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Lung imaging — Two dimensional gamma scintigraphy, SPECT, CT and PET ☆

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ABSTRACT

This review will cover the principles of imaging the deposition of inhaled drugs and some of the state-of-the art imaging techniques being used today. Aerosol deposition can be imaged and quantified by the addition of a radiolabel to the aerosol formulation. The subsequent imaging of the inhaled deposition pattern can be acquired by different imaging techniques. Specifically, this review will focus on the use of two-dimensional planar, gamma scintigraphy, SPECT, CT and PET.
This review will look at how these imaging techniques are used to investigate the mechanisms of drug delivery in the lung and how the lung anatomy and physiology have the potential to alter therapeutic outcomes.

Contents

Abbreviations: SPECT, single photon emission computed tomography; CT, computed tomography; HRCT, high resolution computed tomography; PET, positron emission tomography; PK, pharmacokinetics; MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation; MDI, metered dose inhaler; DPI, dry powder inhaler; ^{99m}Tc, technetium; ^{81m}Kr, krypton; ^{133}Xe, Xenon; ^{57}Co, Cobalt; ^{111}In, Indium; ^{123}I, Iodine; $^{13}N_2$, Nitrogen; MCC, mucociliary clearance; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; PCD, primary ciliary dyskinesia; V/Q, ventilation/perfusion; HU, Hounsfield Unit; HFA, hydrofluoroalkane; ITU, intensive therapy unit; TLC, total lung capacity; EBUS, endobronchial ultrasound; OCT, optical coherence tomography.

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1. Introduction

The efficacy of an inhaled active agent depends on many factors including individual anatomical and physiological variations, the effects of pathology, and the inhaler device used. It is important that any variation in pulmonary deposition is quantified, as accurate measurement of the amount of drug to reach the lung allows verification of dose and the ability to relate that dose to clinical effect. Sensitive and reliable methods that allow therapeutic interventions to be studied in detail are required. Ideally the quantification methods need to be translatable to other research centres so that a multi-centre, consensus view on inhaled therapies can be gained.

Inhaled drug deposition can be evaluated by a variety of established non-imaging and imaging methods. The methods that do not involve imaging include the charcoal-block and urinary excretion pharmacokinetic methods. Both these techniques of measuring pharmacokinetics (PK) will allow quantification of the relative pulmonary bioavailability of an inhaled drug [1–5]. The charcoal block method uses charcoal ingestion to block any systemic uptake via the gastrointestinal route, thus quantifying pulmonary bioavailability. The urinary excretion method estimates systemic delivery by comparing 'area under the curve' data between different regimens so it is useful as a measure of relative pulmonary bioavailability. Some research groups have used both PK data and lung imaging to quantify deposition [2,3] and it is generally accepted that PK methods give similar results, for total lung deposition, to lung imaging data [3,6]. PK methods have the advantage over lung imaging techniques of not requiring a radiation dose so it may seem that there is no reason to go to an imaging method to assess lung deposition. The principal limitations of PK data are that these methods may not be suitable for all drugs and the lack of information these methods give on regional deposition of the inhaled drug within the lung in vivo may be important in relation to clinical effect. Imaging studies can be carried out by any drug formulation that can be satisfactorily radiolabelled. A recent workshop on the role of PK methods in establishing bioequivalence for inhaled drugs confirmed the current consensus opinion that the limitation of the PK methods is the lack of reliable information on regional deposition of the inhaled drug [7].

Is regional deposition important? The receptors for different drug groups such as inhaled bronchodilators and corticosteroids have regional differences in density and so it is considered that differing regional deposition patterns may have an important clinical effect [8]. Inhaled aerosols can be targeted to different regions of the lung by manipulating the particle size, the method of inhalation and even perhaps by the carrier gas [9–13]. Usmani et al. [11] have shown that regional targeting of an inhaled β_2-agonist to the proximal airways is more important than distal alveolar deposition for bronchodilation. This group found that by altering the intrapulmonary deposition through the manipulation of aerosol particle size they could enhance inhaled drug therapy. Usmani et al. [11] found that the larger particle sizes (approximately 6 μm and 3 μm MMAD) achieved greater bronchodilation than the smaller particles (1.5 μm MMAD) and concluded that regional deposition of an inhaled drug should be considered when developing future inhaled treatments [14].

