Continuous nebulization therapy for asthma with aerosols of β_2 agonists

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Background: Various studies have demonstrated the benefits of continuous nebulization therapy for delivering aerosols of the β_2 agonists such as terbutaline sulfate or albuterol sulfate to patients with severe asthma and/or impending respiratory failure.

Objective: The purpose of this investigation was to explicate the operational factors associated with the use of nebulizers for extended aerosol respiratory therapy including those factors that affect the prescribed aerosol dosages and the relationship to actual delivery of prescribed drugs to the respiratory airways of the lungs of a patient under treatment conditions.

Methods: Operational characteristics and methods have been investigated for use of long-running nebulizers for continuous nebulization therapy. Factors considered were particle size distribution, setup conditions, aerosolization concentrations and rates, delivery fraction of aerosol reaching patient, and changes in medication concentration during extended operation. With a large volume nebulizer, aerosols can be delivered to the patient without dilution via a standard open mask for up to eight hours without refill. The pneumatic HEART nebulizer with 240 mL reservoir was evaluated.

Results: The nebulizer was operated from a single compressed air or oxygen source and found to provide from 10 to 15 L/min of aerosol with 38 to 50 μL of aerosolized medicine per liter of air (or oxygen) and utilize from 30 to 56 mL/hour of medicinal liquid. The mass median aerodynamic diameter of the aerosol droplets was found to be about 2.0 μm (σ_g = 2.7). Delivery efficiency to the patient mask was about 90%. The aerosolized medicine delivered to the patient can be increased by adjusting the flow rate of the gas source or changing the solution concentration of medicine. Typically, several milligrams of drug can be delivered to the patient as inhaled aerosol per hour of treatment of which about one-quarter can be expected to be deposited in the lungs. During eight hours of operation the concentration of medicinal solution increased by about a factor of two because of water evaporation.

Conclusions: Continuous nebulization therapy is an important means of treating patients with severe asthma. Dosage criteria can be established based on the operating characteristics of the nebulizer system, drug solution concentration, and patient respiration.

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INTRODUCTION

Continuous intravenous isoproterenol has been administered previously with impending respiratory failure associated with severe asthma.[1] This drug and route of administration, however, has been associated with increased cardiovascular risks such as arrhythmias and myocardial ischemia.[2–4] Development of more selective bronchodilators has decreased potential side effects because of their selective receptor activity; repeated treatment has been shown to be effective.[5–13] Various studies have demonstrated the efficacy and safety of continuous nebulization therapy for delivering aerosols of the β_2 agonists terbutaline sulfate or albuterol sulfate to patients with severe asthma and/or impending respiratory failure.[14–27] For example, physicians at the University of Michigan Medical Center and at the University of Missouri-Kansas City School of Medicine found continuous nebulization therapy with terbutaline sulfate to be effective for the treatment of status asthmaticus in pediatric patients who did not improve with the standard therapy of aminophylline, methylprednisolone, and intermittent nebulized terbutaline sulfate.[15,16]

Terbutaline sulfate, a β_2 agonist, can be administered by oral, inhalation, subcutaneous, or intravenous routes. Undesirable side effects may occur depending upon the serum level. When delivered to the patient via aerosol inhalation, there are fewer side effects compared with oral or parenteral administration since there is less drug absorption into the systemic circulation.[17,18] Also, the delivery of aerosolized medicines such as terbutaline sulfate results in greater therapeutic efficacy at lower dosage levels because of its direct effect on β_2 receptors in the lung. The biologic half-life of terbutaline sulfate or other β_2 agonists, however, is relatively short. Peak bronchodilation from the action of drugs such as terbutaline sulfate on the β_2-receptor sites, occurs for up to one and

one-quarter hours.[17] In patients with acute bronchospasm, the use of continuous nebulization may be the preferred method of administering β_2 agonists.[14,19–30]

The purpose of this study was to investigate the operational factors associated with the use of nebulizers for extended aerosol respiratory therapy including those factors that affect the prescribed aerosol dosages and the relationship to actual delivery of prescribed drugs to the respiratory airways of the lungs of a patient under treatment conditions. This was accomplished in this study using the high flow-rate HEART nebulizer (Westmed Inc, Tucson, AZ). The low flow-rate MiniHEART mini-nebulizer was also tested for comparison purposes. These two test nebulizers are shown together in Figure 1. Analysis and characterization of the factors controlling the operation of these nebulizers, the mathematical relationships that describe the aerosolization process, and the expected delivery of respirable aerosols to a patient provide fundamental considerations that apply to all nebulizer systems that may be used for continuous nebulization therapy. Of particular importance are those factors that affect the net delivery of prescribed drugs to the lungs of a patient under treatment conditions.

