The science of nebulised drug delivery

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Effective nebuliser therapy requires a device that repeatedly and quickly delivers sufficient drug to the site of action, with minimal wastage, at a low cost. Clinicians are bombarded with competing claims about different nebuliser systems. In many cases, however, insufficient details are available to make the most appropriate choice. The rapid increase in the number of nebulisers marketed and significant differences in design may result in drug delivery to patients varying by a factor of two or more.[1]

Drug delivery from nebulisers

Most of the prescribed medication for nebulisers never reaches the lungs.[2] Of the dose placed in the nebuliser chamber, perhaps two thirds remains there at the end of nebulisation. Two thirds of the dose released from the nebuliser may be released during expiration and passes into the surrounding air.[3] Some of the inhaled drug will be in particles too large to reach the lung, and some in particles so small that they do not deposit but are simply exhaled again. With many nebulisers only 10% of the prescribed dose may reach the lung.[4]

For bronchodilators, where a small dose may achieve an adequate result, this may not matter. It is more important for drugs with dose related effects (and side effects) such as steroids, and for expensive medications such as rhDNase.[5]

Nebuliser types: how they work[6–8]

Nebulisers used in aerosol drug delivery produce a polydisperse aerosol where most of the drug released is contained in particles 1–5 μm in diameter. Most nebulisers use compressed air for atomisation (fig 1), but some use ultrasonic energy (fig 2). A nebuliser may be distinguished from a simple atomiser by the incorporation of baffles which selectively remove large droplets from the outgoing spray.[9]

Early models were essentially atomisers constructed of glass and operated manually by compressing a hand bulb attached to the air inlet tube.[10] In 1946 pumps providing a continuous flow of air were advocated and the Collinson nebuliser,[11] constructed of ebonite with a plate baffle to filter out particles larger than 5 μm, became the most popular nebuliser in this country. In 1958 Wright[12] described a new nebuliser, considerably more compact than the Collinson, with a moulded perspex top. Now discontinued, it found widespread use in bronchial challenge testing.[13 14]

With the advent of portable, oil free compressors and injection moulding of plastics, a wide variety of disposable nebulisers has become available. Recent advances in their design have considerably altered the amount of drug patients receive.

THE JET NEBULISER

In a jet nebuliser the driving gas passes through a very narrow hole, known as a Venturi, from a high pressure system (fig 1). At the Venturi the pressure falls and the gas velocity increases greatly producing a cone shaped front. This passes at high velocity over the end of a narrow liquid feed tube or concentric feeding system creating a negative pressure at this point. As a result of this fall in pressure, liquid is sucked up by the Bernoulli effect (see Appendix 1) and is drawn out into fine ligaments. The ligaments then collapse into droplets under the influence of surface tension. This primary generation (atomisation) typically produces droplets 15–500 μm in diameter.[15] Coarse

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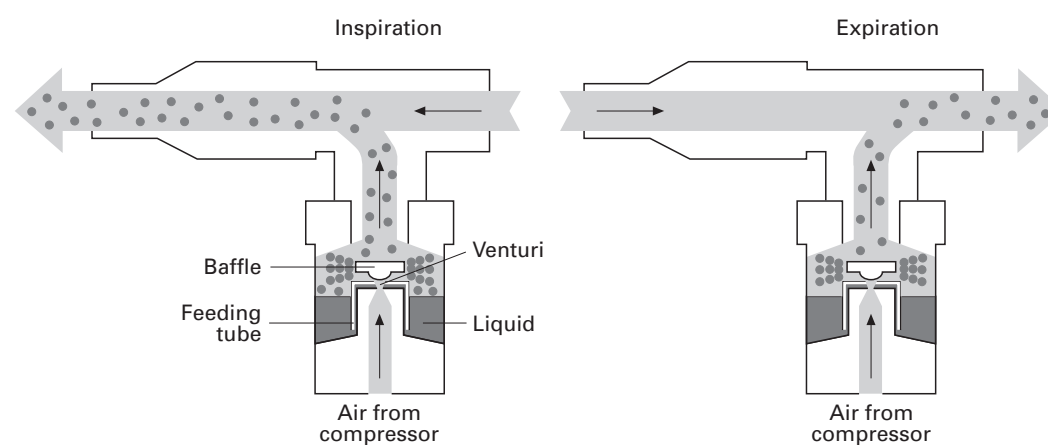
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Figure 1 Conventional nebuliser design. Air from the compressor passes through a small hole (Venturi). Rapid expansion of air causes a negative pressure which sucks fluid up the feeding tube system where it is atomised. Larger particles impact on baffles and the walls of the chamber and are returned for re-nebulisation. Small aerosol particles are released continuously from the nebuliser chamber. On expiration the nebuliser continues to generate aerosol which is wasted.
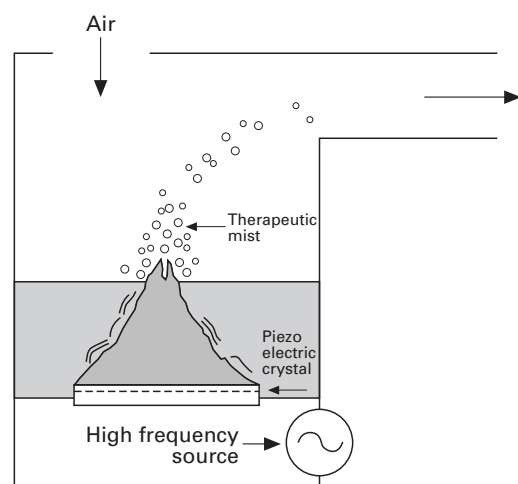
Figure 2   Schematic diagram of an ultrasonic nebuliser showing vibration of fluid with release of particles from the standing waves generated.
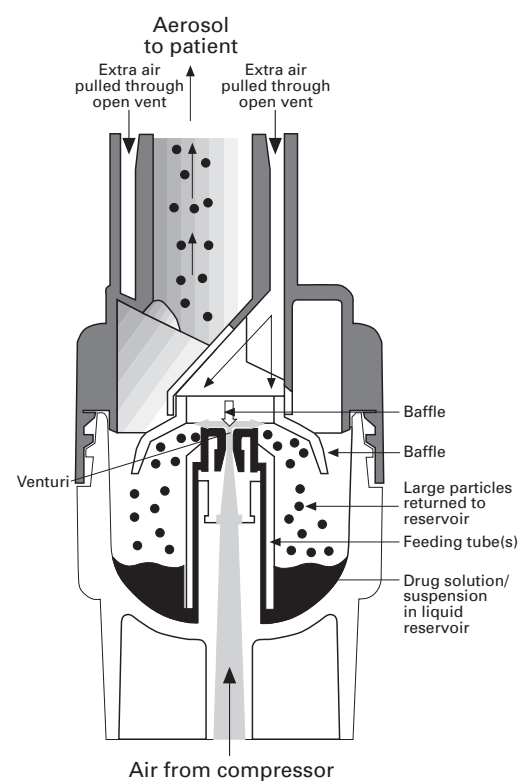

Figure 3   Open vent nebuliser. The diagram illustrates the Sidestream nebuliser which incorporates an open vent on the top of the device. The negative pressure generated as compressed gas expands through the Venturi causes liquid to be sucked up liquid feeding tubes for atomisation. Air is also sucked down through the open vent, increasing the total flow of air leaving the nebuliser chamber via the mouthpiece. More aerosol is being pushed out in a given time.

droplets impact on baffles while smaller droplets may be inhaled or may land on internal walls returning to the reservoir for renebulisation. Baffle design has a critical effect on droplet size.

Concentric liquid feeds minimise blockage by residual drug build up with repeated nebulisation. A flat pick up plate may allow some nebulisers to be tilted during treatment whilst maintaining liquid flow from the reservoir.

Different jet nebulisers have different output characteristics determined by the design of the air jet and capillary tube orifices, their geometric relationship with each other and the internal baffles. For a given design the major determinant of output is the driving gas flow.

