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*REVIEW*

# Airway deposition and airway effects of antiasthma drugs delivered from metered-dose inhalers

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*Airway deposition and airway effects of antiasthma drugs delivered from metered-dose inhalers. R. Pauwels, S. Newman, L. Borgström. ©ERS Journals Ltd 1997.*

**ABSTRACT: Many different metered-dose inhalation devices are becoming available for the treatment of airway diseases. Each of these inhalers differs in its delivery characteristics. An assessment of the efficacy of drug delivery by these inhalers is essential, in view of their therapeutic use.**

**A review of the literature on the relationship between airway deposition and airway effects of drugs delivered from metered-dose inhalers is presented. Nebulizers or spacers are not discussed. The effect of an inhaler depends on the characteristics of the inhaler and the inhalation manoeuvre performed by the patient. This review focuses on the influence of inhaler characteristics on the airway deposition and airway effects. Data from several studies show that there is a significant relationship between the amount of drug deposited in the airways and the airway effects of the drug.**

**Studies on the relationship between airway deposition and airway effect have been troubled by methodological problems, such as the absence of multiple dose comparisons and the difficulty in obtaining steep dose-response curves. The techniques for measuring airway deposition of inhaled drugs, namely the scintigraphic and the pharmacokinetic method, are discussed and compared. The appropriate use of these techniques can help to define and compare the drug delivery characteristics of different devices, thus enabling inhaled therapy to be optimized.**

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Asthma is a chronic inflammatory disorder of the lower airways characterized by variable airflow limitation and airway hyperresponsiveness [1]. Treatment of asthma consists of controller medication that is used regularly, and reliever medication that is used when needed. Many of the antiasthma medications are administered *via* inhalation. The main reasons for administration of these drugs *via* inhalation are that the drug reaches the diseased tissue more easily and that systemic effects can be minimized. High drug concentrations can, thus, be achieved in the effector organ without concomitant high drug concentrations in the systemic circulation. For an optimal balance between the desired and undesired effects of the inhaled drug, the ratio between local bioavailability (L) in the lung and total systemic bioavailability (T) of active drug, the L/T ratio [2], should be as high as possible.

Many different inhalation systems have been developed, and the numbers and types of inhalation devices are increasing rapidly. The aim of this paper is to discuss the methods for *in vivo* assessment of the performance of the different inhalers and to compare the results of these assessments with parameters of clinical efficacy.

Before inhalation, the drug must be aerosolized, as only very fine particles (below approximately 5 μm diameter) will reach the lower airways, and larger particles will to a great extent deposit in the oropharyngeal region before being swallowed [3]. A number of different inhalation systems have been designed to achieve the necessary aerosolization. Drug in solution or suspension can be delivered by nebulizers, which are commonly used in a hospital setting [4], whilst more convenient and portable systems have been designed for everyday ambulatory use. The pressurized metered-dose inhaler (pMDI) was the first portable multidose inhaler and is still the most commonly used [5]. In a pMDI, fine drug particles are usually suspended in a propellant, and a metered-dose is delivered upon actuation.

Another formulation principle is to use a dry powder consisting of drug or a mixture of drug and an inert carrier (usually lactose). Upon inhalation, the dry powder is deaggregated and fine particles are carried into the airways with the inhaled air. A number of dry powder inhalers (DPIs), using different dosing principles, have appeared on the market: *e.g.* Spinhaler® (Fisons, UK) [6] and Rotahaler® (Glaxo, UK) [7], which use single prefilled capsules; Diskhaler® (Glaxo, UK) [8], which is a multidose system using disks with 4 or 8 doses; Turbuhaler® (Astra, Sweden), which is a multidose inhaler that can dispense and deliver up to 200 metered-doses of dry powder [9]; and Diskus®/Accuhaler® (Glaxo, UK), which is based on a continuous strip of prefilled blisters [10].

When designing new inhalers or new formulations, various approaches can be used. The delivery characteristics of the new product could be chosen to be the same as those of the old product. Such an approach is often used when formulating generic drugs. The advantage is that the two products are interchangeable, but the drawback is that no added advantage, with respect

to the L/T ratio, is to be expected when changing from one product to the other. Another approach is to produce an inhaler that delivers as much drug as possible to the lungs. The degrees of pulmonary bioavailability or (preferably) the pharmacodynamic responses for the old and new inhalers are determined, and the nominal dose of the new inhaler can then be adjusted so that both inhalers deliver the same amount of active drug to the lungs, and exert the same effect, or, alternatively the dosing schedule can be adapted. The second approach can increase cost-effectiveness by allowing a decrease in nominal dose, with the same amount of drug reaching the lungs and, possibly, decreasing the systemic absorption and side-effects.

When making the pharmacodynamic evaluation, both the desired local effects and the undesired systemic side-effects should be considered. The pharmacodynamic approach is the optimal one, as a good clinical response in the asthmatic patient is the ultimate treatment goal. Pharmacodynamic comparisons can, however, be complicated; they are rather insensitive and conclusive results are not always obtained. For inhaled steroids, for example, treatment must be given for an extended time and, with the very flat dose-response curve of inhaled steroids, a large number of patients must be included in order to show differences between treatment regimens. If the comparison is made with doses that are on the plateau of the dose-response curve, then important differences between delivery systems could be missed. In view of some of the difficulties of pharmacodynamic studies, a simple and straightforward short-cut by which to compare different inhalers is desirable. We believe that measures of pulmonary bioavailability can, to some extent, be used as such a surrogate parameter, as the effect elicited in the target organ (the lungs) is related to the amount of drug reaching that site. Pulmonary deposition is an absolute requirement for inhaled drugs to work. Although factors other than the quantity of pulmonary deposition are also related to the pharmacodynamic response, it appears logical to postulate that the quantity of drug deposited in the airways is the primary determinant of the local airway response to the drug.

In the present review, we would like to give a short overview of the methods for measuring pulmonary deposition together with the results from a number of relevant deposition studies. Finally, the clinical implications will be discussed.

