Pharmacokinetics of inhaled drugs

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1 A high therapeutic ratio for the inhaled route of administration is achieved by delivering doses which achieve a high local concentration in the lung and relatively low levels of systemic absorption.

2 Pharmacokinetic evaluation of drug absorption from the lungs provides an accurate and reproducible method for comparing different inhaler delivery systems, as well as for evaluating bioequivalence of generic drug formulations.

3 The measurement of drug absorption from the lungs may also be applied to assess the effects of inhalation technique on drug delivery in vivo. For example with salbutamol delivered via a large volume spacer, lung bioavailability has been shown to be altered by factors such as the number of actuated puffs, inhalation-actuation delay and washing procedure.

4 Differences in drug delivery to the lungs between dry powder reservoir and pressurised metered-dose aerosol devices translate directly into commensurate differences in clinical efficacy for delivery of both inhaled β2-adrenoceptor agonists and corticosteroids.

5 For inhaled corticosteroids, pharmacokinetic evaluation using oral charcoal to obviate alimentary absorption may be applied to quantify the relative gut and lung components of systemic bioavailability. In tandem with information on receptor potency and affinity, drug elimination and distribution, these data may help in part to explain observed differences between different inhaled corticosteroids in terms of their systemic bioactivity profiles.

6 Studies are required to evaluate whether pharmacokinetic evaluation of lung absorption is a suitable way of quantifying delivery of nebulised aminoglycoside antibiotics, as for example in patients with cystic fibrosis.

7 Pharmacokinetic evaluation appears to have an established role in the quantification of drug delivery to the lungs and provides important information which is complimentary to other techniques such as radiolabelled deposition. The next decade of research into pharmacokinetics of established and novel drugs and delivery systems is awaited with keen interest, and will hopefully provide a greater understanding into ways of optimising the benefit-risk ratio for inhaled drugs.

Keywords pharmacokinetics inhaled drugs lung bioavailability

Introduction

The inhaled route of administration is the preferred route for delivering preventer and reliever drugs to patients with airflow obstructions. The inhaled route allows the delivery of relatively small doses of drug directly to the airway achieving a high local concentration, whilst at the same time minimising systemic adverse effects. This in turn results in a high therapeutic ratio as compared with systemic delivery by oral or parenteral routes of administration. Over the past decade the delivery of inhaled drugs has been continuously refined by inhaler delivery devices which optimise the deposition of respirable particles.

Why should we be interested in the pharmacokinetics of inhaled drugs? The application of pharmacokinetics...
provides a valuable tool for investigating lung deposition and bioavailability, and hence ways of optimising drug delivery. At the same time, pharmacokinetic techniques can be used to predict and explain the systemic adverse effect profiles of inhaled drugs. The widespread availability of sensitive assay techniques, such as high performance liquid chromatography allows the measurement of plasma and urinary drug levels required for pharmacokinetic evaluation. The purpose of this review is to appraise the literature on pharmacokinetics of commonly used inhaled drugs and how this may be applied to optimising their use in every-day clinical practice.

