
Lung Dose, Distribution, and Clinical Response to Therapeutic Aerosols

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The response to therapeutic aerosols is considered to be a function of the dose deposited at the target site in the lung. The dose, in turn, is dependent upon the system producing the aerosol, the particle size characteristics of the inhaled aerosol, the mode of inhalation, and the calibre of the airways. The influence of the pattern of deposition of the inhaled dose, i.e., selective delivery to the central vs. small, peripheral airways, on the response is not as well defined. Distribution of therapeutic aerosols in the lung has been measured using a variety of tracer methods; correlations with clinical response have been obtained in a limited number of these same studies. Systems used to provide unit doses of therapeutic aerosols are the metered dose inhaler (MDI), containing drug in a pressurized formulation, and the dry powder inhalers (DPI). Efficiency of delivery is on the order of 5–15% for these systems, even under optimal inhalation conditions. Continuous aerosol is provided by the jet or ultrasonic nebulizer with delivery efficiencies ranging from 1 to 5% for the former and approximately 10% for the

latter. The particle size of aerosol from these devices ranges from $< 1 \mu\text{m}$ mass median aerodynamic diameter (MMAD) to $12 \mu\text{m}$ MMAD. However, the “effect” of particle size, once the inspiratory flow rate is taken into account, can be much greater, shifting the deposition pattern to more proximal airways, as does airway narrowing owing to the presence of lung disease. Increased flow rates and changes in airway geometry can alter both the dose deposited and the response and may necessitate the adjustment of dosing levels to meet the needs of the individual patient. By using a variety of methods, deposition efficiency can be improved and medication “targeted” to the lower respiratory tract to minimize local and systemic side effects. Practically, these methods consist of baffling and the addition of valved spacer devices to the MDI. New formulations and delivery systems are being developed to provide finer, and more respirable aerosols, with sustained action. Knowledge of the lung dose and distribution of inhaled aerosols from these systems is critical for the assessment of their performance in vivo.

INTRODUCTION

Aerosols are used in both the diagnosis and the treatment of respiratory diseases (Dolovich et al., 1985). The efficacy of a diagnostic or therapeutic aerosol is mainly determined by the dose deposited in the lower respiratory tract whereas the influence of the distribution of that dose within the lung on response is less clear. The amount of respirable aerosol (the percentage contained in particles $< 5 \mu\text{m}$) provided by the nebulizer system can be determined from the particle size distribu-

tion characteristics of the aerosol and the measurements of the quantity of “useful” aerosol produced by system. Other variables such as the inhalation pattern adopted by the patient (inspiratory flow rate, inspiratory volume, and breath-holding time) and the degree of airway narrowing that varies with type and severity of the lung disease will influence the dose deposited and the distribution of that dose within the lung (Chan and Lippman, 1980) (Figure 1). Because the location of autonomic receptors varies within the lung,

successful therapy may depend upon targeting specific receptor sites in the lung with different types of drugs (Barnes et al., 1983).

DOSE AND RESPONSE

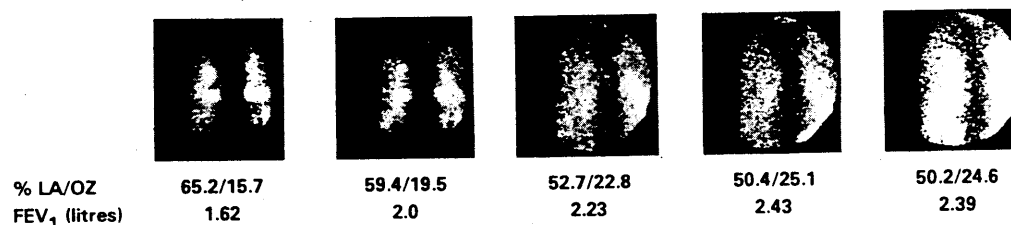
The main criterion for effectiveness of inhaled therapeutic aerosols is the clinical results. The decision to measure responses to single doses, multiple doses, or cumulative doses of a drug is based on study objectives. Responses to treatment can be assessed by a variety of methods

(Table 1) including simple clinical tests, or laboratory or physiologic measurements. For example, a clinical scoring system and measurement of methacholine airway responsiveness have been used in asthmatics to demonstrate the efficacy of inhaled steroid for a period of 1 year (Juniper et al., 1990). A decrease in inflammatory cells in bronchoalveolar lavage fluid has been used as an outcome to assess a short course of inhaled steroid delivered from a metered dose inhaler (Howarth et al., 1990).