RECENT ADVANCES IN JET NEBULISER DESIGN
Conventional jet nebulisers are highly inefficient as much of the aerosol is wasted during exhalation. Between 93% and 99% of the primary droplets are caught on the internal baffles and structures, resulting in a low output.[15] Recent designs have attempted to reduce these inefficiencies.

Continuous entrainment of gas through the nebuliser (open vent nebulisers)
Conventional jet nebulisers produce a fixed flow of gas containing aerosol. Some recent designs (for example, Sidestream; Medic-Aid, Pagham, UK) incorporate an extra open vent into the nebuliser in such a way that negative pressure generated by the expansion of compressed air at the Venturi sucks air into the chamber via the vent as well as fluid from the feeding tubes for atomisation (fig 3). This results in a continuously greater air flow through the chamber which pushes more small particles out to be inspired, in a given time, leading to shorter nebulisation times. The contribution of enhanced air flow through the nebuliser in reducing particle size, due to greater solvent evaporation, remains to be determined. Because lower compressed air flows are needed to generate the same respirable

output, cheaper lower specification compressors can be used. If the extra inlet channel (the vent) is blocked, preventing additional flow of air through the chamber, a similar amount of drug exits the nebuliser, but over a much longer time. Because of the high flow of aerosol from this device, young children with low inspiratory flow may receive less drug than anticipated.

With continuously operated nebulisers at least 50% of the aerosol is wasted during exhalation. Intermittent nebulisation, during inspiration alone, reduces aerosol waste and contamination of the environment (fig 4). Manual interrupters, however, require coordination by the patient, but the increased efficiency results in longer treatment times. In order to combine the convenience of continuous operation and the efficiency of intermittent nebulisation, the Pari LC Plus (Pari, Germany) (fig 5) and the Ventstream (Medic-Aid, UK) have been developed.

Entrainment of gas through the nebuliser on inspiration only (breath assisted, open vent nebulisers)
The Pari LC Plus nebulises continuously, but during inspiration a valve situated on top of the device opens, allowing extra air to be drawn through the nebuliser. As with the open vent nebulisers, it is claimed that this air will draw a much greater number of particles into the
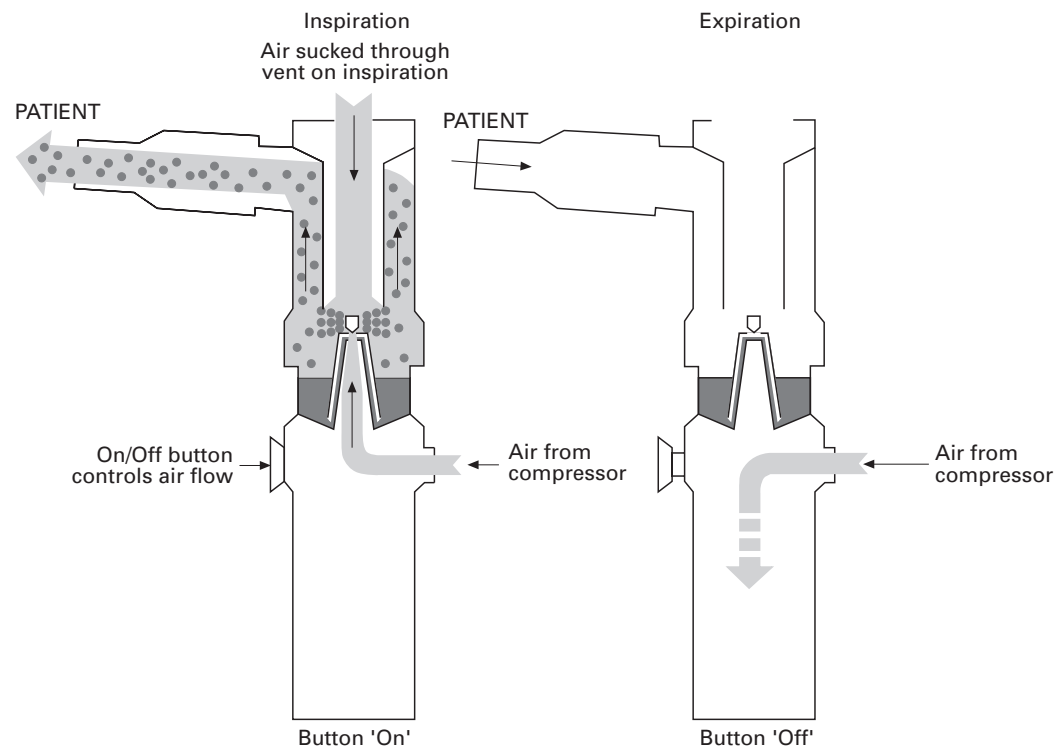
Figure 4   A dosimetric nebuliser (e.g. Pari LL) produces aerosol only when the patient presses a button allowing compressed air to pass through the nebuliser.
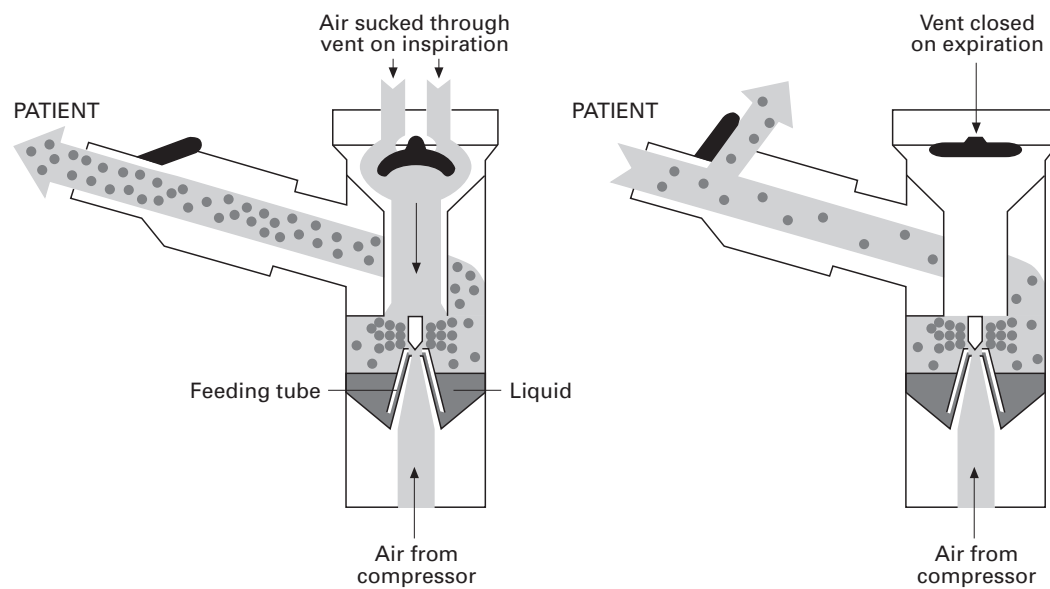

Figure 5   An example of a breath assisted, open vent nebuliser, the Pari LC Jet Plus. On inspiration the valve located at the top of the chamber opens, allowing extra air to be sucked through the vent on inspiration. The main effect of this is to pull more aerosol from the nebuliser on inspiration, increasing the dose to the patient. On expiration the vent closes and aerosol exits via a one-way valve near the mouthpiece. Aerosol lost from the nebuliser on expiration is thus proportionally less than that from a conventional nebuliser. Nebulisation times will be faster and the drug dose received by the patient will be significantly greater than with conventional nebulisers but not as fast as with the open vent nebuliser.

inspired air stream. During exhalation the inspiratory valve closes, decreasing the flow of air through the chamber to that from the compressor only. The result is that loss of aerosol during expiration is similar to that from a conventional jet nebuliser.

The Ventstream nebuliser is similar in design to the Sidestream, but a valve on the side of the device opens only during inspiration, allowing air to be drawn through the nebuliser which increases drug output. On exhalation

this valve closes and exhaled air passes out of the device through a separate expiratory pathway. These "breath assisted, open vent" nebulisers increase the amount of inspired drug. Nebulisation time is shorter than conventional jet nebulisers but not as fast as the open vent design.

