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Human lung deposition data: the bridge between in vitro and clinical evaluations for inhaled drug products?

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Abstract

Regulatory dossiers for new inhaled drug products generally contain in vitro data, which assess delivered dose and particle size distribution, together with clinical efficacy and safety data. Human lung deposition data may be generated using radionuclide imaging techniques or appropriate pharmacokinetic methods, and can act as a 'bridge' via which a seamless transition can be made between in vitro testing in the laboratory and efficacy/safety testing in the clinic. By enabling informed decisions to be made about the evaluation of new devices or formulations in man, lung deposition data permit a long and expensive clinical trials programme to be commenced with much greater certainty of a successful outcome. Human lung deposition data should be considered for supplementing the information required for regulatory dossiers.

Keywords: Inhaled drugs; Lung deposition; Particle size; Clinical response

1. Introduction

As we enter the new millennium, many new inhaler devices and drug formulations intended for pulmonary drug delivery are being developed (Newman, 1997). These involve both drugs required to treat asthma and other respiratory conditions, and drugs for which the lungs act as a portal of entry to the systemic circulation. It is necessary for manufacturers to demonstrate to regulatory authorities that a new product is likely to deliver drug efficiently and reproducibly, and that once delivered, the drug will be both efficacious and safe. Regulators require to see in vitro data which document both emitted dose and particle size distribution (United States Pharmacopoeia, 1996) while pharmacodynamic studies, including controlled clinical trials in patients, are currently considered essential to demonstrate efficacy and safety (Rogers and Ganderton, 1995). Although regulatory guidelines concentrate on topical delivery of asthma drugs, the above considerations also apply to drugs given by inhalation to achieve a systemic effect. A major challenge faced by companies developing new inhaled drug products is to define with confidence the doses that are needed in phase II and/or

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phase III studies in patients. Companies also desire to undertake these studies as soon as possible, in order to bring the product to market at the earliest possible opportunity.

How should companies 'cross the Rubicon' to move from in vitro testing in the laboratory to efficacy and safety investigations in the clinic? This paper will review the available methodologies for assessing the delivery of inhaled drugs, arguing that in order to progress to the testing of clinical response with maximum confidence, companies should supplement in vitro data with human lung deposition data. These data can often be obtained in healthy volunteers, rather than in patients with asthma.

2. Assessment methods for inhaled drugs

2.1. In vitro particle size distribution assessment

Measurement of the in vitro particle size distribution of an inhaler yields parameters such as mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), fine particle fraction (FPF) and fine particle dose (FPD) (Clark et al., 1998). Of these parameters, the FPF and FPD have particular relevance, since they express respectively the percentage of the drug dose and mass of drug contained in 'respirable' particles or droplets, smaller than about 5 μm diameter (Hickey, 1992).

Inertial separation methods are preferred for determining size distributions from pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) (Clark et al., 1998). The devices listed in the Pharmacopoeias for making these assessments are the Andersen sampler, high precision multistage liquid impinger (HPMLI) and Marple-Miller cascade impactor (United States Pharmacopoeia, 1996). While these three systems differ in design, all are based on the same impaction principle, by which particles and droplets of different sizes are collected on a series of stages, each of which represents a discrete size band, when air is drawn through the system at a predetermined rate. The stages may be washed with a solvent, so that the mass of drug associated with each size band may be determined by an analytical method such as high performance liquid chromatography (HPLC) or by ultraviolet (UV) spectrophotometry. An impactor has an induction port or 'throat' through which the aerosol cloud is introduced, which typically takes the form of a right angle tube, either with straight sides or incorporating a glass bulb.

Several optical methods, including laser diffraction and time-of-flight aerodynamic particle size analysis, can be used for assessing size distributions from inhalers (Niven, 1993; Annapragada and Adjei, 1996). These methods can be especially useful for obtaining rapid sequential results, but are generally seen as providing data to support a fuller programme of evaluation using inertial sampling techniques.

The major roles of in vitro particle sizing data are first in the quality control of the pharmaceutical product, and second as a tool to aid rapid product development.

