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 rifamycin (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 12.9–28.7 ng/10⁶ cells. In in vitro study, RTV, a P-gp inhibitor, significantly increase the intracellular concentration of DRV (10.0 vs 1.5.9 ng/10⁶ 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.
cancer patients. The aim of this study was evaluate the plasma concentrations of oxycodone and its demethylates and opioid-induced adverse effects based on cachexia stage in cancer patients receiving oxycodone.

**Patients (or Materials) and Methods:** Seventy patients receiving oxycodone for cancer pain at Hamamatsu University Hospital were enrolled. Cachexia was evaluated using the Glasgow Prognostic Score (GPS). Predose plasma concentrations of oxycodone, oxymorphone, and noroxycodone were determined at the titration dose. Opioid-induced adverse effects were monitored for 2 weeks after the titration.

**Results:** Fourteen patients had a GPS of 0, 27 a GPS of 1, and 29 a GPS of 2. Plasma concentrations of oxycodone and oxymorphone but not noroxycodone in patients with a GPS of 2 were significantly higher than that with a GPS of 0. The metabolic ratios of noroxycodone but not oxymorphone to oxycodone in patients with a GPS of 1 and 2 were significantly lower than in those with a GPS of 0. A higher GPS was associated with a higher incidence of somnolence, while the GPS did not affect the incidence of vomiting. Plasma concentrations of oxycodone and oxymorphone were not associated with the incidence of adverse effects.

**Conclusion:** Cancer cachexia raised the plasma exposures of oxycodone and oxymorphone through the reduction of CYP3A but not CYP2D6. Although the cachexia elevated the incidence of somnolence, alterations in their pharmacokinetics were not associated with the incidence.

**Disclosure of Interest:** None declared.

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**PP203—WHOLE BLOOD CANNABINOID PHARMACOKINETIC PARAMETERS IN HEAVY AND OCCASIONAL SMOKERS. DO ORAL FLUID CANNABINOID MEASUREMENTS CORRELATE WITH WHOLE BLOOD DATA IN HEAVY SMOKERS?**

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**Introduction:** Many issues remain to be solved in regard to cannabinoid disposition, elimination time profiles and correlation between oral fluid (OF) and whole blood (WB) concentrations. Delta-9-tetrahydrocannabinol (THC) in OF is usually indicative of a relatively recent cannabis exposure, but the study of other cannabinoids in OF and WB could also be helpful as a confirmatory test when applied for legal purposes.

**Patients (or Materials) and Methods:** A randomized, blinded, 2-way crossover study was conducted in 48 healthy volunteers (23 heavy and 25 occasional cannabis smokers) who received by smoking each period, in random sequence, a cannabis joint (containing bedrobinol, 11% THC, and traces of cannabidiol - CBD) or a placebo. WB was collected up to 2.5 hours after smoking. An additional WB sample at 3.5 hours, and OF samples were collected in heavy smokers. Storage at –20°C and liquid-liquid extraction preceded analysis by liquid chromatography-tandem mass spectrometry. THC, 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THCCOOH) were measured in WB, THC, THCCOOH, cannabionol (CBN), CBD and delta-9-tetrahydrocannabinolic acid A (THC-A) were investigated in OF. WB pharmacokinetic parameters of THC and its metabolites were compared in heavy and occasional smokers. Correlations for these parameters between OF and WB were studied in heavy smokers.

**Results:** Before smoking, a significant difference (P < 0.001) was found in WB THCCOOH between heavy and occasional smokers: median THCCOOH was 20.1 µg/L (range, 2.50–93.9) and 0.14 µg/L (range, 0–16.6) respectively. No significant difference was found in WB for THC maximal concentrations (Cmax): median Cmax was 86.5 µg/L (range, 37.1–192) and 75.1 µg/L (range, 8.20–168) respectively. Elimination half-lives (t1/2) in WB were also not significantly different: median THC T1/2 were 0.97 hours (range, 0.53–1.87) and 0.84 hour (range, 0.69–1.45) respectively; and median THCCOOH t1/2 were 3.89 hours (range, 1.68–9.16) and 3.33 hours (range, 1.59–17.3) respectively. Differences in the area under the curve (AUC) between both groups, were marginally significant for THC (P = 0.01) but highly significant (P < 0.001) for 11-OH-THC and THCCOOH. No correlation between WB and OF was found in heavy smokers for Cmax or AUC.

**Conclusion:** Our results suggest that the smoking regimen (heavy/occasional) do not influence the elimination kinetic of cannabinoids in WB but do influence the initial THCCOOH level. No correlation was found between WB and OF for THC or THCCOOH parameters.

**Disclosure of Interest:** None declared.

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**PP204—METHADONE KINETICS AND CORRECTED QT TIME DURING HAEMODIALYSIS IN FOUR METHADONE MAINTENANCE TREATMENT PATIENTS WITH END-STAGE RENAL FAILURE**

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**Introduction:** Methadone is known to be associated with prolongation of corrected QT time (QTc). Excretion of methadone is primarily renal in patients with normal renal function. It is unknown to what extent hemodialysis removes methadone. We investigated methadone kinetics and QTc during hemodialysis in methadone maintenance treatment (MMT) patients with end-stage renal disease.

**Patients (or Materials) and Methods:** The Regional Ethics Committee approved the study. Data are given as median (range). Four patients with end-stage renal failure, 1 female and 3 males, 46 (43–53) years, stabilized on methadone were included. Methadone was measured by UPLC-MMS in serum and hemodialysates collected before morning methadone intake, every 30 minutes during 4 hours hemodialysis and before afternoon dose, and in urine sampled at the end of hemodialysis. ECGs were recorded every 30 minutes during hemodialysis, and QT time was measured in lead v2 using tangential method and QTc was calculated with Bazett’s formula. ECGs were read serially for each patient with blinding of numbering. Several routine biochemical tests were performed before and after hemodialysis.

**Results:** The daily methadone dose was 100 (60–120) mg. Serum-methadone increased from Cmin of 1124 (547–1581) nmol/L to Cmax of 1806 (1237–2098) nmol/L after 85 (40–120) minutes. The apparent half-life of methadone was 12 (6.3–25) hours. A total of 2.30 (1.25–3.70) % and 0.14 (0.03–0.26) % of daily methadone intake was collected, respectively, in hemodialysate and urine during 4 hours. Renal clearance of methadone was 0.67 (0.31–1.20) mL/min, methadone clearance of hemodialysis was 17.10 (1.25–3.70) % and 0.14 (0.03–0.26) % of daily methadone intake. Methadone clearance of hemodialysis was 17.30 (1.25–3.70) % and 0.14 (0.03–0.26) % of daily methadone intake. Elimination half-lives (t1/2) in WB were also not significantly different: median THC T1/2 were 0.97 hours (range, 0.53–1.87) and 0.84 hour (range, 0.69–1.45) respectively; and median THCCOOH t1/2 were 3.89 hours (range, 1.68–9.16) and 3.33 hours (range, 1.59–17.3) respectively. Differences in the area under the curve (AUC) between both groups, were marginally significant for THC (P = 0.01) but highly significant (P < 0.001) for 11-OH-THC and THCCOOH. No correlation between WB and OF was found in heavy smokers for Cmax or AUC.

**Conclusion:** Our results suggest that the smoking regimen (heavy/occasional) do not influence the elimination kinetic of cannabinoids in WB but do influence the initial THCCOOH level. No correlation was found between WB and OF for THC or THCCOOH parameters.

**Disclosure of Interest:** None declared.