Factors Affecting Drug Exposure after Inhalation

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Abstract: Administration of drugs by inhalation is mainly used to treat lung diseases and is being investigated as a possible route for systemic drug delivery. It offers several benefits, but it is also fraught with many difficulties. The lung is a complex organ with complicated physiology and specific pharmacokinetic processes. Therefore, the exposure and subsequently efficacy of a drug after inhalation is affected by a number of factors. In this review, we summarize the main variables that may affect drug fate after inhalation delivery, such as physicochemical properties of the drug, pulmonary clearance and metabolism, pathophysiological factors and inhalation device. Factors that have impact on pharmacokinetic processes need to be considered during development as their correct setting can lead to new effective inhaled drugs.

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Introduction

Inhalation route is a way how to deliver a drug for various pulmonary diseases directly to the main place of its effect in the lungs. It has a long tradition, especially for local delivery, but in the meantime it has been also extended for systemic drug delivery. The first and still the most common use of inhaled drugs is the treatment of asthma and chronic obstructive pulmonary disease with beta-sympathomimetics, anticholinergics and corticosteroids. The inhalation delivery may be advantageous for macromolecule drugs that would otherwise have to be injected because the lungs are naturally permeable not only for small molecules but also for peptides and proteins. Inhalation has been tested for systemic exposure of insulin since many years. It has even reached the market in the US and provides patients an option for a needle-free treatment. However, many more drugs such as vaccines, chemotherapy or gene therapy have been tested (Chow et al., 2007).

Inhalation is preferred route of drug administration for local treatment of pulmonary diseases. The drug is delivered directly to the site of action. High drug concentration in the lung is also ensured by avoiding first-pass metabolism of the liver and low enzymatic activity in the lungs. This allows the use of lower dose of the drug and reduces its systemic adverse effects (Rau, 2005; Eedara et al., 2021). Inhalation is well tolerated and usually easy to administer.

One of possible advantages of inhalation delivery is rapid onset of action. Therefore, it is used to treat an acute exacerbation and may also be beneficial for systemic treatment due to highly permeable and perfused epithelium (Hou et al., 2015). This could represent a clear benefit for the treatment of pain (Macleod et al., 2012; Mercadante et al., 2019), migraine (Aurora et al., 2011), nausea and vomiting (Merritt et al., 2002) or epileptic seizures (French et al., 2017).

Like other routes of administration, inhalation has its own limits. One of them is the characteristics of the drug and drug formulation (Borghardt et al., 2018). Aerodynamic particle size has a major effect on deposition and subsequent absorption in the respiratory tract (Heyder, 2004). Other key factors that affect pulmonary administration are lung condition and inhalation device (Borghardt et al., 2018). In patients with lung disease, deposition is thought to be worse due to pathophysiological modification. This may affect the expected kinetic processes. Change in ventilation parameters and breathing patterns may cause incorrect inhalation from an inhaler (Wang et al., 2014). The limit may also be the patient handling the inhalation device.

Due to complexity of pulmonary administration, there are many factors that affect the efficacy of inhaled drugs. Their overview is limited, although administration by inhalation is relatively often studied. Therefore, this review focuses on the main influencing factors such as drug properties (physical and physicochemical properties), pulmonary characteristics (clearance, metabolism and pathophysiology) and inhalation device.

Literature search

The search was done till February 2022 in PubMed and Web of Science databases. The key words used for the searches were pulmonary delivery, pharmacokinetics, drug formulation, inhalation, absorption, mucociliary clearance and lung diseases in various combinations. The publications found were then evaluated in terms of relevance to the purpose of this review.

Pharmacokinetic processes after inhalation

Deposition

Drug formulations are deposited in different parts of the lungs depending on their particle size. The particles larger than 5 μm are deposited in the mouth, throat and upper airways. They are swallowed and subsequently absorbed in the gastrointestinal tract instead of reaching the lungs. The best particle size for achieving the lower airways is 1–5 μm for adults (Prime et al., 1997; Hassan and Lau, 2010). For children, it is assumed that the particle size should be different. It is not generally known how large it should be (Laube et al., 2011; Deng et al., 2018). The particles smaller than 0.5 μm may not deposit at all (Pilcer and Amighi, 2010) as they may be breathed out of the body. After deposition, the particles are cleared from lungs, absorbed or degraded.

Clearance

Multiple processes take place in the lungs due to their complex structure. There are diverse clearance mechanisms in different parts of the lungs such as mucociliary, macrophage and metabolic clearance. Mucocilliary clearance is the key factor for drug particles elimination from the upper airways while macrophages degrade the most of drug in the lower airways (Borghardt et al., 2015). These are physiological mechanisms that remove deposits of various mostly insoluble particles. Clearance processes nevertheless eliminate dissolved drug as well.

