Nebulisers for chronic obstructive pulmonary disease

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Definition of chronic obstructive pulmonary disease

In this paper the term “chronic obstructive pulmonary disease” (COPD) is used as defined in the forthcoming British Thoracic Society guidelines for the management of COPD (1997) as a chronic slowly progressive disorder characterised by airways obstruction (reduced forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC)) which does not change markedly over several months. Most of the lung function impairment is fixed, although some reversibility may be produced by bronchodilator (or other) therapy.

The guidelines indicate that, in practice, a diagnosis of COPD requires a history of chronic progressive symptoms such as cough, wheeze and/or breathlessness without intervening periods of “wellness”, usually a cigarette smoking history of more than 20 pack years, and objective evidence of airways obstruction (ideally verified by spirometric testing) that does not return entirely to normal with treatment.

Acute exacerbations of COPD

Current clinical practice is based largely on tradition rather than on careful clinical trials. Although patients with COPD are considered to have relatively static lung function, most have some reversibility and peak flow will often show a modest rise during the first few days in hospital. For example, Rebuck et al found that, in 51 patients with COPD, the mean peak flow increased from 70 l/min to 95 l/min (36% rise) 90 minutes after treatment with a nebulised bronchodilator, and a later study reported a rise of 19% in mean peak flow from 113 l/min to 134 l/min in 47 patients with COPD after nebulised bronchodilator treatment. These studies demonstrate that patients with acute exacerbations of COPD can respond to high doses of bronchodilator drugs.

Several studies have suggested that patients with acute asthma or COPD may respond better to treatment with a β agonist given by nebuliser than by metered dose inhaler. However, other authors have suggested that treatment with a metered dose inhaler (given through a spacer device) may be as effective as nebulised treatment in the acute situation. It is difficult to compare these results directly as the patient groups and inhaler devices were different and most studies have contained relatively small numbers of patients, making it difficult to draw definite conclusions about the difference between treatments. However, it is generally agreed that the bronchodilatation obtained is largely a reflection of the dose of bronchodilator administered rather than the mode of administration. It is therefore unlikely that treatment with either a nebuliser or a metered dose inhaler will give superior results for most patients provided similar doses are given to the lungs by each device. The question therefore becomes one of convenience and cost.

For low dose bronchodilator therapy – for example, 100–400 µg salbutamol or terrbutaline – treatment with a metered dose inhaler is more convenient whilst a nebuliser can deliver higher doses more easily. A nebuliser has the further advantage of being independent of effort or breathing pattern when a patient is distressed. This means that a patient can begin nebulised treatment using a mask or a mouthpiece while the medical attendant can continue with other tasks. The use of a metered dose inhaler in this situation would require the medical attendant (or respiratory therapist or nurse) to stand by the patient and supervise or administer multiple doses of treatment, possibly more than 20, at one minute intervals. Breathless patients are less likely to be able to inspire slowly or breathe hold for optimum lung deposition from a metered dose inhaler.

The optimum dose of bronchodilator treatment (β agonist or anticholinergic) in acute COPD is not known. Mestitz et al showed that terbutaline was equally effective given by metered dose inhaler or nebuliser and the dose response was still rising at 40 mg. However, doses of β agonist above 5–10 mg tend to be associated with unacceptable side effects such as tachycardia or palpitations. Gross and colleagues showed that the optimum response to ipratropium bromide occurred at 0.4–0.6 mg. A review of practice in Britain shows that salbutamol or terbutaline (5 mg), with or without ipratropium bromide (0.25–0.5 mg), is usually administered to patients with acute airflow obstruction. This would require 50 inhalations of salbutamol followed by 25 inhalations of ipratropium bromide via a metered dose inhaler. Most doctors mix salbutamol and ipratropium bromide respirator solutions in a single nebuliser chamber and administer it immediately. It has recently been suggested that the Turbohaler dry powder device may be used effectively by patients with severe airflow obstruction. This would allow the administration of 5 mg (10 puffs) or 10 mg (20 puffs) of terbutaline almost as conveniently as with a nebuliser.

Nebulised treatment might have a further beneficial effect due to its physical properties. Inhaled droplets may alter mucus viscosity
the airways and nebulised terbutaline or saline may help patients with bronchiectasis to expectorate. However, the maximum bronchodilator response to β agonists and anticholinergic agents may not occur until very high doses are reached (more than 20 puffs of terbutaline or ipratropium bromide). With these doses it is more convenient (and less expensive) to deliver the medication by small volume nebuliser.

Other patients may benefit from the physical properties of nebulised treatment. Nebulised terbutaline aids sputum clearance in patients with bronchiectasis. Differing particle size and particle distribution in the airways may produce different responses to treatment with nebulisers and metered dose inhalers even if the same dose is given. In one study a group of patients with COPD who had a higher peak flow and sputum clearance after nebulised drugs than to the same drugs given by metered dose inhaler and spacer. However, other patients had a higher subjective and objective response to the lower dose of treatment given by metered dose inhaler and spacer. These differences may be due to the different distribution of particles in the airways between patients. The dose of inhaled drug available for systemic absorption also differs between a metered dose inhaler and a nebuliser and this could increase or decrease the systemic effects for the same dose.