THEORY

Nebulizer Operation

The operational characteristics of medical nebulizers are described by the aerosol droplet size distribution using aerosol particle mass median aerodynamic diameter [MMAD, μm] and geometric standard deviation [σ_g], aerosol droplet output concentration [a, μL, or mL of aerosolized liquid per L of air or oxygen mixture], evaporation loss [w, μL, or mL of evaporated water per L of air or oxygen mixture], volumetric flow rate of aerosol [Q, L/min], nebulized liquid consumption [A, mL/h] and operating gage pressure of compressed air or oxygen mixture [p, psig].[31,32] The volumetric flow rate [Q] was measured using rotameters

corrected for operation at 50 psig and also with a spirometer. These measures of flow rate are equivalent to the volumetric flows given by the back-pressure compensated flow meters ordinarily used in medical facilities to operate nebulizers and set flow rate.

For aqueous solutions at low solute concentrations, the MMAD is about equivalent to the droplet volume median physical diameter since the droplet physical density is close to 1 g/cm.[3,31] Outputs of aerosolized liquid were determined gravimetrically by weighing the nebulizers before and after use with the nebulizers operated both under normal room temperature conditions and also when chilled in an ice-water bath. During nebulization in an ice-water bath the vapor pressure of water is low and it was assumed that there was less than 4 μL/L evaporation losses because the reservoir temperature is typically below 4°C.[31] The dif-

ferent consumption rates were contrasted to determine the effective evaporation consumption of water that occurs during normal nebulizer operation without an ice-water bath.

Evaporation Losses During Nebulization

During the course of nebulization, the consumption of nebulizer solution (mL/h) is divided between medicinal solution aerosolized and pure water evaporated from the nebulizer. Both of these portions of the expended solution are related to the volume of compressed air or oxygen mixture that passes through the nebulizer nozzle. During any time period, t (h), the total volume of compressed air or oxygen mixture, v_a (L), that passes through the nozzle is given by:

$$v_a = Q \times t \qquad (1)$$

Figure 1. Photograph of the HEART nebulizer (left) and the Mini HEART nebulizer (right) used in this study.

where Q (L/h) is the gas volumetric flow rate and t (h) is a specific elapsed time of nebulizer operation.

Because the evaporated water does not carry medicinal drug, evaporation results in an increasing concentration of drug in the nebulized solution with elapsed time of operation. The concentration of drug in the nebulized solution after beginning treatment is given by:

$$C_t = C_n \left[\frac{V_o}{V_o - (a + w)Qt} \right]^{w/(a+w)} \quad (2)$$

where C_t (mg/mL) is the concentration of drug in the solution in the nebulizer reservoir after operation for a time, t (h), Q (L/h) is the volumetric flow rate of air (or oxygen mixture), a (mL/L) is the liquid aerosol concentration per liter of air, w (mL/L) is the concentration of evaporated water per liter of air, and C_n is the starting concentration of volume V_o (mL) of solution at t = 0.[32] The evaporation-concentrating process is controlled by the value of the exponent, w/(a + w), in Equation 2. When w is zero (no evaporation) this exponent is also zero, and there is no change in drug concentration in the solution at any time. When the value of $w \ll (a + w)$, there is relatively little evaporation or concentrating; this occurs when a is large compared with w. The liquid consumption rate (mL/h) is A = (a + w)Q. Modern nebulizers have high a/w ratios that minimize the evaporation-concentrating effect.

Drug Dosages and Treatment Regimen

When ordered by the attending physician, continuous nebulization therapy is initiated utilizing a prescribed hourly aerosolization dosage of the chosen medication over a planned treatment period of several hours or until the patient's condition improves. The therapist must prepare the nebulized solution from the stock solution provided by the supplier in accordance with the planned course of therapy. Various flow rates and nebulized liquid concentrations are possible, so the flow rate should be selected based upon the appropriateness to the patient's respiratory minute ventilation. Albuterol sulfate and terbutaline sulfate are commonly used β_2 agonist for continuous nebulization therapy. The usual aerosolization dosage ranges from 2 mg/h to 20 mg/h in adults. This dosage range is about equivalent to 0.03 to 0.3 mg/kg/h for adults. Lin et al[33] observed systemic side effects at aerosolization dosages of 0.4 mg/kg/h. Bennett and Dave,[34] however, successfully used 0.6 mg/kg/h for up to four hours without observing side effects. Since drug effectiveness and minute ventilation both vary with about the three-quarters power of body mass, a high flow rate nebulizer will somewhat automatically compensate for body weight differences. When a low flow-rate nebulizer is used, it is desirable to prescribe the nebulization dosage in terms of mg/kg/h.

Moler et al[15] mixed 40 mg terbutaline sulfate from a 1 mg/mL stock solution with 60 mL of normal saline to produce a 0.40 mg/mL concentration [A = 10 mL/h]. The average aerosolization dosage with their nebulizer and dilution system was 4 mg of terbutaline sulfate per hour. The nebulizer operated at a flow rate of 6 L/min with humidified dilution air set at 10 L/min to provide a combined flow rate of 16 L/min. Other dosages could be achieved with different drug concentrations in the nebulized solution. The conditions used by Moler et al[15] were dictated in part by the operating characteristics of the nebulizer that was used. Likewise, with a high flow-rate nebulizer or a low flow-rate nebulizer, details of the characterization of the output properties and operating conditions are required to establish the aerosolization dosage regimen.