The local (lung) dose of medication together with the response to that dose

J.M.

DEVILBISS646 (2.4 μ)



NANOMIST (0.5 μ)

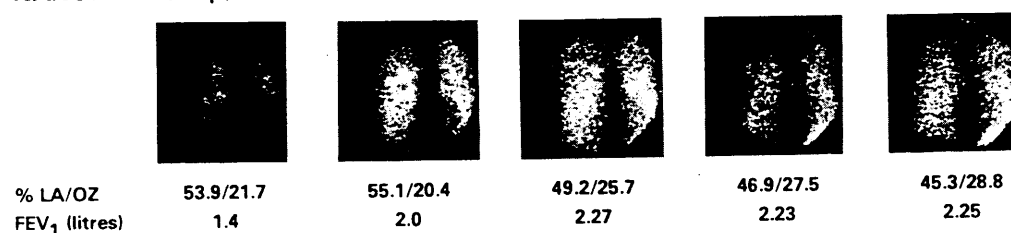


FIGURE 1. Series of lung scans obtained from an asthmatic subject (J.M.) after inhaling increasing doses of bronchodilator (fenoterol) radiolabeled with ^{99m}Tc-sulfur colloid. The drug was administered as two different sized aerosols, 2.4 and 0.5 μ m, on two separate occasions. The percentage deposited on the large, central airways (LA) and peripheral lung or outer zone (OZ) is given under each scan along with the FEV₁ in liters. As bronchodilatation progressed from a baseline of 1.62 or 1.4 L, more aerosol was deposited in the lung periphery and less on the large airways. Hot spots or concentration of radioactivity in the central airways due to airway narrowing were more evident with the larger particle aerosol, particularly at baseline.

TABLE 1. Tests for Assessment of Responses to Inhalant Treatment

Therapeutic effects
Symptom and medication scoring
Pulmonary function
Nonspecific airway responsiveness
Mucociliary clearance
Respiratory (epithelial) clearance
Bronchoalveolar lavage (cells, markers)
Sputum cytology
Bronchial biopsy
Adverse effects
Cardiac function
Metabolic parameters
Tremor

have been measured in a limited number of clinical trials. Using technetium-99m sulfur colloid delivered as a 3- μ m aerosol generated by an ultrasonic nebulizer, Ruffin and co-workers (Ruffin et al. 1978b), in a multidose study performed in our laboratory, demonstrated that only 26.2 ± 5.9 μ g of fenoterol was needed to produce maximum bronchodilatation in a group of mild to moderate asthmatics, and that no greater bronchodilatation in these subjects could be achieved by deposition of four times this amount. These subjects then were on the plateau of their bronchodilator dose-response curve. In another study of cumulative doses of fenoterol (Dolovich et al., 1981a), hand tremor, but not the forced expiratory volume for 1 s (FEV₁) continued to increase as the deposited lung dose exceeded 20 μ g and did not appear to level off even at a lung dose of 120 μ g. Thus, the administration of inhaled beta-2 agonist at doses higher than that producing maximum bronchodilatation leads to an increased risk of systemic side effects characteristic of the drug. It is unclear from a number of studies in the literature whether response is governed solely by the dose delivered, the distribution of that dose in the lungs, or the combination of both the dose and its distribution.

Clinical Trial Methodology—Variables Pertaining to Lung Dose-Response Studies

In order to compare results from various clinical trials, it is important to account for differences in design and methodology (Ahrens, 1991). When the objective is to relate topical lung dose to clinical response, variables affecting the measurement of lung dose need to be considered (Table 2). For example, in patients with more severe lung disease, lung function may be unstable. Thus, reproducibility of the lung dose and distribution may be compromised and results obtained from different doses on different days could vary. These patients may require higher doses of drug to achieve the optimal bronchodilator effect. Thus, there is need to define the degree of impairment of lung function in the population studied.

