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Potential Drug-drug Interaction between Dabrafenib and Insulin Secretagogue Repaglinide

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***SUMMARY*. Type 2 diabetes mellitus (T2DM) can increase the risk of cancer. Therefore, high possibility existed for the co-administration with anti-diabetic drugs and anti-cancer drugs. In this study, drug-drug interaction (DDI) was evaluated between anti-diabetic drug repaglinide and anti-cancer drug dabrafenib. *In vitro* incubation system was used to evaluate the inhibition potential of dabrafenib on the activity of UGT1A1 which was the major drug-metabolizing enzyme (DME) involved in the metabolism of repaglinide. Dabrafenib 100 μM significantly inhibited the activity of UGT1A1 ($p < 0.001$), with 95.5% activity inhibited. Furthermore, inhibition of the activity of UGT1A1 depends on dabrafenib concentration, as the activity was inhibited for 5.1, 13.6, 46.9, 65.4, 79.6, 87.7, 92.8, 95.0, and 94.1% by 0.5, 1, 5, 10, 20, 40, 60, 80, and 100 μM of dabrafenib. In summary, dabrafenib showed strong inhibition towards the activity of UGT1A1 which is the major drug-metabolizing enzyme involved in the metabolism of insulin secretagogue repaglinide. Therefore, clinical drug-drug interaction between dabrafenib and repaglinide should be given much attention.**

RESUMEN. La diabetes mellitus tipo 2 (DM2) puede aumentar el riesgo de cáncer. Por lo tanto, existe alta posibilidad de co-administración con fármacos antidiabéticos y fármacos contra el cáncer. En este estudio se evaluó la interacción fármaco-fármaco (DDI) entre el fármaco antidiabético repaglinida y el fármaco anticanceroso dabrafenib. Se utilizó el sistema de incubación *in vitro* para evaluar el potencial de inhibición del dabrafenib sobre la actividad de la UGT1A1, la principal enzima metabolizadora de fármacos (DME) implicada en el metabolismo de la repaglinida. Dabrafenib 100 μM inhibió significativamente la actividad de UGT1A1 ($p < 0,001$), con un 95,5% de actividad inhibida. Además, la inhibición sobre la actividad de UGT1A1 depende de la concentración de dabrafenib, con la actividad inhibida en 5.1, 13.6, 46.9, 65.4, 79.6, 87.7, 92.8, 95.0 y 94.1% por 0,5, 1, 5, 10, 20, 40 , 60, 80 y 100 μM de dabrafenib. En resumen, dabrafenib mostró una fuerte inhibición hacia la actividad de UGT1A1, que es la principal enzima metabolizadora de fármacos implicada en el metabolismo del secretagogo de insulina repaglinida. Por lo tanto, se debe prestar mucha atención a la interacción farmacológica entre dabrafenib y repaglinida.

KEY WORDS: cancer, dabrafenib, drug-drug interaction, glucuronidation, repaglinide, type 2 diabetes mellitus (T2DM), UDP-glucuronosyltransferase (UGT) 1A1.

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