Arch Bronconeumol. 2012;48(7):240–246

ELSEVIER DOYMA

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

Review

Deposition of Inhaled Particles in the Lungs☆

Ana Fernández Tena, Pere Casan Clarà*

Instituto Nacional de Silicosis, Hospital Universitario Central de Asturias, Facultad de Medicina, Universidad de Oviedo, Oviedo, Spain

ARTICLE INFO

Article history:
Received 26 January 2012
Accepted 1 February 2012
Available online 26 May 2012

Keywords:
Aerosol
Lung deposition
Inhalers

ABSTRACT

Inhaled medication is the first-line treatment of diseases such as asthma or chronic obstructive pulmonary disease. Its effectiveness is related to the amount of drug deposited beyond the oropharyngeal region, the place where the deposit occurs and its distribution (uniform or not). It is also important to consider the size of the inhaled particles, the breathing conditions, the geometry of the airways, and the mucociliary clearance mechanisms.

Currently, mathematical models are being applied to describe the deposition of inhaled drugs based on the size of the particles, the inspiratory flow, and the anatomical distribution of the bronchial tree. The deposition of particles in the small airways gets maximum attention from pharmaceutical companies and is of great interest as it is related with a better control in patients receiving these drugs.

Depósito pulmonar de partículas inhaladas

Palabras clave:
Aerosol
Depósito pulmonar
Inhaladores

RESUMEN

La medicación inhalada constituye el tratamiento de primera línea de enfermedades como el asma o la enfermedad pulmonar obstructiva crónica. Su efectividad está en relación con la cantidad de fármaco que logre depositarse más allá de la región orofaríngea, con el lugar en que se produzca el depósito y con la distribución uniforme o no del mismo. Otros factores trascendentes son el tamaño de las partículas inhaladas, las condiciones de respiración, la geometría de las vías aéreas y los mecanismos de aclaramiento mucociliar.

Actualmente se están aplicando modelos matemáticos que permiten describir el depósito de fármacos inhalados a partir del tamaño de las moléculas, el flujo inspiratorio y la distribución anatómica del árbol bronquial. El depósito de partículas en las vías aéreas pequeñas recibe la máxima atención de las empresas farmacéuticas y es del máximo interés para poder controlar mejor a los pacientes que reciben estos fármacos.

Introduction

The air that we breathe contains more than just nitrogen and oxygen. In addition, there are thought to be small concentrations of other gases (ozone, hydrogen, krypton, argon) and a variable quantity of water vapor depending on the environment in which we find ourselves. We do not know if this is all, although we fear that it is not. What we call "air" also contains enormous quantities of suspended particles, solid as well as liquid, organic and inorganic, bacteria, viruses, antigens, particles that can be more elemental, volatile or solid, simple or combined. All these elements make up the exterior environment where we breathe and live.

Our lungs are tremendous sponges of blood that also act as enormous filters that purify the air we breathe. By the time the oxygen and nitrogen molecules are deposited in the alveoli, we could say that they are practically free of the majority of these "contaminants" and that these local and general defense systems are quite effective during many, many years. This, of course, is true as long as we have taken care not to deliberately deteriorate our lungs by smoking.

The respiratory tract is especially designed, both anatomically and functionally, so that air can reach the most distal areas of the lungs in the cleanest possible condition. Nasal hairs, nasal turbinates, vocal chords, the cilia of the bronchial epithelium, the sneeze and cough reflexes, etc., all contribute to this filtering process. And, on most occasions it is properly done. But human beings are full of paradoxes: an efficient system, designed to avoid certain

☆ Please cite this article as: Fernández Tena A, Casan Clarà P. Depósito pulmonar de partículas inhaladas. Arch Bronconeumol. 2012;48:240–6.

* Corresponding author.
E-mail address: pcasan@ins.es (P. Casan Clarà).

particles from penetrating into the lungs, is at the same time used to intentionally deposit drugs in the airways and even for these to reach the alveoli in the best possible condition. It is thus necessary to get around the defense systems by evading reflex arcs, mucus layers, ciliary movements, etc., so that, with the inspiratory flow, the molecules that can improve diseases are deposited in the lungs. A system that evolved over time in order to filter and clean the air should be dodged in order to deposit other substances that we deliberately want to reach the inside of the organism. Without a doubt, an understanding of anatomy, airway function and the laws of physics that govern flow dynamics, size, shape, and the number of inhaled particles will contribute to the development of this area of expertise. This area is so close to our specialty and has generated great interest, especially for the development of new methods to administer medication.

