Nebulisers: their effectiveness, indications and limitations

Robin Johns *MRCP* ***and C Michael Roberts*** *MA, MD, FRCP*

VM

Figure 1. Mouthpieces are recommended for nebulisation of steroids and anticholinergics to prevent deposition of these agents on the skin or in the eyes

The authors describe the indications and adverse effects of nebulisers and show how careful assessment can identify those patients who will benefit.

Nebulisers are devices used to deliver atomised particles of drug to the airways. Atomisation is achieved using either a pressurised gas source (jet nebuliser) or ultrasonic energy (ultrasonic nebuliser). Nebulisers are in common use for a wide range of respiratory conditions.

How nebulisers work

In a jet nebuliser (see Figure 2) a compressor or pressurised gas source generates air or gas that is forced through a narrow hole (venturi) as a high-velocity jet. An area of low pressure occurs immediately adjacent to this jet that passes over a narrow liquid feed tube. Drug solution is sucked up from a reservoir below the feed tube and atomisation of the solution ensues.[1] The jet, now composed of pressurised gas and atomised solution, impacts on an obstruction known as a baffle; this action generates smaller respirable particles while larger ones fall back into the reservoir of liquid to be reatomised.

Ultrasonic nebulisers (see Figure 3) use a power source to rapidly vibrate an electrically polarised (piezoelectric) crystal within a reservoir of drug solution or suspension. Standing waves are formed on the surface of the liquid. Small droplets break free from these waves and are released as an aerosol. Ultrasonic nebulisers are more expensive and less able to aerosolise the more viscid drug suspensions. They are, however, faster and maintain a more constant aerosol drug concentration than their jet counterparts.

The size of respirable particles generated by a nebuliser is important, as particles that are too large (>5µm) may be deposited in the upper airway and subsequently swallowed, whereas particles that

are too small (<0.5µm) may be exhaled without depositing in the lung at all. Nebuliser design is critical to the generation of particles of respirable size. Comparison of available nebulisers confirms that not all are equal either in the time taken to complete nebulisation or in efficacy of lung deposition.[2]

Choice of nebuliser

A list of available nebulisers and their costs is provided in the *BNF*. Choice must take into consideration effective matching of chamber and compressor, cost, ease of use and ease of maintenance. Currently there are no national recommendations for choice of nebuliser but advice can be sought from the local hospital respiratory team. Nebulisers are available from a number of major medical suppliers and pharmacies, or can be bought via the internet at very competitive prices.

Unlike the units commonly used in hospitals and driven from cylinder air or wall oxygen, those used in the community are lightweight, portable units with their own integral compressor or ultrasonic device. Most require mains electricity as the power source, but some can be powered from batteries including plug-in adaptors for (ironically) car cigarette lighter sockets.

Nebulised drug can be administered either through a mouthpiece (see Figure 1) or mask, and both are considered to be equally effective. Face-masks are preferred for infants, young children and in emergency scenarios for ease of use. Mouthpieces are recommended for nebulisation of steroids and anticholinergics to prevent deposition of these agents on the skin or in the eyes where the latter has been linked with exacerbation of glaucoma.

For a standard nebuliser, only about 10 per cent of aerosolised drug may reach the lungs. Metered-dose inhalers and dry powder inhalers are comparable with nebulisers in terms of particle sizes and deposition rates when used optimally. Unlike nebulisers, however, inhaler devices are effort-dependent, and poor technique can render them ineffective. In

