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The meaning of lung dose

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For a physician to understand how to prescribe appropriate doses of drugs via aerosol requires a basic understanding of the technical issues involved. Drugs are usually prescribed in terms of "nominal dose" (total dose of drug prescribed). This dose is device-specific, as recommended doses are different for different devices. The effective component of the nominal dose is the "lung dose", which is the mass of drug delivered to the lung. A given clinical effect should, in general, be produced by a given lung dose irrespective of the delivery device. However, the effect of a lung dose depends on several factors, including:

1) site of deposition
2) rate of clearance of the drug from airway
3) site of action of the drug.

Confirmation that a particular lung dose will produce a desired clinical effect usually requires that a clinical trial be performed. The lung dose should be reflected by data on lung deposition, but interpreting such data requires that the following are considered:

1) Lung deposition figures can be stated in different ways:
   a) percentage of the nominal dose
   b) percentage of the mass of drug leaving the aerosol-generating device
   c) percentage of the mass of drug entering the mouth or nose.
2) The radiation from an inhaled aerosol is attenuated as it leaves the lung. Approaches vary as to how this correction is done, affecting the quoted data on percent deposition.
3) In children, lung deposition is age-dependent, but the effect of age on delivery is different for different devices.

There are major differences in the efficiency of delivery for different devices with a range of 6–60%. When "adaptive aerosol delivery" nebulizers become available, they should

provide an accurate dose of drug to the lung with very low variability. In summary, the concept of lung dose is useful in understanding the related technical aspects, and it has the potential to allow drugs to be prescribed more accurately.

Introduction

With the proliferation of delivery techniques and devices in recent years, the knowledge needed to provide optimal inhalation therapy has grown accordingly. For optimal treatment using appropriate doses of aerosolized drugs, a physician needs to have a basic understanding of the technical issues involved in aerosol generation, delivery, deposition, and clinical efficacy. Of particular importance are the rapid advances in the efficacy of delivery that have occurred during the last year or two. These advances, allied to the powerful inhaled drugs now available, mean that greater care is needed to avoid toxicity from inhaled drugs.

Different ways that the dose of aerosolized drugs can be expressed

Drugs are usually prescribed in terms of "nominal dose". This dose is device-specific, as recommended doses are different for different devices. Nominal dose is the total dose of drug prescribed. For example, it is the mass of drug in the bowl for a nebulizer or in the metering chamber of a pressurized metered-dose inhaler (pMDI). The mass of drug available for inhalation at the nose or mouth is sometimes called the "delivered dose", and the mass of drug deposited in the lung is called the "lung dose". The lung dose is the effective component of the nominal dose. A given clinical effect should, in general, be produced by a given lung dose irrespective of the delivery device.

The effect of a given lung dose

The effect of a given lung dose will depend on several factors, including:

1) *The distribution of deposition.* If the drug is delivered to the wrong part of the respiratory tract, its effect will be reduced. For example, if histamine is delivered too peripherally, it will have little effect on the airway and may produce toxicity due to increased systemic absorption (1).
2) *The rate of clearance of a drug from the airway.* Clearance occurs by diffusion or active transport, and the rate of clearance is likely to influence the drug's duration of action. For most drugs, little information is available on this important variable.
3) *The site of action of the drug.* The effect of a drug depends on the location of the receptors it affects or the site of action, but, for many drugs, the site of action is unknown and the effect of central as opposed to peripheral deposition is unclear (2).

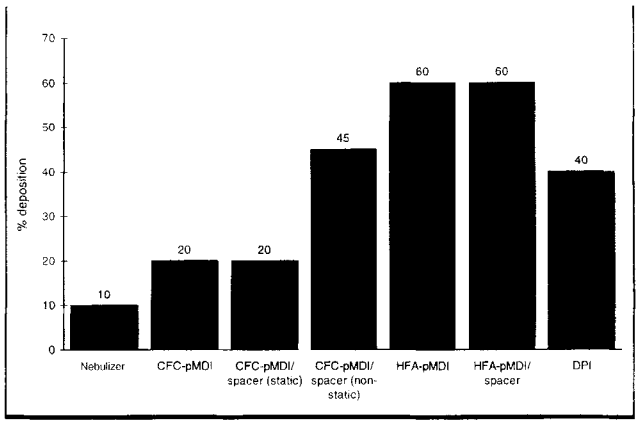


Figure 1. Approximation of optimal percent lung deposition for different devices (9–11, 14, 15). pMDI: pressurized metered-dose inhaler; CFC: chorofluorocarbon; HFA: hydrofluoroalkane; DPI: dry-powder inhaler.

Interpreting lung deposition data

The lung dose should be a reflection of lung deposition, but interpreting deposition data requires that the following are considered:

1) Lung deposition figures can be stated in different ways. Usually, lung deposition is quoted as a percentage of the nominal dose, but it can also be quoted as a percentage of the mass of drug leaving the aerosol-generating device or the mass of drug entering the mouth or nose. The latter two methods of describing lung dose give artificially high percentages.
2) The radiation from a labelled inhaled aerosol is attenuated or absorbed by passage through body tissue as it leaves the lung. A correction can be made for this so that the most accurate estimate can be made of the mass of aerosol in the lung. However, approaches vary as to how this correction is done, affecting the quoted data on percent deposition (3). For example, for a nebulized aerosol, calculating lung deposition by a lung phantom correction method resulted in a mean deposition of 4.3%, as compared with 6.1% by a tissue attenuation method (4).