## Deposition of inhaled drug

When a drug is given by inhalation, the drug particles reaching the patient will be deposited either in the oropharynx or in the airways, and may be absorbed into the systemic circulation either *via* the gastro-intestinal (GI) tract or *via* the airways (fig. 1) [11]. The pulmonary portion will exert the desired effects in the lungs and will then be transported through the lung membrane to reach the systemic circulation, if it is not metabolized in the lung. For the drugs discussed in this review, lung metabolism is negligible and, thus, drug reaching the lungs will be absorbed into the systemic circulation, where it can elicit unwanted side-effects. The portion that was deposited in the oropharynx will eventually be swallowed and will reach the GI tract. The fraction of the drug escaping first-pass metabolism in the gut wall and liver will be partly responsible for the total systemic bioavailability, and can add to unwanted side-effects *via* the systemic circulation.

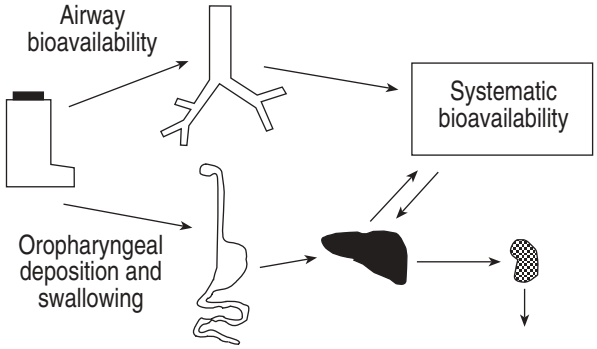


Fig. 1. – Pharmacokinetics of inhaled drugs. The metered dose is partly deposited on the device, partly inhaled into the airways, and partly deposited in the upper airways and swallowed. The inhaled fraction can be absorbed from the airways into the systemic circulation. The swallowed fraction can be partly absorbed from the gastrointestinal tract and partly metabolized in the gut wall and/or liver (first-pass metabolism). The total systemic fraction is derived from the fraction absorbed from the airways and the fraction of the gastrointestinally absorbed drug that is not metabolized during the first pass. The systemically available drug can be removed from the body by metabolism and excretion.

## Methods used for assessing deposition patterns

The degree of lung deposition, or pulmonary bioavailability, can be determined either by gamma scintigraphy, or by specific pharmacokinetic methods. Each method has its advantages and disadvantages, and the results should be interpreted in the light of the method used.

### *Gamma scintigraphy*

The amount of drug deposited in the airways from an inhaler device is determined using the technique of gamma scintigraphy, in which a minute amount of a gamma-ray emitting radiotracer is added to the formulation, in order that its presence in the body can be quantified by gamma camera [12, 13]. The gamma camera images are stored by a data-processing system as a matrix of picture elements or pixels. Lung and oropharyngeal depositions may be expressed as percentages of the metered-dose, delivered dose or nominal dose, and the fraction retained on the inhalation device (actuator in the case of a metered-dose inhaler (MDI), and gelatine capsules or mouthpiece in the case of a DPI) as well as that recovered from the exhaled air may be determined. Anterior and posterior views of the lungs and stomach are usually taken, and a geometric mean count calculated, in order to obtain a measure that is virtually independent of the depth of the material deposited in the body [14]. Corrections must also be made for the attenuation of gamma-rays as they pass through tissue to the detector, and there are several methods that may be applied for this purpose [15–18].

Using the data processing system, "regions of interest" may be drawn around specific lung zones, to give

regional deposition data; the most usual divisions of the lungs are into central, intermediate and peripheral zones, representing mainly large, medium and small airways, respectively [19], or into a central one-third and a peripheral two-thirds of the lung fields [20]. The lung edges are usually defined either by ventilation scans using a radioactive inert gas [21], or by a transmission scan using a large flood field source [18]. An index of regional lung deposition may then be calculated as the ratio of peripheral zone deposition to central lung deposition (lung penetration index), or vice versa [22]. Planar scintigraphic imaging, as described above, is a very powerful technique, since it is the only method that allows total and regional deposition patterns from inhalers to be determined noninvasively in humans. Since the amount of radionuclide required to obtain satisfactory planar images is small, the radiation dose to each subject, expressed as an "effective dose equivalent" [23], need only be a fraction of that received from an abdominal radiograph. Ideally, methodologies for carrying out scintigraphic studies should be standardized, so that results obtained by different centres can be compared [24].

In planar scintigraphy, the lungs are viewed in only two dimensions, and the central, intermediate and peripheral lung zones correspond only loosely to precise anatomical regions. The central zone will, for instance, inevitably include some small peripheral airways and alveoli. More precise information about the anatomical site of deposition can be obtained from three dimensional single photon emission computed tomography (SPECT), possibly enabling better discrimination to be made between two or more treatment regimens [25]. This approach involves sequential images taken from different angles by a rotating gamma camera [26], and the lung outlines in three dimensions are delineated by magnetic resonance imaging. The lung may then be considered as a system of concentric shells centred on the hilum, and it may be possible to relate each shell to specific airway generations. Three dimensional imaging is a powerful tool, but the technology is in its infancy, and in order to obtain adequate data at the present time it seems necessary to use an order of magnitude more radioactivity (and hence to give the subject an order of magnitude higher radiation dose) than that required for planar imaging [27].

Few radionuclides are suitable for the chemical labelling of drug molecules for use in scintigraphic studies. Drugs can be labelled with $^{14}C$ or $^{3}H$, but both of these radionuclides emit only beta particles. Various cyclotron-produced radionuclides, including $^{11}C$ and $^{15}O$, could be tagged onto drug molecules, but have impractically short physical half-lives. Only one drug (ipratropium bromide) has been chemically labelled inside a metered-dose inhaler, using the radionuclide $^{77}Br$ [28]. Hence, scintigraphic studies of aerosol inhalers are generally performed using the widely available radionuclide, $^{99m}Tc$. The earliest of these method involved the use either of placebo Teflon particles [29], or placebo solutions [30] labelled with $^{99m}Tc$, and this approach was developed further by VIDGREN *et al*. [31], who physically incorporated this radionuclide into spray dried particles of disodium cromoglycate. However, none of these methods allowed the distribution of radiolabel in various particle size bands to be matched exactly with that of the micronized drug normally found in commercially marketed inhalers.