The advantages of the "breath assisted, open vent devices" are (1) that the additional airflow through the nebuliser draws more of the small particles generated out to be inspired (increased
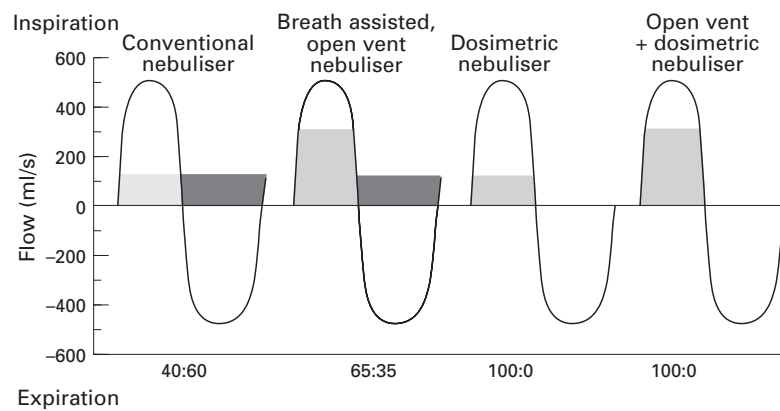
Figure 6 Schematic presentation of identical flow-time traces with nebuliser drug output adapted to a nebuliser/compressor flow of 6 l/min. The nebulised drug output is indicated by the shaded areas. The improvement in potential drug delivery from the new open vent nebulisers is clearly seen. Modified from Nikander[104] with permission.

evaporation from droplets may occur so that smaller particles are produced; (2) there is an increase in the amount of aerosol delivered to the patient and less wastage of aerosol during exhalation (fig 6) so that the dose of drug inspired may be doubled;[1] and (3) lower compressed air flows are needed to generate the same respirable output, allowing cheaper compressors of lower specification to be used.

These systems do have some disadvantages, however. Firstly, they are dependent upon the patient's inspiratory flow for optimum function and more information is needed before they can be recommended for young children. Viscous solutions (such as ceftazidime) may be nebulised slowly if a less powerful compressor is used.

HOLDING CHAMBERS
Another way of reducing wastage of drug produced during exhalation is to use a holding chamber such as the Mizer aerosol conservation device (Medic-Aid Ltd, Pagham, UK; fig 7).[16]

COMPRESSORS
Compressors used to drive gas through the nebuliser chamber vary greatly in power and some will generate a reasonably high free air flow. However, nebuliser chambers have a resistance to flow, and attaching a nebuliser chamber to a compressor will reduce the flow considerably. Different chambers vary greatly in their resistance. To make valid comparisons between compressors, flow should be estimated with the nebuliser attached and should be measured at the outlet of the nebuliser. This is the *dynamic flow* and is critical in determining the droplet size and nebulisation time. More powerful compressors can generate a higher flow through more resistant nebulisers. Unfortunately, some manufacturers often quote only the compressor's maximum static pressure and maximum flow – that is, without the nebuliser chamber in line. This gives a false impression of the capability of the compressor as these values can be approximately twice the dynamic flow.

Smaller, less powerful compressors may not be suitable for all drugs, but there are distinct advantages in having a nebuliser that is small, lightweight and that can run on batteries.

It is important to choose a nebuliser and compressor that work well together. For example, if a "breath assisted, open vent" type of nebuliser is run by a very high flow compressor this may defeat the object of minimising drug wastage on expiration.

ULTRASONIC NEBULISERS
The ultrasonic nebuliser uses a rapidly vibrating piezoelectric crystal to produce aerosol particles (fig 2). Ultrasonic vibrations from the crystal are transmitted to the surface of the drug solution where standing waves are formed. Droplets break free from the crests of these waves and are released as aerosol. The size of droplets produced is inversely proportional to two thirds of the power of the acoustic frequency (see Appendix 1 on page S42 for mathematical relationships). Like jet nebulisers, baffles within the nebuliser remove large droplets and much of the aerosol produced impacts on these, falling back into the drug reservoir.

A more recent design of ultrasonic nebuliser (Omron U1, Omron Healthcare) uses the vibration of the piezoelectric crystal to generate
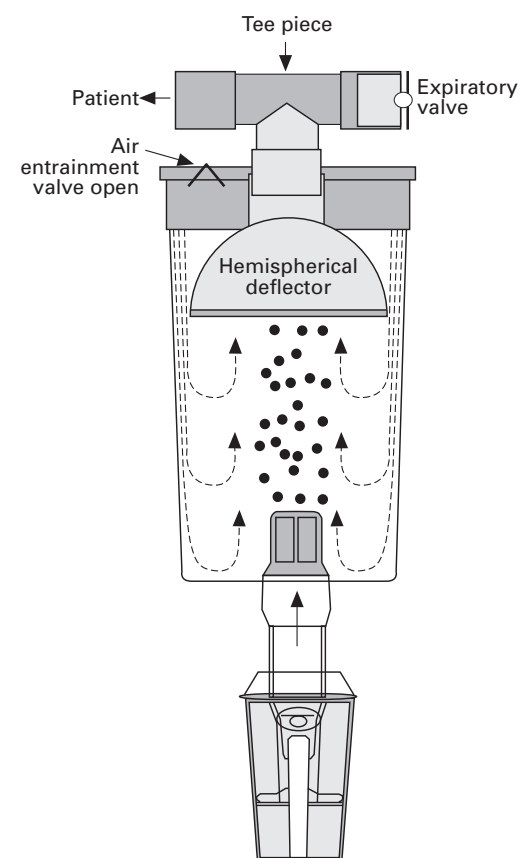
Figure 7 The Mizer aerosol conservation device. Aerosol is continually generated by a conventional nebuliser and passes into the holding chamber. During inspiration a negative pressure is created inside the holding chamber, causing an air entrainment valve to open and air to be drawn in. The entrained air collects aerosol and exits through the Tee piece delivering stored aerosol to the patient. Expired air is diverted away from the chamber by a valve and the chamber fills up with aerosol again.

an aerosol indirectly. Crystals vibrate around a feeding tube, turning it into a peristaltic pump, which forces liquid through a ceramic mesh (pore size 4.6 μm), creating an aerosol.

COMPARISON OF JET AND ULTRASONIC NEBULISERS

Jet nebulisers are by far the most common type of nebuliser used worldwide. Advances in design have improved their efficiency so that the higher mass output and shorter nebulisation times seen with ultrasonic nebulisers[17] may no longer be important discriminating factors. Current ultrasonic nebulisers do not appear to nebulise drug suspensions efficiently, and until newer models are evaluated they should be avoided for this task. The evidence that they may break down complex molecules is conflicting.[18–20] Ultrasonic nebulisers are generally smaller and quieter, and some patients may prefer them for routine bronchodilator treatment.[17]

A summary of the different types of nebulisers is given in Appendix 2 on page S42.

Description of particle size output from nebulisers

Particle size in this article refers to *aerodynamic particle size*, meaning the size of a spherical, unit density particle that settles with the same velocity as the particle in question. A very dense particle will have a different aerodynamic behaviour (an increased aerodynamic size) to an equivalently sized but less dense particle.

Aerosols produced by medical nebulisers are heterodisperse[7] – that is, made up of particles of different sizes. Their particle size distribution may be described statistically (fig 8).[21] Most therapeutic aerosols conform to an approximately log normal distribution which can be described by giving the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). Perhaps a more useful way of describing the aerosol cloud is to determine the total amount of drug contained in particles leaving the nebuliser and the amount of drug contained in particles less than a certain size. Although drug contained in particles less than 5 μm is described as the "respirable" dose, whether all such particles are truly respirable is not certain (table 1).

