Drug-drug interaction with OTC drugs

-The inhibitory effect of NSAIDs and cough suppressants on CYP activities

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<Background and Purpose> In general most of NSAIDs and cough suppressants are available as the over the counter drugs (OTC) without prescription. It has been believed that OTC drugs are relatively safe compared to prescription drugs, therefore, OTC drugs have been widely used for self-medication all over the world. However, the reports concerning to their drug-drug interactions are insufficient in fact, although the information especially for that mediated by cytochrome P450 (CYP) is essential for safe medication. In our previous study, the major OTC drugs such as antihistamines and expectorants showed potent inhibitory effects on CYP activities, suggesting the possibility of clinical drug interactions. To avoid the risks of adverse reaction caused by CYP inhibition, it is important to investigate these interactions. Thus, in the present study we evaluated the inhibitory effects of commonly used NSAIDs and cough suppressants on CYP activities in human liver microsomes.

<Methods> Four NSAIDs (acetylsalicylic acid, isopropylantipyrine, ibuprofen and 2-ethoxybenzamide), two cough suppressants (noscapine, and tipepidine hibenzate), two secretolytic and mucolytic agents (L-carbocisteine and potassium guaiacolsulfonate) and two bronchodilator (diprophylline and methoxyphenamine hydrochloride) were estimated for their inhibitory effects on CYP activities. Pooled human liver microsomes was used as the CYP enzyme source and ethoxyresorfin O-deethlation (CYP1A2), S-warfarin 7-hydroxylation (CYP2C9), S-mephenytoin 4-hydroxylation (CYP2C19), bufuralol 1'-hydroxylation (CYP2D6) and midazolam 1'-hydroxylation (CYP3A) were assayed as the indicator of each CYP activity. The Ki values and inhibition manner of these drugs on CYP activities were evaluated by nonlinear regression analysis.

<Results> Noscapine showed competitive inhibitory effect on CYP2C9 and CYP2C19 activities with Ki values of 13.9 and 2.72µM, respectively. The result against CYP2C9 was consisted with the report that noscapine inhibited warfarin metabolism by the inhibition of CYP2C9. In addition, our result newly showed its potent inhibitory effect on CYP2C19. On the other hand, tipepidine hibenzate inhibited CYP2D6 activity by competitive manner. Its Ki value of 490 nM was close to the reported Cmax values in clinical use. NSAIDs and other cough suppressants employed in this study did not show any remarkable effects on CYP activities.

<Discussion & Conclusion> The results showed that noscapine and tipepidine hibenzate, which are widely used OTC drugs to suppress a cough showed the potent inhibitory effects on CYP2C9/2C19 and CYP2D6, respectively in human liver microsomes. In considering of their Ki values, the drug-drug interactions were predicted during the treatment of these OTC drugs with other drugs that are metabolized by these CYP isoforms. The investigation and the accumulation of these data were clinically important to avoid the risk of adverse reaction by drug-drug interactions. Furthermore, the appropriate human studies are needed to clarify if the clinically important interactions are occurred through these CYP inhibitions.