

From Inhaled Drugs to Exhaled Viruses: A Journey of my 45 years in Aerosol Medicine.

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Summary and Key Messages

Radiolabelled aerosol particles were used to measure regional respiratory tract deposition and clearance of these particles from deep in the lungs and airways. We found that some aerosol particles were not cleared from the airways within one day. We found also that particles > 5µm could reach the airways and even the alveoli. This is important for drug delivery. We also found that the breathing pattern is more important for pulmonary drug deposition than particle size.

By tidal breathing the reopening of collapsed airways is the main mechanism that produces aerosol particles which could be exhaled from the human lungs. This important mechanism is able to distribute influenza and corona viruses between human subjects.

Introduction

The following statements (doctrines) are often found in pharmaceutical and scientific literature:

- Particles > 5 µm cannot be inhaled deep into the lungs.
- Inhaled aerosol particles < 2 µm are deposited in the alveoli, 2-5 µm particles are deposited in the airways and aerosol particles > 5 µm are deposited in the mouth and throat.
- Particles deposited in the airways (bronchi and bronchiole) are eliminated from the lungs within a few hours by mucociliary transport.

These statements were challenged by our investigations.

Aerosol particles cannot only be inhaled but can be generated by and exhaled from the human lungs. In the late 1980s and in 2020s we did several studies to determine the amount and the site of origin of these exhaled particles.

Studies and Results

To study the influence of particle size and breathing pattern on total lung deposition and the regional distribution, radiolabelled particles and gamma camera or whole body scanner were used. Every individual did inhale under controlled conditions Tc99m or In111 labelled monodisperse aerosol particles of a specific size. Directly after inhalation and in specific intervals after the last inhalation the amount of radioactivity and the distribution of the radioactivity had been measured for each subject. In that way total lung deposition, regional distribution and the clearance of these particles out of the lungs could be determined.

It could be shown, that

- a) Aerosol Particles between 4 and 10 µm are mainly depositing in the bronchial airways [1]
- b) The optimal particle size to reach the alveolar space is 2.5 µm and not particles < 2 µm [2,3]
- c) Breathing pattern has a greater influence on regional deposition than particle size [4]
- d) Not all particles which are deposited in the human airways are cleared out of the lungs in one day [5]

In the course of these experimental investigations we found that the human lung functions like an aerosol generator. Tiny aerosol particles (0.2-0.4µm) could be detected in the exhaled air even after washout of the lungs with clean air and with quiet breathing. These investigations suggest that the origin of these

particles is the deep lung and is caused by the reopening of collapsed airways at the beginning of an inhalation.[6] This effect was found in every subject that we studied. On average we found ~ 200 particles/Liter in the exhaled air. However, the concentration of these exhaled particles increased by 2-3 orders of magnitude when a person had a respiratory infection. We continued our experimental work during the corona crisis in 2020 and found that not every infected individual became a so-called 'superspreader', these were infected individuals which exhaled >5000 Particles/L. For patients with a severe corona infection, we found that about 15% of these patients were superspreaders. [7]

In several studies with children we found that they exhaled far fewer particles than adults and we didn't find any 'superspreader' at all.[8] These findings should be considered if such an event would happen again in future.

References:

- [1] Heyder J, Gebhart J, Rudolf G, Schiller C, Stahlhofen W. Deposition of particles in the human respiratory tract in the size range 0.005–15 μm . *J Aerosol Sci* 1986;17:811–825.
- [1] Scheuch G, Siekmeier R. Novel approaches to enhance pulmonary delivery of proteins and peptides. *J Physiol Pharmacol*. 2007 Nov;58 Suppl 5(Pt 2):615-25.
- [3] Brand P, Friemel I, Meyer T, Schulz H, Heyder J, Häussinger K. Total deposition of therapeutic particles during spontaneous and controlled inhalations. *J Pharm Sci*. 2000 Jun;89(6):724-31.
- [4] Apiou-Sbirlea G, Newman S, Fleming J, Siekmeier R, Ehrmann S, Scheuch G, Hochhaus G, Hickey A. Bioequivalence of inhaled drugs: fundamentals, challenges and perspectives. *Ther. Deliv*. 2013 Mar;4(3):343-67.
- [5] Scheuch G and Stahlhofen W.: The recovery of 1 μm aerosol particles from large human airways. *J Aerosol Sci*. 1992, 23, 477-481.
- [6] Scheuch G, Breathing Is Enough: For the Spread of Influenza Virus and SARS-CoV-2 by Breathing Only. *J Aerosol Sci*. 2020; 33.4: 1–5
- [7] Gutmann D, Scheuch G, Lehmkuhler T, Herrlich LS, Landeis A, Hutter M, Stephan C, Vehreschild M, Khodamoradi Y, Gossmann AK, King F, Weis F, Weiss M, Rabenau HF, Graf J, Donath H, Schubert R, Zielen S. Aerosol measurement identifies SARS-CoV 2 PCR positive adults compared with healthy controls. *Environ Res*. 2023 Jan 1;216(Pt 1):114417. doi: 10.1016/j.envres.2022.114417. Epub 2022 Sep 24.
- [8] Schuchmann P, Scheuch G, Naumann R, Keute M, Lücke T, Zielen S, Brinkmann F. Exhaled aerosols among PCR-confirmed SARS-CoV-2-infected children. *Front Pediatr*. 2023 Apr 21;11:1156366. doi: 10.3389/fped.2023.1156366. PMID: 37152322; PMCID: PMC10160682.