Two pitfalls may arise in the description of aerosol particle size (fig 8). One is the use of MMAD and mass median diameter (MMD)
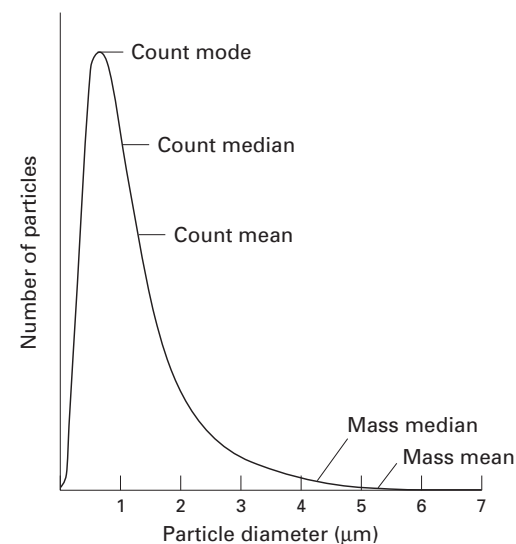
Figure 8   Log normal particle size distribution of an aerosol produced by a nebuliser.

as if they are interchangeable. MMD is measured by some light scattering devices (see below) and only describes the aerodynamic behaviour of particles if they are spherical and of unit density. The second and more serious pitfall is the presentation of count median aerodynamic diameter (CMAD), the diameter of the median *number* of particles in the aerosol cloud, as if it is equivalent to the MMAD (fig 8). A 10 μm diameter drug particle contains the same amount of drug as 1000 particles of 1 μm diameter. Describing the number of particles of a certain size may therefore give a very distorted view of the mass of respirable drug obtained from a nebuliser.

METHODS OF MEASURING PARTICLE SIZE

The two most commonly used methods of aerosol particle size determination are laser based light scattering devices and inertial impaction devices. Unfortunately they measure different things, and each has its own drawbacks. They are not usually interchangeable. Ideally, comparisons of the amount of drug contained in particles of various sizes from different nebulisers should use identical measurement techniques.

Laser diffraction devices, such as the Malvern Mastersizer (Malvern Ltd, Malvern, UK), work by passing a laser beam through the aerosol cloud. Particles diffract the light at an angle inversely related to their diameter. This diffracted light is detected by the machine which uses light scattering theory to compute the particle size distribution. Aerodynamic particle size is not determined by this method, and all particles produced by the nebuliser that pass through the laser are measured whether or not they contain drug. This is acceptable for a drug solution but may give erroneous results for a nebulised suspension. With suspensions the laser diffraction device may describe a seemingly excellent particle size distribution without detecting that only a few of the particles measured, usually larger ones, contain drug. The

Table 1   Aerosols: some definitions

Aerosol	A two phase system made up of a gaseous continuous phase (usually air) and a discontinuous phase of individual liquid or solid particles
Mass median diameter (MMD)	Diameter of a particle such that half the mass of the aerosol is contained in small diameter particles and half in larger
Mass median aerodynamic diameter (MMAD)	Diameter of a sphere of unit density that has the same aerodynamic properties as a particle of median mass from the aerosol
Geometric standard deviation (GSD)	Dimensionless number which gives an indication of the spread of sizes of particles that make up the aerosol. An aerosol with a GSD of 1 is made up of particles of the same size
Heterodisperse aerosol	Aerosol made up of particles of many different sizes (GSD >1.2)
Monodisperse aerosol	Aerosol particles all the same or very nearly the same (GSD <1.2)

Table 2   Deposition of monodisperse aerosols in the aerodynamic size range 1–8 μm

Particle aerodynamic diameter (μm)	% Deposition			% Exhaled
	Oropharynx	Tracheobronchial	Alveolar	
1	0	0	16	84
2	0	2	40	58
3	5	7	50	38
4	20	12	42	26
5	37	16	30	17
6	52	21	17	10
7	56	25	11	8
8	60	28	5	7

new Malvern Mastersizer and the older Malvern 2600 particle sizers use different mathematical theories to compute particle size, and results are not necessarily interchangeable.

Impaction methods of particle size determination include the glass multistage liquid impinger (MSLI),[22] the Anderson impactor, the high performance multistage liquid impinger, and the twin stage impingers described in the British Pharmacopoeia.[23] The MSLI operates by drawing the aerosol through a series of stages, each containing a glass impaction plate and connected by progressively smaller jets. Aerosol velocity therefore increases through each jet resulting in the deposition of smaller particles at each subsequent stage. A filter after the final stage collects the smallest particles. Each stage is washed and the amount of drug collected in each stage assayed. The MSLI is calibrated by passing an aerosol of known particle size through it and computing the cut off diameters above which particles are deposited for each stage. The MSLI determines aerodynamic particle size and allows the amount of drug contained in particles below a certain aerodynamic size to be computed. The high air flow may dry out aqueous particles, in contrast to the high humidity of the respiratory tract, and the size of particles produced from aqueous solutions may be underestimated by this method. Methodology allowing measurements to be performed at high humidities may reduce this error.[24] The importance of in vitro assessment of drug delivery was demonstrated by a recent study which, using a suspension of an inhaled steroid, highlighted the extremely small dose produced in particles within the respirable range, thus helping to explain the poor clinical effect of the preparation.[25]

AEROSOL DEPOSITION

The lung deposition characteristics and efficacy of an aerosol depend largely on the particle or droplet size. Generally, the smaller the particle the greater its chance of peripheral penetration and retention. However, for very fine particles below 0.5 μm in diameter there is a chance of avoiding deposition altogether and being exhaled. In 1966 the Task Group on Lung Dynamics, concerned mainly with the hazards of inhalation of environmental toxins, proposed a model for deposition of particles in the lung.[26] This suggested that particles of more than 10 μm in diameter are most likely to deposit in the mouth and throat, for those of 5–10 μm diameter a transition from mouth to airway
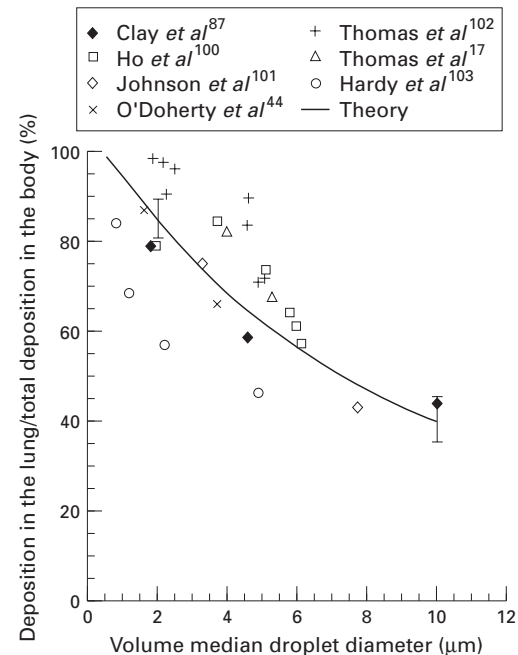

Figure 9   Correlation between mass median diameter of an aerosol cloud produced by nebulisation measured by laser diffraction and percentage thoracic deposition. Reproduced from Clark[31] with permission.

deposition occurs,[27] (table 2) and particles smaller than 5 μm in diameter deposit more frequently in the lower airways and are appropriate for pharmaceutical aerosols. The Task Group model was based on nose breathing and may underestimate the total lung deposition by ignoring mouth breathing.

The velocity of air flow decreases markedly as it travels down the respiratory tract as the total cross sectional area of the airways increases. The speed of inhaled aerosol laden air and turbulent flow is greatest in the nose/mouth, pharynx, trachea and larger bronchi, and it is here that larger particles are deposited by impaction. Within the smaller bronchi, bronchioles, and gas exchanging tissues smaller particles are removed by interception, sedimentation, and diffusion. In addition, particles generated by nebulisers are often electrostatically charged. This charge may induce an equal and opposite charge on the airway wall leading to electrostatic deposition.[28 29] This mechanism is most apparent for particles less than 1 μm in diameter and for long thin particles such as fibres.[30] It is thought to be of less importance for the deposition of therapeutic aerosols in the lung.