A major breakthrough was made in 1988, when KÖHLER *et al*. [32] described a simple method for the direct addition of $^{99m}Tc$ to active drug formulations in metered-dose inhalers. In the original method of KÖHLER *et al*. [32], the radionuclide was added to formulation in additional chlorofluorocarbon (CFC)-11 propellant, resulting in a change in the composition of the formulation, and a corresponding change in the size distribution compared with the unlabelled product. However, subsequent modifications made it possible to add the radionuclide to the inhaler without changing either the composition of the formulation or the particle size distribution [33]. In subsequent *in vivo* studies, the distribution of $^{99m}Tc$ as viewed by gamma camera can then be taken to represent the distribution of drug. Appropriate *in vitro* validation measurements should always be performed in advance of the scintigraphic study, to demonstrate that the $^{99m}Tc$ radiolabel is an accurate marker for the drug substance. These methods of directly labelling the formulation have subsequently become the methods of choice for pMDIs, and analogous methods are used in the study of deposition patterns from DPIs [34, 35]. The radiolabel and drug have a close physical association for the majority of MDI products [36]. Nebulizer solutions are the easiest formulations to radiolabel, since it is generally satisfactory to prepare a mixture of drug and $^{99m}Tc$, such that the radiolabel is distributed uniformly amongst large and small droplets, according to droplet mass [37].

### *Pharmacokinetic methods*

If it is possible to determine how much drug appearing in the plasma or urine from an "inhaled" dose has arrived *via* the lungs or *via* the gastrointestinal tract, then it is possible to obtain data relating to lung and oropharyngeal depositions. The earliest of these methods observed that the disposition of isoprenaline from a pMDI resembled that of swallowed drug [38], implying that the majority of the dose was actually deposited in the oropharynx and subsequently swallowed. For inhaled substances which are not absorbed from the GI tract or are completely metabolized during first-pass through the gut wall and liver, the intact drug will reach the systemic circulation only *via* the lungs. Total systemic bioavailability will, thus, reflect pulmonary bioavailability. Sodium cromoglycate may be tested by this approach, since it undergoes virtually no absorption through the GI tract, and plasma or urine levels are, thus, taken to reflect lung deposition [39].

The GI absorption of some other drugs, including terbutaline sulphate and budesonide, can be blocked almost entirely by administering a suspension of charcoal in water before and after drug inhalation [40]; an experimental situation is, thus, created where systemically available drug represents pulmonary deposited drug. For each substance, the adsorbing capacity of the activated charcoal must be investigated by giving an oral formulation of the drug under study with and without concomitant charcoal administration. Absolute lung deposition, or deposition expressed as a percentage of the

metered-dose, can thus be determined by the "charcoal block" method, if the systemically available amount of drug is compared with that following an intravenous reference dose.

Total systemic bioavailability ($F_{syst}$), after oral inhalation is composed of two components, the pulmonary bioavailability ($F_{pulm}$), and the systemic bioavailability *via* the oral route ($F_{oral}$). Thus, $F_{pulm}$ can be calculated from $F_{syst}$ and $F_{oral}$, according to the following equation:

$$F_{syst} = F_{pulm}+F_{oral}\ (1\text{-ret-}F_{pulm})$$

which, after rearrangement will give:

$$F_{pulm} = (F_{syst}\text{-}F_{oral}(1\text{-ret}))/(1\text{-}F_{oral})$$

where ret is the fraction of the metered-dose retained in the device, and thus (1-ret) the fraction that reaches the patient. The method has been used for determining the pulmonary bioavailability of budesonide [41].

Lung and oropharyngeal fractions of deposited drug may also be separated on the basis that they will be absorbed at different times. The plasma levels of salbutamol between 0 and 60 min [42] and urine levels of salbutamol between 0 and 30 min [43] after inhalation are derived almost entirely from the fraction deposited in the lungs. However, both these measures only yield indices that are assumed to be related in some way to lung deposition, and do not allow lung deposition to be determined in absolute terms or as a percentage of the metered-dose.

Other *in vivo* techniques giving information about deposition include the measurement of drug recovery either from mouthwashings [44] or from bronchoalveolar lavage (BAL) [45], and the determination of total body deposition from the quantity of aerosol measured in the inhaled air minus the quantity in the exhaled air [46].

### *Comparison of gamma scintigraphy and pharmacokinetic studies*

The relationship between scintigraphic data and the results of pharmacokinetic bioavailability studies are incompletely understood at the present time, since there have been few comparative studies. However, two studies have compared gamma scintigraphy and the charcoal block method. In the first of these studies [47], lung deposition of terbutaline sulphate from the Turbuhaler® DPI averaged 26.9% in a group of six healthy volunteers by gamma scintigraphy, and 21.1% by the charcoal block method. In the second study, lung deposition was assessed in eight healthy volunteers for terbutaline sulphate delivered from a MDI used at fast and slow inhalation rates, and from a MDI connected to a Nebuhaler® (Astra, Sweden) spacer device [48]. Overall, there was no significant difference between the estimates of whole lung deposition obtained by the two methods, but the charcoal block method gave a lower value for lung deposition than gamma scintigraphy for the fast inhalation rate from the MDI.

For both studies, the discrepancy between techniques was ascribed to the rapid mucociliary clearance of drug deposited in central airways of the lungs, which was detected by scintigraphy, but which was not subsequently absorbed. Gamma scintigraphy measures what is deposited in the lungs, whilst pharmacokinetic assessments of bioavailability measure what is absorbed across the lung surface. It was concluded that while gamma scintigraphy and the charcoal block method do not measure precisely the same quantity, either method could be used to assess the pulmonary deposition of terbutaline sulphate. Neither the charcoal block method, nor any other pharmacokinetic technique, provides any data concerning the regional distribution of drug within the airways. Furthermore, each pharmacokinetic method is specific to a particular drug or group of drugs. However, pharmacokinetic methods do not use ionizing radiation, and there is no risk of making an inadvertent change to the formulation in the process of adding a radiolabel, as is possible with gamma scintigraphy.

