DISPOSITION OF TELITHROMYCIN IN LUNG SURFACE AND ALVEOLAR MACROPHAGES

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Telithromycin (TEL), a ketolide antibiotic agent, has a wide antimicrobial spectrum against bacterial pathogens of respiratory infection and high distribution characteristics from blood to lung. There is little detailed information about the distribution characteristics of TEL in lung. In the present study, the distribution characteristics of TEL from blood to lung and the uptake characteristics of TEL by alveolar macrophages (AMs) were examined. In vivo pharmacokinetic experiment, TEL was orally administered to rats. The concentrations of TEL in epithelial lining fluid (ELF) and AMs were significantly higher than that in plasma at 0.25-8 h after administration, and the AUC_{0-8 h} ratio of ELF to plasma was 2.2 and AMs to plasma was 60.1. In vitro transport experiment, TEL was added to Calu-3 cells monolayers as cultured lung epithelial cells and then incubated at 37 °C for 0.5-2 h. The apparent permeability coefficient (P_{app}) of TEL from basolateral to apical side was approximately 4.3 folds larger than that from apical to basolateral side. The P_{app} from basolateral to apical side was significantly decreased by coexistence of rhodamine123 and verapamil as P-gp substrate. These results suggest that the distribution of TEL from blood to ELF is influenced by lung epithelial cellular P-gp. In vitro uptake experiment, TEL was added to NR8383 cells as cultured AMs and then incubated at 37 °C for 2 h. The ratio of concentration of TEL in NR8383 cells for concentration in culture medium (I/E ratio) was 39.7. The I/E ratio was significantly decreased by coexistence of rotenone and FCCP as ATP depletors, clarithromycin and mannose. These findings suggest that TEL is taken up by AMs via mechanism same as macrolides or mannose receptor mediated endocytosis. The present study indicates that the high distribution of TEL to AMs is due to the high distribution characteristics from blood to ELF as well as the high uptake by the AMs themselves.

BIODISPOSITION OF HIGHLY-BRANCHED CYCLIC DEXTRIN AS BIODEGRADABLE DRUG CARRIERS

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Highly-branched cyclic dextrin (Cluster Dextrin®; CDin) produced from starch, is a glucose polymer which has a cyclic structure in the molecule. Despite its large molecular weight (462 kDa), CDin is highly water-soluble and easily digested with enzymes such as α-amylase. FITC-labeled CDin (FCDin) was successfully synthesized by the modified method of de Belder and Granath. A systemic kinetic analysis of FCDin in rats was carried out by using both a spectrofluorometer and a specific high-performance size-exclusion chromatography (HPSEC). Intravenously administered FCDin was rapidly eliminated from the blood circulation followed by an appreciable excretion into the urine. HPSEC analysis showed that FCDin was quickly degraded into small molecules (~ 6 kDa) in the plasma. Sugar hydroxyl groups were partially activated by periodate oxidation in order to acquire the aldehyde groups to which guest molecules can be bound. The rate of enzymatic degradation of FCDin was controlled by the degree of oxidation. It was found that high NaIO₄-treatment extended the blood persistence of FCDin injected intravenously. The prolongation of the circulation time resulted in the high liver uptake followed by a marked fecal excretion. Fluorescence microscopic examination of paraffin section of the liver revealed that NaIO₄-oxidized FCDin was accumulated mainly in the sinusoidal endothelial cells. It was suggested that CDin is a liver-specific drug carrier whose biodegradability is controllable with attaching a guest molecule by the NaIO₄-oxidation method.