Patients (or Materials) and Methods: Patients treated with DRV for HIV infection were enrolled in this study. Efficacy of drug therapy was evaluated by relative change of copy number of HIV in blood, and the blood samples were taken when the relative copy number of <200 copies/mL. The concentrations of DRV in plasma and PBMC were analyzed using HPLC-fluorescence detection method. Then, in vitro uptake study using human leukemia cell line, MOLT-4, was performed. The intracellular concentrations of DRV were measured after exposure to DRV (3.0 μg/mL in medium) or the combination of DRV and ritnavir (RTV) (3.0 and 1.0 μg/mL in medium, respectively) for 2 hours.
Results: The effective concentrations of DRV in plasma showed great variation of 0.88 to 5.57 μg/mL, while the concentrations in PBMC were maintained within a relatively-narrow range 12.9–28.7ng/10^6 cells. In in vitro study, RTV, a P-gp inhibitor, significantly increase the intracellular concentration of DRV (10.0 vs 15.9 ng/10^6 cells).
Conclusion: Our results suggested that the concentration of DRV in PBMC could be better indicator for clinical efficacy of DRV compared with that in plasma. In in vitro study, we found that RTV could promote the intracellular accumulation of DRV, and it was thought to be due to the P-gp inhibitory activity of RTV. Those results mean that coadministration of RTV have possibility to increase intracellular concentration of DRV and result to sufficient clinical efficacy of DRV regardless the concentration of DRV in plasma.
Disclosure of Interest: None declared.

PP200—METABOLIC PROCESS OF VORICONAZOLE TO ITS N-OXIDE IS SATURABLE IN CLINICAL DOSE RANGE

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Introduction: Triazole antifungal agent voriconazole (VRCZ) has a nonlinear pharmacokinetics. VRCZ is extensively metabolized hepatically to major inactive metabolites VRCZ N-oxide (VNO). Few clinical reports revealed the influence of VNO on the metabolic process of VRCZ. The present study aimed to evaluate metabolic process of VRCZ in patients taking plasma concentration of VNO.
Patients (or Materials) and Methods: Fifty-eight Japanese patients receiving oral or intravenous VRCZ for prophylaxis or fungal infections at Hamamatsu University Hospital were included in the study. Predose plasma concentrations of VRCZ and VNO were monitored at day 5 or later. The relationships between plasma exposure parameters of VRCZ and VNO were evaluated. CYP2C19 genetic polymorphism (G636A and G681A on exon 4 and exon 5) were determined using PCR-RFLP method for assessing the influence of major metabolic enzyme of VRCZ.
Results: A large interindividual variation was observed in the plasma concentrations of VRCZ and VNO. Dose-normalized VRCZ concentration had a strong correlation with VRCZ concentration and a straight line passing through nearby the origin of the coordinates was obtained. No significant correlation between the plasma concentrations of VRCZ and VNO was observed. Plasma concentration ratio of VRCZ to VNO (VRCZ/VNO) was strongly correlated with VRCZ concentration. No significant difference was observed in the plasma concentrations of VRCZ and VNO and VRCZ/VNO between the CYP2C19 genotypes.
Conclusion: Metabolic process of VRCZ to VNO is saturable in clinical dose range. Our findings indicated that nonlinear pharmacokinetics of VRCZ depends on its metabolic saturation
Disclosure of Interest: None declared.

PP201—AN OPEN-LABEL, RANDOMIZED, SINGLE-CENTRE, FOUR-WAY CROSSOVER STUDY TO EVALUATE THE PHARMACOKINETICS OF SINGLE, ORAL DOSES OF RETIGABINE/EZOGABINE IN HEALTHY ADULT TAIWANESE SUBJECTS

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Introduction: Retigabine (RTG)/ezogabine, *N*-[2-amino-4(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester, is a novel antiepileptic compound. In 2011, RTG was approved by the FDA and European Commission as adjunctive treatment for partial onset seizures in adults aged ≥18 years. The global pivotal studies did not include Asian countries. The purpose of this study was to characterize the pharmacokinetics (PK) of single 50, 100, 200, and 400-mg doses of RTG and *N*-acetyl metabolites of RTG (NAMR) in healthy Taiwanese subjects.
Patients (or Materials) and Methods: Sixteen subjects were randomized to the study (ANE116798, NCT01462669), which comprised a screening visit, 4 treatment periods, and a follow-up visit. The following PK parameters were determined for RTG and NAMR: Cmax, AUC0-inf, Tmax, and t½. Safety and tolerability were measured using adverse event (AE) reports, vital signs, electrocardiograms, clinical laboratory measurements and Columbia Suicide Severity Rating Scale. Dose proportionality of RTG was assessed by fitting AUC0–inf and Cmax to a power model. A point estimate and 90% CI for the slope of the regression line obtained by regressing log(PK parameter) on log(dose) was calculated. As a secondary analysis, an analysis of variance was performed using loge-transformed dose-normalized AUC0–inf and Cmax by including periods and treatments as fixed effects and subjects as a random effect. All doses were compared with the 50 mg reference dose.
Results: *Safety*: No subject was withdrawn from the study owing to AEs and no serious AEs were reported. AEs reported most frequently in this population were somnolence, dizziness, and nausea, and the incidence of AEs increased with RTG dose. *PK:* Cmax value increases were approximately dose proportional from 50 to 100 mg, but less than dose proportional at 200 and 400 mg. AUC0–inf appeared to increase more than dose proportionally between 50 mg and the higher doses of 100, 200, and 400 mg. This was believed to be due to an underprediction of t½ at the 50-mg dose. AUC0–8, which represents the dosing interval of RTG with a 3-times-daily dosing regimen, was added as a post hoc PK parameter, since this truncated AUC is not confounded by determination of t½. AUC0–8 increased proportionally across the range of 50 to 400 mg.
Conclusion: Single oral doses of RTG (50–400 mg) were generally well tolerated in Taiwanese subjects. The PK parameters for RTG and NAMR in the current study in Taiwanese subjects are consistent with single-dose PK parameters obtained at these doses in healthy Western subjects.
Disclosure of Interest: M. Buraglio: Shareholder of share option, full-time employee.

PP202—CANCER CACHEXIA RAISES THE PLASMA CONCENTRATION OF OXYMORPHONE THROUGH THE REDUCTION OF CYP3A BUT NOT CYP2D6 IN OXYCODONE-TREATED PATIENTS

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Introduction: Cachexia decreases CYP3A metabolism of oxycodone, while its influence on CYP2D6 metabolism remains to be clarified in