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Title: Laninamivir's prolonged intrapulmonary retention: Intrapulmonary pharmacokinetics (PK) and the intracellular disposition to support the long-lasting efficacy after an inhaled administration of its prodrug laninamivir octanoate (LO)

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Body: Background: A single inhaled dose of LO, a long-acting neuraminidase inhibitor, exhibits efficacy to patients with influenza virus infection. However, the relation between PK and its long-lasting efficacy has not fully been investigated. Purpose: Intrapulmonary PK in healthy volunteers and the intracellular drug disposition in mice were evaluated to support its long-lasting efficacy. Methods: Each subject underwent bronchoalveolar lavage (BAL) at specified time intervals from 4 to 240 hrs after an inhaled LO dosing (40mg). Plasma, BAL fluid and alveolar macrophage (AM) were analyzed to determine drug concentrations. Microautoradiographic localization in the respiratory tissues in mice and the drug uptake and release were evaluated using primary cultured airway epithelial cells. Results: In healthy volunteers, laninamivir concentration in epithelial lining fluid (ELF) and AM were higher than those in plasma and lasted for 240 hrs. Laninamivir in ELF decreased with a longer half-life (~ 6 days) and notably exceeded the IC50 values for viral neuraminidase at all time points. In mice, the labeled LO mainly located on the epithelial cells for a long period. LO uptake in epithelial cells increased without saturation and the intracellular laninamivir was released very slowly, which was regarded as a rate-limiting step in the cellular retention. Conclusion: ELF concentration profiles and prolonged high intrapulmonary retention of laninamivir support its long lasting efficacy to treat patients with influenza virus infection by the single inhalation.