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Rivaroxaban Showed Strong Inhibition on the Activity of HuMan Carboxylesterase (CES)1

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***SUMMARY*. Rivaroxaban, sold under the brand name Xarelto, has been clinically used as an anticoagulant medication. This study aims to investigate the inhibition of rivaroxaban on the activity of important phase I drug-metabolizing enzyme (DME) carboxylesterase 1 (CES1). Human liver microsomes (HLMs)-catalyzed hydrolysis of the probe substrate 2-(2-Benzoyl-3-methoxyphenyl) benzothiazole (BMBT) was utilized as the probe reaction of CES1, and 100 μM of rivaroxaban was added to determine the inhibition of rivaroxaban on the activity of CES1. 100 μM of rivaroxaban inhibited about 75% activity of CES1 ($p < 0.05$). Furthermore, concentration-dependent inhibition of rivaroxaban on the activity of CES1 was determined, and the results showed that 5, 10, 20, 40, 60, 80, and 100 μM inhibited 2.8, 14.7, 31.4, 37.5, 57.2, 67.6, and 72.4% activity of CES1, respectively. In conclusion, all these results indicate the potential drug-drug interaction (DDI) between rivaroxaban and drugs mainly undergoing CES1-catalyzed metabolic elimination.**

RESUMEN. Rivaroxaban, vendido bajo la marca Xarelto, se ha utilizado clínicamente como medicamento anticoagulante. Este estudio tiene como objetivo investigar la inhibición de rivaroxaban en la actividad de la importante enzima metabolizadora de drogas en fase I (DME) carboxilesterasa 1 (CES1). Se utilizaron microsomas hepáticos humanos (HLM) para medir la hidrólisis catalizada de (2-benzoil-3-metoxifenil) benzotiazol (BMBT) como reacción sonda de CES1 y se añadieron 100 μM de rivaroxaban para determinar la inhibición de rivaroxaban en la actividad de CES1; 100 μM de rivaroxaban inhibieron aproximadamente el 75% de la actividad de CES1 ($p < 0,05$). Además, se determinó la inhibición dependiente de la concentración de rivaroxaban sobre la actividad de CES1, y los resultados mostraron que 5, 10, 20, 40, 60, 80 y 100 μM inhibieron el 2,8, 14,7, 31,4, 37,5, 57,2, 67.6 y 72.4% de la actividad de CES1, respectivamente. En conclusión, todos estos resultados indican la posible interacción fármaco-fármaco (DDI) entre rivaroxaban y fármacos que se someten principalmente a la eliminación metabólica catalizada por CES1.

KEY WORDS: carboxylesterases (CES), drug-drug interaction, drug-metabolizing enzymes (DMEs), rivaroxaban.

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