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REVIEW OF THE CURRENT PRACTICE OF THE INHALATIONAL USE OF POSITRON EMITTERS

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ABSTRACT

Purpose: In this paper, I am reviewing the current state of art of use of PET imaging in inhalational studies, exploring the potential for this imaging modality in the respiratory field.

Inhalational delivery is a commonly used method of drug administration, especially for conditions that affect the lung where optimal lung drug exposure is desired, for example steroids in chronic obstructive pulmonary disease or bronchial asthma [2] or for conditions where the kinetics of systemic therapy has limited access to lungs in conditions such as idiopathic pulmonary fibrosis [3].

Approach: I searched the literature, using PubMed and MEDLINE databases, for papers and publications looking into the inhalational use of positron emitters over the last two decades.

Results: There has been a quest recently to administer drugs through inhalational methods as an alternative to systemic administration allowing more effective dosing levels with reduced systemic toxicity [4]. Nuclear imaging methods such as Single Photon Emission computed tomography (SPECT) and PET, have been used to assess aerosol delivery to the lung. Higher sensitivity, the ability for dynamic acquisition and physiological respiratory gating confers an advantage to PET [7].

The biodistribution in the lungs of a number of radiolabeled agents administered via inhalation such as [11C] triamcinolone, [18F] fluticasone, [11C] zanamivir has been evaluated using PET [8-11]. Inhalational biodistribution of FDG has also been investigated in conditions such as cystic fibrosis and lung inflammation [11].

Conclusions: There are currently continuing advancements in radiotracer development and imaging technologies which offer promising avenues for enhancing drug delivery via inhalation.

KEYWORDS: Positron Emission Tomography; Inhalational.

INTRODUCTION

Introduction and Rationale: Inhalation is a commonly used method of drug administration, especially for conditions that affect the lung where optimal lung drug exposure is desired, for example steroids in chronic obstructive pulmonary disease and bronchial asthma [1] or for conditions where the kinetics of systemic therapy has limited access to lungs in conditions such as idiopathic pulmonary fibrosis [2].

There has been a quest recently to administer drugs through inhalational methods as an alternative to systemic administration allowing more effective dosing levels with reduced systemic toxicity [3]. Studies looking at drug delivery have shown that inhalational exposure is variable based on the inhalational device, particle size and patient compliance [4, 5].

Nuclear imaging methods such as Single Photon Emission computed tomography (SPECT) and Positron Emission Tomography (PET) have been used to assess aerosol delivery to the lung. Higher sensitivity, the ability for dynamic acquisition and physiological respiratory gating confers an advantage to PET over SPECT [6]. The biodistribution in the lungs of a number of radiolabeled agents administered via inhalation such as [11C] triamcinolone, [18F] fluticasone, [11C] zanamivir has been evaluated using PET [7-10]. Inhalational biodistribution of FDG has also been investigated in conditions such as cystic fibrosis and lung inflammation [10]. Reviewing the literature, I believe there is a strong case for further developing the inhalational route as a drug delivery mechanism in various pulmonary conditions. The unique ability of PET to study the uptake kinetics of the inhaled tracers in vivo places this imaging modality at the forefront of future research in the field. For example, a research group from Hull, UK have used radiolabeled formulations to validate a range of inhalation drug delivery devices allowing monitoring of output and investigation of the potential for clinical use with data sets on dry powder inhalers, nebulizers and, more recently, vape devices. An interdisciplinary team of chemists, physicists, engineers and clinicians have developed the devices and phantoms in Hull, UK [11] and their studies have shown that vapes offer a novel accessible delivery system for aerosols, providing higher device output than traditional nebulisers, reducing the required activity and potentially minimizing radiation dose to staff and improving patient compliance [12].

In the next few sections, I will shed some light over the history of and current clinical use of inhaled positron emitters and how they make a difference compared to the traditional imaging techniques when assessing pulmonary disease. This is to give an overview and a context to the reader who is keen on the role of imaging in pulmonary drug delivery helping them understand the promising role of PET in pulmonary drug delivery research.

