

Anatomy and physiology in delivery: can we define our targets?

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Studies have shown that the receptors for β -agonists, inflammatory markers, and mast cells are distributed throughout the airways. Thus topical delivery of drug for the management of asthma requires an even spread throughout the lungs. Particles of 2–5 μm in diameter have the greatest potential to be deposited throughout the lungs during inhalation, by impaction and sedimentation. Inhaled products, therefore, are formulated such that almost half of the dose emitted during inhalation contains particles less than 5 μm in diameter. This is known as the fine-particle dose. Studies in adults (volunteers and asthmatic patients), using radiolabeling techniques, have shown that although the amount of drug deposited in the airways (total lung dose) from different inhaled products varies, the percentages of this amount distributed throughout the central, intermediate, and peripheral zones are fairly consistent. All that varies, therefore, is the density of the spread. Studies in children indicate that lung deposition is lower than in adults. Nevertheless, all factors which affect lung deposition in adults do so also in children. The lower lung deposition in children indicates the use of adult doses, and the importance of inhaler device and of inhalation technique. The even distribution of inhaled drug throughout the required therapeutic areas highlights the importance of the total lung dose.

Topical therapy to the therapeutically active sites of the airways is achieved by inhalation. However, the process of delivering drugs to these sites is not simple and is related to many factors associated with the inhaled product and the patient. The difficulties that adults have when using an inhaled product have been widely recognized for more than 20 years (1–3), and similar problems occur when children use their inhalers despite the assistance of their parents (4). Recently, some breath-actuated inhaled products and

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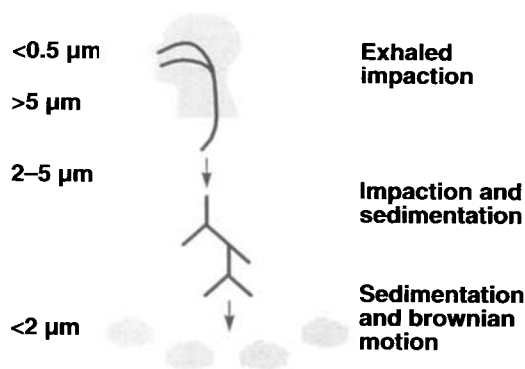


Figure 1. Deposition processes during inhalation.

spacers have been introduced to overcome many of the difficulties experienced by patients.

The characteristics of the emitted dose from an inhaled product determine how much drug is deposited in the lungs. These characteristics are determined by the formulation, the inhaled device, and use by the patient. The patient factors include inhalation technique, especially coordination of dose release with inhalation, and the inspiration rate. The age of children and their size are additional factors which determine the delivery of drugs to the lungs.

Particle size and lung deposition

Various studies have shown that particles within a size range of 2–5 μm are those most likely to be deposited in the lungs. Rees et al. (5) demonstrated that when 10 asthmatic patients inhaled terbutaline, there was little bronchodilation when formulations containing drug particles of $>5 \mu\text{m}$ in diameter were inhaled. Particles above 5 μm in diameter are most likely to be deposited in the mouth and throat; thus, most of these are eventually swallowed. A study of eight patients with mild asthma who inhaled isoproterenol particles of 2.5 and 5 μm in diameter showed that the percentage increases (from baseline) in FEV₁, SGaw and FEF_{25–75}, and the decrease in FRC, were greater for the smallest particles (6). These lung-function results also suggest a fairly even spread of drug throughout the airways for both formulations. Zanen et al. reported that the bronchodilator response to inhaled β -agonists is reduced when the particles are too small (7). They reported that the spirometric response was greater after inhalation of salbutamol particles of 2.8 μm in diameter than particles of either 1.5 or 5 μm in diameter. This study of seven patients with severe airflow obstruction was repeated by these authors in patients with mild asthma (8), and similar results were

reported. If the particles are too small, they will be preferentially deposited in the alveoli where there is no smooth muscle and thus no bronchodilation (9). Putting more drug into these regions would not be beneficial and would merely increase rapid systemic drug delivery. The net effect of this would be to increase side-effects, especially for high inhaled doses.

