

Population Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics Modeling of Oxypurinol in Hmong Adults with Gout and/or Hyperuricemia

Ya-Feng Wen¹, Richard Brundage¹, Youssef Roman², Kathleen Culhane-Pera³, and Robert Straka¹

¹University of Minnesota Twin Cities

²Virginia Commonwealth University

³Minnesota Community Care

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Abstract

Aim: Quantify identifiable sources of variability, including key pharmacogenetic variants in oxypurinol pharmacokinetics and their pharmacodynamic effect on serum urate. **Methods:** Hmong participants (n=34) received 100 mg allopurinol twice daily for 7 days followed by 150 mg allopurinol twice daily for 7 days. Serum urates (SU) were obtained pre- and post-allopurinol. Serum oxypurinol concentrations were obtained at times 0, 2, 4, and 6 hours after the last dose. A sequential population pharmacokinetic pharmacodynamics (PKPD) analysis with non-linear mixed-effects modeling evaluated the impact of anthropometrics, concomitant medications, and genetic variants on oxypurinol PKPD parameters. Allopurinol maintenance dose to achieve target SU was simulated based on the final PKPD model. **Results:** A one-compartment model with first order absorption and elimination best described the oxypurinol concentration-time data. Inhibitory of SU by oxypurinol was described with a direct inhibitory E_{max} model using steady-state oxypurinol concentrations. Fat-free body mass, estimated creatinine clearance and *SLC22A12* rs505802 genotype were found to predict differences in oxypurinol clearance. Oxypurinol concentration required to inhibit 50% of xanthine dehydrogenase activity was affected by *PDZK1* rs12129861 genotype. Most individuals with both *PDZK1* rs12129861 AA and *SLC22A12* rs505802 CC genotypes achieve target SU with allopurinol below the maximum dose, regardless of renal function and body mass. In contrast, individuals with both *PDZK1* rs12129861 GG and *SLC22A12* rs505802 TT genotypes would require more than the maximum dose, thus alternative medications. **Conclusion:** The proposed allopurinol dosing guide uses individuals' fat-free mass, renal function, and *SLC22A12* rs505802 and *PDZK1* rs12129861 genotypes to achieve target SU.

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Authors : Ya-Feng Wen, Pharm.D.¹, Richard C. Brundage, Pharm.D., Ph.D.¹, Youssef M. Roman, Pharm.D., Ph.D.², Kathleen A. Culhane-Pera, M.D., M.A.³, Robert J. Straka, Pharm.D., FCCP¹

Affiliations :

1. Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, USA
2. Department of Pharmacotherapy & Outcomes Science, School of Pharmacy, Virginia Commonwealth University, Richmond, VA 23298, USA

3. Minnesota Community Care, St. Paul, MN 55107, USA

Corresponding Author :

Robert J. Straka Experimental and Clinical Pharmacology University of Minnesota College of Pharmacy 308 Harvard St SE, Minneapolis, MN 55455 Email: strak001@umn.edu ORCID iD: 0000-0002-9541-7823

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What is already known about this subject

- Allopurinol exhibits large variability in pharmacokinetics and pharmacodynamics.
- Patient characteristics and concomitant medications have been identified as sources of the variability but have not accounted for all of it.
- The impact of genetic variants has been explored but no significant association has been established with population pharmacokinetics and pharmacodynamics analysis.

What this study adds

Genetic variants in *SLC22A12* were associated with oxypurinol clearance and variants in *PDZK1* were associated with urate-lowering effect of oxypurinol.

The allopurinol maintenance dose to achieve target serum urate level depends on patients' body mass, renal function, and genetic variants in *SLC22A12* and *PDZK1*.

ABSTRACT

Aim : Quantify identifiable sources of variability, including key pharmacogenetic variants in oxypurinol pharmacokinetics and their pharmacodynamic effect on serum urate.

Methods : Hmong participants (n=34) received 100 mg allopurinol twice daily for 7 days followed by 150 mg allopurinol twice daily for 7 days. Serum urates (SU) were obtained pre- and post-allopurinol. Serum oxypurinol concentrations were obtained at times 0, 2, 4, and 6 hours after the last dose. A sequential population pharmacokinetic pharmacodynamics (PKPD) analysis with non-linear mixed-effects modeling

evaluated the impact of anthropometrics, concomitant medications, and genetic variants on oxypurinol PKPD parameters. Allopurinol maintenance dose to achieve target SU was simulated based on the final PKPD model.

Results : A one-compartment model with first order absorption and elimination best described the oxypurinol concentration-time data. Inhibitory of SU by oxypurinol was described with a direct inhibitory Emax model using steady-state oxypurinol concentrations. Fat-free body mass, estimated creatinine clearance and *SLC22A12* rs505802 genotype were found to predict differences in oxypurinol clearance. Oxypurinol concentration required to inhibit 50% of xanthine dehydrogenase activity was affected by *PDZK1* rs12129861 genotype. Most individuals with both *PDZK1* rs12129861 AA and *SLC22A12* rs505802 CC genotypes achieve target SU with allopurinol below the maximum dose, regardless of renal function and body mass. In contrast, individuals with both *PDZK1* rs12129861 GG and *SLC22A12* rs505802 TT genotypes would require more than the maximum dose, thus alternative medications.