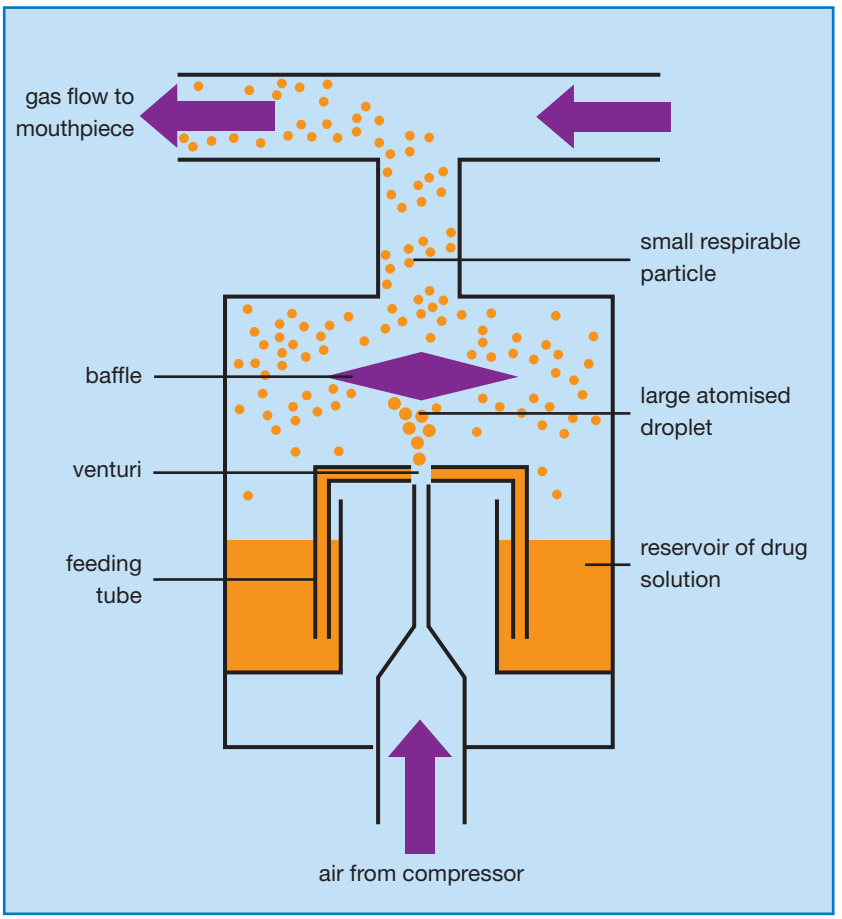

Figure 2. Jet nebuliser design. Compressed air or pressurised gas is forced through a narrow hole (venturi). Negative pressure adjacent to this fast-flowing jet sucks liquid up from a reservoir into the jet via feeding tubes. The liquid is atomised into large particles that impact on a baffle to generate smaller respirable particles

circumstances when inhalers cannot be used effectively, nebulisers can deliver guaranteed larger doses of drug to the lungs.

Indications for nebulisers

Nebulisers can be used to administer a number of drugs for specific conditions, as listed in Table 1. The only categorical indications for nebuliser use are when the drug needed is not available in any other form or when the patient is unable to use alternative delivery devices, *eg* some children and older patients, and in emergency department patients *in extremis*. Relative indications are when large volumes of drug need to be delivered or when convenience dictates.

The evidence for the beneficial use of nebulisers in other settings is extremely limited. Even within the emergency room, where nebulisers are routinely used to deliver large doses of bronchodilators, there is no benefit compared to similar doses delivered via spacer devices in terms of hospital admission rates and time to discharge.[3]

It remains conventional practice to administer bronchodilators via nebuliser to extremely ill patients who may not be able to easily use a spacer device and where equal dose delivery may be impractical. To deliver an equivalent amount of nebulised salbutamol (5mg) would require 50 separate actuations of a 100µg metered-dose inhaler.