Factors That Affect the Deposition of Aerosolized Drugs

Particle Size and Shape

The size and shape of particles are primordial factors that condition their deposition in the lungs. The size is defined by what is called the mass median aerodynamic diameter (MMAD) or diameter of a particle of mass equal to the average particle diameter of a population, meaning the diameter of a particle in which 50% of the aerosol mass is greater and the other 50% is smaller.[1] Depending on their size and shape, the particles can be deposited by means of four mechanisms:

- *Impaction.* This is the physical phenomenon by which the particles of an aerosol tend to continue on a trajectory when they travel through the airway, instead of conforming to the curves of the respiratory tract.[2] Particles with enough momentum (product of the mass and velocity) are affected by centrifugal force at the points where the airflow suddenly changes direction, colliding with the airway wall. This mainly happens in the first 10 bronchial generations, where the air speed is high and the flow is turbulent.[3] This phenomenon mainly affects particles larger than 10 μm, which are mostly retained in the oropharyngeal region, especially if the drug is administered by dry powder inhalers (DPI) or metered-dose inhalers (MDI).[4]
- *Interception.* This is mainly the case of fibers, which, due to their elongated shape, are deposited as soon as they contact the airway wall.
- *Sedimentation.* This is the physical phenomenon by which particles with sufficient mass are deposited due to the force of gravity when they remain in the airway for a sufficient length of time. This predominates in the last 5 bronchial generations, where the air speed is slow and the residence time is therefore longer.[3]
- *Suspension.* This is the phenomenon by which the particles of an aerosol move erratically from one place to another in the airways. This happens as a consequence of the Brownian diffusion of particles with an MMAD smaller than 0.5 μm when they reach the alveolar spaces, where the air speed is practically zero. These particles are generally not deposited and they are expelled once again upon exhalation.

The particles of aerosolized drugs usually have a uniform shape and are symmetrical on several planes. They rarely are smaller than 1 μm, and therefore the predominating mechanisms are impaction and sedimentation.[5]

It can generally be considered that particles with an MMAD higher than 10 μm are deposited in the oropharynx, those measuring between 5 and 10 μm in the central airways and those from 0.5 to 5 μm in the small airways and alveoli. Therefore, for topical respiratory treatment it is best to use particles with an MMAD between 0.5 and 5 μm. This is what is known as the breathable fraction of an aerosol.[6]

Airflow Velocity

Because particles are transported through the airway by an air current, their trajectories are affected by its characteristics. The air flow in the lungs is determined by the tidal volume and respiratory rate. Sbirlea-Apiou et al.[7] demonstrated that in the first four generations of the airway, the deposition increases for any size particle as the inspiratory flow increases. However, the opposite is true in the last generations of the airway, where the deposition of particles is inversely proportional to this flow. This is due to that fact that the increased inspiratory flow reduces the residence time of the particles in the airway, therefore the effects of the severity and of the Brownian movement will be quite lower. Obviously, a minimal inspiratory flow is necessary to drag the particles toward the interior of the bronchial tree.

Airway Geometry

The probabilities of particle deposition by impaction increase when the particles themselves are larger, the inspiratory airflow is greater, the angle separating the two branches is wider and the airway is narrower.[8]

In pathologies such as chronic bronchitis or asthma, which may alter the lung architecture with the appearance of bronchoconstriction, inflammation or secretion accumulation, the deposition of aerosolized drugs is modified. The smaller caliber of the airway increases air speed, producing turbulence in places where the flow is usually laminar. The airway obstruction also means that the air tends to be displaced toward unobstructed areas, and therefore the drug will also tend to be deposited mostly in healthy areas of the lung.[9]

Degree of Humidity

The particles of aerosolized drugs can be hygroscopic to a greater or lesser extent. Hygroscopicity is the property of some substances to absorb and exhale humidity depending on the setting in which they are found. This means that they can get larger or smaller in size upon entering into the airway, with the consequent modification in the deposition pattern compared to what was initially expected. The diameter that a particle reaches after hygroscopic growth depends on its initial diameter, the intrinsic properties of the particle, and the environmental conditions in the airways. The mole fraction of water vapor contained in the airway has been demonstrated to be an important factor related with the increase in the MMAD of the aerosol particles.[10] In general, it is considered that hygroscopic growth does not have much of an effect in particles with MMAD less than 0.1 μm; meanwhile it is very intense in particles with MMAD larger than 0.5 μm.[11]

The hygroscopicity of molecules can be used to try to favor the deposition of inhaled drugs. Studies have been developed in which an aerosol was administered with a submicrometric or nanometric MMAD in order to reduce extrathoracic loss, taking advantage of later growth due to hygroscopicity, which enabled the particles to be retained within the lungs.[12,13]

Mechanisms for Mucociliary Clearance

Once deposited in the airways, the particles can be carried by the mucociliary system, degraded or absorbed into the systemic circulation or the lymph ducts.[9] The first of these mechanisms is