Wastage of drug from nebulisers: a review

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Jet nebulisers are traditionally the oldest devices used to generate therapeutic aerosols. Originally made of glass and operated by manually compressing a handbulb in a similar manner to a perfume spray, they are now mass-produced by injection-moulding of plastic and operated by a continuous flow of compressed air or oxygen from a cylinder, compressor or even a footpump.

In spite of their bulk, the popularity of jet nebulisers has not waned even though smaller, more portable devices have been introduced such as metered-dose inhalers and dry-powder inhalers. This is probably because they are simple to use, require neither hand-lung coordination nor a controlled inhalation manoeuvre, and are consequently suitable for small children and severely dyspnoeic patients. In addition, nebulisers may be used to administer large doses of drugs or even mixtures of drugs conveniently, including some drugs which are not available in other aerosol-generating devices. Also there may be psychological benefit when the patient observes a visible mist which is inhaled during tidal breathing.

Although it is generally accepted that nebuliser therapy is effective in the treatment of chronic obstructive airways disease, grave concern has been expressed over its indiscriminate use without adequate supervision[1]. In the treatment of asthma, this concern in part arises from patients' misplaced confidence that nebuliser therapy will correct a life-threatening exacerbation. Further concern results from the magnitude of bronchodilator dose required for use with nebulisers compared with equivalent doses from metered-dose inhalers. For example, the standard dose of terbutaline from a metered-dose inhaler is 250 μg per puff (2 puffs = 0.5 mg) compared with the 5 mg dose placed in a nebuliser. Consequently there is a tenfold difference between the standard two puffs from a metered-dose inhaler and one inhalation treatment from a nebuliser.

It is often assumed that the starting dose (i.e. the dose placed in a nebuliser) represents that delivered to the lung, but several studies have shown that this is not the case and as little as 1% has been reported as delivered to the lung[2].

There are three main sites of wastage of respirator solution during nebuliser therapy which may account for the magnitude of the original dose placed in the device prior to use.

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Nebuliser wastage

During nebulisation, the solution is drawn up a feed-tube within the nebuliser and broken up into droplets by the compressed air. The aerosol produced is heterodisperse in size and is filtered within the nebuliser by baffles to remove the largest droplets. These large droplets coalesce on the baffles and may fall back into the reservoir to be recirculated[3]. However, some of the solution remains trapped on the baffles and is not recirculated; this represents a significant proportion of the original dose. Further, the trapped solution is more concentrated than the original solution due to evaporation of solvent. We have found that the volume of respirator solution trapped in this manner is directly related to the original volume used[4]. Although it is common practice to use a 2 ml fill with nebulisers to minimize administration time, by so doing over 50% of the volume is trapped in the nebuliser. If, however, the volume fill is increased to 4 ml, 60% is released as aerosol and only 40% retained in the nebuliser. The trapped droplets of respirator solution may be encouraged to fall back into the reservoir of the nebuliser by tapping the walls to dislodge them, though in practice this is rarely done. It is also common practice to stop the nebuliser as soon as aerosol release becomes sporadic, but at this point much respirator solution may still be left in the nebuliser.

Aerosol released during exhalation

Most nebulisers are operated continuously during therapy, the compressed air source being switched off at the end of nebulisation only. However, the aerosol released from the nebuliser is only available for inhalation while the patient is breathing in and any aerosol released from the nebuliser during exhalation is wasted. As inhalation occupies one-third of the respiratory cycle (and often less in disease), at least two-thirds of the aerosol released from the nebuliser is not available for inhalation. Consequently, of the 60% of the dose which left the nebuliser (following a 4 ml fill), only one-third (20% of the original dose) is available for inhalation.

Aerosol wastage during exhalation may be eliminated by using a triggering device which allows the compressed air driving the nebuliser to be diverted away from the nebuliser except when directed by the patient. A few makes of nebuliser are supplied with such devices, usually in the form of a T-piece situated near the air inlet of the nebuliser, but their use requires considerable hand-lung coordination and may not be suitable for many patients. Triggering devices may be particularly useful in the nebulisation of antibiotics, where the aerosol released from the nebuliser during exhalation has to be vented away.

Extrapulmonary aerosol deposition

Twenty percent of the original starting dose of respirator solution may be inhaled by the patient. How-

Table 1. Fate of a 4 ml dose of respirator solution during continuous nebulisation

Site of wastage	*Remaining dose*	*Remedy*
40% retained in nebuliser	60%	Tap walls of nebuliser
66% released in exhalation	20%	Use triggering device
25% aerosol exhaled	15%	Breath-hold
20–60% aerosol too large to reach airways	7–12%●	Minimize aerosol size

● Dose to lung.

ever, not all of this aerosol will deposit in the lungs. Several factors affect the site and amount of aerosol retained in the lung. Residence time of the aerosol within the respiratory tract directly affects the amount of aerosol deposition[5]. It has been found that for nebulised aerosols inhaled during tidal breathing (14 breaths per minute with inspiration lasting one-third of the respiratory cycle and a tidal volume of 700 ml), one-quarter of the aerosol was exhaled without depositing[6]. This fraction represents aerosol which although inhaled remained airborne and was immediately exhaled. It has been found for aerosols from metered-dose inhalers that the inclusion of a breath-hold interval between inspiration and expiration increased the amount of aerosol deposited in the lung[7]. This may well also apply to nebulised aerosols though in practice it may be difficult for patients to accomplish. Consequently, allowing for exhaled aerosol, only 15% of the original starting dose is deposited in the body.

The amount of inhaled aerosol depositing in the lungs is directly related to the size of the aerosol droplets. In a patient without obstructive airways disease, the droplets should be smaller than 10 μm to reach the lungs[8]. In the presence of airways obstruction even smaller droplets are required and the optimum therapeutic size is thought to be 5 μm or smaller[9]. Nebulisers produce droplets of varying sizes, the differences depending both on the make of the device and also on the flow rate of compressed air used to drive the nebuliser. The droplet size may be halved by increasing the flow rate of compressed air used to drive the nebuliser from 4 to 8 litres per minute[10].

In a recent study it was shown that only 44% of an inhaled aerosol with a mass median diameter (MMD) of 10.3 μm reached the lungs during inhalation, while 79% of an aerosol with a MMD of 1.8 μm deposited in the lungs[6]. The remaining aerosol was deposited in the oropharynx and swallowed. Therefore only between 7% and 12% of a dose of respirator solution placed in a nebuliser is likely to reach the target organ, the lung. Small beta-agonist aerosols have been found to achieve better bronchodilatation than larger aerosols[9] although the magnitude of dose normally used with nebulizers may mask this effect. The sites and amounts of respirator solution lost during nebulisation are summarized in Table 1.

Conclusion

At least 88% of a standard dose of respirator solution is therefore lost during therapy. Methods of reducing this wastage, namely using a 4 ml fill, tapping the walls of the nebuliser during therapy, using a triggering device, and also minimizing aerosol size have been suggested. We advocate that nebulisers should be selected on the basis of their output characteristics such as aerosol size and rate of aerosol formation, and also that nebulisers should be used under optimum conditions of driving gas flow rate to minimize both administration time and droplet size. The manufacturers of respirator solutions should also indicate whether the chemical properties of their preparations necessitate the use of particular types of nebuliser.

The application of these ideas will depend on the compliance of the patient and also the awareness and interest of the medical and nursing staff in ensuring that the patient obtains maximal benefit from this form of therapy.

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