## Effect of inhalation technique and device on airway deposition

Our leading hypothesis is that the amount of drug reaching the airways is a critical factor for the pharmacodynamic effects of inhaled drugs. However, different ways of performing the inhalation affect the lung deposition. The inhalation process can be described in three steps: 1) dose delivery from the inhaler; 2) pulmonary deposition of some of the delivered dose; and 3) functional response to the deposited dose. The first step involves the priming and handling of the device and the inhalation flow used during inhalation. The second step is influenced by factors such as co-ordination of actuation and inhalation, and also physiological factors, including airway narrowing, airway closure and mucous plugging. Finally, the third step involves factors such as potency, partial or full agonistic activity, and whether the inhaler constituents can induce irritation or even bronchoconstriction. Different devices have their advantages and disadvantages with regard to the three steps, and each inhaler should be judged with this knowledge in mind.

All currently available inhalers are flow-dependent; pMDIs should be used at a flow as low as possible [48–50], and DPIs will deliver a larger pulmonary dose at a high inhalation flow than at a low flow [35, 51, 52]. Pressurized metered-dose inhalers have to be shaken before each inhalation, otherwise the dose reaching the patient will vary markedly between doses but also over the life-span of the inhaler [53]. The pulmonary deposition of the dose delivered varies between inhalers, from about 5% for Spinhaler® up to 20–30% for Turbuhaler® (table 1). Differences in total or regional deposition between inhalers could affect the clinical response [57, 58].

### *Lung deposition values*

Values from a number of lung deposition studies are listed in tables 1 and 2, selected to give representative values. When data are available on inhalation flow, or other inhalation parameters, these are given in the

Table 1. – Lung deposition after inhalation of different substances *via* dry powder inhalers

| Inhaler | Substance | $\dot{V}'_I$ L·min$^{-1}$ | LD % | [Ref.] | Comments |
|---|---|---|---|---|---|
| Spinhaler® | DSCG | 60 | 11.5 | [54] | HV (n=7) |
| | | 60 | 5.5 | [34] | HV (n=10) |
| Pulvinal®+ | Salbutamol | 28 | 11.7 | [35] | HV (n=10) |
| | | 46 | 14.1 | | |
| Easyhaler®† | Salbutamol | 57.8 | 28.8 | [55] | HV (n=8) |
| Rotahaler® | DSCG | - | 6.2 | [54] | HV (n=7) |
| | Teflon particles | Fast | 9.1 | [56] | Pts (n=9) |
| Turbuhaler® | Terbutaline | 28 | 9.1 | [51] | Pts (n=10) |
| | | 57 | 16.8 | | |
| | Terbutaline | 55 | 26.9* | [47] | HV (n=6) |
| | | | 21.1** | | |
| | Terbutaline | 58 | 21 | [57] | HV (n=8) |
| | Budesonide | 58 | 28 | [52] | HV (n=10) |
| | | 36 | 15 | | |
| | Budesonide | 52 | 32 | [41] | HV (n=24) |
| Diskhaler® | Salbutamol | - | 12.4 | [20] | HV (n=10) |
| | | | 11.4 | | Pts (n=19) |
| | Salbutamol | - | 11.3 | [18] | HV (n=6) |

$\dot{V}'_I$: inhalation flow; LD: lung deposition; DSCG: disodium cromoglycate; HV: healthy volunteers; Pts: patients. *: measured by scintigraphy; **: measured by charcoal block method; +: Chiesi, Italy; †: Orcon, Finland.

Table 2. – Lung deposition after inhalation of different substances *via* pMDI

| Inhaler | Substance | $\dot{V}'_I$ L·min$^{-1}$ | LD % | [Ref.] | Comments |
|---|---|---|---|---|---|
| pMDI | Isoprenaline | - | <10 | [38] | HV |
| | Ipratropium | - | ~16 | [59] | HV (n=4) |
| | Teflon | 20 | 13 | [49] | 20% VC, Pts (n=15) |
| | particles | 120 | 5 | | |
| | Terbutaline | - | 2.9 | [60] | Pts, range 0.8–10.1% |
| | Teflon | 30 | 14.3 | [50] | 20% VC, BHT=10 s Pts (n=10) |
| | particles | | 14.3 | | 50% VC |
| | | | 13.8 | | 80% VC |
| | | | 11.8 | | 20% VC, BHT=4 s |
| | | | 6.5 | | 50% VC |
| | | | 6.8 | | 80% VC |
| | Teflon | 30 | 12.8 | [50] | 20% VC, BHT=4 s, Pts (n=8) |
| | particles | | 7.5 | | 50% VC |
| | | | 7.2 | | 80% VC |
| | | | 8.4 | | 20% VC |
| | | | 7.0 | | 50% VC |
| | | | 6.0 | | 80% VC |
| | Terbutaline | 86 | 8.2 | [40] | HV (n=11) |
| | DSCG | - | 9.2 | [61] | HV (n=7) |
| | Budesonide | 40 | 15 | [41] | HV (n=24) |
| | DSCG | 30 | 8.8 | [62] | HV (n=10), 5 mg dose |
| | Salbutamol | - | 21.6 | [20] | HV (n=10) |
| | | | 18.2 | | Pts (n=19) |
| | Salbutamol | - | 24.1 | [18] | HV (n=6) |
| | Terbutaline | 34 | 16.7 | [57] | HV (n=8) |
| | Terbutaline | 37 | 10.7* | [48] | HV (n=8) |
| | | | 11.2** | | |
| | | 151 | 10.4* | | |
| | | | 7.2** | | |
| pMDI | Salbutamol | - | 18.6 | [63] | Pts, good co-ordination, (n=10) |
| BA pMDI | | | 17.5 | | |
| pMDI | | | 7.2 | | Pts, bad co-ordination, (n=8) |
| BA pMDI | | | 20.8 | | |
| SmartMist†/ | Salbutamol | 30 | 14.1 | [64] | HV (n=9) |
| pMDI | | 90 | 18.6 | | |
| | | 270 | 7.6+ | | |
| Gentlehaler# | Salbutamol | - | 18.8 | [65] | pMDI, pts (n=10) |
| | | | 19.6 | | Gentlehaler |

pMDI: pressurized metered-dose inhaler; VC: vital capacity; BHT: breathholding time; BA: breath actuated. *: measured by scintigraphy; **: measured by charcoal block method; +: late actuation; †: Aradigm, USA; #: Schering, USA. For further definitions see legend to table 1.

tables; unfortunately, many investigators have not reported these parameters. The effect of adding a spacer to a pMDI will not be discussed here, as this was covered in a recent review [66].

