Delivery of inhaled bronchodilators by breath-actuated jet nebulizer: The potential for improved adherence with clinical guidelines

The first breath-actuated nebulizer only generates aerosol during patient inhalation to improve compliance and reduce medication waste

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Patient titration to the lowest efficacious dose

Clinical recommendations relating to the management of bronchoconstrictive diseases, such as asthma and chronic obstructive pulmonary disease (COPD), propose that the clinician titrate the patient to the minimum dose for effective control of the disease.[1-3] A beta-2 adrenergic agonist (for asthma or COPD) and anticholinergic medications (for COPD), such as salbutamol and ipratropium bromide respectively, can be delivered by pressurized metered dose inhaler (pMDI) with spacer/valved holding chamber for non-severe disease[1,4] but may require treatment by nebulizer in the event of a severe exacerbation.[5] This change in delivery approach may be preferred: (a) where a patient is perceived to require very high doses of inhaled bronchodilator medication; (b) if a patient needs an inhaled drug that cannot be given by any other means; (c) for patients who are unable to use other devices or (d) in situations such as acute severe asthma where patient cooperation with other devices may be problematic.[6]

How various jet nebulizer types can be used to achieve patient titration

The approach to patient titration is highly problematic with conventional jet nebulizers because they continue

to deliver medication that is wasted during the time that the patient exhales, which can typically be two-thirds of each respiratory cycle for tidal breathing.[7] Figure 1 is an idealized flow-time profile for a tidally-breathing adult with a 33% duty cycle and a breathing rate of 12 cycles per minute (5 s per cycle), inhaling medication from a continuously operating jet nebulizer. This diagram illustrates the wasted aerosol that typically escapes to contaminate the local environment during each exhalation. Furthermore, if the patient removes the nebulizer mouthpiece during treatment, the nebulizer continues generating aerosol that goes directly to waste. Even with

breath-enhanced jet nebulizers, in which the aerosol output is intentionally increased by entraining additional air during the inhalation portion of each breathing cycle (Figure 2), substantial wastage of medication to the ambient surroundings during exhalation still takes place.[7]

The potential for reducing waste of medication during exhalation has resulted in several initiatives to improve nebulizer performance. The simplest arrangement is to direct the flow from the nebulizer containing aerosol via a 'T'-piece into a reservoir bag during exhalation, where a portion of it can be retained until the next inhalation.[8] However, this type of system inevitably causes some re-breathing of air stored in the reservoir, a feature that is undesirable from the perspective of retaining good oxygen saturation in the bloodstream. A one-way valve may be incorporated between the T-piece and nebulizer to direct exhaled flow away from the reservoir to avoid this complication.[7,8] However, whichever system is adopted, during the time that exhalation takes place, the suspended droplets are subject to deposition on the walls of the bag, due to the influence of gravity (sedimentation), as well as losses associated with turbulent deposition during transport into and out of the reservoir (Figure 3).[9] It is important to note that such nebulizers, despite claims that they conserve aerosol until it can be inhaled, cannot be considered dosimetric because there is still wasted medication. Furthermore, the nebulizer will continue to operate should the patient take the mouthpiece out of the mouth during treatment, a situation that can arise frequently in the treatment of patients with COPD, unless the caregiver monitors the patient continuously throughout treatment.

An innovative approach to the problem of linking medication delivery to patient inspiration has been adopted in the mechanically-operated, breath-actuated jet nebulizer (BAN). By virtue of its design, it also takes advantage of air entrainment during the inhalation portion of each breathing cycle to help increase delivery of respirable fine particles.[10] The AeroEclipse-II BAN (Trudell Medical International) is currently the only member of this particular class of devices. It is actuated when the inhalation flow rate exceeds 15 L/min.[11] and, at the end of the inhalation, cuts off aerosol generation

Figure 1

Idealized, tidal-breathing, adult flow, rate-time profile showing continuous delivery of aerosolized medication from a continuous, non-breath-enhanced jet nebulizer

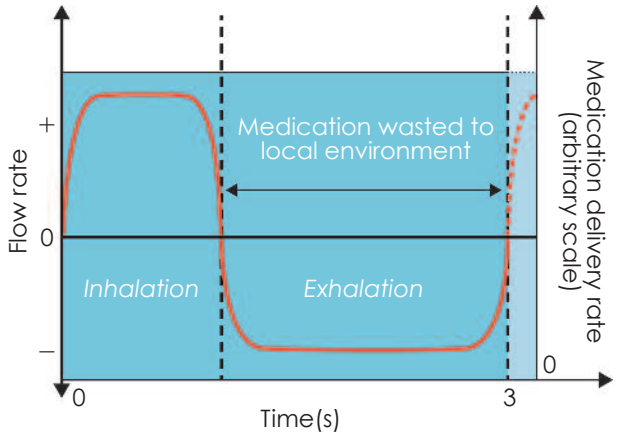


Figure 2

Idealized, tidal-breathing, adult flow, rate-time profile showing increased delivery of aerosolized medication during inhalation from a continuous, breath-enhanced jet nebulizer, with associated waste of medication during exhalation