Inhaled β₂-adrenoceptor agonists

Following inhalation of salbutamol, most of the dose (60–80%) is delivered to the oropharynx and hence to the gut after swallowing, with a much smaller fraction (10–20%) reaching the lungs. The polarity of salbutamol at salivary pH results in only negligible buccal absorption, and the swallowed fraction undergoes extensive first-pass conjugation in the intestinal wall and liver. Since there is no first-pass conjugation in the lung, this means that initial plasma levels of unchanged salbutamol will reflect the dose delivered to the lung. Direct measurement of plasma salbutamol given by pressurised metered-dose inhaler shows that maximal plasma concentration (C_max) is achieved within 5–10 min of inhalation, consistent with rapid absorption from the lung [1,2]. It is however, unclear what proportion of this initial absorption originates from alveolar or bronchial sites. This approach provides a simple method to compare the relative drug deposition of salbutamol from different inhaler devices by making a direct measurement of lung absorption. In an initial study it was shown that enhanced delivery of salbutamol from a low velocity modified vortex metered-dose actuator (Spacehaler, Evans) resulted in a greater plasma C_max compared with an ordinary actuator [2]. As one might perhaps predict, the higher plasma concentration of salbutamol was associated with a leftward shift in the dose-response curve for extrapulmonary β₂-mediated responses. The same methodology was subsequently used to compare two nebuliser delivery systems, namely the Hudson Updraft II and the Ventstream. In vitro studies had shown that the Ventstream produced a significant increase in output of respirable particles compared with the Hudson [3]. Since the Ventstream also increases the drug delivery by matching the nebuliser output to inspiratory tidal flow rate, one might expect to find a difference in lung deposition of salbutamol when comparing the two nebuliser systems. In a study of asthmatic patients (FEV1 55% predicted) [3] the Ventstream produced an enhanced delivery of salbutamol across a dose range of 1.25 mg, 2.5 mg and 5 mg, resulting in an approximate two-fold improvement in lung absorption as assessed by plasma C_max or area under the concentration-time profile (AUC) (Figure 1). This was associated with a difference between nebulisers in AUC values for bronchodilator and systemic responses. Furthermore, each nebuliser exhibited linear pharmacokinetics with doubling doses of salbutamol.

The pharmacokinetic approach may also be applied to evaluate the bioequivalence of different formulations of inhaled salbutamol. In one such study no differences were found in lung absorption of salbutamol comparing three different formulations of inhaled salbutamol given by pressurised metered dose inhaler [4]. However, in a comparison of a non-CFC metered-dose inhaler formulation of salbutamol (Airomir, 3M) with a CFC metered-dose inhaler formulation (Ventolin, Allen & Hanburys), a 1.3-fold greater ratio for C_max was found [5] (Figure 2). This probably reflects the lower aerosol

![Figure 1](image-url)
particle plume velocity with the non-CFC formulation, as has been demonstrated in vitro [6]. This observation is in keeping with the similar finding of enhanced lung absorption with a modified actuator device (Spacehaler), which also had a reduced aerosol plume velocity [2]. Salbutamol delivered by CFC containing metered-dose aerosol (Ventolin) and dry powder inhaler (Ventodisk, Allen & Hanburys) results in comparable lung bioavailability, suggesting that both types of inhaler devices can be prescribed on a microgram equivalent basis [5] (Figure 2).

In a study of salbutamol delivered via a large volume spacer device observed values for \( C_{\text{max}} \) were 1.9-fold greater using single puffs without delay compared with the same dose as multiple puffs (4 puffs at a time), and 1.8-fold greater compared with the same dose using an inhalation delay of 20 s [7]. These effects were mirrored by commensurate differences in extrapulmonary \( \beta_2 \)-adrenoceptor activity (Figure 3). The effects of multiple actuations and inhalation delay are similar to those observed in vitro for salbutamol, corticosteroids and cromoglycate delivered by large volume spacer [8–10]. In vitro studies have also shown that reduction in electrostatic charge within the spacer using an antistatic lining is associated with a significant improvement in delivery of respirable particles [11]. The pharmacokinetic technique was applied to show that washing the spacer is an effective way of eliminating such electrostatic charge and hence optimising drug delivery [7].

An alternative, albeit indirect, method of evaluating pharmacokinetics of inhaled \( \beta_2 \)-adrenoceptor agonists is to measure urinary excretion. One application of this technique involved the measurement of urinary excretion of inhaled terbutaline, using oral activated charcoal to eliminate the gastrointestinal component of systemic bioavailability [12]. This enables calculation of a percentage for lung deposition if a standard intravenous injection of the same drug is used as a pharmacokinetic internal standard for comparison. There appears to be good agreement between estimates of lung deposition of terbutaline using pharmacokinetic and technetium radiolabel aerosol methods.

