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POPULATION PHARMACOKINETIC MODELING OF THE INTERACTION BETWEEN THE P-GLYCOPROTEIN INHIBITOR PSC-833 AND MITOXANTRONE IN PEDIATRIC LEUKEMIA PATIENTS. *S. Kshirsagar, PhD, T. Blaschke, MD, D. Verotta, PhD, N. Lacayo, MD, G. Dahl, MD, B. Sikic, Stanford University, University of San Francisco, Palo Alto, CA.*

AIM: PSC 833 is a safer and more potent P-glycoprotein inhibitor than its parent drug, cyclosporine. It has significant pharmacokinetic (PK) interactions with common chemotherapeutic drugs. To examine and quantify this interaction, we modeled the change in clearance of the antileukemic drug mitoxantrone (MTX) upon the co-administration of PSC.

METHODS: PSC and MTX PK data on 14 patients were obtained from a Phase I clinical trial with pediatric patients having acute leukemia. On day 1, patients received MTX as an IV infusion of 10mg/m² over 15 min. From day 2 to 5, the dose was halved and PSC was given as a 2mg/kg loading dose over 2h along with a continuous infusion at varying dose levels (8, 10, 12.5 and 15 mg/kg/day) for 5 days. Both the PSC and MTX data were fit to 2-compartment models. The effect of PSC on MTX clearance was modeled as follows:

$$CL_{MTX} = CL_0 + (CL_1 - CL_0) * PSC / (PSC + EC_{50})$$

where CL₀ is the baseline clearance, CL₁ is the asymptotic value of CL (when PSC → ∞) for large concentrations of PSC.

RESULTS: The population parameter estimates (%CV) obtained using NONMEM were:

$$CL_{PSC} = 1.2 \text{ L/h (58\%)}, V_{1PSC} = 2.4 \text{ L}, V_{2PSC} = 41.5 \text{ L (473\%)}$$

$$CL_0 = 16.5 \text{ L/h (47\%)}, CL_1 = 6.12 \text{ L/h (64\%)}, EC_{50} = 0.5 \text{ mg/L},$$

$$V_{1MTX} = 23.2 \text{ L}, V_{2MTX} = 98.5 \text{ L}.$$

CONCLUSIONS: We successfully modeled PSC and MTX PK and their interaction in pediatric leukemia patients. Our model allows us to estimate CL_{MTX} at different PSC concentrations. PSC has a large effect on CL_{MTX} (73% reduction).

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PHARMACOKINETIC INTERACTION BETWEEN VORICONAZOLE AND METHADONE AT STEADY STATE IN METHADONE PATIENTS. *P. Liu, PhD, G. Foster, PhD, R. Labadie, MPH, E. Somoza, MD, PhD, A. Sharma, PhD, Pfizer Inc, Cincinnati Addiction Research Center, Groton, CT.*

AIM: Voriconazole (VORI), a triazole antifungal agent, is metabolized by the cytochrome P450 CYP2C19, CYP2C9 and to a lesser extent by CYP3A4. Methadone (METH), a μ-opioid receptor agonist, is primarily metabolized by the CYP3A4. This study was conducted to evaluate the pharmacokinetic (PK) interactions between these two compounds.

METHODS: A randomized, subject and investigator blinded, placebo controlled, parallel group multiple dose study was conducted in 23 male methadone patients. Subjects continued to receive individualized maintenance dose of METH alone (30–100 mg QD) for 2 days after entering the study. Therapeutic dose of VORI (400 mg BID on day 1 followed by 200 mg BID) or placebo were co-administered for the next 5 days. The steady state PK of VORI and METH following 5 days of co-administration (Day 7) were compared to those of METH alone (Day 2) and VORI alone in a reference study (conducted in 34 healthy subjects).

RESULTS: VORI increased the daily mean steady state area under the concentration-time curve (AUC_{0–24}) of pharmacologically active enantiomer R-METH by 47.20% (90% CI: 37.65–57.41%), and peak concentration (C_{max}) of R-METH by 30.69% (90% CI: 22.17–39.81%). The magnitude of increase in S-METH exposure was greater than that of R-METH (AUC_{0–24}: 103.36%; C_{max}: 65.39%). METH appeared to have no effect on the steady state VORI PK.

CONCLUSIONS: Caution should be exercised with METH due to the moderate increase in R-METH exposure by VORI.