Clark[31] has recently considered the question of whether measurements of particle diameter have any relevance to clinical practice by reviewing studies of radiolabelled deposition of drug in the lung and droplet particle size measured by laser diffraction. Figure 9 plots lung aerosol deposition as a percentage of the total deposited in the patient versus the mass median droplet diameter (MMD) of the nebulised aerosol cloud. A reasonable correlation was found between the MMD and lung deposition. However, the data presented only represent the fractionation of the aerosol cloud between the

Table 3 Definitions used in describing aerosol output

Aerosol output	Mass per minute of particles in aerosol form produced by the nebuliser
Nebulisation time	Time from starting nebulisation until continuous nebulisation has ceased
Respirable particles	Particles <5 μm aerodynamic diameter
Respirable fraction	Proportion of respirable particles in the aerosol output expressed as a percentage
Respirable output	Mass of respirable particles produced per minute (aerosol output × respirable fraction)
% Mass emitted	$\frac{(\text{Mass of drug added} - \text{mass of drug remaining}) \times 100}{\text{mass of drug added}}$
Rate of nebulisation	(Mass of drug added − mass of drug remaining)/nebulisation time
Residual volume	Volume of liquid remaining in the nebuliser reservoir when nebulisation has ceased

oropharynx and the lung, and the author found insufficient data in the same papers to study the relationship between particle size and penetration of aerosol into the lung periphery.

The deposition profiles for an inhaled nebuliser cloud as predicted from the model of Rudolph *et al*,[32] which assumes oral breathing, are shown in fig 10. On the assumption that the model is correct for healthy subjects, it was concluded that oropharyngeal deposition decreases with decreasing median droplet diameter, falling from 60% of the inhaled dose at 10 μm to virtually zero at 1 μm.[31] Central airway deposition peaks at 6–7 μm and peripheral airway deposition at 2–3 μm. Interestingly, the dose reaching the peripheral airways, as a fraction of the total inhaled, varies by less than 8% over the median droplet diameter range 1–5 μm. Particle deposition in the lung periphery is diminished in patients with bronchoconstriction[32 33] and the optimum particle size for lung deposition in children and those with airways obstruction is less clear. In Rudolph's model the curves in fig 10 would be moved to the left by greater impaction in the central and upper airways of such patients. It may be better to use finer aerosols when a high degree of airway obstruction is present.

With many drugs the mass of material reaching the site of action is directly related to the

therapeutic effect. The ideal particle size to achieve deposition in the lung is subject to continuous speculation, but the largest particles capable of penetrating into the lung are considered to offer the greatest therapeutic advantage and particles with a diameter in the range of 1–5 μm diameter are generally accepted as the pharmaceutical industry's target. Small individual particles may be exhaled and carry very little mass (one 10 μm diameter particle has the same mass as 1000 particles with a diameter of 1 μm). Generation of small particles in high concentration is difficult and delivery time is prolonged.

Nebuliser output
In order to measure nebuliser output and to compare different nebulisers it is important to use measures relevant to patients and to standardise how those measurements are made.[6] The British Standards Institute has recently published a specification for gas powered nebulisers for the delivery of drugs, giving definitions and a method for determining their output.[34] Some definitions are given in table 3. Minimum standards are required of a nebuliser (see Appendix 3 on page S43), and the nebuliser manufacturer must supply certain information. However, the standard ignores the effect of the patient's breathing pattern on the *actual* dose of drug inhaled. This is essential information for the clinician who will otherwise have an inappropriate view of the ability of a nebuliser to deliver drug to the patient.

MEASUREMENT OF DRUG OUTPUT
The mass of aerosol released has in the past been measured simply by weighing the nebuliser before and after nebulisation (the gravimetric method).[3 35] This is highly inaccurate for jet nebulisers and overestimates the drug output as weight loss due to evaporation is not taken into account (fig 11).[36 37] The use of weight loss as a measure of aerosol output can only be used if the concentration of drug
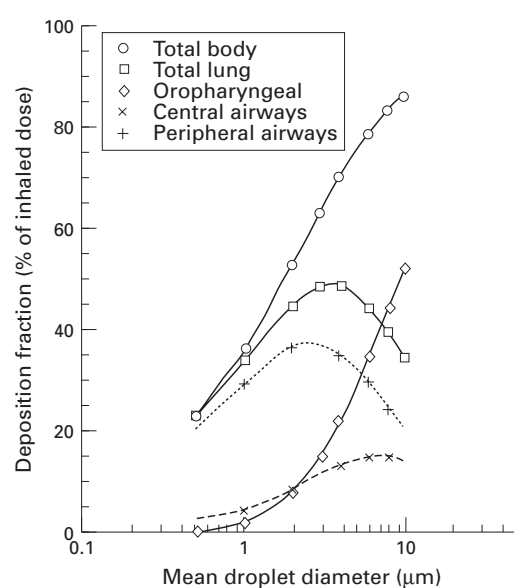
Figure 10 Deposition profiles predicted from an empirical model for an inhaled aerosol cloud produced by nebulisation with a geometric standard deviation of 2.2. Reproduced from Rudolph[32] with permission.
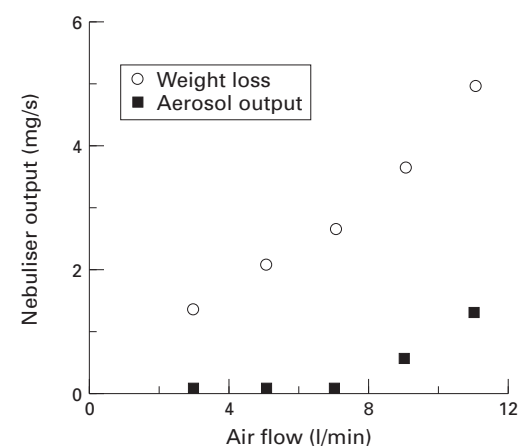
Figure 11 Effect of air flow on rate of weight loss and aerosol output from a Wright jet nebuliser. Simultaneous measurements of weight loss and aerosol output over 20 second activation periods at flows of 3, 6, 9, and 11 l/min were made and mean values calculated. Reproduced from Dennis et al[40] with permission.

Table 4 Factors affecting output of drug solutions from jet nebulisers

Factor	Positive effect	Negative effect
Increase driving gas flow/ compressor rating	Smaller particle size, shorter nebulisation time	More expensive compressor
Increase volume fill	Greater proportion of drug nebulised	Longer nebulisation time
Decrease residual volume	Greater proportion of drug nebulised	Longer nebulisation time
Increase baffles	Smaller particle size	Longer nebulisation time
Decrease solution viscosity (e.g. warm solution)	Smaller particle size	Minor effect
Use an "open vent" nebuliser	Shorter nebulisation time	Nebuliser cost
Use nebuliser with manual interrupter/ assisted "open vent"	No drug wasted in expiration. Increased dose to patient	Coordination required. Longer treatment time
Use "breath assisted open vent" nebuliser	Greater (twice or more) drug delivery to patient	Effectiveness has only been shown in adults using bronchodilator solutions

remaining in the nebuliser at the end of nebulisation is also measured. This is then multiplied by the residual volume to give the mass of drug remaining in the nebuliser which is subtracted from the mass of drug placed in the chamber at the start to give the output expressed as percentage mass emitted.[38 39] However, we have recently shown that this method also underestimates nebuliser output by up to 100% (Barry and O'Callaghan, unpublished observations).

An alternative in vitro method of assessing nebuliser output is to collect the aerosol onto a filter or into an impactor and to assay the drug or a chemical tracer added to the nebuliser solution.[40] It is important that the tracer behaves in the same way as the drug to be nebulised. In the laboratory the ideal method is to collect the aerosol leaving the nebuliser, assay the amount of the specific drug present, and perform particle size analysis as described above. The importance of taking breathing patterns into account is discussed later in the section on "reality testing".

