Potential Drug Utilization Risk of 3-n-Butylphthalide (NBP) Due to the Inhibition on the Activity of Human Carboxylesterase (CES)

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SUMMARY. 3-n-butylphthalide (NBP) is a drug clinically utilized to treat acute ischemic stroke in China. The present study aims to evaluate the safety of NBP through determining the inhibition of NBP on the activity of one of important drug-metabolizing enzymes (DMEs) carboxylesterase (CES). Human carboxylesterase (CES) 1 was selected to be the evaluating CES isoform. In vitro human liver microsomes (HLMs)-catalyzed biotransformation of 2-(2-benzoyl-3-methoxyphenyl) benzothiazole (BMBT) to its metabolite 2-(2-hydroxy-3-methoxyphenyl) benzothiazole (HMBT) was used as the probe reaction to determine the inhibition of NBP on the activity of CES1. 100 μM of NBP exhibited significant inhibition on the activity of CES1 (p < 0.01). Furthermore, we tried to evaluate the concentration-dependent inhibition of NBP on the activity of CES1. To ensure the accuracy of experiments, three separate experiments were carried out, and the results showed that NBP indeed showed concentration-dependent inhibition on the activity of CES1 for three separate experiments. In the Lineweaver-Burk plot, we found the horizontal axis was the location of intersection point for Lineweaver-Burk plot. The slopes of the lines in the Lineweaver-Burk plot were calculated, and used to draw versus the concentration of NBP. The equation of fitting line was $y = 0.0048x + 0.1905$ ($r^2 = 0.99$). Using this equation, the inhibition kinetic parameter ($K_i$) was calculated to be 39.7 μM. This study demonstrated the necessary monitoring for drug-drug interaction (DDI) related with the clinical utilization of NBP.