There is some limited evidence to suggest that corticosteroids might be more effective in chronic asthma or chronic obstructive pulmonary disease (COPD) when administered via nebuliser. In one study in patients with asthma, budesonide (Pulmicort) given by jet nebuliser was associated with increased peak expiratory flow rate, reduced symptom scores, and reduced use of rescue beta-agonists compared to inhaler and spacer.[4]

In a separate retrospective cohort study of 2178 patients with asthma or COPD who were over 50 years of age, administration of steroids via nebuliser was associated with less visits to the emergency department and less use of systemic steroids than the period prior to their use.[5]

A Cochrane review of the evidence in asthma, however, concludes there is insufficient evidence to make a recommendation for use of nebulised steroids,[4] and no evidence for benefit with nebulised beta-agonists in either acute[3] or chronic asthma.[6]

The more justifiable use of nebulisers may be in the administration of drugs that cannot otherwise be delivered directly to the lungs. For example, nebulisers are employed to administer mucolytic and antimicrobial agents in bronchiectasis and cystic fibrosis. In this setting, they are particularly useful in being able to administer large volumes of drug, and to aerosolise agents that are often in viscous solutions.

Nebulised hypertonic saline has been shown to improve mucociliary clearance and lung function in patients with cystic fibrosis.[7] Nebulised antibiotics are useful in reducing exacerbation rates in both patients with cystic fibrosis

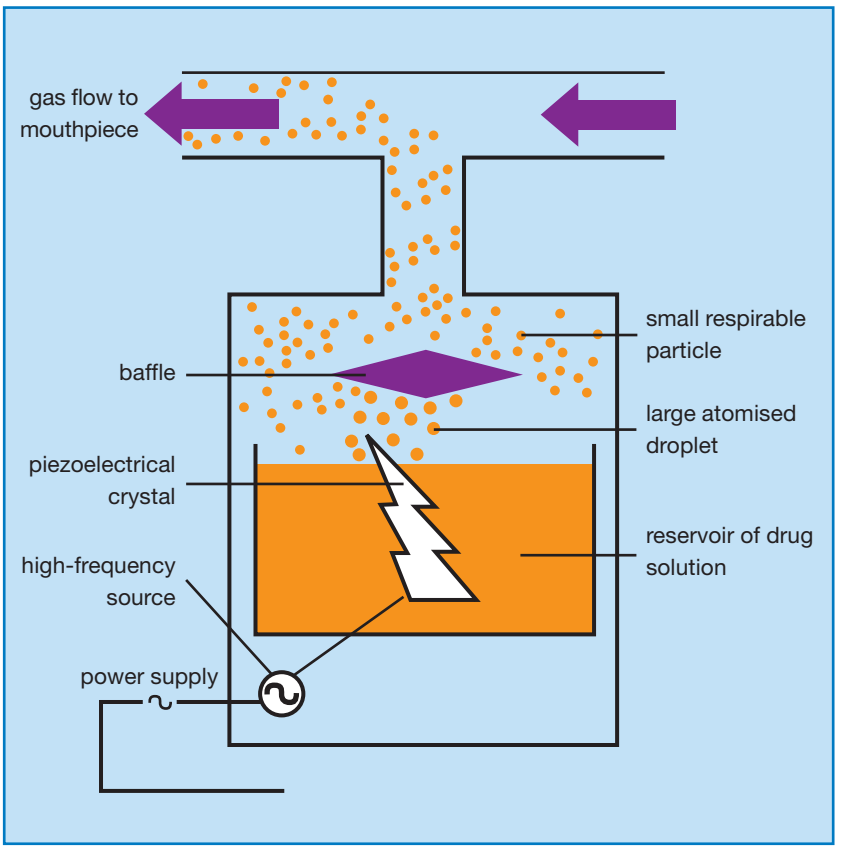

Figure 3. Ultrasonic nebuliser design. A power supply is used to drive a high frequency source that vibrates a piezoelectrical crystal within a reservoir of liquid. Large droplets break free from standing waves that form on the surface of the liquid, and these impact on a baffle to create smaller respirable particles

and those with bronchiectasis colonised with *Pseudomonas*.[8] Nebulised recombinant human DNase/dornase alpha (Pulmozyme) breaks down DNA in viscid sputum and is used to improve sputum clearance and pulmonary function in both conditions.

