31C11-1

PREDICTION OF DRUG-DRUG INTERACTION CAUSED BY INTESTINAL CYP3A4 AND P-GP
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CYP3A4 and P-glycoprotein (P-gp) are present in the human intestine and mediate intestinal first-pass metabolism and
efflux transport of oral drugs. We presented the novel method for predicting intestinal drug-drug interactions (DDIs)
mediated by CYP3A4 at the 1st APISSX Meeting and, for DDIs mediated by P-gp, at the 8th International ISSX
Meeting. To predict the risk of drug-drug interactions (DDIs) mediated by intestinal CYP3A4 and/or P-gp, we
calculated the ratio of inhibitor dose (Dose,i) to the inhibition constant (Ki), termed the drug interaction number (DIN).
CYP3A4 specific substrates which exhibit low bioavailability were selected and the clinical DDI data of these
substrates were analyzed. From the analysis, we concluded that CYP3A4 inhibitors with a DIN below 2.8 L have a low
risk of interacting with substrates which exhibit intestinal first-pass metabolism and those with a DIN above 9.4 L have
a high risk. Similarly, from the analysis of clinical DDI studies of P-gp specific substrates, we concluded that P-gp
inhibitors with a DIN below 10.8 L have a low risk of interacting with P-gp substrates and those with a DIN above 27.9
L have a high risk. Clinical DDI data for CYP3A4 and P-gp dual substrates were also collected. The rules derived from
the analyses of CYP3A4 specific and P-gp specific substrates were found to apply to dual substrates as well. In
summary, DIN is useful for classifying the risk of DDI for inhibitors mediated by intestinal CYP3A4 and P-gp.

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ANTIBODY-FREE QUANTIFICATION METHOD FOR AMYLOID β-PEPTIDES BY UPLC-MS/MS
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Abnormalities of amyloid β-peptide (Aβ) kinetics are proposed to closely relate to pathogenesis of Alzheimer’s
disease (AD). Quantification of various species of Aβ is essential for elucidation of AD pathology, and development of
therapeutic drugs and diagnosis for AD. Enzyme-linked immunosorbent assay (ELISA) is widely used so far, however
ELISA is disturbed by cross-reactivity of Aβ antibody and/or Aβ binding protein. Because highly selective and sensitive
MRM analysis using LC-MS/MS is used for small compounds, the purpose of this study was to develop antibody-free
quantification method of Aβ by MRM analysis using UPLC-MS/MS. hAβ(1-40) and hAβ(1-42) mixed with
\[^{15}N\]hAβ(1-40) and \[^{15}N\]hAβ(1-42) as internal standard were measured simultaneously by UPLC-MS/MS. Each
calibration curve demonstrated linearity in the range of 5-1000 fmol for either hAβ(1-40) or hAβ(1-42). Our developed
method show greater sensitivity by 2-5 fold than the reported method using immunoaffinity purification and
LC-MS/MS. hAβ(1-40) in mouse brain were recovered by guanidine hydrochloride homogenization and solid-phase
extraction, and the recovery rates determined by \[^{15}N\]hAβ(1-40) were 68-99%. hAβ(1-40) (1.5 pmol) microinjected
into the mouse brain was detected by the optimal sample preparation and developed UPLC-MS/MS method. These
results indicate that our established method has enough selectivity and sensitivity to detect hAβ in vivo without using
antibody, and can be applied to various Aβ species without preparing antibody specific for each species. Furthermore,
the developed quantitative strategy using UPLC-MS/MS with MRM mode can be used for not only investigation of Aβ
kinetics but also searching for biomarkers for AD diagnosis.