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SEMI-AUTOMATED IN VITRO DRUG-DRUG INTERACTION ASSAYS UNDER A QUALITY CONTROLLED CONDITION

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We established semi-automated in vitro drug-drug interaction assays for new drug applications (NDAs) in human liver microsomes on the activities of nine isoforms of cytochrome P450 (CYP), using the selective markers which are recommended in the draft guidance for drug interaction studies provided by FDA in 2006. All metabolic reactions were executed by an automation system, Freedom EVO (Tecan, Switzerland), whose pipetting performance was optimally-adjusted. The metabolic reaction using an automation system could execute accurately as same as manual reaction, because it was possible to control the pipetting for 5 μL of methanol in the precision of 5% or less. Furthermore, determination of the metabolites after reactions were performed by liquid chromatography with electrospray ionization tandem mass spectrometry (LC/MS/MS) methods, which were validated with Good Laboratory Practice (GLP) Standard. As a result, we established the assay methods under the quality controlled condition. The assays contain the evaluation of reversible and irreversible inhibitory potentials, and we determine their inhibitory parameters, IC₅₀ and Kᵢ, or Kᵢ(upp) and kₙact, depending on their inhibitory mechanisms. In this presentation, we will show the results obtained from semi-automated assay compared with those from manual reaction by using erythromycin, known as a potent MBI inhibitor on CYP3A4, as an example of NDAs. And we will also show the assay data for other isoforms of CYP, which were executed by Freedom EVO system.

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EFFECT OF BYAKKOKANINJINTO ON THE PHARMACOKINETICS OF TETRACYCLINE AND CIPROFLOXACIN

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Kampo preparations are frequently prescribed with Western drugs for the treatment of chronic diseases. Therefore, it is important to clarify the drug interactions concerning Kampo preparations. Byakkokaninjinto (TJ-34), which is used for the treatment of heat stroke and febrile disease, contains large amount of Ca²⁺. On the other hand, tetracycline (TC) and ciprofloxacin (CPFX) forms insoluble complex by chelation with divalent and trivalent metal ions. In the present study, we investigated the effect of TJ-34 on the pharmacokinetics of TC and CPFX in human volunteers. Twenty healthy male volunteers received a single oral dose of 250 mg TC or 200 mg CPFX in the presence and absence of 3 g TJ-34. Blood and urine sample were collected over 24 h for the quantitation of TC and CPFX using HPLC and the pharmacokinetic parameters were estimated using non-compartmental analysis. For both TC and CPFX, Cmax and AUC were significantly reduced in the presence of TJ-34, whereas tmax and elimination from plasma did not change. In addition, renal clearance (CLR) was not affected by TJ-34 for both drugs, although significant reduction was observed in the fraction of urinary recovery as unchanged form (f₀) for TC. These results suggest that TJ-34 reduces the extent of absorption but has no effect on the elimination process of the two drugs. Reduction in absorption of the two drugs may be the result of chelation with Ca²⁺ included in TJ-34. We recommend that the dose timing of the Kampo preparation should be carefully controlled to avoid therapeutic failure for patients receiving the treatment especially with tetracycline.