For patients with HIV, nebulised pentamidine (Pentacarinat) may be effective as secondary prophylaxis against *Pneumocystis* pneumonia.[9] It is, however, less effective than oral co-trimoxazole, with higher relapse rates mainly in the relatively poorly ventilated upper lobes. Nebulised hypertonic saline helps provide deep cough-induced sputum for the diagnosis of *Pneumocystis*.

Nebulised morphine has been utilised to palliate breathlessness in terminally ill patients with lung cancer, COPD and interstitial lung disease. Similarly, nebulised local anaesthetics such as lidocaine have been used to palliate dyspnoea and cough. The evidence for effectiveness is poor outside of a few trials in cancer patients, and a recent Cochrane review concluded that there was little benefit of nebulised morphine on the perception of dyspnoea associated with severe interstitial lung disease.[10]

Nebuliser assessment

The decision to consider nebulised therapy in primary care is most likely to occur within the context of COPD and occasionally chronic severe asthma. The National Institute for Health and Clinical Excellence (NICE) guideline concerning management of COPD[11] is clear and suggests that nebulisers should only be considered in patients with distressing or disabling breathlessness despite maximal therapy.

Continued prescription of medication is only justified if its use is associated with a reduction in symptoms, an increase in the ability to undertake activities of daily living, an increase in exercise capacity, or an improvement in lung function. While the measurement of FEV_1 (forced expiratory volume over one second) is critical to the diagnosis of COPD it varies little with bronchodilator administration but sometimes functional improvement may be demonstrated with an increase in vital capacity or forced vital capacity.

The key judgement for most is the patient's perceptions of benefit, including reduced symptoms and fewer visits to their GP or hospital.[12] To best estimate any benefits or otherwise of nebulised therapy, a formal trial with recording of symptoms and functional changes, together with lung function, is advised.

An example of a nebuliser trial for bronchodilator therapy is shown in Table 2. Peak flow readings are measured twice daily (with additional spirometry at the start and end of the trial in COPD patients) over four weeks. During the first week bronchodilators are administered via inhaler plus large volume spacer. During the subsequent three weeks, different combinations of bronchodilator are used via nebuliser to identify the most effective agents.

There are no independently validated outcomes for a positive trial, so each case should be taken individually with reference to the NICE parameters above. One practical

Indication	Common disease setting	Nebulised drug	Drug effect
bronchial narrowing	asthma/COPD	salbutamol/ terbutaline	bronchodilator
bronchial narrowing	asthma/COPD	ipratropium bromide	bronchodilator
airway inflammation	asthma/COPD	budesonide/ fluticasone	anti-inflammatory
airway inflammation	asthma	cromoglicate	anti-inflammatory
viscous/retained secretions	cystic fibrosis/ bronchiectasis	normal saline (0.9%)	loosens secretions
viscous/retained secretions	cystic fibrosis/ bronchiectasis	hypertonic saline (3-7%)	loosens secretions
viscous/retained secretions	cystic fibrosis	DNase/dornase alpha	liquifies secretions by DNA lysis
airspace *Pseudomonas* colonisation/ infection	cystic fibrosis/ bronchiectasis	colistimethate sodium/ tobramycin	reduces exacerbations
Pneumocystis pneumonia prophylaxis	HIV	pentamidine	reduces relapse rates
(terminal) dyspnoea	COPD/lung cancer	morphine	may relieve dyspnoea
(terminal) cough and dyspnoea	COPD/lung cancer	lidocaine	may relieve cough and dyspnoea

Table 1. Potential indications for nebuliser therapy

approach is for the patient to maintain a symptom diary with daily entries that may reveal a pattern of use and response, or otherwise, to treatment. Nebuliser prescription should then only be recommended if the patient also perceives potential benefit.

