Effect of SHR0302 on the Pharmacokinetics of CYP3A4, CYP2C8, CYP2C9, and CYP2C19 Probe Substrates in Healthy Volunteers: A Cocktail Analysis

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March 24, 2023

Abstract

Aim: This study evaluated the effects of SHR0302 on the pharmacokinetics of cytochrome P450 (CYP) probe substrates. Methods: We performed a single-center, open-label, three-period drug-drug interaction (DDI) study in 24 healthy subjects (NCT05392127). Subjects received a single oral dose of 5 mg warfarin (CYP2C9), 20 mg omeprazole (CYP2C19), and 15 mg midazolam (CYP3A4) on day 1, 8, and 22, and received 0.5 mg repaglinide (CYP2C8) on day 7, 14, and 28. Multiple oral doses of 8 mg SHR0302 were administered once daily from day 8 to day 28. Results: The exposure of S-warfarin and repaglinide were comparable before and after SHR0302 administration. AUC of midazolam was not affected by SHR0302, whereas the administration of SHR0302 slightly decreased the Cmax of midazolam by 7.6% (single dose) and 15.7% (once daily for 14 days). The AUC0-t, AUC0-inf, and Cmax of omeprazole were slightly decreased after a single dose of SHR0302 by 19.2%, 21.8%, and 23.5%, respectively. In the presence of SHR0302 for 14 days, the AUC0-t, AUC0-inf, and Cmax of omeprazole were marginally reduced by 3.0%, 16.4%, and 8.3%, respectively. According to the induction mechanism of the CYP enzyme, for the investigation of the induction effect, the results of multiple administration of the perpetrator were more reliable than those of the single dose. Conclusion: The results demonstrated that co-administration of SHR0302 is unlikely to have a clinically meaningful effect on the exposure of drugs metabolized by CYP3A4, CYP2C8, CYP2C9, and CYP2C19 in healthy subjects.

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