Mucociliary clearance is the first line defense mechanism of the mucous layer, the airways and the cilia (Munkholm and Mortensen, 2014). Insoluble particles are trapped and transferred to the mouth by the cilia waving cells, and then are swallowed into the gastrointestinal tract. This mechanism is more common and faster for larger particles, in general they are completely removed within 24 h (Edwards et al., 1997).

Macrophages play an important role in the immune response. They removed insoluble or slowly dissolving particles from the alveolar region and transported them to the cilia mucus. The ability of macrophage phagocytosis is dependent of aerodynamic particle size (optimally 1–3 μm) (Edwards et al., 1997) and surface charge. Macrophages have negatively charged surface, so the particles with a charged surface are thought to be more susceptible to phagocytosis. Soluble and hydrophilic particles have the ability to avoid macrophages (Patel et al., 2015; Liu et al., 2020). Perhaps because they dissolve faster than they are captured by macrophages. The

particles that macrophages do not recognize can deposit in the alveoli for years (Edwards et al., 1997). However, macrophages may be the delivery target of some inhaled drugs. For example, for the treatment of infectious diseases (Rojanarat et al., 2012; Zhang et al., 2018).

Absorption

The absorption rate depends on the dissolution rate (Borghardt et al., 2015) and on the hydrophilicity of the drug (Dugas et al., 2013). Drug absorption is more rapid from the alveolar space than from the tracheo-bronchial region due to higher perfusion and thinner airway wall (Brown and Schanker, 1983; Mobley and Hochhaus, 2001; Chillistone and Hardman, 2017). Absorption half-life of small lipophilic molecules from the alveoli is about 1 to 2 minutes, and they are absorbed by passive diffusion through epithelial cell membrane. Small hydrophilic molecules have absorption half-life approximately 65 minutes, and they are most likely to be transported via tight junctions or specific transporters (Patton et al., 2004, 2010; Bacle et al., 2021). The macromolecules are usually absorbed via tight junctions and transcytosis. Transport by endocytic vesicles is promoted by cationic charge of the compounds. In general, the absorption time of the drug is dependent on the molecular weight. Small peptides and proteins are usually absorbed faster compared to subcutaneous administration and with increasing size the absorption gets slower (Patton et al., 2004, 2010; Bacle et al., 2021).

Metabolism

Metabolic processes take place in the lung as in other tissues in the organism. Drug metabolism enzymes are the same as in the intestine or the liver but their expression is generally less in the lungs. Therefore, considerably lower doses may be administered compared to the oral route to achieve similar systemic exposure (Taylor, 1990; Upton and Doolette, 1999).

The most relevant metabolizing enzymes in the lungs are CYP1A1, CYP1B1, CYP2E1 and CYP2B6 (Borghardt et al., 2018; Pasqua et al., 2022). CYP1A1 and 1B1 are mostly elevated in smokers (Kim et al., 2004). Their substrates are e.g. theophylline or zolmitriptan that have been studied for inhaled delivery. CYP2E1 metabolizes anesthetics such as isoflurane, enflurane and halothane, one of the most common used for the administration of inhaled drugs (Guengerich, 2020). Lungs further contain several other drug metabolizing enzymes as aldehyde oxidases, glucuronosyltransferases, hydrolases, esterases, and peptidases (Pasqua et al., 2022). Carboxylesterases have been shown to rapidly hydrolyse mycophenolate mofetil to the active molecule after pulmonary administration (Dugas et al., 2013). Small natural peptides (< 3,000 D) can be very strongly enzymatically hydrolyzed by peptidase. Therapeutic peptides should be chemical modified to be resistant to peptidases (Patton et al., 2004). As the expression of drug metabolizing enzymes is relatively low, drug metabolism is expected to be minor after inhalation.

Although the impact of active drug transporters on drug distribution after pulmonary delivery could be envisaged (Endter et al., 2007; Patton et al., 2010), the real impact seems to be limited as several studies demonstrated high bioavailability of substrates of MDR1 from rat and mice lungs (Tronde et al., 2003a; Manford et al., 2008). It suggests a minor role of P-glycoprotein in absorption from the lungs.

Physicochemical properties

The Lipinski's Rule of Five is a widely accepted method to predict ADME (absorption, distribution, metabolism, and excretion) properties of oral drug candidates. There are only a few studies that compared bioavailability of inhaled drugs on the market with the Lipinski's rule. Inhaled drugs on the market correlate with the Rule probably as they were first administered orally (Choy and Prausnitz, 2011). However, optimal physicochemical property for delivery of inhaled compounds have not been defined, yet (Ritchie et al., 2009; Strong et al., 2018).

