Aerosol inhalation delivery of ceftriaxone in mice

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The pulmonary route of drug administration is a noninvasive and effective approach to deliver therapeutic agents both locally and systemically. The main benefits from the inhalation delivery are rapid onset of action, in contrast to oral application, and ease of administration, non-invasive needle-free systemic delivery and high patient acceptability, in contrast to injections. In the present work, aerosol formation and pulmonary delivery are studied for the antibiotic drug ceftriaxone, which is currently delivered mainly by injection. For this purpose, an inhalation set-up designed and built by us was used, which includes: a generator of dry aerosol particles, inhalation chambers, and measuring equipment that allows determining the delivered inhalation dose in real time. Studies have been performed on the pharmacokinetics of ceftriaxone after inhalation, intravenous and intraperitoneal administration.

Chromatographic measurements show that inhaled ceftriaxone is accumulated in the respiratory system. The absorption to blood from the respiratory system can be described by the first-order kinetics with the rate constant k_{resp} = 0.050±0.005 min^{-1}. The lung-to-blood adsorption is characterized by the first-order rate constant k_{lung} = 0.025±0.005 min^{-1}, while the absorption to blood through peritoneal barrier is characterized by the first-order rate constant k_P = 0.035±0.005 min^{-1}. The elimination rate constant is determined from aerosol delivery experiments to be k_e = 0.025±0.005 min^{-1}, which is in good agreement with that measured for intravenous and intraperitoneal administration.

To investigate the antibacterial efficiency of the ceftriaxone aerosol form, outbred male mice were infected with the archival strains of *K. pneumoniae* 82 and *S. aureus ATCC 25 953*. After the intraperitoneal injection of bacterial suspension, all the infected animals demonstrated increased bacterial burden, however, aerosol treatment, as well as injection delivery, caused a significant reduction of the bacterial concentration in animals. Aerosol, intravenous and intraperitoneal treatment of infected animals resulted in approximately equal therapeutic effects. Thus, the developed ceftriaxone aerosol form is efficient against *K. pneumonia* and *S. aureus* in mice.

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