Drug Delivery

When a drug aerosolization dosage is prescribed in mg/h, it is understood that a patient cannot actually inhale all of the aerosolized medicine, and, of that which is inhaled, only a portion is actually deposited in the airways of the lung. There may be losses in the tubing or mask. The aerosol generated during the exhalation phase of the breathing cycle is not inhaled and is lost. To optimize the delivery rate, the volumetric flow rate (L/min) of the nebulizer should not exceed two times the patient's minute ventilation. This is because the average inspiratory rate is about two times the minute ventilation when exhalation and inhalation each represent about half of the breathing cycle.

Since nebulizers usually produce polydisperse droplets with median aerodynamic diameters in the range of 2 μm to 5 μm, aerosol therapy should be transoral to avoid 40% to 80% nasal deposition. The expected regional deposition of orally inhaled nebulizer aerosol droplets is a function of droplet aerodynamic or diffusive size (Fig 2).[35,36] For aqueous droplets with low concentration of dissolved drug or salts, the aerodynamic and diffusive diameters are approximately equal to the droplet geometric diameter. Some droplets larger than 3 μm in diameter may deposit in the mouth, oral pharynx, and laryngeal region. Also, most of the inhaled particles with aerodynamic diameters in the range from 0.1 μm to 1 μm are not deposited in the respiratory tract but are exhaled. If low flow rate nebulizers are used with large volumes of dry diluting air, the aerosol droplets may shrink by evaporation into this smaller size range prior to entering the respiratory tract, and thus decrease deposition and increase the probability of being exhaled. Droplets smaller than 0.1 μm actually exhibit increased deposition in the alveolar region than bigger particles by the mechanism of Brownian diffusion (Fig 2), but high-output pneumatic nebulizers yield little aerosol in this submicrometer diameter range.

Assuming that the aerosolization volumetric flow rate does not significantly exceed the patient's inspiratory demand and equipment losses are small, the aerosolization dosage provides a practical measure of dose versus effectiveness of treatment. In other words, if it is known from experience that a specific treatment protocol yields the desired clinical effect, then
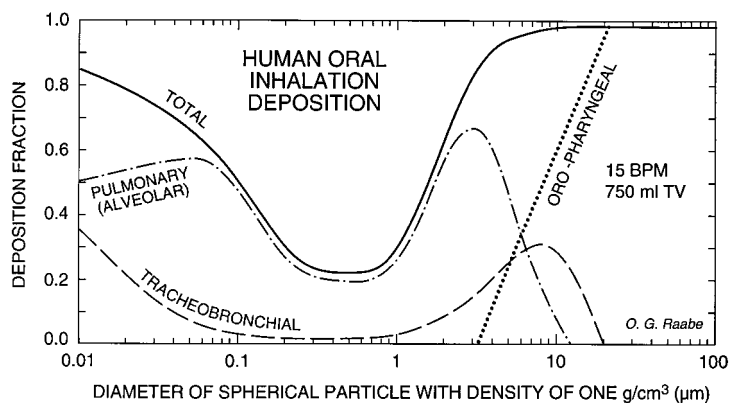
Figure 2. Overview of the deposition in the respiratory tract of aerosol particles inhaled by mouth as a function of particle geometric diameter for spherical particles of density 1 g/cm^3 equal to the aerodynamic equivalent diameter for particles larger than 0.5 μm and the diffusive diameter for particles smaller than 0.5 μm (Adapted and reproduced with permission from Bronchial Asthma, Principles of Diagnosis and Treatment, 2nd ed, Grune & Stratton, 1986, from Raabe et al).[35]

that prescribed treatment is applicable even though the actual delivery of drug to the lungs may be far less than the amount nebulized.

Preparation of medicinal solution is based on nebulization conditions. For an aerosolization dosage of D (mg/h), the concentration of the solution, C_n (mg/mL), is given by:

$$C_n = \frac{D}{A} \text{ (mg/mL)} \qquad (3)$$

for an average liquid output of A (mL/h) from the nebulizer. In this working calculation the evaporation of liquid is tacitly but intentionally ignored. To prepare the solution at this concentration, the stock solution of the medicinal drug at a concentration of C_m (mg/mL) must be diluted with saline.

The volume of stock solution of medicinal drug, V_m (mL), that is required for T (h) of treatment is given by:

$$V_m = (D \times T)/C_m \text{ (mL)} \qquad (4)$$

where D (mg/h) is the prescribed drug aerosolization rate and T (h) is the total planned treatment time. The total volume of solution required is the product of the liquid output rate of A (mL/h) and the treatment time, T (h) as:

$$V_t = A \times T \text{ (mL)} \qquad (5)$$

where V_t (mL), is the total volume of solution to be nebulized over the time duration of treatment, T (h). The volume of physiologic saline required to dilute the drug stock solution is given by:

$$V_s = (A \times T) - V_m \text{ (mL)} \qquad (6)$$

where V_s (mL) is the volume of saline and V_m (mL) is the volume of medicinal drug stock solution combined to prepare the total volume of solution.