2.2. Pharmacokinetic (PK) studies

The quantification of drug concentrations in blood or in urine primarily provides information about systemic exposure. In the case of inhaled asthma drugs which act locally on the airway surface, it is considered that PK data have limited relevance to clinical efficacy (CPMP, 1995). However, for the drugs administered by inhalation in order to achieve a systemic effect (for instance insulin or morphine), PK data may be a key predictor of therapeutic response.

A problem inherent in the use of PK methods as a means of assessing the delivery of drugs to the lungs is that systemic drug levels can result not only from drug absorbed through the lungs, but also from drug which is deposited in the oropharynx and then absorbed via the gastrointestinal (GI) tract. Systemic levels can be used to quantify whole lung deposition for compounds which have negligible oral bioavailability (e.g. sodium cromoglycate, (Auty et al., 1987)), for which oral bioavailability is accurately known (e g budesonide, (Thorsson et al., 1994)) or for which GI absorption can be blocked by co-administration of charcoal (e.g. terbutaline sulphate,

(Borgström et al., 1996)). Since GI absorption is expected to occur later than pulmonary absorption, plasma levels (Newnham et al., 1993) or urine levels (Hindle and Chrystyn, 1992) of albuterol within the first 30 or 60 min following inhalation have also been used as indices of lung deposition. Generally, however, PK methods for assessing drug deposition in vivo are highly drug-specific, and are unable to provide any information about the regional pattern of distribution within the airways.

2.3. Imaging methods

Radionuclide imaging methods involve radiolabelling the drug formulation or drug molecule with an appropriate radionuclide, and then visualising and quantifying the deposition pattern by external imaging. The most widely used imaging method is gamma scintigraphy, which views the lungs in two-dimensions from anterior and posterior projections using a gamma camera and data processing system (Newman, 1998a). Gamma scintigraphy enables lung deposition to be quantified accurately for any inhaled drug product, and also provides data on regional deposition by dividing the lungs into a series of zones, primarily representing airways of different sizes. In gamma scintigraphic studies, the radionuclide ^{99m}Tc (half life 6 h) is generally used to radiolabel the drug formulation. Pre-study validation tests must be carried out to prove that drug and radiolabel match one another across different size bands, and that the drug delivery characteristics of the product have not been altered during the labelling procedure (Newman, 1996). Guidelines relating to experimental aspects of scintigraphic studies have recently been published as part of a British Association for Lung Research (BALR) consensus statement (Snell and Ganderton, 1999).

The imaging techniques of single photon emission computed tomography (SPECT) (Perring et al., 1994) and positron emission tomography (PET) (Berridge and Heald, 1999) have both been used to quantify drug delivery from inhalers, and have the advantage of viewing the lungs in three dimensions. PET imaging involves specific positron-emitting radionuclides such as ^{11}C, which can be chemically incorporated into the structure of the drug molecule. However, at the present time there are significant practical problems associated with conducting SPECT and PET studies to assess human lung deposition from inhaler devices (Newman and Wilding, 1999), and consequently the recent BALR Consensus Statement (Snell and Ganderton, 1999) concluded that gamma scintigraphy is the current imaging method of choice for assessing lung deposition of inhaled drug products.

2.4. Pharmacodynamic data

Pharmacodynamic data are considered to be the 'gold standard' for assessing the efficacy and safety of new inhaled drug products, and form the basis of the clinical trials package in regulatory submissions. For inhaled bronchodilators, a clinical response is relatively easy to measure in asthmatic patients, using the increase in spirometric tests of lung function such as forced expiratory volume in one second (FEV1) within the first 15–30 min of inhalation. An alternative method is to assess the protective effect of the inhaled bronchodilator against the bronchoconstriction induced by inhaled methacholine or histamine, with the primary measure being the PC_{20}, i.e. the provocative concentration of bronchoconstrictor in a nebuliser solution which reduces lung function by 20% (Juniper et al., 1994). However, since the top of the dose response curve of an inhaled beta-agonist such as albuterol may be reached using only one or two metered doses (Barnes and Pride, 1983), single dose comparisons are of limited value. Other study designs, e.g. a four-way randomised cross-over study involving one and two doses of test and reference product (Adams et al., 1994), or a cumulative dose response study (Kleerup et al., 1996), are more valuable. Assessment of the side-effects of inhaled bronchodilators involves the recording of changes in blood pressure, pulse rate, electrocardiogram (ECG) and serum potassium, together with monitoring of finger tremor.

