Enhanced Oral Bioavailability of Acyclovir by Its 12hydroxystearicacid-Acyclovir and Biotin-12hydroxystearicacid-Acyclovir Conjugates in Mouse Model: Analysis by LC-MS/MS

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Purpose
Acyclovir prodrugs, such as 12hydroxystearicacid-acyclovir (12HSACV) and biotin-12hydroxystearicacid-acyclovir (B12HSACV) can increase oral bioavailability of acyclovir.

Methods
To test the hypothesis, we used mouse model and developed bioanalytical LC-MS/MS method employing 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 using acidified dichloromethane-isopropanol (60:40). The sensitivity of LC-MS/MS method was optimized at 3.0 ng/mL as a lower limit of quantitation.

Results
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. But, we do not found any intact B12HSACV. A ~3-fold higher oral bioavailability of ACV was observed in the plasma indicating that this B12HSACV has completely hydrolyzed into 12HSACV and ACV. Intra peritoneal administration this drug produce 40 times higher bioavailability of ACV.

Conclusion
There, we conclude that the terminal ester linkage between biotin and 12HSACV has completely hydrolyzed first by esterase, and subsequently into ACV in the blood. These ACV biotin lipid prodrugs would be a good therapeutic agents for the treatment of viral infection.