This volume is given as:

$$V_t = V_m + V_s \text{ (mL)} \qquad (7)$$

where V_t (mL) is the volume of solution to be nebulized during the treatment time T (h).

METHODS

Nebulizer

The nebulizer setup is shown in Figure 3. This arrangement for continuous nebulization therapy utilizes a standard open mask and a single-patient, disposable nebulizer having a high-output pneumatic nebulization nozzle operated in a large volume reservoir (240 mL) to produce 10 to 15 L/min of relatively high concentrations of therapeutic aerosol in the respirable droplet diameter range.[35,36] The arrangement requires only a single source of compressed air or oxygen mixture. No humidifier is used because high-output nebulizers produce an output flow of liquid aerosol that is large enough to maintain humidity near saturation as a result of the excess water present and the naturally elevated vapor pressure of the small droplets. At room temperature, 100% relative humidity is reached when the absolute humidity exceeds about 20 μL of liquid water evaporated in each liter of air.[31] More
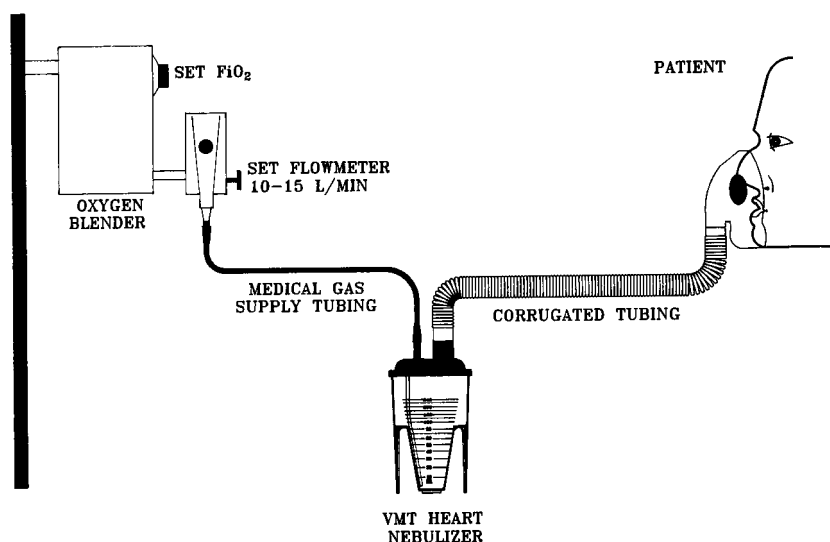

Figure 3. Schematic illustration of the nebulizer system for continuous nebulization therapy.

than enough water vapor and reserve liquid aerosol is produced by the high volume nebulizers to insure saturation conditions.

Mini-Nebulizer

A low flow-rate mini-nebulizer will accommodate continuous nebulization therapy in cases where lower aerosol volumetric flow rates are desired and when large volumes of aerosol and associated humidification are not required. The smaller nebulizer used in this study operated at flow volumetric flow rates from 1 to 2.5 L/min. The liquid reservoir volume was 30 mL. This mini-nebulizer can be used in the same setup shown in Figure 3 in place of the larger nebulizer. Because of the lower flow rate of the smaller nebulizer, the inhaled aerosol is automatically diluted with room air via the vent holes on the sides of the standard open delivery mask. For additional oxygen, a nasal canula can be utilized under the mask. Alternatively, this low flow-rate nebulizer could probably be used with a mechanical ventilator without interference.

Nebulizer Characterization

A detailed characterization of the two nebulizers was conducted so that all aspects of their behavior could be utilized to describe the expected performance over an extended period of operation and so that the quantitative delivery of aerosolized drug to a patient could be accurately predicted. Three different randomly chosen nebulizer units were tested at flow rates of 8, 10, 12, and 15 L/min. Likewise,

three different mini-nebulizer units were tested at 1, 1.5, 2, and 2.5 L/min. Solutions of 1 mg/mL of fluorescein dissolved in physiologic saline were aerosolized and the droplet aerosols were sampled with a multi-jet, 7-stage cascade impactor to measure the droplet aerodynamic size distribution.[37] Impactor stage collection of aerosol droplets was quantified by ultraviolet fluorometry of the highly fluorescent fluorescein salt that serves as a tracer of the drug in the nebulizer solution and the aerosol. Lognormal size distribution functions were fit to the resulting measurements of droplet distribution using log-probability graph paper to evaluate the particle MMAD and associated geometric standard deviation [σ_g] for each nebulization test.[38,39]

Measurements were made of the increasing-concentration effect of evaporation using three randomly chosen high flow-rate nebulizer units each with 240 mL of a solution with 1 mg/mL of albuterol sulfate to which fluorescein was added. The nebulizer units were each connected to 30 cm long 22 mm diameter ventilator tubing and standard open delivery mask and operated for eight hours. The consumption of liquid was periodically determined gravimetrically. Solution concentrations were determined by fluorometric measurements of the fluorescein tracer.

