**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-∞h} (P = 0.02) of enalaprilat compared to CES1 normal metabolizers. CES1 slow metabolizers also had 32.0% lower enalaprilat-to-enalapril AUC_{0-∞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.

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