The physicochemical properties of the drug do not appear to be as a significant factor for lung delivery as after oral administration. Systemic absorption has been described for drugs that did not comply with the Lipinski's Rule and cannot be delivered by conventional route (Uchenna Agu et al., 2001; Ritchie et al., 2009; Siekmeier and Scheuch, 2009). This group includes macromolecules or proteins such as insulin, as well as heparin or interleukin-2 (Siekmeier and Scheuch, 2009; Shute et al., 2018; Dixon et al., 2021).

Pulmonary epithelium is permeable to molecules with high molecular polar surface area unlike the intestinal epithelium and blood-brain barrier (Tronde et al., 2003b). The degree of ionization can affect absorption and transport to the systemic circulation. It is assumed that charged molecules may interact with protein and lipid structures at the delivery site and this may slow down or diminish the rate of absorption. Mucins that are negatively charged can capture the drugs with a positive charge, while negatively charged particles easily penetrate (Sigurdsson et al., 2013; Bacle et al., 2021). The ability to penetrate also depends on the lipophilicity of the particle. Hydrophilic particles diffuse faster through lipophilic mucus compared to hydrophobic molecules. Lipophilicity is even thought to have a greater influence on mucus diffusion compared to charge (Leal et al., 2017; Liu et al., 2020). The mucus layer can form certain specific binding interaction with the trapped particles due to cationic or other selectivity of epithelial channels and thus form a barrier to the passage of the particles (Sigurdsson et al., 2013; Tamai, 2013).

The dissolution rate has main impact on the effectiveness of pulmonary clearance. Inhaled drugs should avoid these clearance mechanisms to ensure their effect (Edwards et al., 1997). Drugs are therefore formulated as liquid or aerosol particles that dissolve much faster than they are mechanically removed by mucus or recognized by macrophages. Thus, these mechanisms appear to be negligible for inhaled drugs (Patton and Byron, 2007; Borghardt et al., 2018).

Inhalation devices and drug formulation

Inhalation devices, excipients, a drug composition and handling with the device by patient may affect the efficiency of the drug. The most often used devices for inhalation delivery are dry powder inhalation system (DPI), metered-dose inhalation system (MDI) and nebulizer systems.

The deposition of the particles is influenced mainly by the physical properties of the aerosol (size, density, shape, hygroscopicity) and by respiratory physiology such as anatomy and breathing pattern (Yeh et al., 1976; Prime et al., 1997; Braakhuis et al., 2014). Humidity of the environment or even due to exhalation into the device may disrupt the formulation of the hygroscopic drugs and can reduce their efficiency. Hygroscopic aerosol is absorbing the water after inhalation which can cause a particle size growing and different deposition patterns (Ferron et al., 1989).

Each inhaler device class has specific drug load capacity, advantages and disadvantages that can affect administration of the drug or compliance with the therapy. An issue of DPI device is inhalation flow. Each DPI has its own minimum and optimal inhalation flow, most often around 30–60 l/min. Thus, the powder disperses into fine particles suitable for inhalation (Hassan and Lau, 2010). The disadvantage of nebulizers is a long time of inhalation connected with a cleaning time after inhalation and low proportion of drug delivery (Pilcer and Amighi, 2010). MDI devices have the most difficult handling technique. The coordination between breath (deep and hard) and manual coordination may be for many patients challenging. Moreover, even within each class of inhalation devices the individual device properties are unique, subsequently the performance in drug delivery differs and therefore different inhalers are not automatically interchangeable (Edsbäcker et al., 2008; Cazzola et al., 2016). However, detailed review of inhalation device characteristics and performance have not been included in this review.

Lung diseases

Lung diseases may have an impact on the fate of inhaled drugs for each process (deposition, absorption and clearance) through a number of interacting mechanisms. Obstructive lung disease (e.g. COPD [chronic obstructive pulmonary disease], asthma, cystic fibrosis) affects the airways. Restrictive lung disease (e.g. pulmonary edema, lung cancers, pulmonary embolus) causes the restriction in lung expansion, which may be caused by involvement the alveoli, blood vessels and/or interstitium. However, lung diseases can affect several different parts at the same time.