Inhaled corticosteroids act much more slowly than inhaled bronchodilators, and their effects must be monitored over a period of at least 4

weeks (Barnes et al., 1998). The response to inhaled corticosteroids is highly variable, so that large numbers of patients must be studied in order that an investigation should achieve appropriate statistical power (Zanen and Lammers, 1995). In order to ensure that clinical response is being assessed on the rising portion of the dose response curve, more than one dose level must be tested. A study meeting these criteria was recently undertaken by Busse et al. (1998), who carried out a comparison of two inhaled corticosteroid products in a total of over 300 asthmatic patients, randomised into six groups of 50–60 patients receiving doses of 100, 400 and 800 μg beclomethasone dipropionate (BDP) daily for 6 weeks. The difficulty of carrying out such studies is obvious, and other models for assessing the clinical response to inhaled corticosteroids are needed urgently. The suppression of serum cortisol levels is generally used as the most easy-to-measure index of the systemic effects of inhaled corticosteroids.

Clinical endpoints for inhaled drugs which act systemically vary widely, and are often based upon changes in biochemical parameters. For instance, the therapeutic effect of inhaled insulin may be assessed from changes in plasma glucose and circulating C-peptide (Laube et al., 1998a).

3. Correlations between particle size data, lung deposition data and clinical response

3.1. In vitro particle size data versus lung deposition

The relationship between in vitro particle size data and lung deposition data is complex. In vitro particle size data and in vivo lung deposition data from 18 inhaled drug products tested in eleven scintigraphic studies were reviewed by Newman (1998b). In these studies, lung deposition was assessed by gamma scintigraphy, and prior to the study, in vitro particle size data were collected from each device in a four-stage liquid impinger operating at a flow rate of 60 l/min. The data show that FPF systematically overestimated whole lung deposition (Fig. 1). This reflects the fact that the inlet 'throat' to an impinger cannot adequately mimic the anatomical complexity of the human upper airway, or the interaction of the aerosol cloud with this region of the respiratory tract. Hence, FPF does not accurately predict the numerical value of human lung deposition. This was a widely held belief, but previously there had been a shortage of clear documentary evidence.

While the correlation between particle size and deposition is sometimes impressive, for instance allowing the relative amounts of lung and oropharyngeal deposition for nebulised aerosols to be predicted from particle size data (Clark, 1995a), this is often not the case. Olsson et al. (1996) assessed whole lung deposition of albuterol (using the charcoal block PK method for a pMDI and three DPIs (Cyclohaler, Rotahaler and Turbuhaler)) in eleven healthy subjects. Inhalations from the DPIs took place with both moderate and weak inspiratory force, at flow rates which were adjusted appropriately for each device. A slow inhalation was taken from the pMDI. FPFs for pMDI and for the DPIs were assessed at each flow rate by an Andersen sampler equipped with a glass bulb inlet 'throat', with the same flow rates through the inhalers being used in vitro as those adopted in vivo. A further set of measurements was made using an anatomical model of the human upper airway as the inlet to the impactor. The results are shown in Table 1. For the glass bulb throat, pMDI and Turbuhaler used with

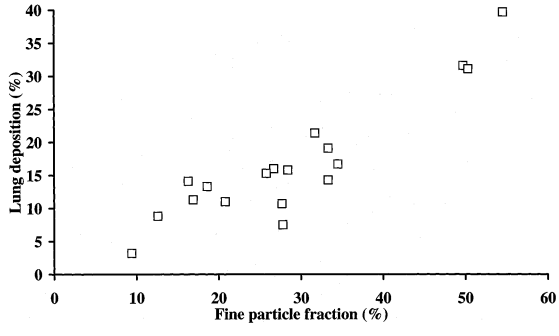

Fig. 1. Comparison of fine particle fraction and whole lung deposition, each expressed as percentage of the metered (ex-valve) dose for eighteen products. Whole lung deposition was quantified by gamma scintigraphy, and fine particle fraction by multistage liquid impinger. Data from Newman, 1998b.

