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Inhaled efficacious dose translation from rodent to human: A retrospective analysis of clinical standards for respiratory diseases

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ABSTRACT

Clinical pharmacologists and toxicologists are often faced with predicting equivalent dosages for humans from biological observations in laboratory animals. Allometric scaling has been used extensively as the basis for extrapolation of drug dosage that might be expected to produce the equivalent biological effects. Allometry is the study of size and its consequences and it is based on the anatomical, physiological, and biochemical similarities between animals. In this review, retrospective analyses have been performed based on data reported in the literature in an attempt to determine the utility of allometric scaling for human dose projections from pre-clinical data for compounds that are delivered by inhalation. The limited pre-clinical efficacy data available on inhaled drugs that are also used clinically supports the current method of scaling using a fixed allometric exponent of 0.67. An example of the utility of the human inhaled dose projections for planning inhaled toxicology studies is also presented.

Contents

1. Introduction

There are many advantages to inhaled administration of drugs for the treatment of respiratory diseases. Inhaled delivery applies the therapeutic agent directly to the site of action; the lungs. A high local concentration of the drug in the lungs offers a significant advantage that minimizes dose and systemic exposure, and maximizes efficacy. This is an important advantage that can greatly increase the therapeutic index (TI). The TI is the ratio of dose of drug that causes a side-effect over the dose of drug that provides efficacy.

As new drugs delivered by the inhaled route are developed, it is essential to appropriately translate the efficacious drug dose from pre-clinical efficacy studies to predict an efficacious human dose for clinical trials. An estimate of the effective human inhaled dose deposited in the lungs also helps to plan the delivered doses used in inhalation toxicology studies required for clinical trials (Degeorge et al., 1997). It is common to use an allometric approach to predict human drug doses from pre-clinical efficacy studies (Boxenbaum & DiLea, 1995). Allometry is the study of size and its consequences (Gould, 1966), and it is based

Abbreviations: TI, therapeutic index; LABA, long acting beta agonist; LAMA, long acting muscarinic antagonist.

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on the assumption that there are anatomical, physiological, and biochemical similarities between animals (Mahmood, 1999). Fig. 1 demonstrates how the allometric scaling concept applies to interspecies scaling for a few physiological parameters, and that these parameters scale with different allometric exponents. Herein an allometric scaling exponent is retrospectively calculated from experimental rodent efficacy data and the known inhaled clinical dose that needs to be deposited in the human lung. This is done for four inhaled compounds currently used clinically; the inhaled corticosteroids mometasone and budesonide, the β-agonist bronchodilator salbutamol, and the anticholinergic bronchodilator ipratropium.

This review attempts to determine the utility of an allometric scaling approach to allow interspecies correlation of inhaled drug dose, a pharmacologic parameter. The limited pre-clinical efficacy data available on inhaled drugs that are also used clinically supports the current method of scaling using a fixed allometric exponent of 0.67 (FDA, 2015). It must be remembered that any allometric approach is empirical and is but a simple and useful correlation (Boxenbaum & DiLea, 1995). One must also keep in mind that the dose predicted by these scaling methods cannot be used in clinical trials without supporting pre-clinical toxicology studies with appropriate safety margins above the predicted efficacious dose (Degeorge et al., 1997; Forbes et al., 2011). Therefore, an example of the process of how the human dose projections are used to plan the pre-clinical inhaled toxicology studies is presented.

