The Fate of Inhaled Drugs: The Pharmacokinetics and Pharmacodynamics of Drugs Administered by Aerosol

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Introduction

Why Inhale?

Inhaled Albuterol: Getting Drug to the Site of Action

Optimizing Inhalation Therapy: Pulmonary Targeting of Inhaled Corticosteroids

Predicting Pharmacodynamic Effects from Pharmacokinetics: Tiotropium

Summary

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Introduction

The respiratory therapist is often responsible for recommending an aerosol generator for delivery of a therapeutic agent, ensuring its proper administrations, and monitoring the response. There are important physical and biologic events that occur between the time of administration of an aerosol and an observed clinical response (eg, improved air flow, tachycardia). Though a sufficient amount of drug targeted for the lung will usually get there and remain there for its intended pulmonary response, a portion of it will probably be absorbed into the systemic circulation, where it will be distributed in the body, often to undergo some degree of metabolism, and ultimately to be excreted (unchanged or metabolized). These events (ie, what the body does to the drug) can collectively be referred to as pharmacokinetics. The observed clinical response (ie, what the drug does to the body) is referred to as pharmacodynamics.¹

In this brief review, some key aspects of the relationship between pharmacokinetics and pharmacodynamics for inhaled drugs will be discussed through examples from the literature, using 3 classes of inhaled drugs to illustrate principles. First, the ability to broaden the therapeutic window via inhaled delivery will be described for albuterol, along with methods to evaluate its relative lung bioavailability. Second, the specific pulmonary targeting (ie, topical to systemic effects) of inhaled corticosteroids (ICS) will be reviewed as an example of how both pharmacokinetic properties and delivery technique can impact optimal therapeutic effect. Finally, a review of how one might predict lung to systemic effects from basic pharmacologic and pharmacokinetic information will be reviewed for the experimental long-acting anticholinergic agent tiotropium.

Why Inhale?

The intended site of action of respiratory therapeutic aerosols is the lung. When utilizing aerosols for respiratory therapy, however, isolating the delivery of the drug to the lung itself (vs, for example, to the oropharynx) will most often optimize its therapeutic window, ie, the difference between a drug’s therapeutic benefit (eg, bronchodilation) and its unwanted effects (eg, tachycardia). The inhaled route for respiratory therapeutics is seen as advantageous in that drug is delivered directly to the site of action and that lower doses can be administered relative to parenteral or oral preparations.² These features, in turn, can broaden the therapeutic window by achieving optimal efficiency and minimizing adverse effects.

Inhaled Albuterol: Getting Drug to the Site of Action

The concept described above was nicely illustrated in a study by Lipworth et al,³ in which a group of asthmatics received salbutamol either orally (2 mg), sublingually (2 mg), or via metered-dose inhaler (MDI) (0.2 mg), with subsequent monitoring of pharmacokinetic and pharmaco-
dynamic end points. For lung function (Fig. 1), forced expiratory volume in the first second (FEV₁) was improved relative to placebo for all routes of administration, with the response following inhalation significantly greater than that following oral or sublingual administration. The time to peak response was also earlier following inhalation (30 min) than with oral or sublingual administration (2 h). The unintended pharmacodynamic response of tremor was also evaluated. Here, an increase in tremor response was confined to the oral and sublingual routes (Fig. 2). Therefore, the improved therapeutic window with inhalation was clearly demonstrated. This report confined pharmacokinetic analysis to the oral and sublingual routes and noted similar profiles, with the exception of an initial delayed absorption following sublingual administration. This is suggestive of minimal buccal absorption, with the systemic levels coming from gut absorption following swallowing of the dissolving sublingual tablet.

Though the above example clearly points to different effects following oral versus inhaled salbutamol, it is also interesting to consider the fate of the inhaled drug itself and methods to determine the relative bioavailability of such drugs to the lungs.

Inhaled therapy, while remaining the optimal choice for many drug classes, is inefficient. That is, only a small fraction of the drug that leaves the aerosol generator actually is deposited in and available to the lung. Despite this inefficiency, the lung-to-systemic effects remain favorable. Methods used to quantify the fate of administrated aerosols include radiolabeled aerosol studies, charcoal ingestion methods, and timed urinary excretion surrogates of lung bioavailability.