Table 1
Mean whole lung deposition and fine particle fraction (both expressed as nominal dose) from an Andersen sampler, fitted with a glass bulb throat and with an anatomical throat model[a]

Device	Inspiratory flow	Lung deposition (%)	Fine particle fraction (%)	Fine particle fraction (%)
			Glass bulb	Anatomical throat
Turbuhaler	Moderate	23.2	41.8	32.2
	Weak	13.9	25.2	25.6
Rotahaler	Moderate	7.0	18.8	14.5
	Weak	3.4	12.9	9.5
Cyclohaler	Moderate	10.7	14.6	12.7
	Weak	7.0	11.4	9.6
pMDI	Slow	13.3	44.7	19.7

[a] Data are shown for three dry powder inhalers (Turbuhaler, Rotahaler and Cyclohaler) and for a pressurised metered dose inhaler (pMDI). Data from Olsson et al., 1996.

moderate effort had similar mean FPFs (44.7 vs. 41.8%), but lung depositions for these two products averaged 13.3 and 23.2% of the dose, respectively.

Hence, the data showed that when a conventional inlet to the impactor was used, in vitro particle size data failed to predict the relative lung depositions from the pMDI and the DPIs, although it is interesting to note that a better agreement was obtained using an anatomical model of the human upper airway as the inlet to the impactor. The discrepancy using the conventional inlet was ascribed mainly to the 'ballistic' nature of the pMDI spray, comprising rapidly moving and rapidly evaporating propellant droplets, which can pass relatively easily through a glass bulb throat to enter the impinger, but which penetrate through the human upper airways much less readily.

Although the correlation between FPF and lung deposition for the DPIs was reasonable in the study by Olsson et al. (1996), this is not always the case. Recent evidence suggests that marked differences between dry powder products in vitro may not be reflected in in vivo data; in a study involving two powder formulations delivered via the Clickhaler DPI, FPFs averaged 61.1 and 32.4% of the dose for 'novel' and 'standard' budesonide formulations (a ratio of 1.9), while lung depositions measured by gamma scintigraphy averaged 34.9 and 26.8% of the dose (a ratio of 1.3) (Warren et al., 1999). Lung deposition data thus provide a way of expressing differences between inhaler devices in vivo, in a manner that may be more relevant to the clinical situation than in vitro testing.

3.2. Lung deposition versus clinical efficacy

Inhaled asthma drugs act locally on receptors on the airway walls (Barnes et al., 1997), whilst inhaled drugs intended for systemic delivery must be deposited in the alveolated regions of the lungs if they are to be absorbed optimally (Adjei and Gupta, 1994). Therefore, it is obvious that the deposition of drug in the lungs must have some type of predictive role for the efficacy of drugs given by the inhaled route. This issue has been explored in several recent reviews (Selroos et al., 1996; Pauwels et al., 1997; Derom and Pauwels, 1998; Snell and Ganderton, 1999), and many good case histories show the predictive value of drug deposition studies for the clinical response to inhaled asthma drugs (Newman, 2000). Fewer examples exist for inhaled corticosteroids than for bronchodilators, but this reflects primarily the difficulty of assessing the clinical response to inhaled corticosteroids reliably, and relating the response to drug deposition in the same subjects. In an important study by Laube et al. (1998b), a group of asthmatic patients inhaled a radiolabelled formulation of sodium cromoglycate (SCG) from a pMDI at slow and fast inhalation rates on different days. Total lung deposition was higher

with slow inhalation (mean 11.8% of dose) compared with fast inhalation (mean 8.6% of dose), and regional lung deposition was more uniform. The patients were then given an inhaled allergen, and the protective effect of SCG against allergen-induced bronchoconstriction was assessed. The improved total and regional deposition pattern brought about by slow inhalation resulted in a smaller fall in FEV1 (mean 5.4%) following allergen challenge compared with a mean 12.6% for fast inhalation.