The lung can also be used as a portal for the delivery of drugs to the systemic circulation [15] and in this context the alveolar zone usually needs to be targeted to gain maximum cross-over to the circulation. Successful peripheral targeting depends on the aerosol properties, the properties of the drug and the physiology and pathophysiology of the patient [16,17]. Quantification of the total and regional lung deposition can be seen as important to the understanding of the therapeutic response for both topical and systemic targeting of an inhaled drug.

The other potent factor that can affect regional deposition is the severity of the lung disease being targeted. Airway obstruction from such factors as inflammation, loss of elastic recoil, increased secretions and sputum plugging, smooth muscle contraction and areas of bronchiectasis will all have a marked effect on regional deposition tending to increase the amount of aerosol deposition in the central airways and to increase inhomogeneity of the deposited drug throughout the lung [18]. Alteration of the in vivo pattern of deposition within the lung, with disease, is of potential importance in judging clinical trial results that compare disease to health.

With the emergence of 'new' inhaled therapeutic agents such as: liposomal vectors for gene therapy; prostacyclins for pulmonary arterial hypertension; cyclosporin for the prevention of post lung transplant rejection; aerosolised vaccinations for influenza, measles, rubella and even anthrax; and therapeutic approaches to lung fibrosis and TB, there may well be an increased need for regional targeting of an inhaled drug and therefore regional quantification of deposition can be seen as essential [19]. It should also be acknowledged that regional deposition information is not just of value to the world of inhaled drugs. There is also a need to understand risk assessment of inhalation toxicology although this is outside the scope of this review. Regional targeting does not also need to just be about peripheral versus central deposition it could also include the targeting of specific lobes or sub-lobar segments. This type of anatomical targeting might be applicable and perhaps more relevant to the clinical scenario, such as when using an inhaled drug to treat cystic fibrosis (CF) where the lung disease is often not homogeneous in nature

There is a clear need to quantify lung deposition patterns of inhaled therapies and that drive has led to the development of several pulmonary imaging techniques based on the use of gamma cameras. The basic principles behind gamma scintigraphy work are the addition of a radiolabel to the aerosol formulation and the subsequent imaging of the inhaled deposition pattern via the use of one or multiple gamma camera detector heads. For gamma scintigraphy, the radiolabel is usually the isotope Technetium (^{99m}Tc). The most straightforward imaging technique is two-dimensional (2D) gamma scintigraphy, also referred to as planar imaging, which gives useful information on the total amount of inhaled drug to reach the lungs and also some information on regional deposition [20].

The introduction of cameras that allowed a 360° rotation provided three-dimensional (3D) imaging data, referred to as single photon emission computed tomography or SPECT, was the next development. The advantage of SPECT over 2D gamma scintigraphy is that SPECT allows the quantification of regional lung deposition with a greater precision than 2D planar imaging [21]. SPECT can also be combined with both low-resolution and high-resolution computed tomography (HRCT). This allows anatomical information to be aligned with the deposition data and offers the possibility of further methods of 3D segmentation. HRCT on its own can describe detailed central airway anatomy which is known to have high inter-subject variation and may be one of the anatomical reasons for individual variance in deposition. Both 2D planar and 3D SPECT gamma camera techniques give some insight into the fate of inhaled aerosols and have been used by many centres to study inhaled drugs such as inhaled bronchodilators, mannitol, tobramycin and interferon gamma [11,22–27]. Positron emission tomography (PET) when applied to the field of inhaled drug deposition, also uses an inhaled radiolabelled aerosol technique and gives 3D imaging data [28] but uses a different method of radiolabelling to planar or SPECT imaging, incorporating positron emitters such as ^{18}F, ^{13}N, ^{11}C and ^{15}O into the drug molecule. The radiolabelling process is significantly more complicated than planar or SPECT imaging but does offer the advantage of direct labelling of the drug molecule providing information not just on deposition but also allows clearance of the drug to be followed over time [9].

This review will focus on the use of two-dimensional planar, gamma scintigraphy, SPECT, CT and PET and how these imaging techniques are utilised to investigate the mechanisms of drug delivery in