### *Pressurized metered-dose inhaler*

The first lung deposition study was performed in healthy volunteers by DAVIES [38], who calculated approximate lung deposition from a difference in isoprenaline metabolism when the drug was administered *via* the intravenous and inhaled routes; a lung deposition of less than 10% was obtained. Radiolabelling of inhaled drug was first used in 1981 to study lung deposition [29, 30, 59]. Ipratropium bromide was used in one of the studies and the bromide ion was exchanged for the gamma-ray emitter, bromine-77 [59]. In this study, lung deposition of about 16% was obtained. NEWMAN *et al.* [50] performed a series of experiments using $^{99m}$Tc-labelled terbutaline spheres in a pMDI; the sizing of the Teflon particles mimicked that of a terbutaline pMDI. Mean lung deposition ranged 6.0–14.3% using different inhalation conditions. A breathholding time of 10 s after inhalation gave a higher deposition than a breathholding time of 4 s. Inhalation at 30 L·min$^{-1}$ gave a higher lung deposition than at 80 L·min$^{-1}$, and actuation at the very beginning of the inhalation was advantageous with respect to the degree of lung deposition. The charcoal-block method was first applied in 1982, when DAVIES [60] measured the degree of lung deposition of terbutaline by pMDI. The values obtained varied markedly, probably due to insufficient administration of charcoal. The first study using a validated charcoal-block method was performed with terbutaline pMDI, and 8.2% of the dose was deposited in the lungs [40].

A flow dependency of deposition from a pMDI was also observed in a study comparing the scintigraphic and the charcoal-block methods [48]. When inhalation flow was increased from 37 to 151 L·min$^{-1}$, total lung deposition decreased from 11.2 to 7.2%, as measured with the charcoal-block method. Values obtained with scintigraphy were 10.7 and 10.4%, respectively. The observed difference in results between methods is probably due to a more central deposition in the lung after inhalation at high flow rate, as discussed above.

No difference was observed in total lung deposition when a group of patients and healthy volunteers were compared using salbutamol

pMDI, although the deposition patterns were more central in the patients [20]. A breath-actuated pMDI, which triggers the inhaler at a specific inhalation flow, and thus avoids the need to co-ordinate inhalation and actuation, has been tested in patients considered to be "good" and "bad "co-ordinators [63]. In "good" co-ordinators, deposition did not increase when changing from pMDI (used with the patients chosen technique) to breath-actuated pMDI. In "bad" co-ordinators, lung deposition increased from 7.2 to 20.8%. Using a microprocessor controlled inhalation system (SmartMist®) with inhalation flows of 30, 90 and 270 $L \cdot min^{-1}$, a scintigraphic study showed that inhalation at 90 $L \cdot min^{-1}$ and early actuation gave the highest lung deposition. At the high flow, combined with late actuation, lung deposition decreased to less than half of optimum [64]. Spacehaler® (Evans Medical, USA) is a pMDI in which the aerosol generated is released at a low velocity. There is conflicting evidence regarding whether or not this device increases pulmonary bioavailability [42, 65].

### *Dry powder inhalers*

The first commercially available DPI was Spinhaler®. The powder is dispersed from a gelatine capsule and deaggregated by the inhalation force. Lung deposition is, thus, flow-dependent [34]. Flow dependency is observed for all currently available DPIs, as the quality of the aerosol cloud depends on the inhalation effort generated by the patient. The dry powder in the formulation is deaggregated at inhalation and, thus, a higher inhalation flow (*i.e.* higher inhalation effort) will generate an aerosol with finer particles than a lower inhalation flow. Due to the flow dependency of DPIs, their inhalation flow characteristics should be determined and it should be shown that asthmatic patients, including those with severe airways obstruction, can achieve a good enough inhalation flow through the inhaler to achieve a satisfactory clinical effect.

Turbuhaler® has been thoroughly investigated with respect to lung deposition, and the general picture is that about 20–30% of the dose reaches the lung, both in healthy volunteers and in patients, at an inhalation flow of approximately 60 $L \cdot min^{-1}$ [41, 47, 51, 52, 57, 67, 68]. At a low inhalation flow, approximately 30 $L \cdot min^{-1}$, lung deposition was lower than at a flow of 60 $L \cdot min^{-1}$, but similar to that after a well-performed inhalation from the corresponding pMDI. The low absolute values observed in one early study were probably due to an unusually low amount of fine particles in the terbutaline batch used [51]; later studies have shown higher values. Diskhaler® uses the same pharmaceutical principle as Rotahaler®, namely ordered mixtures (small particles adhered to larger carrier particles), and the degree of lung deposition is about 11% [18, 20]. No difference in the total degree of lung deposition was observed when comparing a group of patients and a group of healthy volunteers who used the same inhalation technique [20]. This is to be expected, as it is the inhalation flow that determines how much of the nominal dose will reach the lung. The regional distribution is, however, more central in the presence of airway narrowing [69, 70]. Future DPIs may provide a lung dose that does not vary with inhalation flow.

## Airway effects

The lung effects elicited after inhaling an asthma drug aerosol have been investigated in a great number of clinical studies. In this review, however, only a small proportion of the studies will be commented upon; mainly those where different devices were compared in an attempt to establish the relative effectiveness of the devices.

Both cumulative and noncumulative dose designs have been used in the studies, and sometimes the results from the two designs are conflicting; for instance, a difference can be seen with one design but not with the other. A direct comparison and discussion of the two designs in evaluating $\beta_2$-agonists has been presented by BRITTON and TATTERSFIELD [71]. Clinical response tends to be higher after the same total dose has been given as a cumulative dose compared with a single dose. The authors concluded that both designs can be used, but the results from differently designed studies cannot be directly compared.