During inhalation, drug particles are deposited in the lungs by impaction, sedimentation, and diffusion processes, as shown in Fig. 1 (10). During inhalation via the mouth, the airstream immediately encounters a 90° bend, and many large particles will not flow around this. These will be deposited in the mouth and throat and will then be swallowed. Most particles less than 5 μm in diameter are capable of flowing in the airstream around this bend and hence down the trachea. As the trachea branches and the airways undergo bifurcation, particles of 2–5 μm in diameter are most likely to be deposited in the upper regions. Farther down the airways, the airflow is very slow, and the particles present in these regions will settle under the force of gravity. Particles less than 2 μm in diameter will be deposited in the lower airways by this process of sedimentation, underlining the importance of breath-holding after inhalation. The sedimentation velocity of particles below 0.5 μm in diameter is very slow, and these particles are suspended in the air. These particles exhibit brownian motion and thus are dependent on collision for their movement. If these particles come into contact with an airway lining, they will be deposited; otherwise, they will be exhaled.

Site of action

The lung-function improvements of the isoproterenol study (6) and those from the salbutamol particle studies of Zanen et al. (7, 8) suggest that the receptors for β -agonists are distributed throughout the airways. This is consistent with biopsy samples taken throughout the lungs which have shown that the β -agonist receptors are present from the trachea down to the terminal bronchioles (11–13). However, there is no smooth muscle in the alveolar regions; hence, stimulation of these would not cause bronchodilation.

Glucocorticoid therapy by inhalation is the first-line therapy for the management of asthma. There are many markers of the inflammatory process of asthma, including macrophages, T cells, dendritic cells, and eosinophils (14). Examination of lung biopsies has demonstrated that these inflammatory markers are present throughout the airways of asthmatic lungs (15–18). Kraft et al. (16) also showed that

Table 1. Distribution of β -agonists in central, intermediate, and peripheral zones of lungs of asthmatic subjects after inhalation

Inhalation method	Reference	Total (SD) lung deposition percentage of dose	Percentage of total lung dose		
			Central zone	Intermediate zone	Peripheral zone
MDI	21	12.8 (5.7)	40.6	21.9	37.5
MDI+Spacer	21	23.8 (6.6)	38.7	23.8	38.2
DPI	22	14.2 (6.6)	39.4	23.2	37.3
Nebuliser (Turret)	23	9.1 (1.1)	37.7	22.0	40.7
Nebuliser (Inspiron)	23	2.7 (0.2)	40.7	22.0	37.0

there were significantly ($P<0.05$) more of these inflammatory markers in the lower airway when samples were taken from the lungs of patients with symptoms of nocturnal asthma at 4 am than in those taken at 4 pm. Mast cells store and generate a number of substances which have potent inflammatory effects. It has been reported that mast cells are present throughout the bronchial wall, in the epithelium itself, and in the airway lumen (19). Mast cells constitute up to 0.5–3.0% of the total cells recovered via bronchoalveolar lavage (20). Overall, all these studies indicate that, after inhalation, an even distribution of β -agonists, anti-inflammatory agents, and cromones is required throughout the lungs for the management of asthma, rather than targeting these drugs on specific regions of the lungs.

Total lung deposition and drug distribution in the lung

Gamma scintigraphy studies after inhalation of radiolabeled β -agonists by asthmatic patients have demonstrated that the amount of drug deposited in the lungs is dependent on the inhalation technique, the inhaled product, or both. Despite differences in the percentage of the dose deposited in the lungs (total lung dose), the distribution into various regions

of the lungs remains the same, as shown in Table 1 (21–23). Similar results have been shown in healthy volunteers using different inhaled products (24), and with the same product used at different inhalation rates (25).

Radiolabeled terbutaline inhaled from Turbuhaler by healthy volunteers revealed that the mean (SD) total lung dose was 14.8% (3.2%) of nominal dose at an inspiration rate of 35 l/min and 27.7% (9.5%) at 60 l/min (26). The percentage of the total lung dose deposited in the peripheral region of the lung was identical. When the subjects inhaled budesonide via Turbuhaler, the total lung dose was 27.0% (7.6%), and 44.8% of this was deposited in the peripheral regions. Thus, total lung deposition can be affected by the inhalation rate, as previously reported (25). Consistent distribution of drug throughout the airways is also seen after inhalation of the cromones. Radiolabeled nedocromil was inhaled, by healthy volunteers, using an Ultrahaler at a slow and fast inspiration rate and via a MDI (27). The total lung dose was higher for the fast rate, a finding which is consistent with the above reports for other drugs. The mean (SD) total lung nedocromil dose and its distribution throughout the lung zones are shown in Table 2. This table shows that the percentage of the total lung dose of nedocromil deposited in the central, intermediate, and peripheral zones was similar for the three inhalation methods.