FACTORS AFFECTING DRUG OUTPUT (TABLE 4)[7 41]
Driving gas flow [38 39 42]
Increasing the driving gas flow through jet nebulisers will increase the drug output, reduce the particle size,[43] and decrease the nebulisation time. Below a certain flow drug output is negligible (fig 11).[41] Optimum flow will depend upon the nebuliser and drug being used, but is often 6–10 l/min. High driving gas flow rate may not be as important for nebulisers with an "open vent". When comparing different nebuliser/compressor combinations it is important to compare only the *dynamic* flow.[44]

Residual volume of drug
The term *residual volume* is often used to infer drug wastage[43] but *residual mass* of drug is the important factor and may not be directly related to the residual volume of fluid. Nebulisers which leave a low residual mass of drug are preferable. Internal baffles may be used to reduce particle size, but these increase the surface area of the nebuliser and hence the residual volume. Residual volume may be reduced a little by tapping the nebuliser intermittently during operation.[3] Drug solutions with a lower surface tension will adhere less to the nebuliser surfaces, more returning to the nebuliser reservoir for re-nebulisation. Residual volume is effectively less and drug output is increased.

Volume fill
If a nebuliser has a residual volume of 1 ml and 2 ml of drug solution are placed into it and nebulised fully, a maximum of 50% of the drug will be released as aerosol (as 1 ml of the drug solution remains in the chamber). In practice less drug will be released than this due to solvent evaporation. If 4 ml of drug solution are placed in the chamber a maximum of 75% can be released.[42] However, the larger the volume fill the longer the nebulisation time.[38 43]

Concentration of nebuliser solution
Evaporation of solvent during nebulisation leads to a gradual increase in the concentration of the drug solution left behind. This leads to drug wastage and explains why evaporation invalidates the gravimetric method of measuring drug output. Irritation of the respiratory tract from the inhalation of highly concentrated solutions may occur.

Solution viscosity and surface tension
Theoretically, the aerosol particle size should be proportional to the surface tension of the drug solution, but experimental work in this area has been conflicting.[45 46] The primary droplet size is related to surface tension and viscosity, but the baffles in jet nebulisers control the output size. Highly viscous solutions such as some antibiotics[38] nebulise slowly and require powerful compressors. Warming solutions will reduce viscosity and nebulisation time. McCallion *et al*[47] studied two ultrasonic nebulisers and found that the droplet size was proportional to the viscosity of the nebuliser fluid, the more viscous fluids having the lowest outputs. While there was a trend for slightly lower mass median diameter values for fluids of lower surface tension, no clear correlation was established.

Solution temperature
The temperature of the solution may fall by 10 degrees or more during jet nebulisation.[36 42] This increases the solution viscosity and reduces the nebuliser output,[40] although the aerodynamic size of droplets produced falls with decreasing solution temperature.[48] A jet nebuliser, Paritherm (Pari, Starnberg, Germany), incorporates a heating system to warm the aerosol to body temperature.

Environmental conditions
Aqueous droplets produced by jet nebulisers can lose water by evaporation. This causes an increase in the concentration of the solution in the droplets and a reduction in droplet size.[49] Conversely, increasing the humidity of the inhaled air may increase particle size, depending on the tonicity of the particle.[48] The relative humidity of the output of jet nebulisers is 95–99% so aerosol particles generated from an isotonic solution probably change very little in size in the respiratory tract. On the other hand, if a hypertonic solution is aerosolised the droplet size would increase in the lung while hypotonic droplets would evaporate towards isotonicity.

Static charge
Particles produced by both jet and ultrasonic nebulisers may acquire an electrostatic charge.[50 51] This is an important factor in the function of spacer devices[52] but it is not known whether interaction between charged particles and the nebuliser, face mask, or mouthpiece affects drug delivery.

Nebulisation time
It is important to consider the effect of nebulisation time on patient compliance. For instance, it has been shown that 80% of the nebulised dose of sodium cromoglycate from most nebulisers is delivered in the first five minutes.[53] This sort of calculation should be made for each different drug/nebuliser combination. Increasing the length of treatment for more than 5 or 10 minutes may exasperate patients for little therapeutic gain.

Ultrasonic nebulisers
Many of the factors described above apply equally to ultrasonic nebulisers. Analogous to driving gas flow is the vibrational amplitude and frequency of the piezoelectric crystal. In general, higher frequencies generate smaller particles and increasing the nebuliser power (increasing the amplitude of the standing waves) increases the mass output. Residual volume affects ultrasonic nebulisers in the same way as jet nebulisers, except that drug solutions are not concentrated as much by solvent evaporation. Solution characteristics also affect ultrasonic nebuliser output. Highly viscid solutions do not form standing waves as easily and are nebulised poorly. Suspensions are also nebulised poorly, perhaps because drug particles in suspension are vibrated away from the area of droplet generation.

Variation between types of nebuliser
Different commercially available nebulisers vary in the size of droplets they produce and in their nebulisation rate. One study[54] showed that the MMD of six commonly used nebuliser chambers varied from <1 μm to >10 μm with most in the range 4–6 μm. The mass output of the nebuliser chambers under the test conditions varied by a factor of four.

Variation between nebulisers of the same type and "nebuliser ageing"
There is a large variation in output between different nebulisers of the same type.[14 55–57] If the jet is blocked with dirt or drug crystals, nebuliser output will be diminished. Repeated use of a singe nebuliser over time may cause a change at the critical points of droplet generation, most significantly an increase in the diameter of the air orifice. This "ageing" may be due to mechanical wear from the compressed air source or to excessive cleaning. Increasing the diameter of the air orifice usually decreases driving pressure, reducing the air velocity and increasing the droplet size.[55] To maintain stable generation of aerosol the driving pressure should be kept constant despite the resulting increase in volumetric flow.

Summary
Factors affecting nebuliser output are inextricably linked with those affecting particle size and nebulisation time. For instance, nebulisers designed to deliver small particles may have extensive internal baffles. This increases the residual volume, decreasing drug output and increasing recirculation of the nebuliser solution, thus lengthening nebulisation time. Increasing the volume fill improves drug output but lengthens nebulisation time. Increasing driving gas flow rate may help, but for home use a higher performance compressor may be needed. Manipulation of these factors can alter drug output dramatically.

PATIENT FACTORS AFFECTING DRUG DELIVERY
Breathing pattern and tidal volume
In conventional jet nebulisers the aerosol is carried in a volume of air which is dependent upon the driving gas flow. If this is, say, 8 l/min, the patient will breath in approximately 3 litres of aerosol per minute (assuming an inspiratory:expiratory ratio of 2:3). If the
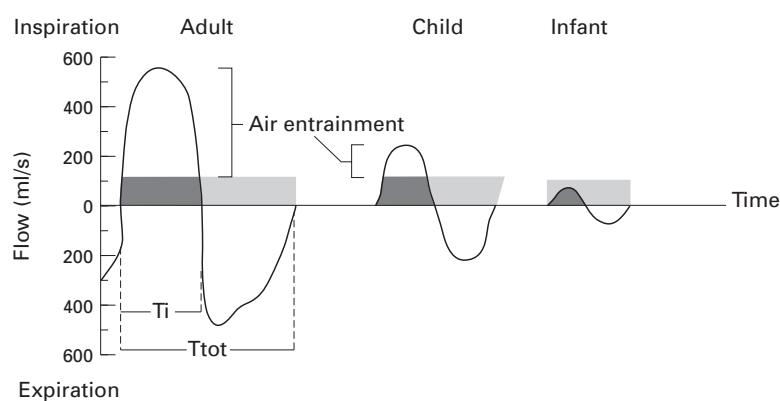

Figure 12   Diagrammatic representation of entrainment using a jet nebuliser with flow-time traces from an adult, a young child, and an infant. In the infant concentrated aerosol is breathed directly from the nebuliser. In older children with a greater inspiratory flow room air is entrained which will dilute the aerosol cloud breathed from the nebuliser. Once dilution of the inspired aerosol occurs the total dose inhaled by a child will be similar to that received by an adult patient. The dose to the child per kg body weight may therefore be much larger. Adapted from Collis[58] with permission.

