LUNG DEPOSITION OF INHALED ALPHA-1-PROTEINASE INHIBITOR (ALPHA-1-PI): PROBLEMS AND EXPERIENCE OF ALPHA-1-PI INHALATION THERAPY IN PATIENTS WITH CYSTIC FIBROSIS AND HEREDITARY ALPHA-1-PI DEFICIENCY

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Alpha-1-proteinase inhibitor (alpha-1-PI; molecular weight: 52 kDa) serves as the most relevant protease inhibitor in the lung. Hereditary deficiency of alpha1-PI as well as its inactivation due to an increased oxidative burden in patients with enhanced inflammation in the respiratory tract (e. g. patients with cystic fibrosis, severe smokers) are at a high risk for the development of lung emphysema and chronic obstructive pulmonary disease (COPD). Since about 15 years treatment with alpha-1-PI (isolated from plasma or produced by recombinant means) is established in clinical treatment. Initially, alpha-1-PI was substituted by means of an infusion therapy (up to weekly infusions). The alternative inhalant administration has the advantages of lower required doses (cost reduction when compared to conventional therapy) and a better convenience and compliance of the patients to be treated. However, this novel therapy requires a nebulisation of the protein without functional inactivation as well as the deposition of sufficient and reproducible doses in the lung periphery.The site of drug deposition within the lungs depends on physical, physiological, and pathophysiological parameters. To ensure an optimised therapy (i. e. sufficient and reproducible dosage at the region of interest) all these parameters should be controlled. For example, the deposition depends on the aerodynamic diameter of the aerosol particle. However, particles made of hygroscopic compounds rapidly enlarge due to the humidity in the respiratory tract which is followed by an increased deposition of the inhaled particles. In addition breathing pattern (e. g. deep or shallow breathing, endinspiratory breathhold) as well as morphological changes caused by lung diseases (e. g. COPD) are important variables affecting the deposition behaviour of inhaled aerosols. In consequence, all these parameters should be considered in a standardised individual breathing manoeuvre. For example, conventional inhalation devices and uncontrolled breathing patterns require a long time for drug administration (up to 1 hour) and allow only a deposition of 10-20% of the drug in the lung periphery. Deposition studies have shown that the optimal particle size for inhalation of ?1-PI is within the range of 2-3 micrometers. An optimal alveolar deposition is achieved at an inhalation flow rate of 250-500 cm3/s together with the largest inhalation volume convenient for the subjects. These settings allow a pulmonary deposition of up to 60% in patients with hereditary alpha-1-PI deficiency and cystic fibrosis. Up to now few studies have demonstrated the feasibility of inhalant administration of alpha-1-PI in patients. Our review describes the underlying problems of inhalant administration of alpha-1-PI and summarises the results of preliminary studies in this novel field of inhalant therapy.