Week 1	bronchodilators via inhaler plus large volume spacer
Week 2	salbutamol 5mg 4 times daily (nebuliser)
Week 3	ipratropium bromide 500mg 4 times daily (nebuliser)
Week 4	combined salbutamol and ipratropium 4 times daily (nebuliser)

Table 2. Nebuliser trial for bronchodilator therapy

Problems with nebuliser therapy

Nebulisers not only have limited beneficial effects but also some less appreciated dangers. High doses of salbutamol may cause tremor, tachycardia, hypokalaemia, hyperglycaemia, and prolongation of the QT interval that can precipitate tachyarrhythmias. Administration of bronchodilators in hypoxic patients may lead to pulmonary venous shunting and exacerbate hypoxia.[13] Nebuliser use in acute severe asthma and COPD should therefore include simultaneous oxygen administration.

Nebulised ipratropium bromide has been linked to worsening narrow-angle glaucoma, and high-dose nebulised corticosteroids with cataract formation and systemic steroid side-effects. The anti-pseudomonal antibiotic colistimethate sodium may cause bronchospasm and should be preceded by administration of salbutamol and initiated at a low dose.

Funding

Nebulisers can be provided by secondary-care units free to patients after specialist recommendation and this should be the usual mechanism of supply. The advent of primary-care airways clinics and general practitioners with a special interest in respiratory disease challenges primary care organisations to provide alternative supply mechanisms.

Some patients opt to buy their own nebuliser machine without seeking guidance on the type or delivery characteristics. The costs of drugs used in nebulisers far outweigh those of the nebuliser purchase itself so should only be provided if assessment suggests benefit. While maintenance of the unit itself is relatively simple, written guidance should be provided to patients on cleaning and the need for an annual service.

Conclusions

Nebulisers are devices able to effectively deliver a variety of aerosolised drugs to the lung. They are indicated when there are no alternative delivery systems for a particular drug or when a patient is unable to use an alternative delivery system such as inhalers. Nebulisers are

most commonly used in airways disease when a larger dose of drug may be delivered more quickly.

In many, but not all, instances, however, nebulisers offer little benefit over simple inhalers and may have significant adverse consequences. Careful assessment should therefore be made of individual response to nebulised therapy to identify those few patients who will obtain meaningful benefit from long-term treatment.

Resources

- Current best practice for nebuliser treatment. The Nebulizer Project Group of the British Thoracic Society Standards of Care Committee. *Thorax* 1997;52 Suppl 2:S1-3 (erratum in: *Thorax* 1997;52:838).
- Management of chronic obstructive pulmonary disease in primary and secondary care. NICE Clinical Guideline 12, 2004.
- British guideline on the management of asthma. British Thoracic Society and the Scottish Intercollegiate Guidelines Network. *Thorax* 2003;58(Suppl): i1-i94.
- asthma.org.uk/all_about_asthma/medicines_treatments/nebulisers.html.

References

1. O'Callaghan C, Barry PW. The science of nebulised drug delivery. *Thorax* 1997;52(Suppl 2):531-44.
2. Loffert DT, Ikle D, Nelson HS. A comparison of commercial jet nebulisers. *Chest* 1994;106:1788-92.
3. Cates CJ, Crilly JA, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev* 2006, Issue 2. Art. No.: CD000052.
4. Cates CJ, Bestall J, Adams N. Holding chambers (spacers) versus nebulisers for inhaled steroids in chronic asthma. *Cochrane Database Syst Rev* 2006, Issue 1. Art. No.:CD001491.
5. Marcus P, Oppenheimer EA, Patel PA, *et al.* Use of nebulized inhaled corticosteroids among older adult patients: an assessment of outcomes. *Ann Allergy Asthma Immunol* 2006;96(5): 736-43.
6. Brocklebank DM, Ram FSF, Muers M, *et al.* Nebulisers versus hand-held