Table 3 lists a number of studies of deposition of radiolabel from the metered dose inhaler (MDI). Labeling techniques used included direct labeling of drug (Atrovent) with ⁷⁷Br, spray-dried drug particles of sodium cromoglycate (SCG) in which the label is incorporated within the particle, radiolabeled monodisperse teflon particles (3.2 μ m) mixed into the drug formulation, and a solution of the radiolabel (^{99m}TcO₄⁻) in the surfactant/chloro-fluorocarbon mixture. The types of sub-

TABLE 2. Factors to Consider When Assessing Clinical Trials Involving the Measurement of Local Drug Dose and Clinical Response

Patient group (age, sex, severity of disease, stability of baseline pulmonary function)
Characteristics of aerosol system (particle size, drug output)
Choice of drug
Radiolabeling technique for drug formulation
Inhalation technique for delivery of drug aerosol
Scanning technique (correction for tissue absorption, calculation of dose)

jects studied also varied. The percentage deposition in the lung ranged from 6.5% to 24.4%. The reduction in the detection of the radioactivity due to tissue absorption is also a factor. For example, for studies from our laboratory (Dolovich et al., 1981b, 1983), taking tissue absorption into account would increase the results by a factor of 1.91. Furthermore, all studies, with the exception of those from our laboratory, were performed with the MDI dose inhaled using the closed-mouth technique (MDI placed in the mouth with the lips closed around the actuator mouthpiece) as opposed to the open-mouth technique (MDI held 4.0 cm in front of the wide open mouth). The latter technique has been shown to double the quantity of drug deposited in the lower respiratory tract (Dolovich et al., 1981b) and increase the bronchodilator response (Thomas et al., 1984). When results given in Table 3 were paired and compared to the deposition data obtained from the MDIs with add-on devices attached (Table 4), significant differences between studies were ob-

tained (Newman et al., 1984, 1986, 1991; Hardy et al., 1991; Hupert and Matthys, 1991), whereas the comparison using the MDI + Aerochamber to the MDI alone showed no difference (Dolovich et al., 1983). Thus, the variations in study design and experimental technique can lead to confusion when comparisons of results are made.

FACTORS AFFECTING DOSE AND RESPONSE

Aerosol Delivery System

Numerous systems are available for delivery of aerosols to the lung. These include jet and ultrasonic nebulizers, powder inhalers, and chlorofluorocarbon-containing (Freon®) pressurized canisters. Aerosols produced by these systems can be delivered to the airways through mouthpieces, face mask, tubing, MDI add-on devices (holding chambers or spacers), and mechanical ventilator circuits. Efficiency of delivery is dependent upon the system used but in general, < 20% of the total

TABLE 3. Lung Deposition from Labeled MDI Aerosols

MDI	Radiolabel	Group	No. of subjects	Percentage of lung deposition ^a	Reference
Atrovent	⁷⁷ Br	normals	7	11.2	Spiro et al. (1984)
		chronic bronchitis	7	11.7	
Intal	^{99m} Tc-SCG (SD)	normals	7	9.5	Vidgren et al. (1987)
	^{99m} TcO ₄ ⁻	normals	10	11.0	Newman et al. (1989)
	^{99m} Tc-Teflon	oad	10	6.5 UT	Newman et al. (1986)
				11.2 CT	
	^{99m} Tc-Teflon	oad	9	8.7	Newman et al. (1984)
Ventolin	^{99m} Tc-Teflon	asthma	9	11.2	Zainudin et al. (1990)
	^{99m} TcO ₄ ⁻	asthma	10	12.8	Newman et al. (1991)
		normals	6	24.4	Biddiscombe (1991)
Placebo	^{99m} TcO ₄ ⁻	normals	7	10.4 ^b OT	Dolovich et al. (1983)
		copd	14	8.7 ^b OT	
		normals	12	6.2 ^b OT	Dolovich et al. (1981b)
				12.3 ^b OT	
Nacystelyn	^{99m} TcO ₄ ⁻	normals	6	12.3	Hardy et al. (1991)

Abbreviations: SD, spray dried; UT, usual (closed mouth) technique; CT, correct (closed mouth) technique; OT, optimal (open mouth) technique; oad, obstructive airways disease; copd, chronic obstructive pulmonary disease.

^aMean (% of metered dose).

^bMultiply by 1.91 to correct for tissue absorption.