Delivery of Aerosol to Patient Via Mask

In order to evaluate the delivery of aerosol from the nebulizer to the pa-

tient during normal use, the total output of aerosol was determined using three randomly chosen high flow-rate nebulizer units each with 240 mL of a solution with 1 mg/mL of albuterol sulfate to which fluorescein tracer was added. The nebulizer units were each connected to 30-cm long, 22-mm diameter ventilator tubing and standard open delivery mask and operated for five minutes. Aerosol reaching the mask was collected with the cascade impactor operated at 17 L/min. The impactor sample was quantified by fluorometrically measuring the fluorescein content of each stage. The consumption of liquid was determined gravimetrically, and the losses in the tubing and mask were determined by washing and fluorometrically measuring the fluorescein content. This provided two measures of nebulization efficiency over eight hours, one by weighing the nebulizer and one by fluorometric measurements.

RESULTS

The measured characteristics of the two types of nebulizer are summarized in Table 1 and Table 2. Both nebulizers demonstrated MMAD (and volume median diameters) that averaged from 1.7 to 2.6 μm. Aerosol output concentrations [a] were uniformly high, spanning from 31.4 to 55.9 μL/L on the average. In all cases the evaporation losses [w] were small compared with the aerosol output [a], so that relatively little solution concentrating occurs during normal operation of these nebulizers.

Table 1. Measured Performance Characteristics of the HEART Nebulizer*

Volumetric Flow Rate Q (L/min)	Pneumatic Pressure p (psig)	Aerosol Concentration a (μL/L)*	Evaporation Concentration† w (μL/L)	Total Liquid Consumption A (mL/h)	MMAD‡ (μm)	Geometric S.D. (σ_g)
8	11.6 ± 0.0	31.4 ± 3.8	11.1 ± 1.3	20 ± 1	1.7 ± 1.1	2.6 ± 0.3
10	16.9 ± 0.1	38.0 ± 2.7	12.1 ± 0.7	30 ± 1	2.0 ± 0.9	2.6 ± 0.3
12	24.6 ± 0.2	45.9 ± 2.5	11.8 ± 0.7	42 ± 2	2.4 ± 0.8	2.7 ± 0.6
15	38.3 ± 0.6	49.9 ± 1.8	12.1 ± 1.1	56 ± 2	1.8 ± 0.6	2.8 ± 0.5
Average			11.8 ± 1.0		2.0 ± 0.9	2.7 ± 0.4

* Errors shown are standard deviations based upon measurements of three different nebulizer units.

† Evaporation was determined by contrasting normal liquid consumption at ambient temperature with consumption when operated in ice water bath.

‡ Mass median aerodynamic equivalent diameter of the aerosol droplet distribution with indicated geometric standard deviation (σ_g).

Table 2. Measured Performance Characteristics of the MiniHEART Nebulizer*

Volumetric Flow Rate Q (L/min)	Pneumatic Pressure p (psig)	Aerosol Concentration a (μL/L)	Evaporation Concentration† w (μL/L)	Total Liquid Consumption A (mL/h)	MMAD‡ (μm)	Geometric S.D. (σ_g)
1	13.1 ± 1.0	25.3 ± 1.1	8.9 ± 1.0	2.1 ± 0.1	2.6 ± 0.8	2.1 ± 0.2
1.5	24.4 ± 2.0	40.0 ± 3.7	8.9 ± 1.0	4.5 ± 0.5	2.4 ± 0.7	2.1 ± 0.1
2	39.2 ± 0.6	53.0 ± 0.6	13.0 ± 1.5	7.9 ± 0.2	2.4 ± 0.7	2.1 ± 0.2
2.5§	52.8§ ± 2.9	55.9 ± 1.5	12.9 ± 3.9	10.3 ± 0.5	2.5 ± 0.7	2.1 ± 0.2
Average			9.1 ± 1.9		2.5 ± 0.7	2.1 ± 0.2

* Errors shown are standard deviations based upon measurements of three different nebulizer units.
† Evaporation was determined by contrasting normal liquid consumption at ambient temperature with consumption when operated in ice water bath.
‡ Mass median aerodynamic equivalent diameter of the aerosol droplet distribution with indicated geometric standard deviation (σ_g).
§ Flow rates above 2 L/min are not normally available in the clinical setting because the available pneumatic pressure usually does not exceed 50 psig.