Factors determining particle aerodynamics through the airways

Studying the factors affecting particle inhalation and movement through the airways are crucial for effective drug delivery and respiratory condition management. This would also influence the imaging characteristics of different inhaled radiolabelled compounds. The following key determinants influence this process:

1. **Particle Size:** The aerodynamic diameter of an aerosol is the major limiting factor determining how far it would reach in the airways, with aerosols less than 2μm in median aerodynamic diameter (MMAD) generally able to penetrate to smaller airways and larger molecules between 2 and 5 μm staying in the more proximal lung [10].
2. **Inspiratory Flow Rate and Breath-Hold Time:** These impact aerosol deposition by influencing particle movement through the airways. The subject's inspiratory flow rate should be 15 Lmin-1 for nebulised aerosols, 30 L min-1 for pressurized aerosols and 60 Lmin-1 for dry powder inhalers [10].
3. **Airway Calibre and disease:** Changes due to mucus secretion, inflammation, or smooth muscle constriction affect particle movement patterns. Presence of smooth muscle constriction in

certain inflammatory conditions, like asthma, will also affect the distribution of aerosols and their delivery to distal airways. This has beendemonstrated by Professor Dolovich studying the effect of inhaled steroids on patients with asthma using inhaled [18F] FDG [10].

Evolution of PET use in inhalational lung studies

The evolution of PET imaging in inhalational lung studies has revolutionized respiratory research, especially with the well-established advantages of PET over SPECT [13]. The enhanced spatial resolution and sensitivity of PET compared to SPECT have enabled the utilization of agents like 68Ga-Gallium for ventilation studies, resulting in quantitative and high-quality respiratory gated images [14].

Another advantage of PET is the relatively short half -life of positron emitters compared to the other radiotracers which allows for multiple / repeated scans on the same day, and low amounts of radiotracer can be used thus limiting the radiation dose to the subject [14].

Another development was the integration of PET/CT with MRI scanners which paved the way for aerosol deposition investigations, enabling dynamic ventilation measurement with gases like Xenon-129[15].

Studies focusing on pulmonary drug deposition and disease monitoring, particularly in conditions like Idiopathic pulmonary fibrosis (IPF), have displayed promising outcomes. In a pre-clinical study, the utilization of lung surrogate phantoms and Andersen cascade impactors has enabled quantification of aerosolized [18F] FDG deposition mimicking human breathing patterns [16].

Current inhalational use of different positron emitters

[18F] FDG

F18 labelled Fluorodeoxy glucose (FDG) is by far the most used positron emitter in clinical practice. Not surprisingly, it has been used extensively in studying lung inflammation and non-oncological pulmonary disease [17]. It also gained momentum as an inhaled radiotracer in evaluating lung function, disease states, and drug delivery efficiency through aerosol administration. In addition, it enables visualization of changes influenced by diseases or interventions, which is crucial for assessing regional lung distribution and drug absorption rates. For example, Dolovich et al used a 1.5-μm aerosol of [18F] FDG to measure ventilation before and after steroid therapy in asthmatic patients. The baseline scan was obtained when the patient became symptomatic following steroid reduction; ventilation was seen to be nonuniform with activity concentrated in the proximal regions of the lung. After 4 weeks of inhaled corticosteroid therapy, deposition was distributed to more distal regions of the lung [10, 18].

In another study, Dolovich clearly demonstrated the difference between the deposition of inhaled [18F] FDG aerosols between healthy volunteers and Cystic fibrosis patients [10].

[11C] Carbon

[11C] Carbon has a half-life of 20 Minutes. Some researchers used it as an inhaled direct-labelled active pharmaceutical ingredient to assess aerosol deposition in the lungs. For example, a group from University Hospitals of Cleveland, Ohio used quantitative PET scans of [11C] triamcinolone acetonide following administration of Azmacort(R) via a commercial metered dose inhaler with an integrated spacer device. Distributions at varying time periods after drug administration were investigated to explore the dynamics and kinetics of the aerosolized drug. Initially, deposition of labelled drug on

conducting airways was found to be higher than those on acinar airways, with the distribution pattern changing slowly with time [19]. This study illustrated the value of positron emitters in designing and evaluating drug formulations.

A group from Austria developed a new in vivo experimental approach to assess the functional impact of P-glycoprotein (P-gp) on the pulmonary delivery of inhaled drugs in rats using [11C] Carbon PET. They measured the intrapulmonary pharmacokinetics of the model P-gp substrates (R)-[11C] verapamil ([11C] VPM) and [11C]-N-desmethyl-loperamide ([11C] dLOP) administered by intratracheal aerosolization in three rat groups. Their study highlights the potential of PET imaging with intratracheally aerosolized radiotracers to assess the impact of membrane transporters on pulmonary drug delivery in rodents and potentially also in humans [20].