The design of comparative studies, particularly the choice of the dose levels compared, is of critical importance in order to draw valid conclusions from the study. The doses of study drug must be chosen on the slope of the sigmoid dose-response curve, and more than one dose level must be included. If a study is performed at only one dose level for each of the devices, it is not possible to verify that the response is on the slope of the dose-response curve if no difference between the two ways of administering the drug is observed. Unfortunately, many of the studies presented in the literature [8, 72–78] have an inadequate design and are, thus, inconclusive. A well-designed comparative study should include at least two dose levels, for at least one of the devices, and it is necessary to show a difference in the response between the two dose levels to draw conclusions. Another way to show that the given doses are on the slope of the dose-response curve is to lower the normal patient dose until a worsening of the lung function and or the symptoms occurs, and then treat the patients with the study drugs at a higher dose level. In this case, different dose levels of the different devices can be used. If the resulting response is still the same, with a difference in doses, a conclusion regarding the relative efficiency of the devices can be drawn.

### *Influence of inhalation technique*

The effect of all inhalation systems is dependent on the way the patient uses the system, as was discussed above. A common property for pMDIs and DPIs is the dependence of the resulting lung dose on the inhalation flow used. In accordance with the dependency of the airway deposition on the mode of inhalation, the effects elicited are dependent on the way the patient uses the inhalation system.

NEWMAN and co-workers [79, 80] performed a number of studies on terbutaline pMDI in order to evaluate the effects of different modes of inhalation on airway deposition and change in forced expiratory volume in one second ($FEV_1$). A slow (30 $L \cdot min^{-1}$) inhalation of 500 μg terbutaline sulphate from a pMDI increased

$FEV_1$ by about 30%, but a fast (80 $L \cdot min^{-1}$) inhalation increased $FEV_1$ by only about 15%.

The results from the effect studies discussed above were compared with similarly designed airway deposition studies [81], and an overall correlation was found between airway deposition and percentage increase in $FEV_1$ for the pMDI.

Similar results were obtained when a fast inhalation, 192 $L \cdot min^{-1}$, from a fenoterol pMDI was compared with a slow inhalation, 64 $L \cdot min^{-1}$ [82]; the increases in $FEV_1$ were 45 and 35%, respectively.

Collectively, a slow inhalation from a pMDI results in a better airway effect, measured as $FEV_1$ response, than a fast inhalation. This is in accordance with the flow dependency of the lung deposition for pMDIs.

For salbutamol Rotahaler®, the effect in asthmatic children (7–14 yrs) when used at different peak inhalation flows has been investigated by PEDERSEN [83]. Salbutamol was inhaled at 30–50, 60–80, and 90–120 $L \cdot min^{-1}$. The improvement in $FEV_1$ after the two fastest inhalations was significantly greater than after the slow inhalation.

For currently marketed DPIs, a lower inhalation effort and a lower inhalation flow will generate a smaller number of fine particles. In an experimental study, it was shown that for Turbuhaler® the quantity of fine (<5 μm) terbutaline particles, delivered from Turbuhaler® at inhalation, influenced the effects elicited [84]. The increase in $FEV_1$ 5 min after inhaling 5 μg of terbutaline sulphate as fine particles was one third of the response elicited after 90 μg was inhaled as fine particles, and 40 μg produced an intermediate value.

Spirometry after inhaling terbutaline sulphate *via* Turbuhaler® at 30 and 60 $L \cdot min^{-1}$ showed that changes in forced expiratory flow at 50 and 75% vital capacity ($FEF_{50}$ and $FEF_{75}$) were significantly higher after inhalation at 60 $L \cdot min^{-1}$, whilst changes in $FEV_1$ were similar [85]. This is in contrast to the results from a study by ENGEL *et al.* [86]. The effects elicited, measured by spirometry, after different inhalation modes were investigated and comparable bronchodilation was achieved when the peak inhalation flow (PIF) through Turbuhaler® varied between 34 and 88 $L \cdot min^{-1}$. The low inhalation flow (34 $L \cdot min^{-1}$) tended, however, to result in a slightly reduced bronchodilatation compared with the three high flow inhalation modes. In another study, the $FEV_1$ response was higher, but not significantly so, after inhaling from terbutaline Turbuhaler® at 60 $L \cdot min^{-1}$ than at 30 $L \cdot min^{-1}$ [51]. The increases in $FEV_1$ were 0.6 and 0.4 L, respectively.

The effect of different PIFs on $FEV_1$ has also been investigated in children (7–15 yrs). The children inhaled 0.25 mg terbutaline at 13, 22, 31 and 60 $L \cdot min^{-1}$ from Turbuhaler® [87]. There were no differences in $FEV_1$ response between 31 and 60 $L \cdot min^{-1}$, but 13 and 22 $L \cdot min^{-1}$ resulted in significantly lower increases in $FEV_1$. It should be noted, however, that the lowest flow, 13 $L \cdot min^{-1}$, resulted in a significant increase in $FEV_1$.

Turbuhaler®, like other currently marketed DPIs, is flow-dependent; a higher inhalation flow will give a better effect. The vast majority of patients, both adults and children above the age of 5 yrs, can generate an adequate inhalation flow [88, 89], and thus achieve an optimal effect from Turbuhaler®.

Fenoterol DPI has been evaluated and a difference, although not significant, in effect elicited was observed when the inhalation flows were 15 and 40 $L \cdot min^{-1}$, respectively [90]. In a study in children, inhalation flows of 17 and 37 $L \cdot min^{-1}$ were obtained; 37 $L \cdot min^{-1}$ was considered a fast flow owing to the high resistance of this device [91]. The resulting $FEV_1$ was significantly higher after the fast flow.

Collectively, the flow dependency for DPIs and pMDIs are reversed. A pMDI should be used at as low a flow as possible, whilst for DPIs a higher flow will give a better effect.

## Comparisons between devices

A number of studies have been performed to compare the relative efficacy of different devices.

### *Terbutaline*

Terbutaline pMDI and Turbuhaler® have been shown to elicit comparable effects on $FEV_1$ in a cumulative dose response study, with doses ranging 0.25–4.0 mg [92]; PIF was 57 $L \cdot min^{-1}$ for Turbuhaler® and 170 $L \cdot min^{-1}$ for the pMDI. Similar results were obtained in a second cumulative terbutaline study, also ranging 0.25– 4.0 mg [93]. PIF was 68 $L \cdot min^{-1}$ with Turbuhaler® and 181 $L \cdot min^{-1}$ with pMDI.