A detailed summary of a selected example of the operation of the high output nebulizer at 10 L/min for eight hours beginning with a full reservoir of 240 mL is given in Table 3. The expected increased concentration with time of operation due to water evaporation will result in a higher delivery rate of medication during the latter part of the treatment than during the beginning. The change of the solution concentration is calculated based on an evaporation loss of 12.1 μL/L (Table 1). The average liquid consumption rate [A] for this nebulizer is 30 mL/h at a flow rate of 10 L/min which will remain constant over the treatment duration. Table 3 assumes a start with 240 mL with drug solution concentration of 1 mg/mL. After one hour of nebulization, this nebulizer delivered 25 mg of medication, which leaves 215 mg of medication in 210 mL of solution. The concentration therefore, increased to 1.03 mg/mL after one hour of nebulization. The medication aerosolization rate will continue to increase gradually as calculated in Table 3. During the full eight hours of operation, essentially all of the medication is aerosolized so that the average aerosolization dosage rate [D] of medication can be assumed to be equal to the total liquid consumption rate [A] of 30 mL/h times the initial solution concentration [C_n] of 1 mg/mL = 30 mg/h. For practical purposes the liquid consumption rate, A, as given in Tables 1 and 2 can be used for aerosolization dosage calculations instead of the aerosol concentration, a.

The results of the experimental measurement of evaporation effects with three nebulizer units equipped with tubing and masks is summarized in Figure 4 showing the measured solution concentrations (and standard deviation, SD, among the three units) as a function of time. The calculated and measured values were found to be in good agreement. The observed maximum increase in medication concentration over eight hours of operation of the nebulizer was about a factor of two.

Gravimetric measurements of the delivery of aerosol from the nebulizers via tubing and mask showed that only 10.3% ± 1.0% SD was lost in carrying the aerosols from the nebulizer to the mask. The fluorometric measurement indicated that only 10.1% ± 1.9% SD of the aerosol was lost. This showed that about 90% of the aerosol generated by the nebulizer is actually delivered to the patient. For the measured particle size distribution, the expected regional deposition of inhaled aerosol in the human airways for transoral inhalation would be about 15% in the tracheobronchial conductive airways and about 50% in the alveolar gas-exchange region (Fig 2).[36] This equates to about one-quarter of the aerosolization dosage being deposited in the

Table 3. Calculated Aerosolization Characteristics of a Typical HEART Nebulizer*

Start Time (hour)	Beginning Volume (mL)	Liquid Consumed (mL/h)	Medication Concentration (mg/mL)	Aerosolization Dosage (mg/h)	Medication Remaining (mg)
0	240	30	1.00	22.8	240
1	210	30	1.03	23.5	216
2	180	30	1.07	24.4	193
3	150	30	1.12	25.5	168
4	120	30	1.18	26.9	142
5	90	30	1.27	28.9	114
6	60	30	1.40	31.9	84
7	30	30	1.65	37.7	50
8	≈0		[≈2.00]	0	
Mean		30	1.32	30	

* Conditions: 10 L/min over eight hours beginning with a normalized medication concentration of 1 mg/mL using Eq. 2. Lower concentrations for aerosolization dosages smaller than 30 mg/h can be derived from this table by multiplying the medications columns (three right columns) by the actual drug concentration of the nebulized solution in mg/mL. Experimentally measured values of concentration are compared to the calculated values in Figure 4.

CONTINUOUS NEBULIZATION THERAPY
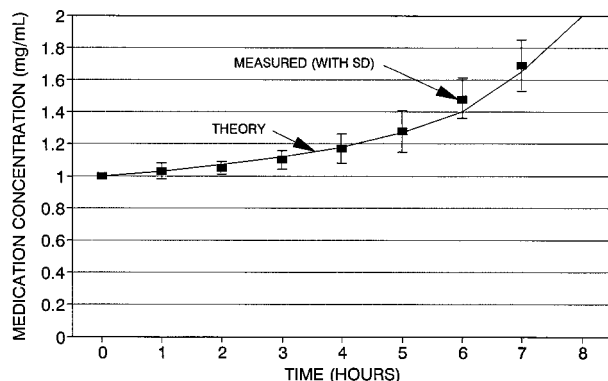### HEART NEBULIZER AT 10 LITERS PER MINUTE

Figure 4. Measured concentration changes (mean and standard deviation, SD of three tests) in an albuterol medication solution during continuous nebulization with the HEART nebulizer system operated at a flow rate of 10 L/min for a period of eight hours compared with the calculated values from Table 3.

lungs over the whole breathing cycle of a patient inhaling by mouth.

Examples of the proper drug concentrations in nebulized solutions with the each of the two sizes of nebulizers are summarized in Table 4. These values were calculated using Eq 3. From these examples, a wide range of therapeutic choices are possible depending upon the individual circumstances. For an albuterol sulfate stock solution at 5 mg/mL the nebulizer solution concentrations obtained with Eqs. 4–7 are shown in Table 5. For a terbutaline sulfate stock solution of 1 mg/mL, the corresponding examples are given in Table 6. The low concentration of the stock solution of terbutaline sulfate in this example limits the range of usefulness of the low flow-rate mini-nebulizer in delivering higher dosages.