In a pharmacokinetic study inhaled terbutaline in a dose of 250 \( \mu \)g produced a lung deposition of 19% when administered by dry powder reservoir device (Turbuhaler, Astra) compared with 8% when delivered by metered-dose inhaler [13]. At the same time a dose ratio of 2:1 was demonstrated in terms of equivalent bronchodilator response comparing 250 \( \mu \)g of terbutaline via a turbuhaler and 500 \( \mu \)g via a metered-dose inhaler. However, such dose ratios are better evaluated by performing proper dose-response studies providing this is done on the steep part of the curve. In one such study, the bronchodilator-dose response (measured as
FEV\textsubscript{1} showed a 1.5-fold dose-ratio comparing terbuta-line given by turbuhaler and metered dose inhaler. Furthermore, the 1.5-fold greater ratio for broncho-dilator efficacy was exactly mirrored by the ratio for hypokalaemic response, inferring that lung deposition determines both airway and systemic effects [14].

Another indirect urinary pharmacokinetic method involves using the measurement of 30 min urinary excretion of salbutamol and its conjugates in order to differentiate between the components of lung and gastrointestinal absorption [15]. This premise depends on the assumption that most of the urinary excretion of unchanged salbutamol in the first 30 min after inhalation is due predominantly to absorption from the lungs. However, it is pertinent to note that in a study where it was possible to detect significant differences in plasma salbutamol between non-CFC and CFC containing metered-dose aerosol formulations, the same was not the case when using 30 min urinary excretion (Figure 2) [5]. Furthermore, the interindividual coefficient of variability is approximately two-fold greater with the urinary compared with the plasma method [4]. This suggests that given the availability of a sufficiently sensitive assay, the direct measurement of plasma salbutamol is the preferred method to quantify absorp-tion from lungs.

On first principles, it might be predicted that lung deposition and hence, bioavailability from the lung, would be altered in patients with airflow obstruction as a consequence of reduced small airway calibre and hence reduced peripheral lung absorption. In this respect there are some data to show that asthmatics with a 50% reduction in predicted normal FEV\textsubscript{1} have an approximate two-fold reduction in fenoterol C\textsubscript{max} compared with normals given the same dose (1.6 ng ml\textsuperscript{-1} in asthmatics vs 3.1 ng ml\textsuperscript{-1} in normals) [1,16]. Furthermore the difference in plasma fenoterol concen-tration between the two groups was associated with a marked difference in the chronotropic response to fenoterol, being greater in the group of normal subjects. This is in keeping with the observation that enhanced absorption from the lung is associated with increased systemic \(\beta\text{-adrenoceptor mediated effects} [2].

The use of plasma pharmacokinetics has also been employed to evaluate the effect of inhaler technique on delivery of terbutaline by the dry powder reservoir inhaler system [17]. These results show that lung volume prior to inhalation had no effect on lung absorption when used with a peak inspiratory flow rate in excess of 601 min\textsuperscript{-1}. At an inspiratory flow rate of 301 min\textsuperscript{-1} drug absorption was reduced to a small degree, and the bronchodilator dose-response curve was not significantly altered. When subjects first exhaled into the turbuhaler prior to inhalation, there was a marked reduction in plasma levels and this was accompanied by a commensurate right shift in the bronchodilator dose-response curve as well as systemic \(\beta\text{-mediated effects}. Improvements in drug delivery to the lung using 30 min urinary salbutamol excretion have been shown with a metered dose inhaler in association with exhaling to residual volume, slow inhalation and breath holding [18].