Lung diseases usually alters the deposition and subsequently absorption of inhaled particles. Obstructive lung diseases increase the deposition of particles on diseased lung lesions due to changes in airway diameter and ventilation conditions (Darquenne, 2012). Systemic absorption is reduced due to less deposition in the alveoli. Overall, this may be beneficial for local treatment (Borghardt et al., 2016), however disadvantageous for systemic drug delivery. Pulmonary vascular disease (emphysema, pulmonary fibrosis, pulmonary embolus) decreases systemic drug

absorption due to dysfunction of air-blood transfer. Loss or damage of functional surface area and blood vessel damage lead to impaired lung perfusion and thus reduced drug absorption. However, chronic airway inflammation and pulmonary edema may increase systemic absorption due to loss of integrity and increased permeability of barriers, which facilitates drug penetration (Patton et al., 2010; Wang et al., 2014).

The mechanism of clearance may also be affected by lung disease. Phagocytosis of alveolar macrophage is decreased in patients with COPD and cystic fibrosis, probably due to inflammatory agents. Mucociliary clearance is impaired in almost all pulmonary disease due to mucus changes (Houtmeyers et al., 1999; Munkholm and Mortensen, 2014), the effect of inflammation mediators and cilia changes. Changes in clearance mechanisms may not have a major impact on the drug efficacy, their dysfunction consequently can alter the deposition patterns of the drug (Apiou-Sbirlea et al., 2010) and even impede the drug from reaching its target.

Interspecies comparison

Since various animal models are used to study the development of inhaled medicinal products, anatomical and physiological differences should be considered. Overall, they can affect all pharmacokinetics processes. Data from the U.S. Food and Drug

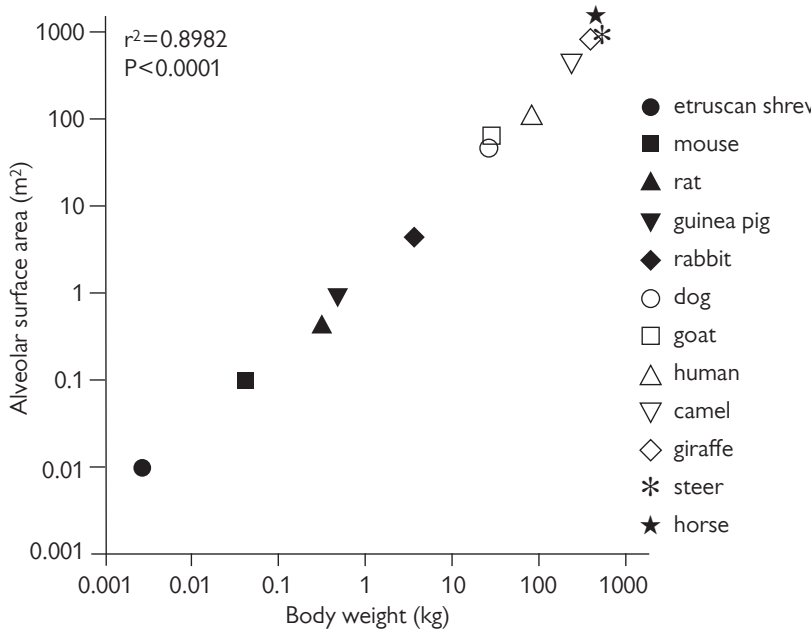

Figure 1 – Allometric plots for alveolar surface area with body weight. On log/log scale, the size of alveolar surface area within a species increases in proportion to body weight. Data obtained from Wirkes et al. (2010).

Administration (2005) are used to convert doses between species. They are based on dose normalization to body surface area, which correlates with biological parameters such as basal metabolism, and thus cover especially elimination phase of pharmacokinetic processes. This is accurate for conversion after administration by the conventional routes (e.g. intraperitoneal), however, more specific routes of administration such as inhalation may be affected by much more factors (e.g. breath rate, alveolar surface area). No dose conversion after inhalation between human and other species has been suggested yet. We compared alveolar surface area and body weight of different mammals (Wirkes et al., 2010) to find a correlation between them that could predict drug absorption. Figure 1 shows on a logarithmic scale allometric relationship of the alveolar surface area within a species to body weight. Based on this observation, we suggest that usually used body weight-normalized dose conversion between species sufficient and no other adjustments are required. However, dose estimation requires careful consideration of all available information and there is currently no uniform and universal approach. Inhalation in particular is complex (different morphological structures, breathing patterns, etc.) and needs to be further investigated.

Conclusion

Inhalation is route of choice for administration of drugs in the treatment of lung diseases such as asthma and chronic obstructive pulmonary disease. Determining the physicochemical and physical properties of the drug, drug formulation and inhalation device can help to optimize the kinetic processes of the drug. The pulmonary kinetic and absorption processes are highly complex. Lung diseases may change the structure of the lungs, their clearance mechanism, perfusion and affect breathing patterns. We observed strong correlation between alveolar surface area and body weight. Based on this observation, traditionally used allometric scaling for conversion of doses between animals and humans can be used without needs of further adjustments.

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