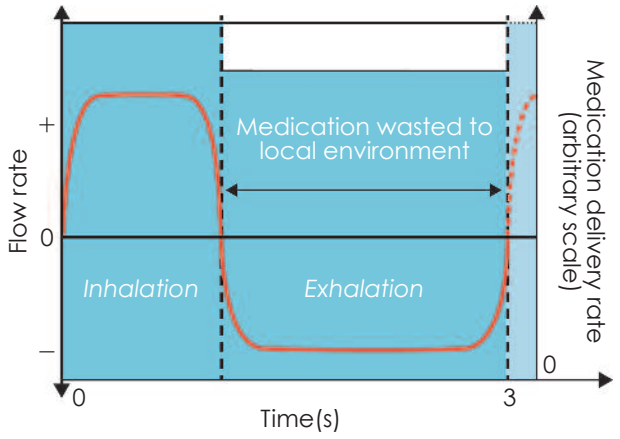
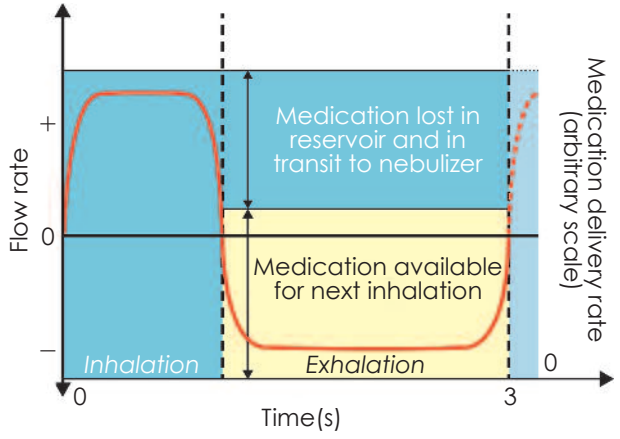


Figure 3

Idealized, tidal-breathing, adult flow, rate-time profile for a jet nebulizer with reservoir, showing partial retention of aerosolized medication during exhalation



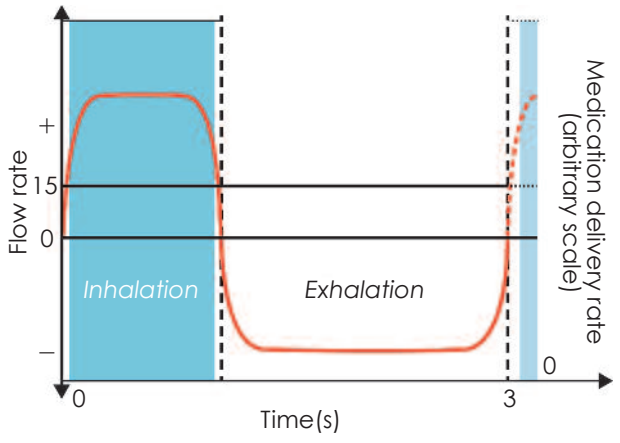
when the flow rate falls below 15 L/min (Figure 4). This low flow rate should help make the current BAN more useable by children in comparison with the predecessor AeroEclipse-I BAN, which required an inhalation flow rate close to 25 L/min for actuation.[11] Dosimetric jet nebulizers have the potential to be more useful in patient titration than continuously operating devices since the mass of medication emitted at the mouthpiece per breathing cycle can be readily quantified.

How does the breath-actuated nebulizer perform as a dosimetric delivery device?

The delivery of medication at a constant feed rate during the inspiratory portion of each breathing cycle is key to achieving dosimetric delivery, as is the ability of the patient to breathe in a reproducible way from one inhalation to the next. In the case of the AeroEclipse-II BAN, the suction force created upon inhalation moves the AeroControl system regulator, (comprising the actuator piston arrangement attached to a flexible membrane) into position with respect to the exits of the liquid and concentric gas supply channels (Figure 5). Patients can be trained to inhale slowly and deeply to trigger actuation and to observe the vertical movement of a green feedback button, which is attached to a moving actuator piston (the button and actuator piston move as respiration takes place), as a way of further improving medication delivery into the distal regions of the lungs. The BAN has been used in the clinic as a dosimetric medication delivery device to deliver narrow therapeutic index drugs, such as methacholine, in bronchial challenge testing.[12]

Figure 4

Idealized, tidal-breathing, adult flow, rate-time profile showing delivery of aerosolized medication only during inhalation from a breath-actuated jet nebulizer, once the initiating flow rate of 15 L/min has been attained



