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# Potential Clinical Adverse Effects of Levosimendan from the Perspective of UDP-Glucuronosyltransferases (UGTs) Inhibition

Jian-Qing ZHANG *, Xian-Jie CHEN, Guo-Feng WANG

*Department of Cardiac Surgery, Zhengzhou Cardiovascular Hospital, Zhengzhou, 450000, Henan, China*

***SUMMARY*. The adverse effects of levosimendan have been frequently reported during the clinical application for treatment of acutely decompensated congestive heart failure. This study aims to investigate the inhibition of levosimendan on the activity of UDP-glucuronosyltransferases (UGTs) which are important phase II drug-metabolizing enzymes (DMEs). UGT1A1, -1A3, -1A6, and -1A9 were selected as the representative UGT isoforms, and recombinant UGT isoforms-catalyzed glucuronidation of 4-methylumbelliferone (4-MU) was chosen as the probe reaction. Levosimendan 100 $\mu$M was used as the screening concentration to determine the inhibition towards four representative UGT isoforms, including UGT1A1, -1A3, -1A6, and -1A9. Levosimendan 100 $\mu$M inhibited 55% activity of UGT1A1 ($p < 0.001$). Fifty % activity of UGT1A3 was inhibited by 100 $\mu$M of levosimendan ($p < 0.001$). Levosimendan 100 $\mu$M did not exert significant inhibition towards UGT1A6. Approximately 60% activity of UGT1A9 was inhibited by 100 $\mu$M of levosimendan ($p < 0.05$).**

*RESUMEN*. Con frecuencia se han informado los efectos adversos de levosimendan durante la aplicación clínica para el tratamiento de la insuficiencia cardíaca congestiva aguda descompensada. Este estudio tiene como objetivo investigar la inhibición de levosimendan sobre la actividad de las UDP-glucuronosiltransferasas (UGT), que son importantes enzimas metabolizadoras de fármacos de fase II (DMEs). se seleccionaron las isoformas UGT1A1, -1A3, -1A6 y -1A9 como UGT representativas, y se eligió la glucuronidación catalizada por la isoforma UGT recombinante de 4-metilumbeliferona (4-MU) como reacción sonda. Levosimendan 100 $\mu$M se utilizó como la concentración de cribado para determinar la inhibición hacia cuatro isoformas de UGT representativas, que incluyen UGT1A1, -1A3, -1A6 y -1A9. Levosimendan 100 $\mu$M inhibió el 55% de la actividad de UGT1A1 ($p < 0,001$). El 50% de actividad de UGT1A3 fue inhibido por 100 $\mu$M de levosimendan ($p < 0.001$). Levosimendan 100 $\mu$M no ejerció una inhibición significativa hacia UGT1A6. Aproximadamente el 60% de la actividad de UGT1A9 fue inhibida por 100 $\mu$M de levosimendan ($p < 0.05$).

*KEY WORDS:* enzyme inhibition, glucuronidation, heart failure, levosimendan (INN), UDP-glucuronosyltransferases (UGTs).

* Author to whom correspondence should be addressed. *E-mail:* much3577@yeah.net



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