inhalers to deliver beta$_2$-agonist bronchodilator drugs in non-acute asthma. *Cochrane Database Syst Rev* 1999, Issue 4.
7. Wark PAB, McDonald V, Jones AP. Nebulised hypertonic saline for cystic fibrosis. *Cochrane Database Syst Rev* 2006, Issue2. Art. No.: CD001506.
8. Ryan G, Mukhopadhyay S, Singh M. Nebulised anti-pseudomonal antibiotics for cystic fibrosis. *Cochrane Database Syst Rev* 2006, Issue 2. Art. No.:CD001021.
9. McIvor RA, Berger P, Pack LL *et al.* An effectiveness community-based clinical trial of respirgard II and fisoneb nebulizers for *Pneumocystis carinii* prophylaxis with aerosol pentamidine in HIV-infected individuals. Toronto Aerosol Pentamidine Study (TAPS) Group. *Chest* 1996;110(1): 141-6.
10. Polosa R, Simidchiev A, Walters AH. Nebulized morphine for severe interstitial lung disease. *Cochrane Database Syst Rev* 2006,Issue 2. Art. No.: CD002872.
11. *Management of chronic obstructive pulmonary disease in primary and secondary care.* NICE Clinical Guideline 12, Feb 2004.
12. Barta SK, Crawford A, Roberts CM. Survey of patients' views of domiciliary nebuliser treatment for chronic lung disease. *Respir Med* 2002;96:375-81.
13. Burggraaf J, Westendorp RG, in't Veen JC, *et al.* Cardiovascular side effects of inhaled salbutamol in hypoxic asthmatic patients. *Thorax* 2001;56(7):506-7.

Dr Johns is specialist registrar in respiratory and general internal medicine at Whipps Cross University Hospital, and Professor Roberts is a consultant respiratory physician and professor of medical education at Whipps Cross University Hospital, and Barts and The London, Queen Mary's School of Medicine and Dentistry, London

InfoPOEMs

InfoPOEMs® Daily Doses of Knowledge™

SSRIs effective for depression after one week

Bottom Line:
Treatment of unipolar depression in adults with SSRIs significantly improves symptoms in as quickly as one week. (LOE = 1a-)

Reference:
Taylor MJ, Freemantle N, Geddes JR, *et al.* Early onset of selective serotonin reuptake inhibitor antidepressant action. *Arch Gen Psychiatry* 2006;63: 1217-23.

Study Design: Systematic review **Funding:** Industry and government **Setting:** Various (meta-analysis)

Synopsis:
Most clinicians believe that it takes two to three weeks of therapy with SSRIs before patients with depression improve. These investigators thoroughly searched multiple databases including MEDLINE, EMBASE, PsychLIT, The Cochrane Registry of Controlled Trials, reference lists of identified articles and other systematic reviews, and conference proceedings for randomised trials comparing SSRIs with placebo for the treatment of unipolar depression in adults. No language restrictions were applied. Where possible, standardised treatment effect sizes were calculated for each study at weekly intervals.

From an initial search yielding 500 citations, 50 trials comprising 6153 participants receiving SSRIs and 3968 receiving placebo met inclusion criteria. The methodologic quality of the individual trials was of moderate to high quality. Only one individual performed the search. Twenty articles provided data that could be analysed for symptom scores at multiple periods. Various methods were used to rate treatment effects. Overall, a statistically significant positive treatment effect of SSRIs compared with placebo was evident in as early as one week. In one model, the degree of improvement was greatest in the first week with a gradual decline in the magnitude of incremental benefit in later weeks. In a different model, the effect was evident in the first week, with stronger effects occurring in later weeks. No formal assessment was performed to check for publication bias or whether the results of the independent trials were homogeneous.

POEM (Patient Orientated Evidence that Matters) editors review more than 1200 studies monthly from over 100 medical journals, presenting only the best as InfoPOEMs. The POEMs process applies specific criteria for validity and relevance to clinical practice. About 1 in 40 studies qualifies.
For more information visit: **www.infopoems.com**