Table 2. Distribution of nedocromil into lungs after inhalation (27)

Inhalation method	Total (SD) lung deposition percentage of dose	Percentage of total lung dose		
		Central zone	Intermediate zone	Peripheral zone
Ultrahaler (fast inhalation)	13.3 (4.8)	33.8	33.8	32.3
Ultrahaler (slow inhalation)	9.8 (3.5)	32.7	31.6	33.7
MDI	7.5 (2.9)	28.0	34.7	37.3

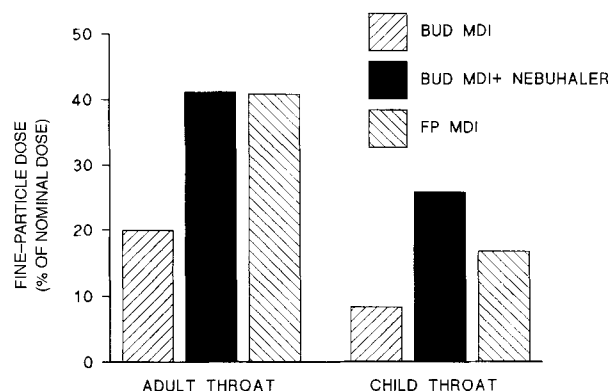


Figure 2. *In vitro* fine-particle dose measured with different sizes of anatomical throat [43]. BUD: budesonide; FP: fluticasone.

All the above studies show that, although the total amount of drug deposited in the lung varies, there is a fairly even distribution throughout the lungs, and thus all that changes is the “thickness of the spread”. Hence, it is the total lung dose that is important rather than the distribution in the different zones of the lungs (28, 29). The differences in the distribution in the different zones for the β -agonists and the chromones (Tables 1 and 2) suggest that the distribution could be drug-specific.

Total lung dose and clinical effect

Zainudin et al. (29) compared the bronchodilatory response and deposition of radiolabeled salbutamol after inhalation via MDI, Rotahaler, and a nebulizer by nine subjects with chronic stable asthma. They showed that the bronchodilator response was related to the total lung dose rather than the distribution of drug throughout the lungs. This is consistent with all the above reports. Furthermore, a study of 10 asthmatic patients reported a greater ($P < 0.01$) total lung dose of terbutaline via Turbuhaler when inhaled at 60 l/min than with an inhalation rate of 30 l/min (30). This effect is consistent with previous reports of the effect of the inhalation rate (25, 27). Greater bronchodilation was reported in these asthmatic patients when inhaling at the higher rate (30). The link between the total lung dose and clinical response was shown in a further study. Borgström et al. (31) showed that the mean (SD) total lung deposition after inhalation of 250 μ g terbutaline from a MDI and Turbuhaler by 13 patients with moderate asthma was 8.1% (2.7%) and 19.0% (7.3%) of the inhaled dose, respectively. Greater bronchodilation was observed after inhalation with Turbuhaler.

Urinary salbutamol excreted during the first 30 min after inhalation has been shown to be an index of total lung deposition (32). A study of 12 patients with stable mild asthma has shown a correlation between this measure and the methacholine dose required to reduce the FEV₁ by 20% (PD₂₀) (33). After inhalation of 100 and 200 μ g of salbutamol by 12 asthmatic patients, the mean (SD) amounts of salbutamol excreted in the urine 30 min after inhalation were 2.25 (0.65) and 5.18 (1.68) μ g, respectively (ratio 1:2.30). The methacholine PD₂₀ values were 3.77 (3.56) and 8.63 (8.16) μ mol, respectively (ratio 1:2.29).