TABLE 4. Lung Deposition from Labeled MDIs Used with Add-on Devices

MDI add-on device	Volume (mL)	^{99m} Tc Label plus drug	Group		Percentage of lung deposition ^a	Reference
Inhalet	50	SCG-SD	normals	<i>n</i> = 7	16.1	Vidgren et al. (1987)
		Nacystelyn	normals	<i>n</i> = 6	9.3	Hardy et al. (1991)
Azmacort	113	TAA	normals	<i>n</i> = 8	5.2 ^b	Dolovich (1989)
Aerochamber	140	placebo	normals	<i>n</i> = 7	9.9 ^b	Dolovich et al. (1983)
			oad	<i>n</i> = 14	9.0 ^b	
Aerovent	140	fenoterol	copd	<i>n</i> = 9	5.7 ^b	Fuller et al. (1990)
Rondo	270	salbutamol	asthma	<i>n</i> = 10	23.8	Newman et al. (1991)
Chiesi	380	fenoterol	normals	<i>n</i> = 5	9.0	Hupert and Matthys (1991)
Inspirease	700	teflon	oad	<i>n</i> = 10	14.8	Newman et al. (1986)
		SCG-SD	normals	<i>n</i> = 7	20.4	Vidgren et al. (1987)
Nebuhaler	750	teflon	oad	<i>n</i> = 9	20.9	Newman et al. (1984)
		SCG-SD	normals	<i>n</i> = 7	14.4	Vidgren et al. (1987)

Abbreviations: SD, spray dried particles; TAA, triamcinolone acetoneide.

^aMean (% of metered dose).

^bMultiply by 1.91 to correct for tissue absorption.

^cBoth lung deposition and response were measured in this study only.

drug metered or placed in the nebulizer reservoir is delivered to the lower respiratory tract. Three systems currently used to deliver pentamidine aerosol illustrate this variability in delivery (Table 5). The rate of production of aerosol from these systems is different and the particle size characteristics range from approximately 1 to 6 μm . Unless starting doses are adjusted, different amounts of respirable drug ($< 5 \mu\text{m}\%$) are available to the patient and clinical outcomes may be affected. Thus, these properties of the nebulizer system should be obtained to ensure adequate delivery of drug (O'Callaghan, 1990).

Aerosol Particle Size

The dose or mass of drug delivered to the lower respiratory tract is primarily a function of the size of the aerosol produced and subsequently inhaled. The size also partly determines the distribution of the aerosolized drug in the lung. Finer aerosols distribute to more peripheral airways but carry less drug (mass), and therefore inhalation of greater amounts of drug

may be required to produce the desired response (Ruffin et al., 1978a). In contrast, large particle aerosols containing more drug deposit in proximal, central airways.

A number of studies of aerosols have related lung responses to particle size. In general, those aerosols with mass medium aerodynamic diameter (MMAD) $< 5 \mu\text{m}$ produce optimal response, whether the aerosol is inhaled from a MDI (Rees et al., 1982) or jet nebulizer (Johnson et al., 1989; Patel et al., 1990). However, it is evident from the studies shown in Table 6 that inhalation of equal drug doses generated as different sized aerosols, can produce equivalent responses despite differences in particle size and initial distribution of the aerosol within the lung (Dolovich et al., 1981a; Mitchell et al., 1987; Wollmer et al., 1987). A factor affecting outcome may be the change in distribution of aerosol occurring during bronchodilator treatment. As bronchodilation increases, drug distribution becomes more uniform and targeted to the peripheral airways (Dolovich et al., 1981a) (Figure 1). A sufficient amount of large parti-

TABLE 5. Characteristics of Three Nebulizers Used to Deliver Pentamidine* (5 mL of 60 µg/mL)

	Respigard II @ 10 L/min	PortaSonic	Fisoneb @ 50% max
Output pentamidine (mg/min)	0.34	0.37	0.58
MMAD (µm)	0.97	1.93	6.13
Percentage < 5 µm	98	85	39
Time to nebulize dose (min)	12	8	7

* Data from Dolovich et al. (1990).

cle drug aerosol may thus reach the appropriate receptors to produce the desired effect.

Inspiratory Parameters

At high inspiratory flow rates (> 1 L/min), less aerosol is inhaled into the lung; the fraction that is inhaled deposits mainly on central airways (Dolovich and Newhouse, 1988). This can result in a reduced clinical response as shown by Newman et al. (1980) for an MDI bronchodilator aerosol inhaled at 80 L/min compared to 25 L/min and similarly by

Ryan et al. (1981) for inhalation of an aerosolized bronchoconstrictor challenge substance using high inspiratory flow rates. However, inhalation from some dry powder inhalation devices requires a high inspiratory flow rate in order to obtain the maximum dose of drug (Auty et al., 1986). With an increased breath holding time at end-inspiration, particles have more time to sediment to airway walls, thereby increasing the dose delivered and the resulting bronchodilatation (Newman et al., 1979; Heyder et al., 1980). Careful monitoring to control inspiratory flow rates during inhalation of a test substance will reduce the variability in the outcome measures.