In the aerosol deposition studies, radiolabeled particles are inhaled, followed by gamma scintigraphy to follow the fate of particles. Among the classic studies reported by Newman et al include the observation that only some 10% of radiolabeled aerosol of Teflon reaches the lung, with the remainder swallowed.⁴

In the charcoal technique, inhaled drug is simultaneously administrated with charcoal, which blocks oral absorption, leaving the recovered fraction attributable to the lung delivery. With this technique, Borgström and Nilsson⁵ reported a lung bioavailability of approximately 10%.

The relative bioavailability of inhaled salbutamol to the lung evaluated by measuring early urinary excretion also serves to illustrate some important pharmacokinetic principles of inhaled drugs. In their simple technique, Hindle and Chrystyn⁶ took advantage of the biphasic renal excretion following inhaled salbutamol. The initial elimination (ie, 30 min) represents the fraction of dose administrated to the lungs, rapidly absorbed via the alveoli, then excreted unchanged by the kidneys. The second phase represents the dose swallowed after impaction in the oropharynx. To support this theory, they showed (Fig. 3) that little drug is excreted in urine 30 minutes after oral ingestion because of the lag time between administration and start of absorption. The urine drug recovery 30 minutes after inhalation, in contrast, was significantly greater. This method was subsequently validated in practice, where 30-minute urine recovery of salbutamol was measured following a variety of inhalation techniques.⁷ For example, they observed significantly greater elimination in the first 30 minutes when drug was inhaled slowly (10 L/min) versus quickly (50 L/min) and with breath-holding (10 s) versus without breath-holding. Thus, the fate of the inhaled salbu-
Optimizing Inhalation Therapy: Pulmonary Targeting of Inhaled Corticosteroids

As seen with the previous example of salbutamol, the route of administration impacts the therapeutic index. Differences in the therapeutic index can also manifest within a given route of administration. This is particularly true for inhaled therapy, with several illustrative and relevant examples coming from the clinical investigations of inhaled corticosteroids. Specifically, different formulations and different delivery devices can produce meaningful differences in topical activity by affecting the dose deposited in the lung and, for drugs absorbed orally, by affecting the amount of drug deposited in the oropharynx and subsequently swallowed.

The primary goal in optimizing the therapeutic window of an ICS is to maximize its action in lung tissue while minimizing systemic exposure that primarily leads to adverse effects. In maximizing therapeutic effect, the potency of a given ICS (related to steroid receptor binding affinity) and the amount of drug reaching the lung are important factors. In the broad sense, efficacy relates to the molecular and cellular activity that reduces airway inflammation and airway hyperresponsiveness. Clinically, the effects translate into improved symptoms, reduced need for oral steroids, and general improvement in lung function.

The goal to minimize systemic exposure is embedded in avoiding clinically problematic effects, including hypothalamic-pituitary-adrenal axis suppression, inhibition of bone formation and growth, and a variety of other metabolic, hematologic, and central nervous system effects. In setting the safety threshold of an ICS, the amount of drug...
that becomes available in the systemic circulation is a primary concern.

The key concepts in determining the therapeutic window of an ICS are best understood by understanding the potential fate of an ICS following administration. As illustrated in Figure 4, therapeutics aim at optimizing effect in the lung while minimizing systemic concentration. Important pharmacokinetic properties of a drug that would foster a wider therapeutic index include slow absorption from the lung, low oral bioavailability, and rapid systemic clearance.

First, prolonged exposure of an ICS in the lung itself may enhance the local anti-inflammatory effect. A surrogate of pulmonary retention can be evaluated by monitoring the differences between drug half-life following inhalation and intravenous administration. Here, a longer half-life after inhaled delivery would indicate that the rate of pulmonary absorption limits the ultimate excretion from the body. Second, low oral bioavailability, or the fraction of ingested dose that reaches the systemic circulation, is affected by physiologic effects of gastrointestinal absorption and inactivation by “first pass” metabolism in the liver. More importantly, however, there are several important factors in the hands of the practitioner that can minimize systemic effects by minimizing the amount of drug that reaches the gastrointestinal tract. These include selection of a device that minimizes oropharyngeal deposition, utilizing a spacer device, and mouth rinsing and expectoration after treatment. The impact of such interventions was illustrated by Selroos and Halme, who reported a difference in the pharmacodynamic systemic measure of serum cortisol following budesonide when the drug administration was followed by mouth rinsing or not (Table 1). This illustrates the potential impact of aerosol administration techniques on the subsequent pharmacokinetic (reduce oral bioavailability) and pharmacodynamic (reduce serum cortisol) response.