Studies in children

Inhalation studies using gamma scintigraphy in children are not normally carried out for ethical reasons. One study by Tal et al. (34) involved seven asthmatic infants aged 3–48 months. This study revealed that the total lung dose ranged from 0.35% to 5.1% of the dose; the total lung dose in two adults was 19%. All subjects (infants and adults) inhaled radiolabeled salbutamol from a MDI via an Aerochamber spacer fitted with a face mask. This study also revealed that there was an even distribution of drug throughout the infants’ lungs, a finding which is consistent with all the above reports in adults. In a second study (35), in six infants aged 4–30 months, Lodrup et al. found that 14% of a nominal 500 μ g terbutaline dose was retained on a filter placed between the mouth of the infant and a nebulizer. The range in the infants was 9–19%, and increased with age. Gamma scintigraphy studies in children with cystic fibrosis (36, 37) and with bronchopulmonary dysplasia (38) have also reported that the total lung deposition, when expressed as a percentage of the nominal dose, is lower than that reported for adults. All these lung deposition doses do not take into account the smaller lung volume of children.

The lower total lung deposition in asthmatic children has also been reported for inhaled sodium cromoglycate (39). After inhalation of 20 mg sodium cromoglycate by nine boys aged 9–26 months, only 0.13–0.61% of the dose was excreted in the urine. Since oral absorption of sodium cromoglycate is negligible, this represents the amount of drug delivered to the systemic circulation via the lungs and excreted in the urine. Higher urinary excretion of sodium cromoglycate has been reported after inhalation of 20 mg of sodium cromoglycate by seven healthy adults (40); the mean (SD) urinary sodium cromoglycate was 1.94% (0.70%) of the dose.

One reason for the reduced total lung dose in children could be the size of their throats. Studies have shown that

there is a link between the *in vitro* fine-particle dose and the *in vivo* total lung dose (41, 42). Berg (43), using similar *in vitro* methods, showed that the fine-particle doses of a budesonide MDI, a budesonide MDI attached to a spacer, and a fluticasone MDI, were all higher when an adult-sized anatomical throat was used than a child-sized throat (Fig. 2). A study using *in vitro* methods and the breathing patterns of children and infants through an Aerochamber showed that the fine-particle dose could be insensitive to tidal volume (44), but that more drug was emitted from this device when the tidal volume was 200 ml, than with 50 and 100 ml. However, the Spacer Chamber, which is a bigger spacer, was sensitive to tidal volume; thus, there could be a link between tidal volume and the volume of a holding chamber or spacer which is dependent on the size of the two in combination. Similar effects have been reported for tidal volume (45).

Another factor to consider, for the reduced total lung dose in children, is the inhalation rate. In one study, 16 children, aged 8–15 years, with exercise-induced asthma, inhaled through a formoterol or placebo dry-powder inhaler at two different rates (46). The decreases in their FEV₁ after exercise at 12 h after the placebo and the doses inhaled at 30 and 60 l/min were 34%, 23%, and 15%, respectively. The greater protection with formoterol inhaled at the higher flow rate would be consistent with a greater total lung dose, as is consistent with the results reported above for adults (25, 27, 30). A recent study in children with cystic fibrosis has highlighted this correlation between inhalation rate and lung deposition for some dry-powder inhalers (37). This

study revealed that the younger the child, the lower the inhalation rate and the smaller the amount of drug deposited in the lungs. When adjusted for body weight, the lung deposition in all children was similar.

The inhalation method will affect deposition of drug in the lungs, especially in infants, who are too young to understand instructions. Nasal breathing will be a major factor with a face mask, while administration during crying will also limit lung deposition (47). Clarke et al. (48) showed that administration of 800 µg salbutamol via Babyhaler with a face mask to 12 sleepy, wheezy infants significantly decreased bronchial hyperresponsiveness; thus, nasal breathing will deliver some drug into the lungs.

Conclusion

The above reports show that inhaled products or devices which emit particles in the size range of 2–5 µm distribute drug evenly throughout the lungs, and that the amount deposited in the lungs is related to the clinical response. Thus, total dose is the key factor. Studies in children show that the percentage of the dose deposited in their lungs is smaller than in adults. However, these values do not reflect the smaller lungs and body weight of children. The studies suggest that all factors which affect lung deposition in adults apply to children, and support the use of adult doses for children.

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