In children, a similar increase in $FEV_1$ was obtained from terbutaline Turbuhaler® and pMDI using a cumulative design [94]. The pMDI dose started at 0.125 mg and the Turbuhaler® dose at 0.25 mg. In total, 2.0 mg was given; six inhalations from the pMDI and five from Turbuhaler®. Although the total dose was the same, the extra dose given *via* pMDI could have increased the response further for this device.

In a single-dose study, the increase in $FEV_1$ was evaluated after inhaling 0.5 mg terbutaline *via* Turbuhaler® or 2×0.25 mg *via* pMDI [95]. The lung function after Turbuhaler® was higher at all time-points, reaching significance after 15 min and also after 360 min.

Terbutaline Turbuhaler® and pMDI were compared with respect to the bronchodilating effect after exercise-induced bronchoconstriction [73]. A dose of 0.5 plus 0.5 mg was given to children after exercise, and it was found that the effects on reversing of the exercise-induced asthma were similar after Turbuhaler® and pMDI.

Terbutaline pMDI (2×0.25 mg) and Turbuhaler® (0.5 mg) were compared in a single-dose study in mild-to-moderate asthmatic patients, in which lung deposition was also determined [74]. $FEV_1$ was similar, but there was a slight tendency towards a greater increase in specific airway conductance ($sG_{aw}$) after inhalation *via* Turbuhaler®. Lung deposition was 8.8% after pMDI and 22.6% after Turbuhaler®. The discrepancy between the difference in deposition but similarity in effects could be due to administration of terbutaline doses that were too high, thus reaching the flat part of the dose-response curve. As discussed above, the design of the study was inconclusive. To evaluate whether too high a dosage was the reason for the discrepancy observed, a follow-up study, also including 0.25 mg terbutaline,

was performed [68]. The degree of lung deposition was then about 10 and 20% for pMDI and Turbuhaler®, respectively, and similar to the values in the preceding study. On the effect side, it was now shown that 0.25 mg given by Turbuhaler® gave a significantly higher $FEV_1$ response than 0.25 mg given by pMDI. In the follow-up study, the difference in $FEV_1$ between 0.5 mg given *via* Turbuhaler® and pMDI was again nonsignificant. Other recorded spirometric parameters, $FEF_{25}$, $FEF_{50}$, $FEF_{75}$, PEF, $_sG_{aw}$, and forced vital capacity (FVC), showed a similar pattern. Thus, the difference observed in pulmonary deposition was reflected in the effects exerted. In this group of patients, a terbutaline dose of 0.25 mg given *via* Turbuhaler® gave a close to maximal effect. The two studies taken together are a good illustration of the necessity to perform comparative studies on the rising part of the dose-response curve.

In another group of patients attending the emergency department with acute severe asthma, inhalation of terbutaline *via* Turbuhaler® was compared to pMDI plus Nebuhaler® [96]. Terbutaline, 2.5 mg, was given twice with a 15 min interval. The effect on $FEV_1$ was significantly higher for Turbuhaler® than for pMDI plus Nebuhaler®. Thus, in this group of asthmatic patients with severe airflow limitation, a difference in effect could still be observed even if the dose of terbutaline administered was much higher than in the study in mild-to-moderate asthmatics discussed previously [68].

In an open study with a cumulative design, doses of 0.125, 0.125, 0.25, 0.5, 1.0 and 2.0 mg were given *via* pMDI and Turbuhaler® at 30 min intervals. The mean relative dose potency in favour of Turbuhaler® was 1.5 [97].

Collectively, cumulative studies comparing pMDI and Turbuhaler® have failed to show significant differences with regard to effects. Single-dose studies, however, including different dose levels, have shown production of a significantly better effect by Turbuhaler® compared with pMDI; the degree of lung deposition of terbutaline sulphate was reflected in the lung effects produced.

### *Salbutamol*

A number of studies have compared the efficacy of salbutamol when inhaled *via* Rotahaler®, Diskhaler®, Turbuhaler® and pMDI. In a cumulative (100, 200, 400 and 800 µg) salbutamol study, it was shown that the increase in $FEV_1$ was lower when the drug was given with Rotahaler® than with pMDI [7]. The difference, in effect, was in the order of two. In a second cumulative study, the bronchodilating properties of salbutamol, delivered *via* pMDI or *via* Rotahaler®, were investigated in the dose range 0.1–2.4 mg with pMDI, and twice the dose range with Rotahaler® [98]. Almost identical $FEV_1$ response curves were obtained with the two modes of administration. Thus, in this study, when inhaling salbutamol from Rotahaler® the same dose was needed as *via* pMDI. In a study comparing the $FEV_1$ response after inhaling 200, 400 or 600 µg from Rotahaler® and 200 µg from pMDI, no difference could be observed in the response elicited between any of the doses [72]. This inconclusiveness was probably due to the inadequate choice of doses.

Rather conflicting results were obtained in a study where PEF was evaluated after administration of 50, 100, 200 and 400 µg of salbutamol with Rotahaler®, and 200 µg with pMDI [99]. The three low powder doses gave similar increases in PEF, whilst the 400 µg dose almost doubled the response. The 200 µg pMDI dose resulted in a response similar to the three low powder doses, but the authors claim that there was no difference between the 400 µg powder dose and the 200 µg pMDI dose.

In a study using a single-dose design, 200 µg salbutamol was given *via* pMDI and 200 and 400 µg was given *via* Rotahaler® [100]. There was an increase in effect between the two Rotahaler® doses, indicating that the study was performed on the increasing part of the dose-response curve. The 200 µg pMDI dose gave a similar increase in $FEV_1$ as twice the amount (400 µg) given *via* Rotahaler®, and the author concluded that twice the dose of salbutamol is needed to achieve the same effect when given *via* Rotahaler® compared with pMDI.

In spite of an inconclusive design, the effect of 200 µg salbutamol delivered *via* a pMDI was claimed to be equivalent to 400 µg delivered *via* Diskhaler® when using a single-dose design [8]. Autohaler® has been compared to an ordinary pMDI in a single-dose study [75]. Only one dose level was used, and salbutamol 200 µg was given using both devices. In spite of this, the authors concluded that the efficacy of the two devices was very similar. In another single-dose study, in children, 200 µg salbutamol given *via* Autohaler® was compared to 400 µg given *via* Rotahaler® [76]. No significant difference in PEF was observed between the two formulations.