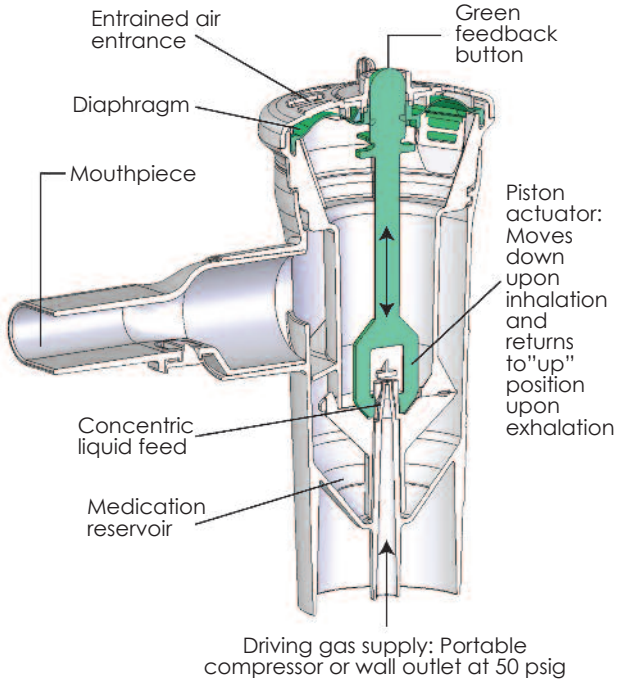
Assessment of dosimetric delivery taking the mechanical breath-actuated nebulizer as an example

The laboratory-based assessment of drug delivery from a dosimetric jet nebulizer is primarily undertaken in device development to verify that the basic criterion of a steady medication delivery rate throughout a hypothetical treatment can be met. This process is undertaken by connecting the mouthpiece of the device via a filter to a breathing device, set to simulate adult tidal-breathing.[13] The BAN is operated for a given period of time with an appropriate volume-fill. The mass of medication is collected on the high-efficiency filter, recovered at regular intervals (typically minute-by-minute) and assayed for the emitted mass of active drug substance available to be inhaled. A secondary, but also important, characteristic for a BAN is establishing that the total emitted mass is a linear function of the fill volume in the reservoir. Achievement of this goal can be easily checked by repeating the test procedure at various fills within the known range for dosimetric operation.

These attributes have been assessed for the AeroEclipse-II BAN and its predecessor (AeroEclipse BAN) in a series of investigations with a variety of formulations.[11,13-15] The data in Figure 6 are a summary from a more recent study with salbutamol sulfate solution and budesonide suspen-

Figure 5

Cross-section through the AeroEclipse-II BAN, showing the AeroControl system regulator associated with breath-actuation of nebulization



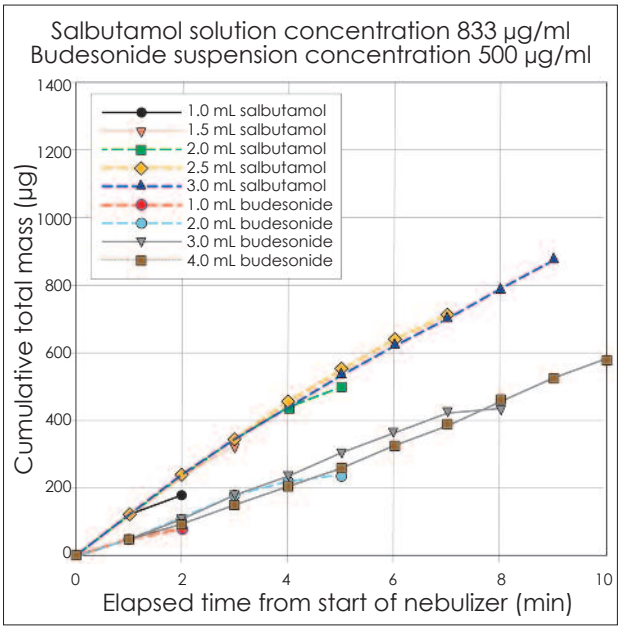
sion, simulating adult tidal breathing [tidal volume = 600 ml; duty cycle = 33%; rate = 10 breaths/min (2 s inhalation/cycle)].[16] Previously, similar experiments with methacholine had confirmed the linear relationship between medication delivery rate and solution concentration within a wide range from 0.25 to 15.75 mg/mL typically used in bronchoprovocation challenge testing.[13]

Conclusions

The ability of a jet nebulizer to deliver inhaled medication in a highly reproducible fashion, breath-by-breath, is possible purely by mechanical operation of the precision-manufactured components involved with droplet generation. This article has outlined how such a BAN can provide dosimetric delivery of both solution- and suspension-based formulations, based on laboratory evidence. The fact that this nebulizer only generates aerosol during patient inhalation will improve compliance, as medication will not be wasted should the user remove the nebulizer from their mouth during a course of treatment in order to rest or converse with someone nearby. Since this work was undertaken, a further advance in the design of the BAN, to be presented at the European Respiratory Congress in September 2011, has enabled equivalent performance to be achieved using portable compressors, a development that is anticipated to be useful for the treatment of patients in the home as well as in the hospital.

Figure 6

Medication delivery from the AeroEclipse-II BAN, showing the near-to-linear relationship between cumulative total emitted mass with elapsed time for a solution (salbutamol) and suspension (budesonide) product, independent of fill volume



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