**Inhaled corticosteroids**

Surprisingly little has been published on the pharmacokinetics of inhaled corticosteroids. This probably reflects the lack of widely available sensitive assays for measuring plasma levels. Earlier studies with tritium labelled inhaled budesonide showed a plasma elimination halflife of 2.0 h [19]. Calculated values for oral budesonide showed a systemic bioavailability of 11% indicating a high degree of first-pass hepatic metabolism (89%) of the swallowed dose. For the inhaled route the systemic bioavailability was calculated at 73% indicating a considerable absorption from the lung of the unchanged drug. This is in keeping with in vitro studies showing extensive biotransformation in the liver but not at all in the lung [20]. For beclomethasone dipropionate partial biotransformation to beclomethasone-17-monoprop-ionate, an active metabolite, occurs in both liver and lung. Precise pharmacokinetic evaluation of the degree of liver and lung first-pass metabolism of beclome-thasone dipropionate in humans is not available. However, in terms of hepatic first-pass metabolism of the swallowed dose, data from a recent study using oral activated charcoal, revealed approximately 60–70% first-pass hepatic inactivation [21]. Fluticasone propionate like budesonide has no lung first-pass inactivation for both drugs, the main determinant of systemic bioavailability is that derived from the lung. Mouth rinsing, to reduce local adverse effects, will act to attenuate further the small component of gut bioavailability.

[Figure 4](#) Schematic representation of the relative lung and gut components comprising total systemic bioavailability for inhaled budesonide (BUD) and fluticasone propionate (FP), both given via the same inhaler device. Because of extensive hepatic first-pass but no lung first-pass inactivation for both drugs, the main determinant of systemic bioavailability is that derived from the lung. Mouth rinsing, to reduce local adverse effects, will act to attenuate further the small component of gut bioavailability.
The differences in the hepatic first-pass inactivation therefore explain the observation that for budesonide the addition of a large volume spacer to a metered dose inhaler will increase systemic bioactivity (by increasing lung absorption), whilst for beclomethasone dipropionate the addition of a spacer reduces systemic activity (by reducing gut absorption). In other words, for beclomethasone dipropionate the reduction in gastrointestinal absorption with the spacer outweighs the concomitant increase in lung absorption, because of the low degree of hepatic first-pass inactivation. Thus, for fluticasone propionate like budesonide, the use of a large volume spacer would increase systemic bioactivity, because lung absorption is the major determinant, and this would be increased with the spacer. In any event, mouth-rinsing should be routinely employed when using inhaled corticosteroids to reduce local adverse effects such as oropharyngeal candidiasis. This in turn acts to reduce further the component of gut bioavailability.

Detailed studies have evaluated the plasma pharmacokinetics of inhaled budesonide in children and adults. In a study of adult healthy volunteers a single 1000 μg dose of budesonide was given via a turbuhaler or metered dose inhaler along with intravenous administration of a 500 μg dose of budesonide as a reference [23]. The same treatments were also administered with concomitant oral charcoal to obviate gastrointestinal absorption and hence evaluate the bioavailability from the lung. The pharmacokinetic profile for both inhaler devices showed rapid absorption with a $t_{\text{max}}$ for budesonide of 0.3 h and elimination half-life of 2.3 h. In the presence of charcoal-block the lung bioavailability was calculated at 32% for the turbuhaler vs 18% for the metered dose inhaler. Comparative values for total bioavailability in the absence of charcoal (i.e. lung plus gut) were 38% for the turbuhaler against 26% for the metered dose inhaler, giving a clear indication of the relative lung and gut components.

In asthmatic children given inhaled (1000 μg) and intravenous (500 μg) doses of budesonide without charcoal, total systemic bioavailability was calculated at approximately 30% of the nominal inhaled dose from a tube spacer (Inhalet) and 15% from a nebuliser (Pari-inhalerboy) [24]. Data from the same study revealed a value for clearance of budesonide which was 40% higher than comparable values in adults, along with a shorter elimination half-life of 1.5 h. The higher clearance and shorter half-life of budesonide in children would seem to be advantageous in terms of reducing the burden of systemic adverse effects.