Table 1. Serum Cortisol Following Budesonide Inhalation With and Without Mouth Rinsing

<table>
<thead>
<tr>
<th>Drug and Dose</th>
<th>Mouth Rinse</th>
<th>Serum Cortisol (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide 1.6 mg</td>
<td>Yes</td>
<td>440 ± 63</td>
</tr>
<tr>
<td>Budesonide 1.6 mg</td>
<td>No</td>
<td>375 ± 56</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>65 ± 58*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*p = 0.007.

Predicting Pharmacodynamic Effects from Pharmacokinetics: Tiotropium

Tiotropium is an experimental anticholinergic agent that is being developed as a once-daily inhaled bronchodilator. Its long duration of action is best explained by its prolonged binding to muscarinic receptors. For example, the half-lives of the drug-receptor complex at the M3 receptor (responsible for airway smooth muscle relaxation) is orders of magnitude longer for tiotropium (34.7 ± 2.9 h) than for ipratropium (0.26 ± 0.02 h).

In a discussion of the relationship between predicted lung and systemic levels of drug, Disse et al. used basic pharmacologic principles to predict local concentrations and their impact on receptor binding and potential response in humans. This approach addressed the following questions.

What are the relative amounts in the lung versus systemic circulation?

As a quaternary ammonium compound, tiotropium has a positive charge and would be expected to have minimal systemic absorption following inhalation. In patients, plasma levels are indeed low, at approximately 2 pg/mL at trough (ie, before dosing), with transient postinhalation peaks measured at approximately 14 pg/mL. Such concentrations correspond to approximately 4.2 pM and 30 pM, respectively.

In order to predict tiotropium concentrations in the lung’s epithelial lining fluid, estimations were made by assuming that 4 μg of the inhaled 20 μg dose (20%) is contained in fine particles likely to reach the lung. Again, assuming a volume of epithelial lining fluid of 20 mL, a tiotropium concentration of approximately 2 μM would be estimated.

What impact do these concentrations have on receptor binding?

From classic pharmacology, receptor occupancy can be estimated as a function of drug concentration based on the following:
where \([RD]/[Rt] = [D]/(K_D + [D])\)

where \([RD]\) is the concentration of drug-receptor complex, \([Rt]\) is the total number of receptors, and \([D]\) is the concentration of free drug. \([RD]/[Rt]\) reflects the proportion of occupied receptors. \(K_D\) is the equilibrium dissociation constant for the drug-receptor complex. A kinetically determined \(K_D\) of 14 pM has been established for tiotropium.

Given this, one could predict, assuming an equilibrium state, that less than one quarter of systemic receptors would be occupied. The value is probably less, as a true equilibrium state is probably not reached. Near full receptor occupancy would require much higher concentrations, such as those estimated for the lungs. Thus, this approach gives an appreciation for what might be predicted for lung and systemic responses, namely, a good therapeutic effect in the airway, with minimal systemic adverse effects.

What might be the impact of these estimations?

It has been postulated that, given the high post-junctional neurotransmitter tonus, acetylcholine is still likely to elicit a near full cholinergic response if \(<\) 50% of receptors are occupied by an antagonist such as tiotropium. Thus, one can predict minimal systemic effects. In the lung, however, much higher topical levels lead to near full receptor occupancy and thus probably explain the long duration of bronchodilation\(^{14,15}\) and bronchoprotective\(^{16}\) effects. These differences are important in the ultimate determination of a drug’s therapeutic index (ie, its safety to efficacy or risk to benefit). This will ultimately be confirmed or refuted in long-term clinical trials.

Summary

Prior to a drug achieving its effects (ie, pharmacodynamics), there are numerous events within the body that determine its ultimate fate. The effects of the “body on the drug” has been referred to as pharmacokinetics—how the favorable lung-to-systemic effects predicted from this exercise translate into practice.

Inhaled drugs have enjoyed the major feature of having “local” effects on the target organ of the lung. Broadly, lower doses can be used and adverse effects are often less than with oral or parenteral administration. Nevertheless, key features of respiratory drugs and their administration can impact their fate and ultimate utility. This review has provided some relevant examples of basic pharmacokinetics principles as related to inhaled products, with emphasis on those factors that help to partition lung-to-systemic effects.

REFERENCES