The pMDI and DPI are the two most widely used types of portable inhaler, but have very different delivery characteristics which lung deposition studies are able to investigate. In the case of pMDIs, both lung deposition and clinical response are enhanced by slow inhalation. Different considerations apply, however, for drugs delivered by DPIs. Currently marketed DPIs are breath-actuated, relying upon the patient's inspiratory effort to generate the aerosol. For most of these devices, drug delivery to the lungs is enhanced by fast inhalation, which increases the deaggregation of drug/lactose complexes or of pure drug pellets, leading to higher fine particle dose and subsequent higher lung deposition in vivo (Timsina et al., 1994). These differences in turn result in the therapeutic effects of drugs delivered from most DPIs being enhanced by fast inhalation i.e. maximum inspiratory effort (Groth and Dirksen, 1983; Pedersen, 1986).

Although clinical response data are relied upon heavily, they are often misleading, since they may not reflect major differences in drug delivery. For instance, in a charcoal block study by Borgström et al. (1996), lung doses averaging 47 and 109 μg terbutaline sulphate from the Turbuhaler gave essentially the same bronchodilator response, presumably because both doses were on the plateau of the dose-response curve. In the study by Busse et al. (1998) mentioned in Section 2.4, the dose responses to inhaled BDP were very flat (Fig. 2), so that daily doses of 100 μg by CFC and 800 μg by HFA pMDIs resulted in mean FEV1 increases of 14 and 23% respectively. However, the HFA product was delivered much more efficiently to the lungs (Leach et al., 1998), so that the relative HFA:CFC lung doses differed by a factor of at least 20:1. Lung deposition data are much more sensitive than clinical response data and a combination of lung deposition data and clinical response often provides a much better understanding of the drug delivery process than clinical data alone.

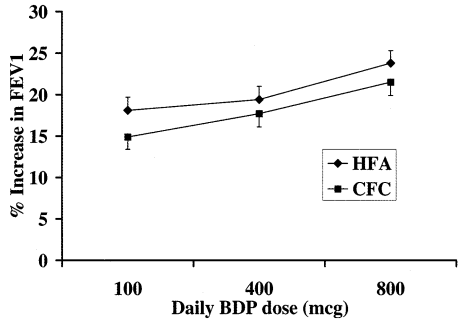

Fig. 2. Responses to daily doses of 100, 400 and 800 μg beclomethasone dipropionate (BDP) given from pMDIs containing either CFC propellants or HFA-134a. Responses were measured as the percentage increase in FEV1 after 6 weeks in a total of over 300 patients, each randomised to receive one of the treatments. Data from Busse et al., 1998.

The alveolar depositions of an inhaled peptide drug, given as two different size distributions on different days, were directly proportional to the areas under the curve for plasma concentrations

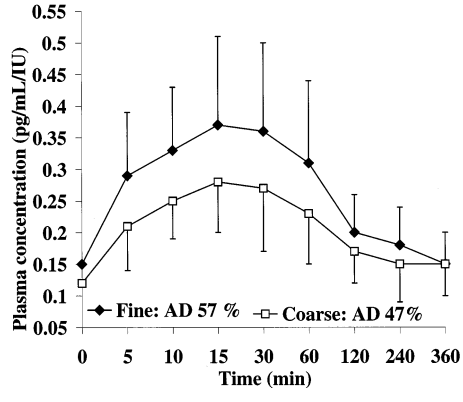

Fig. 3. Plasma concentrations of an inhaled peptide plotted versus time. The inhaled peptide was administered in two size fractions ('fine' and 'coarse' particles). The area under the plasma concentration versus time curve was directly related to alveolar drug deposition (AD), expressed as percentage of whole lung deposition. Data redrawn from Newman et al., 1998a.

plotted versus time (Fig. 3). Changes in particle size were shown to alter the deep lung penetration of the inhaled peptide and subsequent absorption, providing direct evidence that inhaled peptides need to be delivered to the alveolated lung zones for optimal bioavailability (Newman et al., 1998a).