The charcoal-block method has also been used to investigate the pharmacokinetics of plasma budesonide given as a 1000 μg dose via a turbuhaler to asthmatic children. It was found that charcoal reduced the systemic absorption (as AUC(0,4 h)) by approximately 20%. The absorption of the same dose of budesonide was higher comparing turbuhaler with nebuliser (both without charcoal) being two-fold greater [25]. Allowing for greater oropharyngeal deposition of budesonide with a turbuhaler than with a nebuliser, these data suggest an almost two-fold greater lung delivery of budesonide when comparing the two devices. Interestingly, this ratio for lung deposition appears to translate into a commensurate dose-ratio for clinical efficacy. In a double-blind randomized double-dummy cross-over study of 241 stable asthmatic children, halving their dose of budesonide via the nebuliser resulted in a clinical relapse in 126 cases [26]. Of these 126 patients, 64 were randomized to continue with their usual budesonide dose via the nebuliser, with the other 62 being randomized to use half their usual dose via the turbuhaler. After 9 weeks of evaluation, there were no differences between the two groups in terms of symptom control, spirometry, peak flow rate or exercise challenge. A similar degree of corticosteroid dose-reduction for turbuhaler vs nebuliser has been reported during step-down therapy to identify the lowest maintenance dose of inhaled budesonide over a prospective 4 year period of follow-up in asthmatic children [27]. This suggests that at least with inhaled budesonide, greater lung deposition with the turbuhaler allows lower maintenance doses during the step-down phase of the management guidelines.

The pharmacokinetics of inhaled corticosteroids may also determine the systemic adverse effect profile, particularly for drugs such as budesonide and fluticasone propionate which have high hepatic first-pass, but no lung first-pass metabolism. Fluticasone propionate has approximately 2–3 times greater glucocorticoid potency than budesonide [28]. Thus if lung absorption is the major determinant of systemic bioactivity, one might expect to find commensurate differences between the two drugs in terms of their respective systemic bioactivity. This hypothesis was investigated in a comparison of single inhaled doses of budesonide and fluticasone ranging from 400–2000 μg, both given by metered-dose aerosol with mouth rinsing to asthmatic adults in a placebo controlled double-blind randomized cross-over study [29]. Suppression of overnight urinary cortisol excretion, a sensitive marker of adrenal activity, showed approximately two-fold greater suppression with fluticasone 500 μg than with budesonide 400 μg. For a 08.00 h serum cortisol and ACTH, at doses above 1000 μg on the steep part of the dose-response curve there was three-fold greater adrenal suppression with fluticasone than with budesonide on a μg equivalent basis. Similar differences in systemic activity have been found comparing single inhaled doses of fluticasone and budesonide (400–1250 μg) given by spacer to asthmatic children, with three-fold greater suppression of urinary cortisol excretion [30].

Thus it is evident that lung absorption of a corticosteroid with enhanced potency produces greater systemic activity on the steep part of the dose-response curve. The plasma elimination half-life of inhaled budesonide is 2.3 h compared with 14.4 h for inhaled fluticasone [23,31]. The longer elimination half-life for fluticasone should result in greater steady-state accumulation during repeated dosing. This is supported by a study where there was a large step-up in adrenal suppression between single and repeated doses of fluticasone 1000 μg twice daily (25% vs 55% suppression), whereas with budesonide 800 μg twice daily this effect was much less pronounced (26% vs 34% suppression) [32]. Other factors which may contribute to greater steady-state
suppression with fluticasone include a more prolonged receptor residency time [33] and greater lipophilicity [34] compared with either budesonide or beclomethasone dipropionate. The higher degree of lipophilicity for fluticasone may result in enhanced systemic tissue retention in fat stores, in effect acting as a reservoir in the body at steady-state.

**Inhaled sodium cromoglycate and nedocromil sodium**

The pharmacokinetics of inhaled sodium cromoglycate and nedocromil sodium has been extensively evaluated both in normal subjects and in patients with obstructive airways disease. After inhalation of sodium cromoglycate there is rapid absorption from the alveolar vascular bed with peak plasma levels being reached within 20 min [35–38]. However absorption appears to occur at two different rates with an initial fast phase from the alveoli and a later slow phase from the bronchial epithelium. This slower phase of absorption is probably due to the high degree of hydrophilicity of sodium cromoglycate which results in a lesser propensity for absorption from the bronchial epithelial barrier compared with the endothelium of the alveolar vascular bed. Thus, inhaled sodium cromoglycate exhibits absorption rate-limited or ‘flip-flop’ kinetics, as has been shown by comparison of elimination after intravenous and inhaled dosing [35–37].