Airway Disease

Reduction in airway calibre due to disease increases deposition in the central airways. The extent of airway narrowing correlates with pulmonary function. In general, the more severe the airway narrowing, the lower the FEV₁ and measurements of airflow capacities of the smaller, peripheral airways (Dolovich et al., 1976; Kim et al., 1988). Patients with greater

TABLE 6. Effect of Aerosol Particle Size on Bronchodilator Response

Study	Asthmatic population	Drug	Aerosol particle size (µm)	Outcome
Dolovich et al. (1981a)	mild to moderate	fenoterol	0.55 2.4	Equal response for equivalent lung doses
Clay et al. (1986)	mild, 5/8 smokers	salbutamol	1.8 4.6 10.3	Lung dose greater for 4.6-µm aerosol, distribution more central for larger aerosol; no difference in response
Mitchell et al. (1987)	chronic, severe stable	salbutamol	1.4 5.5	Equal lung doses with equivalent response
Johnson et al. (1989)	moderate	ipratropium bromide	3.3 7.7	Equivalent response for unequal doses, probable receptor effect
	moderate	salbutamol	3.3 7.7	Greater lung dose from 3.3 µm with greater response
Wollmer et al. (1987)	moderate	terbutaline	0.25 ^a 4.20 ^a	Equivalent response for equal doses inhaled whether drug deposited centrally or peripherally

^a Data from Corkery et al. 1988. *Respir. Care* 33:676-685.

impairment due to chronic disease or an acute exacerbation (Svedmyr, 1991) may require more drug to achieve an optimal clinical response (Jenkins et al., 1987; Tarala et al., 1980). Thus it may be advantageous to titrate the dose to achieve the maximum response for an individual patient. Stratifying patients according to the severity of their disease thus becomes important when testing a drug in a clinical trial.

Aerosol Dose

One method of measuring topical lung dose is by external detection of an inhaled radiotracer. Values for lung doses are about 10% for metered dose inhaler taken by the optimal technique (Table 3) and between 1% and 15% for aerosol administered from a jet or ultrasonic nebulizer. Variability in these measured values may reflect differences in methodology.

One method of increasing the mass of drug deposited in the lung from an MDI aerosol is to attach a valved holding chamber (add-on device) to the MDI (Table 4). The patient then inhales the aerosolized drug dose from the device rather than directly from the MDI. Valved holding chambers such as the Aerochamber (140 mL) were designed to select only the respirable fraction (contained in particles $< 2.8 \mu\text{m}$) of the MDI aerosol for inhalation (Corr et al., 1982). The larger particles, which otherwise deposit in the

mouth and throat, are lost in the device owing to impaction on the chamber walls and the one-way valve positioned between the mouth and chamber, but distal to the exhalation ports (Dolovich et al., 1983; Dolovich, 1989). Additional evaporation of the chlorofluorocarbons in the brief time between MDI actuation and inhalation results in an increased number of particles $< 3 \mu\text{m}$ in diameter and particularly, in particles $< 1 \mu\text{m}$. The benefit resulting from the increased mass of drug contained in particles $< 1 \mu\text{m}$ in diameter (Table 7) may be offset by their lower deposition efficiency in the lung, and this may partially explain why the lung deposition (and also clinical response) with the Aerochamber is the same as that for a properly used MDI.

The overall effect of the Aerochamber is the production of an aerosol with a smaller MMAD than the original aerosol and reduced total output, reflecting loss of large non-respirable particles in the chamber. In addition, the particles decelerate in the chamber, making the aerosol easier to inhale. The advantages to the patient using an add-on device are that (a) coordination of actuation with inhalation is unnecessary, unless the add-on device does not contain a one-way valve, and (b) a reduction in deposition in the mouth and throat of large particles is achieved. This latter benefit results in a lower incidence of side effects, particularly with the use of steroid aerosols (Salzman and

TABLE 7. Berotec MDI vs. Berotec MDI + Aerochamber (AC): Aerosol Size Characteristics and Dose Output to Filter

	MDI	MDI + AC	MDI vs. AC + MDI: percent change
MMAD (μm)	3.49 ± 0.25	2.65 ± 0.17	-24
GSD	1.66 ± 0.06	1.90 ± 0.12	+14
percent mass $< 5 \mu\text{m}$	75.5 ± 5.24	83.8 ± 0.67	+11
percent mass $< 3 \mu\text{m}$	39.6 ± 3.78	56.4 ± 2.19	+42
percent mass $< 1 \mu\text{m}$	16.7 ± 2.17	26.0 ± 2.24	+56
Filter (μg fenoterol)	106.7 ± 13.8	33.6 ± 14.4	-69

Pyszczyński, 1988). Values of lung deposition with a number of add-on devices have been measured and found to range, as a percentage of the metered dose, from 5.2% to 23.8% (Table 4). As mentioned earlier, this variability may be the result of differences in labeling techniques, calibration procedures, and subjects studied.