EVIDENCE FROM CLINICAL TRIALS OF BRONCHODILATOR TREATMENT IN COPD

Given the different (medication and inhaler skills) of different patients, and the variable performance characteristics of different inhaler and nebuliser devices, it is hardly surprising that clinical trials of home nebulisers in COPD have yielded conflicting results. Some authors have shown that nebulisers were superior to metered dose inhalers based on improvements in spirometric values and symptoms. Some other studies nebulisers and metered dose inhalers were found to be equally effective. Some of the differences in these studies can be explained by differences in patient groups and doses and devices. For example, Jenkins et al excluded patients who did not have a satisfactory response to conventional metered dose inhaler treatment, whereas these are presumably the patients who are most likely to benefit from high dose nebuliser treatment. There are also methodological problems with home nebuliser trials as there is no perfect placebo for a nebulised treatment (nebulised saline might alter airway calibre or mucus clearance). Morrison et al compared nebulised saline with nebulised ipratropium bromide and fenoterol in a double blind, randomised, placebo controlled study. The mean daily peak flow (PEF) rose by 19% (from 164 to 196 l/min) on the active nebuliser treatment compared with nebulised saline supplemented by "rescue" metered dose inhaler bronchodilator therapy. This improvement in PEF was sustained identical to that observed by O’Driscoll et al. These studies suggest that there is, indeed, a small population of patients with severe COPD who derive greater subjective and objective
benefit from a high dose nebulised broncho-
dilator than from lower dose metered dose
inhaler treatment.

**PATIENT ASSESSMENT**

Details of home nebuliser assessment for
patients with COPD are given in the guidelines
on page S10. The key steps are:

1. An assessment by a respiratory specialist to
confirm the diagnosis of COPD and to explore
other treatment options. An assessment needs
to be made also of a patient’s ability to use
hand held inhalers.
2. A recording of baseline home peak flow
taken twice daily on the patient’s usual inhaled
treatment.
3. A trial of treatment with an oral steroid, if
not already done.
4. A trial of high dose treatment by hand held
inhaler – for example, a dry powder device or
metered dose inhaler and spacer with 1 mg
terbutaline or 400 μg salbutamol and 160 μg
ipratropium bromide four times daily.
5. A formal trial of a home nebuliser – for
e.g., 2.5–5 mg salbutamol or 5–10 mg ter-
butaline four times daily or ipratropium brom-
ide 0.25–0.5 mg four times daily or a
combination of these treatments.
6. A careful assessment of the patient’s re-
sponse to these treatments over at least two
weeks each. Laboratory based single dose re-
versibility studies will not identify patients who
should be given home nebuliser therapy and
such trials cannot identify the best treatment
options for individual patients.6,7
7. After an assessment process the clinician
must decide with the patient if the nebuliser
has produced subjective and ob-
jective benefit. The doctor and patient need to
discuss whether the degree of benefit is suf-
cient to justify the high cost and incom-
venience of home nebuliser therapy.

**SIDE EFFECTS AND OUTCOME**

Safety issues are important when patients are
given high dose treatment at home. There has
been considerable concern about the use of
high dose β2 agonists in patients with asthma
and the same concerns (arrythmias, tachy-
phylaxis, failure to call in an emergency) apply
to patients with COPD. Patients with severe
airflow obstruction taking high doses of
therapy are more likely to die of their disease
than patients with milder disease taking stand-
ard doses. This is likely to be a marker of
disease severity rather than an effect of the
drugs themselves. Studies of asthma deaths
have found no evidence for direct toxicity of the
bronchodilator drugs.8,9

Little is known about the long term prognosis
of patients with COPD who use home nebu-
lisers. The drugs might be toxic in high doses,
especially in patients with coexistent cardiac
disease, due to an intrinsic cardiac effect or to
indirect effects such as hypokalaemia. How-
ever, deaths from arrhythmias have not been
widely reported among home nebuliser users. It
is suggested that ECG monitoring is a sensible
precaution when the first dose of nebulised bronchodilator is given to a patient with known
ischaemic heart disease or cardiac arrhythmias.
Perhaps the greatest danger is over reliance by
patients on home nebulisers rather than the
summoning of medical help in an emergency.
The frequency with which this happens is not
known. Other theoretical hazards include the
development of tachyphylaxis during pro-
longed administration, although there is no
evidence for this in clinical practice,10 and
the risk (which largely applies to hospitalised
patients with acute COPD) of giving prolonged
nebulised treatment driven by pure oxygen to
patients who have type II respiratory failure
thus worsening carbon dioxide retention. Care-
ful attention to limiting the duration of nebu-
lisation and the use of air driven nebulisers in
selected patients should avoid this hazard,
which in practice is rarely a significant problem.
The life expectancy of patients with severe
COPD is mainly determined by the severity of
their airflow obstruction.4 A recent study has
shown that the five year survival of patients
using nebulisers and metered dose inhalers was
similar.11 These patients had similar FEV1,
values on entry to the study (0.88 l) and the
five year mortality was approximately 46%,
most deaths being due to respiratory failure or
lung cancer with the risk of death being directly
related to the patient’s initial FEV1. These data
provide some reassurance as they suggest that
the excess mortality amongst nebuliser users in
cross sectional studies is probably due to disease
severity rather than treatment.

If ipratropium bromide is used, patients with
prostatism should use the smallest possible dose
to reduce the risk of acute urinary retention
and patients with a history of glaucoma should
use a mouthpiece rather than a face mask. If a
face mask must be used every care should be
taken to keep the droplets of medication away
from the eyes. For example, the mask should
be taped over using adhesive tape.

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