The urinary excretion of sodium cromoglycate given by dry powder inhaler (Spinhaler, Fisons) has been used to evaluate the effect of airway calibre on lung bioavailability in patients with obstructive airways disease compared with normal controls [39]. Urinary excretion as a measure lung bioavailability is possible, because when sodium cromoglycate is given orally less than 2% is absorbed, and when given by the intravenous or inhaled route the drug is also excreted unmetabolized. It was found that urinary excretion of sodium cromoglycate was markedly reduced in patients with chronic bronchitis but not in asthmatics as compared with normal controls. The explanation for this may be the combined effects of a lower FEV\(_1\), and a lower inspiratory flow rate in the chronic bronchitic compared with asthmatic group, resulting in reduced lung bioavailability. However in another study looking at lung bioavailability of sodium cromoglycate given via a spinhaler, there was a reduction in plasma \(C_{\text{max}}\) and AUC comparing asthmatic patients vs normal volunteers, and this was also mirrored by urinary excretion [40]. There was a large inter-subject variability in plasma concentration of sodium cromoglycate which was attributed to differences in inhalation technique, particularly with respect to inspiratory flow rate and breath holding.

In a study of normal subjects using the spinhaler there were clear differences in plasma concentration time curves for three different peak inspiratory flow rates [37]. For example, mean inspiratory flow rates of 57.1 min \(^{-1}\) and 184.1 min \(^{-1}\) resulted in an approximate three-fold difference in AUC(0,240 min), and was mirrored by similar differences in \(C_{\text{max}}\). There were however, no differences in plasma concentration-time curves when comparing inhalation from a spinhaler with and without a 10 s breath hold at the end of inspiration. In the same study pharmacokinetics of sodium cromoglycate delivered as a solution directly into the airways was investigated in patients undergoing diagnostic bronchoscopy. The plasma concentration-time profile was found to be similar to those obtained after normal inhalation and values for \(C_{\text{max}}\) and AUC(0,240 min) were intermediate between the higher two inspiratory flow rates for the spinhaler. Comparison of the AUC values after bronchoscopic administration with those by spinhaler indicates that only 10% of the nominal dose reaches the airways. Furthermore comparison of the AUC after bronchoscopic administration with that after intravenous infusion suggests that approximately 70% of the drug was bioavailable in terms of absorption from the lungs.

The effects of bronchoconstrictor challenge with methacholine, histamine and adenine monophosphate (AMP) on the pharmacokinetics of inhaled sodium cromoglycate have been evaluated in a series of studies from the same laboratory. Methacholine challenge resulted in a 23% lower FEV\(_1\), and a 2.8-fold higher central: peripheral lung deposition ratio (with technetium-99m) in comparison with saline [41]. Inhalation of methacholine was associated with significant increase in \(C_{\text{max}}\) but not in AUC for plasma cromoglycate. The greater \(C_{\text{max}}\) after methacholine is difficult to explain if initial rapid absorption occurs from the peripheral alveolar vascular bed, particularly since technetium studies suggested increased central deposition after methacholine inhalation.

The effects of inspiratory flow rate on pharmacokinetics of sodium cromoglycate given by spinhaler and its protection against AMP challenge were evaluated in asthmatic subjects [42]. Values for \(C_{\text{max}}\) and AUC showed proportional attenuation with associated reduction in inspiratory flow rate. Furthermore, both inspiratory flow rate and AUC correlated significantly with the degree of protection afforded against AMP induced bronchoconstriction. This shows that the inspiratory flow rate used to inhale sodium cromoglycate dry powder is an important determinant of protection against bronchial challenge. The smaller degree of lung absorption at lower inspiratory flow rates probably reflects a reduction in fragmentation of particles in the spinhaler device and hence a lower delivered mass of respirable particles.

