunteers
- Effect does not seem to be related to diuresis
Nebulised frusemide

- Jensen et al 2008
  - 20 COPD- crossover RCT
  - Statistically significant benefit in BORG
- Sheikh Motahar Vahedi 2013
  - 100 COPD during exacerbation- RCT
  - Statistically significant benefit in mean VAS for dyspnoea
- Wilcox 2008
  - 15 patients with lung cancer- randomised to receive either nebulised saline or frusemide
  - No benefit seen
Others....

• Cannabinoids

• Levomepromazine

• Herbal remedies
Summary

• Assess clinical stage of patient when considering ration of pharm/non-pharm management
• Consider using steroids, frusemide, nebulisers followed by non-pharm measures
• Use opioids as first line palliative pharm management
• Consider starting on 5mg BD MR morphine (with laxative) and do not increase for 6 days
• If element of anxiety, only use BDZ in short term whilst starting long-term anxiolytic/treating depression
Palliative Care in Respiratory Disease

Edited by Claudia Bausewein, David C. Currow and Miriam J. Johnson