4. Lung deposition data: the bridge from in vitro to clinical testing

Drug deposition assessed from imaging studies or suitable PK studies can predict the clinical response to inhaled drugs, while the predictive nature of in vitro particle size data is more debatable. However, none of these methods is considered able to substitute fully for clinical response data for new inhaled drug products at the present time. A manufacturer introducing a new inhaler or formulation needs at the very least to conduct a phase III clinical trial in order to prove the efficacy and safety of their product. However, lung deposition data can act as a bridge to help cross the wide gulf that exists between the in vitro testing and the clinical trials programme, enabling more informed decisions to be made about the conduct of clinical studies than would otherwise be the case, and allowing the clinical trials programme to proceed with greater confidence of a successful outcome. Three case histories will be presented to support this argument.

4.1. Example 1: the Respimat, a new 'soft mist inhaler'

One category of novel inhaler device is the so-called 'soft mist inhaler'. These are multidose devices capable of delivering accurately metered doses of <100 μl drug solution in a manner analogous to a pMDI. These devices work by a variety of principles, including the forcing of liquid through a very fine nozzle under pressure, and ultrasonics (Clark, 1995b). One of these devices is the Respimat (Boehringer Ingelheim), which is being developed for the delivery of a range of bronchodilator and corticosteroid products for the therapy of asthma and chronic obstructive pulmonary disease (Zierenberg et al., 1996).

The Respimat is intended as a therapeutically equivalent alternative to a CFC-based pMDI, but it was anticipated that the Respimat spray would have both a finer particle size and a slower velocity than the pMDI spray. Andersen sampler data showed that the Respimat had an FPF of 66% when delivering a fenoterol formulation, a value approximately twice that for the corresponding pMDI formulation when measured under equivalent conditions of temperature and humidity (Zierenberg, 1999). Compared with the pMDI, the Respimat had a slower spray velocity at the nozzle (10 vs. 50 m/s), and the spray was generated over a longer period (1.2 vs. 0.1 s). In developing the Respimat, Boehringer Ingelheim needed to conduct a phase II study to compare the new device with a pMDI, but knew that the doses used from the two devices could not be the same. However, armed only with in vitro data, and knowing that these data do not always predict in vivo behaviour accurately, especially for the comparison of aerosols with widely differing physical characteristics, the Company was faced with the question of predicting the doses that would be needed for the phase II study. To aid their decision making, a lung deposition study was conducted in twelve healthy subjects using the imaging technique of gamma scintigraphy. Drug formulations were radiolabelled with ^{99m}Tc, which was shown to be an accurate marker for the drug substance. The study showed that whole lung deposition of fenoterol averaged 39.2% of the metered (ex-valve) dose from the Respimat and 11.0% from the pMDI (Newman et al., 1998b).

These human lung deposition data provided the confirmatory evidence which enabled Boehringer Ingelheim to proceed to the phase II study with confidence. In that study (Maesen et al., 1997; Van Noord et al., 2000), 62 asthmatic patients were randomised at two study centres to four out of eight possible treatments: placebo, 12.5, 25, 50, 100 and 200 μg fenoterol by Respimat, versus 100 and 200 μg fenoterol by pMDI. The improved lung deposition provided by the Respimat gave clinically significant improvements in lung function with lower drug doses than the pMDI; 12.5 and 25 μg doses delivered by the Respimat were equivalent to 100 μg delivered by the pMDI, while

Table 2
Median (range) deposition data for AM-MDPI and Turbuhaler (Newman et al., 2000a)[a]

Device Targeted PIFR[b]	AM-MDPI 90 l/min	AM-MDPI 60 l/min	AM-MDPI 45 l/min	Turbuhaler 60 l/min
Lungs (%)	32.1 (9.4–41.0)	25.0 (12.1–37.4)	19.9 (8.8–26.6)	21.4 (4.7–29.2)
Oropharynx (%)	57.0 (45.1–81.7)	61.6 (42.2–77.6)	60.9 (49.5–68.3)	71.9 (54.8–80.0)
Mouthpiece (%)	9.5 (5.5–23.2)	15.6 (1.2–20.0)	17.3 (11.8–43.0)	11.6 (5.3–22.0)
Exhalation filter (%)	0.8 (0.2–1.8)	0.6 (0.2–3.0)	0.2 (0–0.9)	0.2 (0–0.7)
Peripheral/central zone ratio (P/C ratio)	0.9 (0.6–1.3)	1.0 (0.8–1.3)	1.0 (0.7–1.5)	0.9 (0.5–1.6)

[a] Deposition in the lungs and oropharynx, retained on the device mouthpiece and recovered from an exhalation filter, are expressed as percentages of the metered dose. The P/C ratio (ratio of deposition in peripheral lung to that in central lung) is given as an index of regional lung deposition.
[b] Denotes peak inhaled flow rate.

all five Respimat doses were equivalent to the 200 μg pMDI dose.