In another study following histamine inhalation which produced a 20% fall in FEV\(_1\), initial absorption of sodium cromoglycate from lung was significantly increased as evidenced by lower values for \(C_{\text{max}}\) and absorption half-life [43]. This phenomenon was observed in both histamine non-responsive (control normal subjects) and hyperresponsive subjects and was therefore independent of bronchoconstriction. The suggested mechanism for enhanced initial absorption of sodium cromoglycate was an increase in permeability of the bronchial epithelium due to histamine. This in turns
The pharmacokinetics of inhaled nedocromil sodium are similar to those of sodium cromoglycate in that it exhibits two absorption components consistent with a ‘flip-flop’ model [45]. As is the case with cromoglycate, the terminal half-life of nedocromil represents the absorption half-life, with absorption from the lungs becoming rate limiting. After inhalation of 4 mg dose by a pressurised metered dose inhaler, differences were observed between normal volunteers and asthmatic patients in terms of a prolonged $t_{\text{max}}$ and lower values for $C_{\text{max}}$ and AUC in the asthmatics [45]. The calculated bioavailability for inhaled nedocromil was 9.2% of the nominal dose in normals vs 5.7% in asthmatics. As with cromoglycate absorption of an oral dose is less than 2%. With inhalation of both cromoglycate and nedocromil, forced expiration and deep inspiration results in enhanced drug absorption [46,47]. It has also been found that significant increases in plasma nedocromil concentration occurs following exercise but not after valsalva manoeuvres or hyperventilation, suggesting that enhanced bioavailability occurs as a consequence of an increase in lung volume with exercise [48]. In a comparison of an intravenous and inhaled nedocromil during AMP challenge no relationship was found between either $C_{\text{max}}$ or AUC and protection against AMP bronchoconstriction [49]. Since inhaled but not systemic administration of nedocromil produced protection, there is no direct relationship between plasma levels and degree of protection afforded against challenge.

Other inhaled drugs

The nebulised route of delivery now has an established role for delivering antibiotics to the lung in patients with the chronic bronchial sepsis as well as to delivery pentamidine prophylaxis for patients with HIV infection. The type of nebuliser is important in determining the size of particles and preferred site of distribution for delivery of the drug. For example, in delivering nebulised pentamidine it is more preferable to produce peripheral deposition to the alveolar compartment of the lung. It would therefore seem appropriate in these situations to apply the pharmacokinetic technique for evaluating drug delivery in order to compare different nebuliser systems, as has successfully been done with nebulised salbutamol [3].

