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In Vitro Evidence for the Inhibition of Diphenidol on Carboxylesterases

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***SUMMARY*. Diphenidol is an important drug clinically used to treat ENT (ear, nose, throat) diseases. So far, no adverse effects have been reported. The present study aims to investigate the adverse effects of diphenidol through determining the inhibition of diphenidol on the activity of carboxylesterases (CES), including CES1 and CES2. *In vitro* human liver microsomes (HLMs)-catalyzed hydrolysis of 2-(2-benzoyl-3-methoxyphenyl) benzothiazole (BMBT) was used to determine the inhibition of diphenidol on the activity of CES1. *In vitro* HLMs-catalyzed hydrolysis of fluorescein diacetate (FD) was used to determine the inhibition of diphenidol on CES2. Diphenidol 100 μM was used as the initial screening concentration. Diphenidol 100 μM did not show inhibitory on the activity of CES1. In the contrast, 100 μM of diphenidol inhibited 75% activity of CES2 ($p < 0.001$). In conclusion, high attention should be given for drug-drug interaction between diphenidol and drugs mainly undergoing CES-catalyzed hydrolysis metabolism.**

RESUMEN. El diphenidol es un fármaco importante utilizado clínicamente para tratar enfermedades otorrinolaringológicas (oído, nariz y garganta) y hasta ahora, no se han reportado efectos adversos. El presente estudio tiene como objetivo investigar los efectos adversos del difenidol a través de la determinación de la inhibición del difenidol sobre la actividad de las carboxilesterasas (CES), incluyendo CES1 y CES2. Para determinar la inhibición del difenidol sobre la actividad de CES1 se utilizó la hidrólisis *in vitro* catalizada por microsomas de hígado humano (HLMs) de 2-(2-benzoil-3-metoxifenil) benzotiazol (BMBT). Se utilizó la hidrólisis catalizada por HLMs *in vitro* de diacetato de fluoresceína (FD) para determinar la inhibición del difenidol sobre CES2. Diphenidol 100 μM no mostró inhibición de la actividad de CES1. En contraste, 100 μM de difenidol inhibió el 75% de actividad de CES2 ($p < 0,001$). En conclusión, se debe prestar mucha atención a la interacción fármaco-fármaco entre el difenidol y los fármacos que sufren principalmente el metabolismo de la hidrólisis catalizada por el CES.

KEY WORDS: diphenidol, drug-metabolizing enzymes (DMEs), carboxylesterases, drug-drug interaction

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