DISCUSSION

Aerosolized bronchodilators, ie, β_2 agonists or anticholinergics, have been shown to be an effective means of treating severe reversible airway disease. The delivery of these medications to the receptor sites in the lower respiratory tract has allowed physicians to give safe, rapid, and effective medications with fewer side effects. Blood levels of the drug are generally very low. This avoids the higher concentration of drugs in the serum with

oral or parenteral administration and the potential side effects. The duration of action of β_2 agonists is relatively short and requires frequent administration. Giving high doses of aerosol over short periods of time can increase side effects. Ideally, a method of continuous aerosolization to avoid the peaks and valleys of drug concentration would decrease potential side effects and possible subtherapeutic levels in acutely ill patients.

Lin et al[40] have conducted a randomized study of the administration of aerosolized albuterol sulfate, using the HEART nebulizer, compared continuous with intermittent nebulization and showed improvements of pulmonary function with continuous therapy with-

out significant side effects. They reported that continuous nebulization therapy was particularly useful for patients with initial FEV_1 of less than 50%.

Chipps et al[41] successfully used the HEART system for continuous nebulization therapy with terbutaline sulfate for 23 episodes of acute bronchospasm. Eighteen of the cases showed significant improvement, while five required mechanical ventilation. They also used the HEART nebulizer for continuous nebulization therapy in conjunction with a mechanical ventilator.

Reisner et al[42] compared intermittent and continuous nebulization of albuterol using small Airlife nebulizer (American Pharmaseal Co., Valencia, CA) in combination with an infusion pump and found that continuous nebulization yielded continued improvement in acute asthma cases beyond two hours of treatment.

Rudnitsky et al[43] used the HEART nebulizer for continuous therapy in emergency cases of severe asthma with acute bronchospasm. They reported that continuous nebulization therapy was superior to intermittent nebulization in management of the most severe cases. For adult patients with peak expiratory flow rates (PEFRs) less than 200 L/min, significantly higher PEFRs ($P = .01$), and clinically important improvement occurred in those receiving continuous nebulization therapy compared with those receiving the same dosage by intermittent nebulization. In addition, there was a marked and sig-

Table 4. Illustrative Drug Concentrations of Nebulized Solutions (C_n mg/mL, Eq. 3) Required to Achieve Various Aerosolization Dosage Regimens*

	Nebulizer Flow Rate (L/min)	Drug Solution Concentration (mg/mL)			
		Drug Dosage 2.5 mg/h	Drug Dosage 5 mg/h	Drug Dosage 10 mg/h	Drug Dosage 15 mg/h
MiniHEART	1.5	0.6 mg/mL	1.1 mg/mL	2.2 mg/mL	2.5 mg/mL
	2	0.3 mg/mL	0.6 mg/mL	1.3 mg/mL	1.9 mg/mL
	2.5	0.25 mg/mL	0.5 mg/mL	1.0 mg/mL	1.5 mg/mL
HEART	10	0.08 mg/mL	0.17 mg/mL	0.33 mg/mL	0.50 mg/mL
	12	0.06 mg/mL	0.12 mg/mL	0.24 mg/mL	0.36 mg/mL
	15	0.04 mg/mL	0.09 mg/mL	0.18 mg/mL	0.27 mg/mL

* Drug dosages expressed as milligrams of drug aerosolized per hour of continuous nebulization therapy, **D** (mg/h).

Table 5. Volumes of Drug Stock Solution of Albuterol at 5 mg/mL (medicine) and Physiologic Saline in Nebulized Solution Required for One Hour of Continuous Nebulization Therapy to Achieve Various Aerosolization Dosage Regimens with the HEART and MiniHEART Nebulizers*

	Flow Rate, Q L/min, and liquid output, A (mL/h)	Solution Constituents (mL)		
		Drug Dosage 5 mg/h	Drug Dosage 10 mg/h	Drug Dosage 15 mg/h
MiniHEART	1.5 L/min (4.5 mL/h)	3.5 mL saline & 1 mL medicine	2.5 mL saline & 2 mL medicine	1.5 mL saline & 3 mL medicine
	2 L/min (8 mL/h)	7 mL saline & 1 mL medicine	6 mL saline & 2 mL medicine	5 mL saline & 3 mL medicine
	2.5 L/min (10 mL/h)	9 mL saline & 1 mL medicine	8 mL saline & 2 mL medicine	7 mL saline & 3 mL medicine
HEART	10 L/min (30 mL/h)	29 mL saline & 1 mL medicine	28 mL saline & 2 mL medicine	27 mL saline & 3 mL medicine
	12 L/min (42 mL/h)	41 mL saline & 1 mL medicine	40 mL saline & 2 mL medicine	39 mL saline & 3 mL medicine
	15 L/min (56 mL/h)	55 mL saline & 1 mL medicine	54 mL saline & 2 mL medicine	53 mL saline & 3 mL medicine

* Drug dosages expressed as milligrams of drug aerosolized per hour (mg/h). The sum of the saline and medicine volumes equals the nebulizer liquid output in one hour, A (mL/h).