The dimensions of the Aerochamber were determined based upon measurements of the MMAD of the aerosol exiting tubes of various lengths and diameters (Figure 2) as well as from dose output measurements (Figure 3). It can be seen

that, although the MMAD approached that of the original aerosol with increasing chamber volume, there appeared to be no advantage to increasing the length beyond 11 cm at a fixed diameter of 3.2 cm. Measurements of drug output, both in terms of absolute levels and as a percentage of the original MDI dose, showed a plateauing at a volume of approximately 140 mL. Although the percentage of respirable particles in the 1–5- μm size interval continued to increase with increasing chamber volume, the advantages in terms of portability of the 140-mL device out-

Effect of Holding Chamber Geometry on MDI Aerosol Characteristics
(MDI: Fluorescein solution placebo)

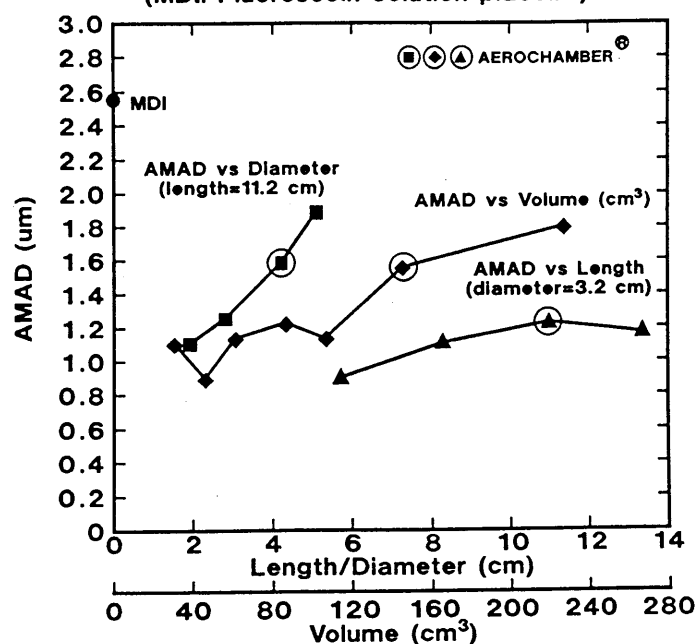


FIGURE 2. Effect of the dimensions (diameter, length, and volume) of a valved holding chamber (HC) on the particle size characteristics of a MDI aerosol. The values for the Aerochamber (volume 140 mL) are denoted by the circle symbols. Owing to geometry, the influence of the diameter of the holding chamber on the activity median aerodynamic diameter (AMAD) of the aerosol exiting the HC is greater than that of its length. By extrapolation, a HC with a volume of approximately 400 mL will deliver an aerosol with the same AMAD as the original aerosol (closed circle on the vertical axis).

Effect of Holding Chamber Geometry on MDI Aerosol Characteristics (MDI: Fluorescein solution placebo)