Table 5 Effect of aerosol particle size on bronchodilator response

Study	Patients	Aerosol characteristics	Result
Dolovich et al[80]	6 stable asthmatics	MMAD 0.55 μm vs 2.4 μm	Equal response
Clay et al[81]	6 stable asthmatics	MMAD 1.88 μm vs 4.6 vs 10.3 μm	Slight increase with smaller particles
Johnson et al[82]	8 stable asthmatics	MMAD 3.3 μm vs 7.7 μm	Increased FEV$_1$ and increased radiolabelled deposition with smaller particles (3.3 μm)
Mitchell et al[83]	8 stable asthmatics	MMAD 1.4 μm vs 5.5 μm	Equal deposition (radiolabelled) and effect (FEV$_1$)
Hadfield et al[84]	10 stable asthmatics	MMAD 11.3 μm vs 16 μm	No difference
Douglas et al[35]	40 chronic asthmatics	MMAD 4 μm vs 11 μm	No difference
Wollmer et al[85]	5 chronic asthmatics	"Central" vs "peripheral"	Equal change in FEV$_1$
Persson et al[86]	12 stable asthmatics. Dry powder inhaler	90, 40 or 5 μg of terbutaline in particles <5 μm	Increased bronchodilation with larger respiratory dose (90 μg dose)
Clay et al[87]	6 stable asthmatics	MMAD 1.8 μm vs 4.6 μm vs 10.3 μm	Increased lung deposition (radiolabelled) with smaller particles (1.8 μm)
Patel et al[88]	8 mild asthmatics	MMAD 2.5 μm vs 5 μm	Increased bronchodilatation with smaller particles (2.5 μm)

MMAD = mass median aerodynamic diameter; FEV$_1$ = forced expiratory volume in one second.

patient's inspiratory flow is greater than the driving gas flow, air will be entrained, diluting the aerosol (fig 12). The effect of this is that infants and children inhale a much larger dose than adults when computed as dose per kilogram.[58] Once children are over six months of age the dose inhaled is independent of body size and the per kilogram dose inhaled gradually reduces as they grow.[59] Use of an aerosol holding chamber may reduce the dilutional effect of air entrainment.[60 61]

The breathing pattern may also affect deposition. Fast inspiration encourages inertial impaction of drug in the upper airways and more central deposition.[62] Slow inspiration lessens the threshold levels of response in bronchoprovocation tests,[63 64] possibly due to increased lung delivery.

Nose breathing
The nose is an excellent filter of inhaled particles and nose breathing reduces the lung deposition of aerosols by half,[65] most of the aerosol being deposited in the anterior third of the nose.[66 67] Data are only available for adults, however, and little is known of the particle retaining properties of the nose in childhood.

Face mask or mouthpiece
The use of a face mask with a nebuliser or spacer device has been shown to be an effective method of drug delivery to children too young to use a mouthpiece.[68 69] Potential problems with face masks are that some of the drug will land on the face, some may be inhaled through the nose, or a seal may not be achieved leading to leakage of the drug. It has been shown in vitro, using a lung model to represent the breathing pattern of a child, that holding the face mask only 2 cm from the face may reduce drug delivery by 85%.[70] It is likely that a mouthpiece, in patients old enough to use one reliably, will increase lung deposition of drug compared with a face mask.

Drug solutions and suspensions
A true molecular solution is defined as a mixture of two or more components which form a homogeneous molecular dispersion in a one phase system. Poor drug solubility in water may be enhanced by addition of a co-solvent, appropriate control of pH, and sometimes the addition of surfactants. Additives such as citrate or phosphate buffers may also be included, or preservatives such as EDTA or benzalkonium chloride. Their use and the acidity and tonicity of nebulised solutions have been linked to bronchoconstriction in some patients.[71 72]

A suspension consists of insoluble solid particles dispersed in a liquid medium. Pharmaceutical companies usually try to formulate flocculated suspensions[73] for nebulisers because, although these sediment down rapidly, they do not form a "cake" and are easy to redisperse.

Particles of drug within a suspension acquire a "fluid envelope" during nebulisation. Depending on the nebuliser used and the initial size and shape of the drug particles they may then be too large to escape the baffle system, resulting in very poor output, or the drug may be released in large droplets which have a high chance of upper airway deposition. In either case treatment may be ineffective.[25]

Importance of breathing pattern when assessing nebuliser performance: "reality testing" of nebulisers
Smaldone[74] coined the term "reality testing" of nebulisers which takes into account the breathing pattern of the patient and gives a more accurate reflection of the amount of drug a patient will actually receive. In a study using the gravimetric technique to determine nebuliser output[75] the Marquest Respirgard (6 ml volume fill) was reported to release 80% of the mass of the drug solution placed in it. However, when the drug contained in an aerosol released from a nebuliser is measured on filters, much lower nebuliser efficiencies (approximately 30%) result.[76] Both of these standard methods fail to take the breathing pattern of the patient into account. Using a breathing simulator with a tidal volume of 750 ml Smaldone[77] found that, at 20 breaths per minute and a duty time of 0.5, only 10% of the drug placed in a nebuliser would reach the patient. These results are much closer to radioisotope studies which suggest that only about 5% of drug placed within the Respirgard will be deposited in a patient.[74] Further refinement of in vitro techniques should result in closer correlation with actual lung deposition measured by radioisotope deposition and pharmacokinetic methods.

Lung deposition measured by radiolabelled aerosols

Measuring the lung deposition of radiolabelled aerosol takes into account the particle size distribution of the aerosol cloud and other factors such as airway calibre and breathing pattern. Studies using standard two dimension gamma scintigraphy have found the mean percentage of the dose deposited in the lung from a jet nebuliser to be between 2%[78] and 12%.[79] Studies of a number of jet nebulisers in terms of bronchodilator response and intrapulmonary deposition have shown marked differences, presumably reflecting variations in nebulisation rate, output, and droplet size (table 5).[35 80–88]

It may appear logical to assume that the efficacy of an aerosolised drug should be related to the local airway dose. In many studies, however, although regional distribution of a radiolabelled aerosol throughout the lung has been carefully determined, it has not been related to clinical efficacy.[89] Exceptions include a study by Clay *et al*[81] who found that nebulised bronchodilators achieve better lung deposition with smaller particles (1.8 µm) than larger particles (10.3 µm) and cause correspondingly greater bronchodilatation. Although lung deposition may be optimised by using drug particles of 2–5 µm aerodynamic diameter, it has been difficult to show that targeting specific airways is crucial for bronchodilator efficacy as such small doses are required for maximum bronchodilatation. Differences in the therapeutic effect of bronchodilators delivered in particles of 2–5 µm in diameter appear to be small. This may not be so with other drugs such as steroids and antibiotics which have a different therapeutic ratio.[89]

Although interesting information can be derived from radioisotope studies, it may be difficult to distinguish between aerosol deposition in the large airways and lung parenchyma. Use of a new technique – single photon emission computed tomography (SPECT)[90] – provides three dimensional images of an inhaled radio-aerosol. This may be better than planar scintigraphy in showing distribution of aerosol in different parts of the lung.

Pharmacokinetic evaluation of lung deposition

There is accumulating evidence from pharmacokinetic studies to suggest that absorption across the lung vascular bed is an important determinant of systemic bioactivity and adverse effects.[91] For example, systemic absorption of inhaled salbutamol occurs predominantly from the vascular bed of the lung rather than the gut, with peak plasma concentrations being achieved within five minutes.[92] Salbutamol absorbed from the intestine undergoes extensive sulphate conjugation, probably in the intestinal mucosa. Similarly, on the basis of data from mouth rinsing and charcoal block studies[93 94] it can be inferred that the systemic bioavailability of inhaled corticosteroids is mainly determined by absorption across the lung vascular bed. Thus, a nebuliser delivery system which improves lung deposition would, at the same time,

be expected to increase lung bioavailability and hence overall systemic absorption.

The pharmacokinetic method has been used in a comparison of two nebulisers (the Hudson Up-draft II and the Ventstream[1]). Lung deposition of drug from the Ventstream should theoretically be greater as it produces a larger output of respirable particles and matches the nebuliser output to breathing pattern (see above). Measurement of plasma salbutamol levels suggested that the Ventstream delivered approximately double the amount of drug.