Table 6. Volumes of Drug Stock Solution of Terbutaline Sulfate at 1 mg/mL (medicine) and Physiologic Saline in Nebulized Solution Required for One Hour of Continuous Nebulization Therapy to Achieve Various Aerosolization Dosage Regimens with the HEART and MiniHEART Nebulizers

	Nebulizer Flow Rate, Q L/min, and liquid output, A (mL/h)	Solution Constituents (mL)		
		Drug Dosage 2.5 mg/h	Drug Dosage 5 mg/h	Drug Dosage 7.5 mg/h
MiniHEART	1.5 L/min (4.5 mL/h)	2 mL saline & 2.5 mL medicine	0 mL saline & 5 mL medicine	NA†
	2 L/min (8 mL/h)	5.5 mL saline & 2.5 mL medicine	3 mL saline & 5 mL medicine	0.5 mL saline & 7.5 mL medicine
	2.5 L/min (10 mL/h)	7.5 mL saline & 2.5 mL medicine	5 mL saline & 5 mL medicine	2.5 mL saline & 7.5 mL medicine
HEART	10 L/min (30 mL/h)	27.5 mL saline & 2.5 mL medicine	25 mL saline & 5 mL medicine	22.5 mL saline & 7.5 mL medicine
	12 L/min (42 mL/h)	39.5 mL saline & 2.5 mL medicine	37 mL saline & 5 mL medicine	34.5 mL saline & 7.5 mL medicine
	15 L/min (56 mL/h)	53.5 mL saline & 2.5 mL medicine	51 mL saline & 5 mL medicine	48.5 mL saline & 7.5 mL medicine

* Drug dosages expressed as milligrams of drug aerosolized per hour (mg/h). The sum of the saline and medicine volumes equals the nebulizer liquid output in one hour, A (mL/h).
† Level not achievable because the maximum drug concentration is the stock at 1 mg/mL.

nificant improvement in heart rate reduction, higher discharge rate, and lower admission rate in the group that received continuous nebulization therapy ($P < .05$).

Papo et al[44] showed in a prospective randomized study that continuously nebulized albuterol was safe and resulted in more rapid clinical improvement than intermittent nebulization therapy. Respiratory therapy attention at bedside and duration of hospital stay were subsequently less for patients receiving treatment with continuously nebulized aerosols.

The usefulness of continuous aerosolization therapy has been established.[7] The standard small-volume, hand-held nebulizer that has previously been used such as by Moler et al[15] and by Reisner et al[42] needs additional airflow (diluting air) to provide adequate volume for meeting the patient's respiratory demands. A higher flow-rate nebulizer provides a useful alternative. Its performance characteristics give desirable aerosol output and particle size distribution with a variety of flow rates that are important for therapeutic efficacy. The larger reservoir can provide up to eight hours of aerosolized solution without refill. The oxygen or air source of at least 10 L/min is sufficient to match inspiratory needs of most patients. This can be increased to 15 L/min if needed for patients with higher inspiratory requirements. Even a mini-nebulizer, however, might achieve the same medication dosages as a larger high flow-rate nebulizer by using an appropriate concentration of the nebulized solution and volumetric flow rate. Dosage regimens for continuous nebulization therapy can be established and implemented using a high flow-rate nebulizer such as described in detail by Ferrante and Painter.[45]

Studies have shown that it is important to have an optimal particle size distribution in order for aerosolized medicine to be delivered to the receptor sites. The two nebulizers in this study each generate particles that are primarily in the desirable aerodynamic equivalent diameter range of 1 to 5 μm

for optimal deposition (Fig 2) and the particle size distributions for both high flow-rate and low flow-rate nebulizers was remarkably consistent over the whole range of various operational flow rates (Tables 1 and 2). Although the concentration of nebulized solution increases with time, the effect does not appear to be clinically significant (Fig 4). Other types of nebulizers that may have a smaller ratio of aerosol output to water evaporation [a/w] could have much more serious concentration problems and may not be suitable for continuous nebulization therapy.

CONCLUSION

In summary, continuous nebulization therapy has been shown in various published studies to be an important means of treating patients with severe asthma that can be labor efficient, may reduce length of hospitalization, and reduce subsequent admissions. Dosage criteria can be established based on the operating characteristics of the nebulizer system, drug solution concentration, and patient respiration. Normally, the nebulization rate of drug is used to prescribe the treatment although it is understood that deposition of drug in the lungs of the patient is about one-quarter of the nebulizer output. Dosage planning, equipment set-up, operation and monitoring are readily accomplished with modern high output nebulizers such as the HEART. Further use and evaluation of continuous nebulization therapy for β_2 agonists may be desirable for pediatric and adult patients with severe reversible airway disease.

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