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OPTIMIZING PLASMA SAMPLING OF ORAL (PO) MIDAZOLAM (MDZ) AS A BIOMARKER FOR CYP3A ACTIVITY. *L. S. Lee, PharmD, J. S. Bertino, Jr., PharmD, A. N. Nafziger, MD, MHS, Clinical Pharmacology Research Center, The Research Institute, and Department of Medicine, Bassett Healthcare, Cooperstown, NY.*

BACKGROUND: MDZ AUC is used to measure CYP3A activity and requires 5 to 8 blood samples. The aim of this study was to determine if minimized plasma sampling can be used to assess baseline CYP3A activity with PO MDZ.

METHODS: 45 healthy adults taking no drugs known to affect CYP3A were included (data from 4 previous studies). Subjects received PO MDZ 0.075mg/kg. Plasma concentrations were collected at various time points (C_{hr}) and analyzed by LC/MS/MS. MDZ AUC_{0–∞} was determined by non-compartmental analysis. MDZ C_{0.5, 1, 2, 4, and 6} and AUC_{0–∞} from 20 randomly selected subjects were log-transformed into normally distributed data and used to generate models to predict MDZ AUC (AUC_{pred}). Models were validated using the MDZ data of the remaining 25 subjects and evaluated for bias and precision using mean prediction error (MPE) and root mean square error (RMSE) with acceptable limits of ≤5% and ≤15%, respectively.

RESULTS:

Sampling Time (hr)	Log of AUC _{pred}	R ²	%MPE	%RMSE
0.5, 6	1.67 + 0.21(logC _{0.5}) + 0.66(logC ₆)	0.97	-1.0	12.1
0.5, 2, 6	1.11 + 0.21(logC _{0.5}) + 0.43(logC ₂) + 0.3(logC ₆)	0.99	-3.5	13.1

CONCLUSIONS: Two limited sampling models, using MDZ C_{0.5 and 6} or MDZ C_{0.5, 2, and 6} were acceptable and predictive of MDZ AUC. These models could reduce costs and inconvenience of greater numbers of samples when PO MDZ is used as a CYP3A biomarker.

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THE RATIO OF 1-HYDROXYMIDAZOLAM (1-OH MDZ) TO MIDAZOLAM (MDZ) PLASMA CONCENTRATIONS IS NOT AN ACCURATE MEASUREMENT FOR CYP3A ACTIVITY WHEN USING ORAL (PO) MDZ. *L. S. Lee, PharmD, A. N. Nafziger, MD, MHS, J. S. Bertino, Jr., PharmD, Clinical Pharmacology Research Center, The Research Institute, and Department of Medicine, Bassett Healthcare, Cooperstown, NY.*

BACKGROUND: The ratio of 1-OH MDZ to MDZ plasma concentrations has been proposed as an index to reduce sampling when measuring CYP3A activity. The aims of this study were to 1) assess if this ratio can be used to predict MDZ AUC when used as a CYP3A probe and 2) determine an optimal sampling strategy for the use of this ratio.

METHODS: Data from 3 previous studies in 41 healthy adults were used. Subjects abstained from any drugs known to affect CYP3A. Plasma samples were collected at specified time points (C_{hr}) after PO MDZ (0.075mg/kg) administration. 1-OH MDZ and MDZ concentrations were analyzed by LC/MS/MS. MDZ AUC_{0–∞} was determined by non-compartmental analysis. 20 subjects were randomly selected for the training set and the remaining 21 subjects for the validation set. The ratios of 1-OH MDZ to MDZ C_{0.5, 1, 2, 4, and 6} and AUC_{0–∞} were log-transformed. Stepwise multiple linear regression was used to derive equation models to predict MDZ AUC (AUC_{pred}).

RESULTS: One equation using C₂ was statistically significant but had a low regression coefficient (R²=0.32): Log(AUC_{pred})=4.43–0.75[log(1-OH MDZ C₂/MDZ C₂)]. This equation did not meet the acceptable limits of bias and precision (Mean prediction error=-9.8%, Root mean square error=52.3%).

CONCLUSIONS: The ratio of 1-OH MDZ to MDZ plasma concentrations does not correlate with MDZ AUC and cannot be used to accurately predict MDZ exposure when PO MDZ is used as a CYP3A biomarker.