Salbutamol Easyhaler®, using two different inhalation techniques but only one dose level, was compared to a conventional pMDI using 200 µg as the test dose [77]. Easyhaler® was actuated before and at inhalation, and both techniques showed an increase in $FEV_1$ similar to that of pMDI. Easyhaler® has also been compared to salbutamol pMDI in a cumulative dose-response study [101]. The cumulative dose was 720 µg and Easyhaler® was actuated before and at inhalation. No difference in $FEV_1$ was observed between the three dosing regimens, and the authors concluded that the three ways of administering salbutamol were clinically equally effective. Salbutamol, delivered *via* pMDI and Easyhaler® has also been compared in a single-dose design at a dose of 200 µg. No difference in $FEV_1$ response was observed [78].

In a well-designed study, LÖFDAHL *et al.* [102] compared the effect of 50, 100 and 200 µg of salbutamol given *via* Turbuhaler® with 200 µg given *via* pMDI. The authors conclude that at an equal nominal dose, 200 µg salbutamol given *via* Turbuhaler® showed a significantly better response than when given *via* pMDI. No difference was observed between 50 and 100 µg given *via* Turbuhaler® and 200 µg given *via* pMDI.

In another study, 50 and 200 µg doses of salbutamol, given *via* Turbuhaler®, were compared with 100 and 400 µg given *via* pMDI [103]. The high doses from pMDI and Turbuhaler® showed a better $FEV_1$ response than the two low doses, thus confirming that the study was performed on the slope of the dose-response curve. There were no significant differences between the two ways of administering the drug either for the two low

or for the two high doses. Thus, it was concluded that half the dose given *via* Turbuhaler® will produce the same effect as the full dose given *via* pMDI. Collectively, due to inconclusive study designs, no clear picture of the relative effects of salbutamol when given *via* pMDI, Rotahaler® or Diskhaler® is seen; if anything, Rotahaler® and Diskhaler® seem to be less efficient formulations than the corresponding pMDI. Conversely, the higher efficacy of Turbuhaler® compared to pMDI, derived from the terbutaline studies, was also confirmed for salbutamol.

*Budesonide*

The relationship between pulmonary deposition and pulmonary effects is much more difficult to evaluate for anti-inflammatory medication than for bronchodilators. As is the case for bronchodilators, the pulmonary deposition can be assessed *in vivo* using the scintigraphic or the pharmacokinetic technique. Efficacy can only be measured in well-designed clinical trials measuring change in symptoms, lung function and consumption of short-acting bronchodilators over a number of weeks. It is very well known that such clinical parameters are very insensitive to dose-response effects of inhaled steroids, and only large scale clinical trials using a considerable number of patients have been able to show a dose-response curve for steroids. To compare different steroids and different inhalation devices will require huge clinical trials. Nevertheless, a few well-designed studies have been published.

Budesonide pMDI plus Nebuhaler® was compared with budesonide Turbuhaler® in asthmatic patients for 4 weeks, and the Turbuhaler® treatment produced a significantly better morning PEF than the pMDI [104]. In addition, the number of coughs within 5 min after inhalation from pMDI plus Nebuhaler® or Turbuhaler® was higher after pMDI. The doses given were 400–800 μg *b.i.d.* No difference in $FEV_1$ or evening PEF was observed. In another study, 127 children, shown to need a previously determined dose of budesonide (given *via* pMDI plus Nebuhaler®), to control their asthma, were given either half the standard budesonide dose by Turbuhaler® or the standard dose of budesonide by pMDI plus Nebuhaler® [105]. No difference in the effect produced could be observed between the two treatment groups. The only significant difference was an increased need for $\beta_2$-agonist as rescue medication in the pMDI plus Nebuhaler® group. The effect data must be compared to plasma concentrations of the drug after inhalation from a pMDI plus Nebuhaler® or Turbuhaler®, which showed that Turbuhaler® gave rise to twice the plasma level of drug as compared with pMDI plus Nebuhaler® [106].

The criticism that can still be formulated for the study comparing Turbuhaler® and pMDI plus Nebuhaler® in children is that two different doses were not selected for each of the devices. This was partly circumvented by selecting the children that deteriorated after halving the dose of budesonide administered *via* pMDI and Nebuhaler®, thus showing again that doubling the dose *via* pMDI plus Nebuhaler® or administering half of the dose *via* Turbuhaler® resulted in an improved control of asthma. Collectively, half the dose of budesonide *via* Turbuhaler®, produced at least the same effect as the full dose given *via* pMDI plus Nebuhaler, indicating that the degree of lung deposition is reflected in the effects exerted.

*Other medications*

No studies have been published on the efficacy of the inhalers used for beclomethasone, flunisolide, triamcinolone acetonide or fluticasone with regard to pulmonary deposition and the resulting clinical effect.

## Concluding remarks

Methods to measure the pulmonary deposition of inhaled drugs have now been validated and shown to be sufficiently sensitive to study the efficacy of inhalation techniques and inhalation devices in delivering drugs into the airways. There is, in general, a good relationship between pulmonary deposition and pulmonary effects both for bronchodilators and steroids, although the documentation is still rather limited and more extensive for bronchodilators. This might be explained by the difficulty in obtaining a dose-response relationship for the clinical effects of inhaled steroids. The development of an increasing number of inhalation devices will result in an increasing demand for studies comparing the efficacy of the different devices. The need for comparative clinical trials using the different devices will remain, but the methods for measuring pulmonary deposition could help in optimizing inhalation therapy with regard both to inhalation technique and inhalation device.

Further studies are clearly needed to substantiate the relationship between pulmonary deposition and therapeutic effect for a number of antiasthma drugs. It is obvious from a review of the literature that an appropriate design must be selected for these studies. A well-designed comparative study should include at least two dose levels, for at least one of the devices, and it is necessary to show a difference in the response between the two dose levels to draw conclusions. Another way to show that the doses given are on the slope of the dose-response curve is to lower the normal patient dose until a worsening of the lung function and or the symptoms occurs, and then treat the patients with the study drugs at a higher dose level. In this case, different dose levels of the different devices can be used.

New and better methods should also be developed to measure the localization of the inhaled drugs in airways of different sizes and in the alveoli.

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