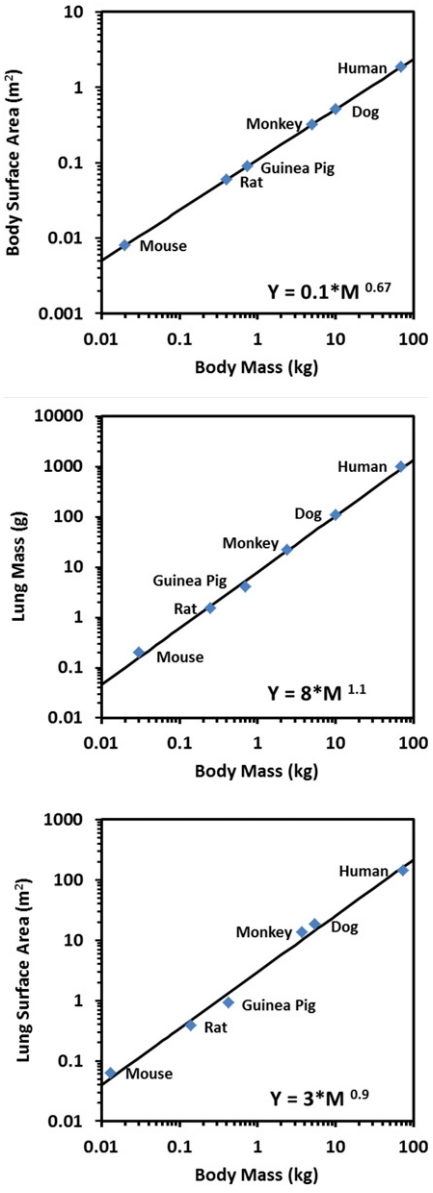

Fig. 1. Allometric plots for the physiological parameters body surface area, lung mass, and lung surface area scale log-linearly with body mass. Power function curve fits for each parameter in lower right hand corner of each graph. Data from (Chappell & Mordenti, 1991), (Snipes, 1989), and (Gehr et al., 1981).

2. Aerosol dose definitions

There are many ways in which the dose can be expressed for drugs delivered by inhalation. This can lead to confusion when comparing results from studies performed in different laboratories. Recently, it was recommended that delivered dose and deposited dose be adopted as the standard terminology (Alexander et al., 2008; Forbes et al., 2011). The delivered dose is the amount of drug inhaled by the animal and the deposited dose is the amount of drug deposited in the lungs. In general, an "inhaled dose" to a toxicologist is a delivered dose and an "inhaled dose" to a pharmacologist is a deposited dose. It is therefore important to clarify if the "inhaled dose" is a delivered or deposited dose. The delivered dose differs from the dose generated by the inhalation device (or metered dose) by an amount that is retained by the inhalation device (some of the drug aerosol particles stick to the walls of the device). The delivered dose differs from the deposited dose (or dose deposited in the lungs) by the pulmonary deposition fraction or the amount of aerosol that can make it into the lungs (i.e. does not get stuck in the back of the mouth, or in the nose if delivered by nose-only inhalation). To convert the delivered dose to the deposited dose, one must know the pulmonary deposition fraction (Alexander et al., 2008; Forbes et al., 2011). Airway geometry makes the pulmonary deposition fraction not only species dependent, but also highly dependent on the particle size distribution of the aerosol (Scheuch & Siekmeier, 2007). Throughout this manuscript we will assume for simplicity in all rodent, canine, nonhuman primate, and human dose calculations, the pulmonary deposition fractions are 10%, 25%, 30%, and 40% (Snipes, McClellan, Mauderly, & Wolff, 1989), respectively. These pulmonary deposition fraction values do not necessarily reflect the actual pulmonary deposition fraction of pharmaceutical aerosols. The inherent limitations associated with using these pulmonary deposition fraction values has been reviewed at length (Forbes et al., 2011). These pulmonary deposition fraction values should be replaced with more accurate values based on the animal species and the experimentally measured aerosol particle size distribution for the drug, if available (Olsson, Borgstrom, Lundback, & Svensson, 2013).

3. Pre-clinical studies for inhaled drugs

Pre-clinically, inhaled compounds are optimized to increase the TI which requires in vivo efficacy and side effect measurements. Initially, these measurements can be made in separate assays. Usually the drug is delivered topically to the lungs for the efficacy measurement and systemically for the side-effect measurement. Final determination of a TI for an inhaled drug, where efficacy and side effect are measured in the same animals after inhaled administration, requires dose/response studies that achieve exposure at least 10 times greater than the efficacious dose deposited in the lungs. At these supramaximal efficacious levels, either a measureable side effect is induced or the targeted safety margin (TI > 10) is confirmed.

Conformation of an appropriate safety margin enables inhaled toxicology studies. The outcome of the toxicology studies will be used to set the maximum dose allowed in clinical trials. The inhaled human deposited efficacious dose projected from the pre-clinical efficacy studies reassures that the maximum dose allowed in the clinical trials by the toxicology studies is not a sub-efficacious dose. A TI calculated from animals dosed by inhalation derisks the toxicology studies, but it is not