COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Pharmaceutical Sciences Seminar

Wednesday, December 9, 2020
Join Zoom Meeting
https://umich-health.zoom.us/j/98309148599
4:00-5:00 pm

"Effect of CES1 genetic variation on enalapril pharmacokinetics in healthy subjects"

Presented by:

Lucy Her
Ph.D. Candidate
Department of Pharmaceutical Sciences

Background and Objective: Enalapril is an angiotensin-converting enzyme inhibitor prodrug and needs to be activated by carboxylesterase 1 (CES1) to exert its intended therapeutic effect. A previous in vitro study demonstrated that the CES1 loss-of-function genetic variant, G143E (rs71647871), significantly lowered the enalapril activation. A prospective open-labeled pharmacogenetics-pharmacokinetics-pharmacodynamics (PGx/PK/PD) study with healthy volunteers (n=21) was conducted to determine the clinical impact of the CES1 G143E variant on enalapril activation in human.

Methods: Volunteers were stratified to CES1 normal metabolizer group (G143E non-carriers, n = 15) and slow metabolizer group (G143E heterozygotes, n = 6) based on their CES1 G143E genotypes. Study subjects received enalapril 10 mg daily for seven consecutive days prior to a 72 h PK/PD study. Plasma concentrations of enalapril and its active metabolite enalaprilat were quantified by an established LC-MS/MS method.

Results: CES1 slow metabolizers had 27.5% lower C_{max} (P = 0.03) and 30.9% lower $AUC_{0-\infty h}$ (P = 0.02) of enalaprilat compared to CES1 normal metabolizers. CES1 slow metabolizers also had 32.0% lower enalaprilat-to-enalapril $AUC_{0-\infty h}$ ratio (P = 0.003). The average maximum reduction of systolic blood pressure in CES1 normal metabolizers was approximately 12.4% lower at the end of the study compared to the baseline (P = 0.001). There was no statistically significant blood pressure reduction observed in the slow metabolizers (P > 0.05)
Conclusions: The CES1 loss-of-function G143E variant markedly impaired enalapril activation in human.

Seminar Privacy Policy: Seminars will not be recorded.

We ask that you not record the seminars on your personal device, out of respect for privacy. Similarly, we encourage people not take screen shots. However, should you choose to do so, you should get permission from the speaker before using any of their content in a public setting (e.g., lab meeting, classroom). If your shots include pictures of other people, you should also obtain permission from each person before showing these images or posting them in any public forum.

For more information on the weekly PharmSci department
Seminar series, please view our website:
https://pharmacy.umich.edu/pharmsci/seminars