There have been a number of studies which have attempted to evaluate pharmacokinetics for inhaled delivery of aminoglycoside antibiotics. The polarity of gentamicin is such that it is poorly absorbed from the gastrointestinal tract. Hence plasma levels of gentamicin following inhalation will directly reflect absorption from the lungs. However, with cromoglycate, a high degree of hydrophilicity may result in a greater propensity for absorption across the endothelium of the alveolar vascular bed compared with the bronchial mucosa. In one study, serum levels of gentamicin 1 h post-dosing ranged from 3.0 to 12.0 $\mu$g $\text{ml}^{-1}$ after intramuscular administration and 1.3 to 6.8 $\mu$g $\text{ml}^{-1}$ after intratracheal administration, both given in a daily dose of 240 mg [50]. In a study of four patients, 40 mg of nebulised gentamicin achieved mean levels of 22.2 $\mu$g $\text{ml}^{-1}$ in tracheal aspirate and 0.2 $\mu$g $\text{ml}^{-1}$ in serum [51], although no details of nebuliser apparatus or sampling times are available. Thirty minutes after intratracheal administration, mean peak serum concentration of gentamicin was 1.04 $\mu$g $\text{ml}^{-1}$, with levels in bronchial secretions at 4 h (43 $\mu$g $\text{ml}^{-1}$) exceeding minimum bacterial inhibitory concentrations. Serum gentamicin levels have also been measured 1 h after an 80 mg dose given via a nebuliser, via oral aerosolisation or via a tracheotomy tube, both with intermittent positive pressure breathing [52]. Serum gentamicin levels were 0.1 to 0.94 $\mu$g $\text{ml}^{-1}$ after tracheal aerosolisation and 0.1 to 0.16 $\mu$g $\text{ml}^{-1}$ after normal inhalation. Moreover, 1 h after nasotracheal administration of gentamicin levels ranged from 1.2 to 4.0 $\mu$g $\text{ml}^{-1}$. Serum concentration of gentamicin, were evaluated 1 h after intramuscular (1.5 mg kg$^{-1}$), intratracheal (40 mg) and oral nebulised (40 mg) administration to children with cystic fibrosis [53]. Mean serum concentration of gentamicin was much lower after aerosolised (0.20 $\mu$g $\text{ml}^{-1}$) than intratracheal (0.53 $\mu$g $\text{ml}^{-1}$) routes. Both aerosolised and intratracheal routes gave adequate bronchial levels above minimum bacterial inhibitory concentration. Nebulised delivery of tobramycin in a single-dose of 120 mg achieved sputum levels in excess of 100 $\mu$g $\text{ml}^{-1}$ in patients with cystic fibrosis [54].

Taken together, these studies suggest that therapeutic nebulised doses of gentamicin achieve adequate levels in the bronchial tree with only minimal systemic absorption. It is unclear whether it is possible to evaluate lung delivery of gentamicin with different nebulisers using pharmacokinetic methods, since this would require a proper concentration-time profile to quantify accurately lung absorption.

Delivery of nebulised morphine to the lung has been suggested as a way of avoiding hepatic first-pass metabolism and an alternative method for achieving rapid analgesia compared with the oral or parenteral route of administration. It has also been suggested that it may relieve breathlessness in patients with associated bronchial carcinoma by a direct action on airway nociceptive receptors. In a recent study the pharmacokinetics of morphine were compared when given by the intravenous, oral and nebulised routes of administration to 10 healthy subjects [55]. Nebulised delivery of morphine was associated with an initial rapid absorption from the lung with a $t_{\text{max}}$ of 10 min and a time profile...
similar to that of the intravenous route. The systemic bioavailability of morphine calculated from the AUC was 5% of the nebulised dose and 24% of the oral dose. The calculated value for bioavailability of the nebulised dose was similar to that from radiolabelled aerosol studies. However it is conceivable with more efficient nebulisers which boost inspiratory phase delivery, or with dosimetry, that the bioavailability would be significantly enhanced. Whether the nebulised route provides more rapid analgesia compared with the oral route requires confirmation from clinical studies.

**Conclusions**

Delivery of drugs by the inhaled route results in a high therapeutic ratio with delivery of relatively low doses achieving a high local concentration. The application of pharmacokinetic techniques allows accurate and reproducible quantification of drug delivery by measuring plasma levels to reflect lung absorption, although this is dependent on sufficiently sensitive assays. This technique may be applied to compare different inhaler devices such as dry powder, pressurised aerosol and nebulised formulations. It may also be used to evaluate the bioequivalence of different drug formulations, as for example with salbutamol. Other applications include the pharmacokinetic measurement of drug delivery to the lung to assess inhalation technique in patients, and this has resulted in providing important information on the use of large volume spacers. Pharmacokinetic evaluation with inhaled corticosteroids using techniques such as the charcoal-block method may be used to assess the relative gut and lung components of systemic bioavailability. This along with information on drug elimination and distribution provides a rational explanation for observed differences at steady-state in the systemic bioactivity profile between inhaled corticosteroids. Further possible applications of the pharmacokinetic technique include the assessment of delivery of nebulised antibiotics via different nebuliser systems, as for example, in patients with cystic fibrosis.

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