4.2. Example 2: a novel dry powder inhaler

Many new dry powder inhalers (DPIs) are currently being developed, especially for asthma therapy. One of these is the ASTA Medica AM-MDPI device, a novel multidose device containing doses in a bulk powder reservoir, which are accurately metered immediately prior to inhalation (Berner et al., 1998). A lung deposition study was conducted in 13 healthy subjects comparing the AM-MDPI with the Turbuhaler DPI for the delivery of budesonide. The Turbuhaler was considered as the most appropriate comparator, as it is probably the most widely used DPI device in Europe. The AM-MDPI was tested at three different inhaled flow rates on different days (90, 60 and 45 l/min), since it was anticipated that lung deposition would be flow rate dependent. Drug formulations were radiolabelled with ^{99m}Tc, which was shown to be an accurate marker for the drug substance.

The scintigraphic data are shown in Table 2. While the AM-MDPI showed the expected flow rate dependence of lung deposition, an index of regional lung deposition (the peripheral lung zone/central lung zone deposition ratio, P/C ratio) was independent of inhaled flow rate. Overall, the data showed that lung deposition of budesonide from the AM-MDPI at flow rates of 60 or 45 l/min was comparable to that from the Turbuhaler (Newman et al., 2000a), and was superior when tested at the highest inhaled flow rate. The AM-MDPI showed less variability in lung deposition than the Turbuhaler. This finding was consistent for all flow rates. The information obtained from this lung deposition study provided the evidence needed to enter a phase III 'head to head' comparison of Turbuhaler and AM-MDPI with a degree of confidence superior to that based upon in vitro data alone. The phase III study was subsequently conducted in 315 patients with mild to moderate asthma, randomised into two parallel groups, who received budesonide either by AM-MDPI ($n = 159$) or Turbuhaler ($n = 156$). Treatment consisted of 200 μg budesonide given every 12 h for 4 weeks. Just under half the patients studied were glucocorticosteroid-naive. The lung deposition study also saved time in the drug development process by allowing the phase III study to commence sooner than would otherwise have been the case.

4.3. Example 3: systemic delivery of inhaled drugs

The lower respiratory tract is seen as a key target area for some inhaled drugs such as small macromolecules (e.g. insulin, calcitonin) and drugs intended for pain control (e.g. morphine, ergotamine) (Byron and Patton, 1994). Successful delivery of drugs to the systemic circulation via the pulmonary route requires suitable inhaler devices capable of reproducibly delivering a high proportion of the dose to the lung periphery, from

which absorption can occur. A novel pMDI actuator (Aerosol Drug Delivery System, ADDS, Sheffield Pharmaceuticals, Inc.) has been developed (Armer et al., 1999), which triggers automatically in a specific portion of the subject's inhalation, and which utilises a flow control chamber to manipulate the discharged plume by reducing momentum compared with a conventional pMDI. A human lung deposition study was carried out to assess the deposition of ergotamine tartrate from the ADDS device in 12 healthy subjects. Three doses (total delivered dose 129 μg ergotamine tartrate) were given from the ADDS. The drug formulation was radiolabelled with ^{99m}Tc, which was shown to be an accurate marker for the drug substance. On a separate day, six doses (total delivered dose 2052 μg ergotamine tartrate) were given by Medihaler pMDI (3M HealthCare). The Medihaler dose was not radiolabelled, but plasma concentrations of ergotamine tartrate from both ADDS and Medihaler were determined. The relative delivered doses from ADDS and Medihaler were selected on the basis of in vitro data suggesting they would lead to similar fine particle doses.

