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Bioavailability and biodistribution of acyclovir, and its produgs 12hydroxystearicacid-acyclovir and biotin-12hydroxystearicacid-acyclovir were studied in mouse model by using LC-MS/MS technique

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Acyclovir (ACV) is one of the most widely used antiviral agent for the treatment various virus infections including herpes simplex virus. ACV prodrugs, 12hydroxystearicacid-acyclovir (12HSACV) and biotin-12hydroxystearicacid-acyclovir (B12HSACV) have shown high antiviral activity against HSV1 and HSV2. Therefore, we hypothesize that these prodrugs may increase systemic bioavailability including brain. To test the hypothesis, we used mouse model and developed bioanalytical LC-MS/MS method by using mouse plasma for determination of ACV, 12HSACV and B12HSACV. The multiple reaction monitoring (MRM) transitions for ACV, 12HSACV and B12HSACV were optimized with proton adducts [M+H]+ at m/z 226.2/152.3, 508.2/490.7, and 735.7/257.3, respectively. These analytes were extracted from mouse plasma with acidified dichloromethane-isopropanol (60:40). Lower limit of quantitation was optimized at 3.0 ng/mL. The method was linear over the range of 3-1000 ng/mL (r2=0.9843-0.9928, accuracy≤9.8%, %CV≤18). We found ~3.5 ng/mL of ACV and 14ng/mL of 12HSACV in mouse plasma after oral administration of B12HSACV. We observed three-fold higher bioavailability of ACV and intact intermediate (12HSACV) in the plasma when we administered B12HSACV orally. We also observed 40 fold higher bioavailability of ACV when we give it intra peritoneal. These results indicating that B12HSACV is completely hydrolyzed into 12HSACV and ACV by breaking its terminal ester linkage between B12HSACV and 12HSACV first, and subsequently into ACV. Therefore, we conclude that the intermediate of B12HSACV in plasma can transit into the brain then hydrolyzed into ACV. These ACV biotin lipid prodrugs would be an excellent therapeutic agents for the treatment of viral infections.

Biography

Ravinder Earla Ph.D., Research Associate, University of Missouri-Kansas City. Ravinder Earla has published more than 17 original research articles in reputed journals. He is involved on ocular drug delivery, drug metabolism, prodrug synthesis. He is experienced on LC-MS/MS bioanalytical research of drugs and metabolites in various biological matrices. Currently, he is working on nicotine metabolism in HIV-1-positive and HIV-negative smokers' plasma using ESI-LC-MS/MS assay with SPE technique as well as methamphetamine metabolism in monkey plasma. Further, he has more than 6 years of industrial experience where he worked for bioavailability and bioequivalence (BA/BE) regulatory submission projects.

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