Factors affecting lung deposition

For any given device, there are many factors that affect deposition. Most of these factors have different effects for different devices. The more important factors are as follows:

1) *Inhalational technique.* For standard "T-piece" nebulizers, the inspired dose is most influenced by the time of inspiration in comparison with the total time of the inspiratory cycle, as aerosol clearly cannot be inhaled during expiration (5). For pMDIs, the greatest lung dose is achieved with a submaximal inspiratory flow and longer breath-hold (6). In contrast, for DPIs such as the Turbuhaler, higher deposition is produced by higher inspiratory flows (7).
2) *Cooperation and coordination.* In very young children, poor cooperation will result in little or no aerosol being inhaled (8). Poor technique at any age will compromise aerosol delivery.
3) *Age.* Even in cooperative children, lung deposition is age-dependent, but the effect of age on delivery is different for different devices (9–11). For "T-piece" nebulizers, the inspired dose is reduced if inspiratory flow is below the nebulizer output, but this usually occurs only for children under 1 year of age (5). For pMDI/spacers, lung deposition is reduced in young children; tidal volume is low in very young children, and this increases the time taken to clear large spacers (12) and reduces output due to sedimentation or the effects of electrostatic charge. For children under 5 years, inspiratory flow is insufficient or too variable to use a DPI reliably. However, good lung deposition can be achieved in individual children aged under 5 years (11).

Dose delivered by current devices

Over the last few years, there have been substantial improvements in delivery systems. Most of the efficacy data come from studies in adults, but data are now becoming available for children. There are major differences in the efficiency of delivery for different devices (9–11, 14, 15) with a range of approximately 6–60% in cooperative subjects (Fig. 1). An important point is that the very high variability of deposition seen with most devices is not shown in this figure.

In adult studies, recent technological advances in nebulizers, pMDIs, and pMDI/spacers have resulted in at least a twofold increase in lung deposition for these devices. For nebulizers, deposition has increased from 5–10% for "T-piece" nebulizers to around 15–20% for "inhalation-augmented" or "Venturi" nebulizers (13). For a hydrofluoroalkane (HFA)-beclomethasone preparation delivered with an inhalation-activated pMDI, 60% of the nominal dose is deposited in the lung (14). These very high deposition levels will not necessarily apply to other HFA preparations. For pMDI/spacers delivering chlorofluorocarbon salbutamol, the use of detergent to minimize electrostatic charge, allied with an optimal inhalation technique, increased mean lung deposition from around 12% to 45% (15). Dry-powder devices (DPI) have achieved lung deposition of up to 30% (2, 16).

In older children, a few studies have recently reported lung deposition data in children over the age of 5–6 years, and these data suggest that the percent deposition in this age group is similar to that in adults. For "T-piece" nebulizers, lung deposition was approximately 5–10% (9). For detergent-treated pMDI/spacers, lung deposition was as much as 45% (5), and for DPIs, similar lung deposition to reported adult levels has been reported (10).

In younger children and infants, data on lung deposition are few, but suggest that lung deposition is generally markedly reduced in the very young. "T-piece" nebulizers deposited 1–2% of the dose in the lung (9), but *in vitro* studies in this age group have suggested that "Venturi" nebulizers will more than double delivery (17). Detergent-treated pMDI/spacers have achieved lung deposition of around 10% (11). DPIs are not recommended in this age group, due to low or variable inspiratory flows (10).

With regard to future advances in delivery technology, further advances in lung deposition can be expected in the next few years. "Adaptive aerosol delivery" nebulizers promise to provide an accurate dose of drug to the lung with very low variability (18). Meanwhile, important questions require urgent attention. For example, should the dose of inhaled steroids be substantially reduced if spacers are treated with detergent?

Matching the lung dose to the size of the child

Given the paucity of data, the child's lung dose is a real challenge for clinicians. Paediatricians have to deal with patients who have a 30-fold range in body weight, lung volume, and airway surface area (19). The main question is whether the reduced levels of lung deposition that can be expected in small children are matched by the children's

smaller size. There are several complex issues involved. Firstly, what is the appropriate lung dose of a particular drug at a particular age? There are very few, if any, data on this with respect to inhaled drugs in children. With oral drugs in children, doses with respect to weight are usually inversely related to body size, and current dosing schedules for inhaled drugs do probably result in disproportionately higher doses in young children. These schedules have been developed generally by extrapolation from pharmacokinetic, aerosol, and clinical studies in older subjects. They were not developed from lung deposition data in the age group in question, as such data were not available when the schedules were devised. Another issue is whether there are sufficient deposition data in children to assist in determining better drug dosage schedules. Since laboratory studies of aerosol deposition are likely to represent an optimal level of drug delivery, further data would be needed to optimize dosage schedules. Current deposition data do point to the need for caution with drug doses in the very young, particularly with the newer and more potent inhaled steroids.

Clinical trials

Confirmation that a particular lung dose will produce a desired clinical effect usually requires that a clinical trial be performed. Meticulous attention to detail is needed for clinical trials. Until recent years, in many clinical trials, insufficient attention was given to the detail of aerosol delivery, adversely affecting the reliability of the results.

In summary, the concept of lung dose is useful, as understanding of the related technical aspects may allow drugs to be prescribed more accurately.

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