An alternative method to blood sampling involves the measurement of early urinary excretion of salbutamol and its sulphate metabolite in order to differentiate between lung and gut bioavailability.[95]

Clinical evaluation

Clinical efficacy studies are ultimately the most relevant measure of the effectiveness of a medication, although they may not be easy to apply to an inhaled drug. For example, although bronchodilatation is characteristically rapid after administration of a single dose of a β_2 agonist, comparisons between different delivery devices may be obscured by a shallow dose-response curve. However, incorrect conclusions may be drawn from clinical efficiency studies unless information on the dose available for inhalation (in vitro studies) or lung dose achieved (pharmacokinetic and radioisotope studies) are available. For example, in a recent paper on the emergency treatment of asthma Campbell and colleagues[96] state that 5 mg of salbutamol given by an oxygen-driven nebuliser was more effective than either 5 mg of terbutaline via a spacer or 200 µg salbutamol via a metered dose inhaler. Review of the method provides a different interpretation. New spacers were used and 20 doses of terbutaline were administered by multiple actuations of the metered dose inhaler into them, then allowing the patient to inhale (personal communication). It is known that multiple actuations of metered dose inhalers into a spacer substantially reduces the amount of drug available compared with repeated inhalation of a single actuation[97] and that new spacers release less drug than old ones.[98] If one can extrapolate from in vitro work with other drugs it is likely that the amount of terbutaline available for inhalation from the spacers was nearer 2 mg than the 5 mg supposed.

Importance of drug targeting[99]

The ability to deliver drug directly to its site of action is one of the attractions of nebuliser therapy. Apart from "in the lungs", we do not always know exactly where we want the drug to be deposited. Receptor sites for β agonists occur predominantly in the small airways and for anticholinergic drugs in the larger airways. Both inhaled steroids in asthma and antibiotics in cystic fibrosis should presumably be delivered to the sites of inflammation and infection, respectively, but the optimum deposition pattern is not known. This issue

needs to be considered before the best nebuliser for a particular treatment can be determined.

Conclusions

Using the appropriate device and conditions it is possible to nebulise virtually any drug and in almost any dose. For β_2 agonists, where only a small airway dose is required to achieve maximum bronchodilatation, variation in drug delivery between devices may be less critical. By contrast, the use of very expensive drugs such as rhDNase or drugs with important side effects such as steroids demands greater knowledge of the delivery systems used.

Nebulisers vary greatly in the size of droplet they produce, their nebulisation time, and drug output. This may have a marked effect on the therapeutic response. Similarly, one cannot assume that different drugs nebulised within the same nebuliser under identical conditions will have the same output characteristics. Ideally, all nebuliser and compressor combinations and all ultrasonic nebulisers should have their output characteristics determined for all drugs used. It is surprising that such basic information is not demanded by regulatory authorities when drug dose delivered may vary by 100% or more.

In order to evaluate nebuliser output a number of factors may be measured in vitro including the amount of drug contained in particles likely to reach the airways. It is clear that this in vitro analysis must also include the effect of the patient's breathing pattern.

Laboratory evaluation will help in the choice of which nebuliser to use for specific patients and drugs, and may be supplemented by measures of lung deposition by pharmacokinetic and/or radioisotope methods. Such an evaluation, prior to clinical studies, may reduce the number of unnecessary trials on patients.

Appendix 1[8]

THE BERNOULLI PRINCIPLE

For a gas or liquid travelling in streamline motion in a tube, the sum of pressure energy plus gravitational potential energy is constant.

$$P + 0.5\rho v^2 + \rho gh = \text{constant}$$

where P = pressure in the tube, ρ = gas or liquid density, v = gas or liquid velocity, g = gravitational acceleration, and h = height above some reference level.

GENERATION OF PARTICLES BY ULTRASONIC NEBULISATION

Mercer described the threshold of amplitude for the generation of capillary waves required for aerosol generation by

$$A = 4v/f\lambda$$

where A = threshold amplitude, v = viscosity of liquid, f = frequency of acoustic signal, and λ = capillary wavelength.

The mean diameter of droplets is proportional to the capillary wavelength λ, where

$$\lambda = (8\pi\gamma/\rho f^2)^{1/3}$$

where γ = surface tension, ρ = density of liquid, and f = frequency of acoustic signal.

Liquid particles of radius r have a surface area S and a volume V given by:

$$S = 4\pi r^2$$

$$V = {}^4/_3\pi r^3$$

If the particle is made up of a solution with mass density ρ, the mass of the particle is given by:

$$M = \rho \times {}^4/_3\pi r^3$$

Appendix 2: Types of nebuliser

Conventional jet nebuliser (e.g. Acorn)
Constant output of aerosol from the nebuliser during both inspiration and expiration. A large amount of drug is wasted as it is produced during expiration.

Conventional jet nebuliser with spacer attachment (e.g. Mizer)
Aerosol is continuously generated by a conventional jet nebuliser and passes into a spacer/holding chamber. Concentrated aerosol from the spacer is inhaled during inspiration. Expired air is diverted away from the chamber by a valve, allowing the chamber to fill up with aerosol during this period.

Manual flow interrupter jet nebuliser (e.g. Pari LL)
The patient can exercise control over the input of flow of compressed air into the nebuliser allowing nebulisation to coincide with inspiration.

"Open vent" jet nebulisers (e.g. Sidestream)
An additional vent is incorporated into the nebuliser chamber. Negative pressure generated by expansion of compressed air at the Venturi sucks air into the chamber via the open vent. This markedly increases the air flow out of the nebuliser pushing more small particles out to be inspired in a given time. Nebulisation times are shorter but the total amount received by the patient is similar to that for a conventional jet nebuliser.

"Breath assisted, open vent" jet nebulisers (e.g. Ventstream, Pari LC Plus)
An open vent in the nebuliser is fitted with a valve system which allows extra air to be pulled through the nebuliser on inspiration, pulling a greater number of aerosolised particles into the inspired air stream. During exhalation the inspiratory valve closes, decreasing flow of air through the chamber to that from the compressor only. The result is that loss of aerosol during expiration is similar to that from a conventional jet nebuliser while that during inspiration is significantly enhanced.

Ultrasonic nebulisers

Ultrasonic vibrations from a piezoelectric crystal are transmitted to the surface of the drug solution where droplets break free from the crests of standing waves and are released as an aerosol.

Appendix 3: British standard BS7711 part 3: Respiratory therapy equipment. Specification for gas powered nebulisers for the delivery of drugs

This specifies minimum performance and safety requirements for gas powered nebulisers for the delivery of drug to patients through the respiratory system.

The minimum standards required of a nebuliser are:

- leakage not exceeding 5% of the maximum fill;
- if intended for use with an anaesthetic breathing system or a ventilator connections must be compatible;
- the nebuliser (or packaging if used for single use) must be marked with the manufacturer's identity, lot number, and recommended driving gas flow, and the maximum filling level of the liquid container must be marked;
- the respirable fraction of aerosol must be at least 50% at each of the recommended flows.

The nebuliser manufacturer must supply the following information:

- a description of intended use;
- suitability of the nebuliser for use in anaesthetic breathing systems and/or ventilators;
- minimum, maximum, and recommended driving gas flows, and the driving gas pressures corresponding to these;
- the respirable output at minimum, maximum, and recommended flows;
- the distribution of aerosol particle size at the manufacturer's recommended driving gas flow;
- the residual volume (by weight) left in the nebuliser at each driving gas flow;
- any contraindications to the use of the nebuliser.

Comment

Important factors in relation to patient usage not addressed in the standard include:

- The effect of the patient's breathing pattern on the dose of drug inhaled.
- Suggested nebulisation times for given volume fills and operating flows.
- The effect of specific drugs (e.g. steroid suspensions) on nebuliser performance.
- The inaccuracy of estimating drug output by weight loss which will overestimate drug delivery.

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