The scintigraphic data showed that a mean 59 μg ergotamine tartrate was deposited in the lungs (representing a mean 46% of the delivered dose, and 34% of the metered (ex-valve) dose), with a mean 69 μg deposited in the oropharynx (Newman et al., 2000b). Plasma concentrations of ergotamine tartrate (Fig. 4) reached a peak from the ADDS within 2 min, attributed to rapid pulmonary absorption, while the maximum plasma concentration from the Medihaler was reached at 5 min, probably resulting from buccal absorption. The maximum plasma level from the ADDS was similar to that from the Medihaler, despite the 16-fold smaller dose.

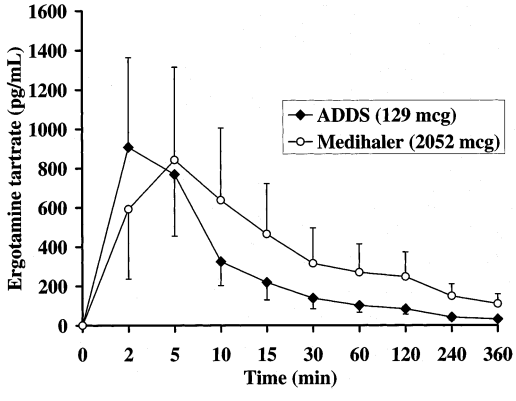

Fig. 4. Plasma levels of ergotamine tartrate following administration of 129 μg by ADDS device and 2052 μg by Medihaler (from Newman et al., 2000b).

The data showed proof of concept in vivo for the ADDS device as an efficient pulmonary delivery system, to support promising in vitro data, and more importantly provided the key information regarding the doses of ergotamine tartrate delivered from the ADDS device that were likely to be clinically effective.

5. Discussion

No method for assessing inhaled drug delivery is perfect, and in practice data from a variety of sources are required. While in vitro data and clinical efficacy testing form the core of regulatory dossiers for new inhaled drug products, the three case histories presented above show the power of lung deposition data to act as a bridge between in vitro data obtained in the laboratory and the demonstration of clinical efficacy/safety in patients. In each case human lung deposition data enabled the pharmaceutical company concerned to make decisions concerning the clinical trials programmes with greater confidence, and in at least one of the examples with greater speed. All three case histories involved healthy volunteers as the study population, and data in healthy subjects will generally suffice to clarify the relative drug deliveries in vivo from two inhaler devices. Similar whole lung depositions are to be expected in healthy volunteers and asthmatic patients, although deposition patterns within the lungs will be more central in asthmatics, owing to the presence of airways obstruction (Melchor et al., 1993).

Although gamma scintigraphy was used to quantify lung deposition in the three case histories, a PK method would be a suitable alternative for some products. PK methods have a potential advantage of not requiring the drug formulation to be manipulated in any way during the radiolabelling process. However, while gamma scintigra-

phy can be applied to assess the deposition of any drug or formulation, PK methods are specific to particular drugs or particular classes of drugs that behave in a given manner. For instance the charcoal block method can only be used to assess lung deposition of drugs whose oral absorption can be readily blocked by pre-administration of oral charcoal. In addition, PK methods such as the charcoal block technique provide no information about the regional lung deposition of inhaled drugs. Therefore, the imaging technique of gamma scintigraphy will usually be the method of choice for lung deposition measurements of inhaled pharmaceutical products, although the three-dimensional imaging methods (SPECT and PET) may play an increasingly important role in the future.

It has been suggested (Ganderton, personal communication) that lung deposition data should be considered as the final step in the development pharmaceutics for inhaled drug products. However, in each of the three case studies, the lung deposition study was a phase I clinical investigation. In reality, lung deposition data have a function in both pharmaceutical development and in a clinical trials programme, which is why we consider the 'bridge' analogy to be the most appropriate positioning of lung deposition data. This accords with recent comments by Florence (1999) to the effect that "gamma scintigraphy is clearly a technique which can bridge the gap between measures of quality derived from good design and testing in the laboratory, and performance of the dosage form in the patient". We believe that the acquisition of lung deposition data should not be seen as an additional burden to drug development, but rather as an opportunity to define a clinical trials programme with greater precision, and to make a relatively seamless transition from in vitro testing. When used in this context, lung deposition data should be considered for supplementing in vitro data in regulatory dossiers.

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