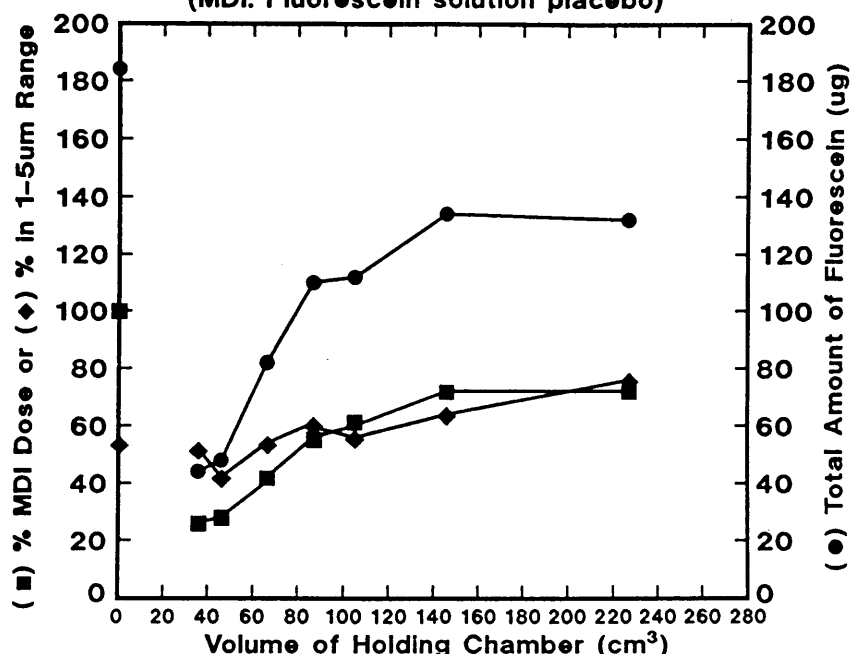


FIGURE 3. Effect of holding chamber (HC) volume on the size characteristics (percentage of particles in 1–5- μ m range) and available drug (percentage of original MDI, absolute dose in micrograms) from an MDI. The values for the MDI without HC attached are shown by the closed symbols on the left vertical axis. The amount of available drug from the holding chamber increases with increasing volume up to 140 mL. No further increase in drug output was measured with a larger volume HC but, as the volume increased further, the percentage of drug contained in particles in the 1–5- μ m range increased and, by extrapolation, would be 100% or all of the aerosol from the MDI used alone at a HC volume of approximately 400 mL.

weighed this gain and, indeed, the clinical data support this.

A plateau of the dose response curve is readily reached with inhaled beta agonist. In the recent study by Newman et al. (1991), both lung doses and FEV₁ responses were measured after inhalation of radiolabeled salbutamol from an MDI and compared to the MDI with an attached add-on device, the Rondo (Tables 3 and 4). Mean lung doses measured after the MDI inhalation were 12.3%, increasing to

23.8% with the Rondo. The distribution of the drug dose between the central/peripheral airways was the same for both inhalations. However, this doubling of the dose did not produce an increase in the FEV₁ response. A possible explanation is that these moderate asthmatics achieved the plateau of their dose-response curve with 12.3% of the drug administered. Therefore the addition of further drug would not change the response. This is similar to findings with other MDI add-on

devices. For example, the increased doses measured with the larger 700-mL In-spirease have not resulted in an improved clinical response when compared to the MDI used with the smaller, 140-mL Aerochamber (Konig et al., 1988; Crimi et al., 1989).

Drug Formulation

The location of receptors in the lung for different classes of drug can influence the response. A study comparing an anticholinergic agent (ipratropium bromide) to an adrenergic agent (salbutamol) illustrates this point. The response to cumulative doses of ipratropium delivered either as 3.3- or 7.7- μ m aerosols was identical, whereas the responses to salbutamol delivered from the same two aerosol systems resulted in a significant difference in clinical outcomes for the finer aerosol (Johnson et al., 1989). This is not surprising, as the receptors for ipratropium bromide are located in central airways while the receptors for salbutamol are mainly in the peripheral lung (Barnes et al., 1983).

SUMMARY

There exists some uncertainty as to the relevance of the topographical distribution of the lung dose to the clinical response. In general, the greater the dose inhaled, the greater the response, unless the plateau of the dose-response curve has been reached. There are several reasons for measuring the lung dose and distribution for the aerosolized drugs being tested (Table 8). It is one way of assessing the performance of the delivery system. Adjustments to the dose of medication can be made according to findings in the individual patient. In some instances, it is appropriate to target therapy to the peripheral airways (Selroos, 1986) and the success of the delivery system in doing this can be measured. The use of

TABLE 8. Reasons for Measuring Lung Dose /Distribution of Inhaled Aerosols

Performance of aerosol delivery system
Dose adjustment
Targeting of aerosol therapy
Design of more efficient delivery systems
Assessment of topical/systemic treatment via aerosol
With new drug formulations
With new (aerosol) formulations of existing drugs

new drug formulations (Farr et al., 1985) as well as new aerosol formulations of existing oral or intravenous drugs can be assessed by direct measurements of deposition. Furthermore, it can be beneficial to the process of developing efficient delivery systems for topical and/or systemic treatment with aerosolized drugs by knowing both the dose to the lung as well as the clinical response.

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