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Dry Powder Inhalation Exposures of the Endotracheally Intubated Rat Lung, Ex Vivo and In Vivo: The Pulmonary Pharmacokinetics of Fluticasone Furoate.

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Abstract

Abstract Background: The isolated perfused rat lung (IPL) is a suitable model for studying lung-specific pharmacokinetics (PK) of inhaled drugs. So far, little has been known, however, whether the PK measured in the ex vivo organ corresponds to the PK measured in similarly exposed animals in vivo, in particular the endotracheally intubated rat (EIR). The purpose of the current research was to compare the PK of inhaled corticosteroid fluticasone furoate (FF) in the IPL and the EIR. Method: Aerosols of FF with mass median aerodynamic diameters ranging from 2.2 to 3.2 μm were generated with the DustGun aerosol generator. The IPL, perfused in the single-pass mode, was exposed via inhalation to 5.6 and 46 μg of FF. Following inhalation, the perfusate was repeatedly sampled for 100 min, after which the lungs were recovered for quantitation of remaining FF. Two groups of EIR were also exposed via inhalation to 7 μg of FF. One group was immediately euthanized for determination of the initial deposition of FF in the lungs. From the second group, four venous blood samples were drawn up to 4 hr after exposure. The animals were then sacrificed for determination of FF remaining in the lungs. Results: Following inhalation, FF was slowly disappearing from both the IPL and the lungs of the EIR, with a half-life of pulmonary retention of 4.3-4.9 hr for all three exposure series. For the low exposure levels, the concentration curve of FF in the IPL perfusate was similar in shape to that in venous blood of the EIR, with a C(max) of 1.0 and 0.8 nM for the IPL and the EIR, respectively. Conclusions: The results indicate that the IPL and the EIR, when used jointly in PK studies, can provide a detailed characterization of inhaled drugs or toxicants.