[68Ga] Gallium

Ventilation / perfusion (V/Q) PET using Galligas / [68Ga] Gallium is a relatively new technique being used in some centres to replace the conventional V/Q Scintigraphy, coming with all the above-mentioned superiority of PET over gamma scintigraphy and SPECT, namely improved sensitivity / spatial resolution and the prospect of respiratory gated acquisition [21]. Main current clinical indications are diagnosis of pulmonary embolism, radiotherapy field planning and preoperative evaluation for lung cancer surgery [22].

A group from Brest University, France, has evaluated the technologist' dose profile from [68Ga] V/Q PET in their institution compared to the usual V/Q scintigraphy and the other widely used PET tracers in clinical practice, namely [18F] FDG and [68Ga] Ga-DOTATOC. They found that while the total effective dose the technologist is exposed to in V/Q PET is about 2.4 times higher than the dose for a conventional V/Q scintigraphy procedure, the technologist radiation exposure for V/Q PET is equivalent to the exposure of other PET procedures, both in terms of total effective and finger doses [22].

[15O] Oxygen

[15O] Oxygen was one of the first clinically used inhaled positron emitters. It has a half-life of only 2 minutes and has been used to assess perfusion for different organs [6]. This can be traced back to the 1980s, when Mintun MA et al validated a method for the measurement of the local cerebral metabolic rate for oxygen (CMRO2) with PET. They used data from a single inhalation of [15O] -labelled CO for cerebral blood volume (CBV), an intravenous injection of [15O] H2O for cerebral blood flow (CBF), and a single inhalation of [15O] O2 for the final calculation of CMRO2 and the extraction of oxygen (E). They validated their technique in baboons by comparing the PET-measured (E) with (E) measured using an intracarotid injection of [15O] O2. The correlation between these two techniques was excellent [23].

Use of inhaled [15O] PET has been applied in cardiology as well. In 2001, a group from France used [15O] O2 to calculate quantitative measurements of the metabolic rate of oxygen (MMRO2) and oxygen extraction fraction (OEF) in patients with cardiomyopathy and left ventricular (LV) dysfunction, comparing them to healthy volunteers. Significant correlations were observed among OEF and LV Ejection fraction (P = 0.002), MMRO2 and LVEF (P = 0.03) [24].

DISCUSSION

The two main positron emitters in clinical use at the moment are [18F] FDG and [68Ga] Gallium. As discussed above, building on the extensive use of [18F] FDG in systemic inflammatory conditions, its

inhalation has been specifically used to illustrate the inflammatory response underpinning some of the most common pulmonary diseases, for example asthma and cystic fibrosis. Dolovich et al have published extensively in the matter over the last two decades. Despite this, I don't think PET imaging is in routine clinical use to assess non-oncologic lung disease, neither well-established in the guidelines. This may be attributed to the relatively higher cost and more complexity of the scan technique compared to conventional imaging.

On the other hand, [68Ga] Gallium seems to be a frontrunner alternative in ventilation / perfusion imaging. V/Q PET/CT is now possible by substituting 99mTc with 68Ga, a positron-emitting radionuclide, using the same carrier molecules as conventional V/Q imaging. Ventilation imaging can be performed with 68Ga-carbon nanoparticles using the same synthesis device as Technegas, yielding "Galligas". Perfusion imaging can be performed with ^{68}Ga-macroaggregated albumin (^{68}Ga-MAA) [21, 25]. Compared with conventional V/Q scintigraphy, the advantages of 68Ga-labeled V/Q PET/CT include superior image quality and faster acquisition. These may improve the outcomes of patients with suspected pulmonary embolism through more accurate diagnosis. [25]

CONCLUSION

The role of positron emitters and PET imaging in inhalational studies is paramount in advancing our understanding of drug delivery mechanisms and respiratory health.

PET imaging has proven its value in understanding disease pathology, with a deeper comprehension of how inhaled substances interact with the airways. In addition, insights from inhalational PET studies can lead to improved drug delivery methods for respiratory conditions. There are currently continuing advancements in radiotracer development and imaging technologies which offer promising avenues for enhancing drug delivery via inhalation.

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