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Drug-Drug Interaction Between Uricosuric Agent Benzbromarone and Irinotecan

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***SUMMARY*. Gout is a disease in which defective metabolism of uric acid induces arthritis, and benzbromarone is a uricosuric drug clinically used to treat gout. The present study aims to determine the inhibition of benzbromarone on the activity of SN-38 glucuronidation, trying to indicate the potential drug-drug interaction between irinotecan and benzbromarone. Benzbromarone 100 μM can completely inhibit human liver microsomes (HLMs)-catalyzed glucuronidation of SN-38. Recombinant UGT1A1-catalyzed glucuronidation of 4-MU was used as the probe reaction, and the results showed that 100 μM of benzbromarone completely inhibited the glucuronidation metabolism of 4-MU. Concentration-dependent inhibition of benzbromarone on the glucuronidation metabolism of 4-MU was demonstrated. The intersection point was located in the vertical axis of Lineweaver-Burk plot, showing the competitive inhibition of benzbromarone on UGT1A1. The slopes of lines in the Lineweaver-Burk plot were calculated, and drawn versus the concentrations of benzbromarone. The fitting equation was *y = 35.9x + 85.4,* and the inhibition kinetic constant (Ki) was calculated to be 2.4 μM. In conclusion, clinical irinotecan-benzbromarone interaction should be given much attention.**

RESUMEN. La gota es una enfermedad en la que el metabolismo defectuoso del ácido úrico induce artritis y la benzbromarona es un fármaco uricosúrico clínicamente utilizado para tratar la gota. El presente estudio tiene como objetivo determinar la inhibición de la benzbromarona sobre la actividad de glucuronidación de SN-38, tratando de indicar la posible interacción fármaco-fármaco entre irinotecán y benzbromarona. Benzbromarona 100 μM puede inhibir completamente la glucuronidación catalizada de SN-38 en microsomas hepáticos humanos (HLMs). Se utilizó la glucuronidación catalizada por UGT1A1 recombinante de 4-MU como sonda y los resultados mostraron que 100 μM de benzbromarona inhibían completamente el metabolismo de glucuronidación de 4-MU. Se demostró la inhibición dependiente de la concentración de benzbromarona sobre el metabolismo de glucuronidación de 4-MU. El punto de intersección se localizó en el eje vertical del gráfico de Lineweaver-Burk, demostrando la inhibición competitiva de benzbromarona sobre UGT1A1. Se calcularon las pendientes de las líneas en el gráfico de Lineweaver-Burk y se dibujaron en función de las concentraciones de benzbromarona. La ecuación de ajuste fue *y = 35,9x + 85,4* y la constante cinética de inhibición (Ki) se calculó que era 2,4 μM. En conclusión, debe prestarse mucha atención a la interacción clínica irinotecan-benzbromarona.

KEY WORDS: benzbromarone, colon cancer, drug-drug interaction, irinotecan, UDP-glucuronosyltransferases (UGTs), uric acid.

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