DISPOSITION CHARACTERISTICS OF MACROLIDE ANTIMICROBIAL AGENTS IN LUNG SURFACE AND ALVEOLAR MACROPHAGES
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Macrolide antimicrobial agents have 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 macrolide antibiotics in lung. In the present study, the distribution characteristics of clarithromycin (CAM; as a macrolide) and telithromycin (TEL; as a ketolide) from blood to lung and the uptake characteristics by alveolar macrophages (AMs) were examined. In vivo pharmacokinetic experiment, CAM and TEL were orally administered to rats. The concentrations of antibiotics in epithelial lining fluid (ELF) and AMs were significantly higher than that in plasma at 0.25-24 h after administration, and the AUCo-24 h ratio of ELF to plasma were more than 3 and AMs to plasma were more than 80. In vitro transport experiment, CAM and 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 (Papp) of CAM and TEL from basolateral to apical side was approximately 4 folds larger than that from apical to basolateral side. The Papp from basolateral to apical side was significantly decreased by coexistence of rhodamine123 and verapamil as MDR1 substance. These results suggest that the distribution of CAM and TEL from blood to ELF is influenced by lung epithelial cellular MDR1. In vitro uptake experiment, CAM and TEL were added to NR8383 cells as cultured AMs and then incubated at 37 °C for 2 h. The ratio of concentration of CAM and TEL in NR8383 cells for concentration in culture medium (I/E ratio) were more than 30. The I/E ratio was significantly decreased by coexistence of rotenone and FCCP as ATP depleters. These findings suggest that TEL is taken up by AMs via mechanism active transport system(s).

APPLICATION OF QUANTITATIVE WHOLE BODY AUTORADIOGRAPHY (QWBA) FOR THE DETECTION OF AN IRON-59 LABELLED PRODUCT IN THE RAT
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Quantitative Whole Body Autoradiography (QWBA) has emerged as the preferred technique for the determination of the tissue distribution of radionlabelled drug products as this technique offers many advantages compared to a tissue dissection and scintillation counting approach. We have been able to successfully use QWBA to describe the tissue distribution of an agent labelled with an unconventional isotope, iron-59 (Fe-59). The agent under investigation contained iron in its chemical structure and it was considered necessary to investigate the fate of iron in case of loss from the structure. Fe-59, a high energy beta and gamma emitter with a short half life, was chosen as the radioisotope to tag the molecule. High energy gamma isotopes are generally utilized in other imaging techniques, such as gamma radiation scanning, but are not generally associated with autoradiography as detection may be hampered by the high energy of emission. Additionally, the handling of such high energy emitters requires specific risk assessment and safety procedures to avoid staff exposure to radioactivity not usually present in our laboratories. The distribution of radioactivity in rats dosed intravenously with the Fe-59 labeled agent was determined and compared with the results using a C-14 labelled version of the agent. Distribution of Fe-59 related material mirrored the distribution of the C-14 labelled material, suggesting that the metal ion did not dissociate from the agent during the observation period. In conclusion, to the best of our knowledge this represents the first application of QWBA in the determination of the tissue distribution of a Fe-59 labelled agent. Radioactivity detection and resolution were optimal, confirming the suitability of QWBA for use with a non conventional isotope.