Conclusion : The proposed allopurinol dosing guide uses individuals' fat-free mass, renal function, and *SLC22A12* rs505802 and *PDZK1* rs12129861 genotypes to achieve target SU.

INTRODUCTION

Allopurinol is the first-line urate-lowering therapy (ULT) to prevent gout by lowering serum urate (SU) to a target of 6 mg/dL in all patients who can tolerate the medication.¹ The treat-to-target SU level approach instead of a fixed dose ULT strategy has been recommended by American College of Rheumatology and other organizations.²⁻⁴ Nonetheless, only 20-50% of patients achieve target SU within the US and Europe.⁵ Patients who typically fail to achieve SU targets include those who have high SU (>9 mg/dL), moderate-to-severe chronic kidney disease (CKD stage [?]³), or urolithiasis. Patients with aforementioned conditions have a greater risk for gout flares and tophi formation.^{6,7} Additionally, hyperuricemia (defined as SU [?]^{6.8} mg/dL) is strongly associated with other chronic conditions, including hypertension,^{8,9} type 2 diabetes mellitus (T2DM),¹⁰ metabolic syndrome,¹¹ cardiovascular diseases (CVD)¹² and dyslipidemia with elevated low-density lipoprotein (LDL) cholesterol and hypertriglyceridemia.¹³

To optimize allopurinol use, several strategies have been proposed. One approach projects an allopurinol maintenance dose based on creatinine clearance (CrCl).¹⁴ However, this approach was developed with the specific goal to avoid the allopurinol-induced severe cutaneous adverse reaction (SCAR) and not to achieve target SU. This approach may be sensible because impaired renal function correlated with the development and poor prognosis of allopurinol induced SCAR.¹⁵⁻¹⁷ Given this CrCL-based dose approach, it is understandable that only 19% of patients achieved target SU.¹⁸ Starting allopurinol dose based on estimated glomerular filtrate rate (eGFR) has been proposed.¹⁹ Similarly, the goal was to prevent allopurinol-induced SCAR, with the authors asserting that the starting dose, not the maintenance dose, correlated with the incidence of allopurinol-induced SCAR. Stamp et al¹⁹ reported that dose titration is often required to achieve target SU in patients who tolerate allopurinol. An approach that encourages safe targeting of optimal allopurinol dosage to achieve target SU remains elusive. This situation creates a gap in tools that specifically address the goal of dose optimization with the intended purpose of mitigating acute and chronic complications associated with hyperuricemia and gout.

Genome-wide association studies (GWAS) provide insights on how single nucleotide polymorphisms (SNPs) in key transporter genes can impact treatment outcomes. The *ABCG2* (BCRP) rs2231142C>A is associated with SU-lowering response to allopurinol²⁰⁻²³ and has been suggested as a guide to improve drug dosage and/or selection by identifying patients in need of alternate therapeutic approaches. The *SLC22A12* (URAT1) rs505802C>T is not only associated with the risk of hyperuricemia,²⁴ but also importantly associated with the exposure of serum oxypurinol, the active metabolite of allopurinol.²⁵ These two transporters, BCRP and URAT1, may prove to be important when identifying genomic based sources of variability in response to allopurinol.

Several population pharmacokinetics (PK)^{26,27} and pharmacokinetic-pharmacodynamic (PKPD)²⁸⁻³¹ models have been developed. Despite these models identifying that body mass, renal function, and concomitant

medications, including diuretics and uricosurics, are important factors, none of the studies illustrated a strong association between SNPs and either PK or PD parameters for oxypurinol. Furthermore, most of the studied populations are of European descent.

The aims of this project were to (1) develop a population PKPD model to characterize the relationship between serum oxypurinol and SU, (2) quantify the effects of relevant clinical characteristics and SNPs identified from GWAS on the PKPD effects for oxypurinol, and (3) predict the allopurinol maintenance dose to achieve target SU of <6 mg/dL.

METHODS

Patients and study design

Data from a prospective, open-labeled, genetically-guided, pilot study, *Genetics Of HyperUricemia and Gout Therapy in Hmong (GOUT-H)* (clinicaltrials.gov, NCT02371421) were analyzed. This study was approved by the Human Research Protection Program at the University of Minnesota Institutional Review Board (IRB #1408M53223). Detailed study design was described in previous publication.²⁵ Briefly, 34 Hmong participants with gout and/or hyperuricemia enrolled in the study. After 7 days of allopurinol or febuxostat washout (baseline visit), all the participants took allopurinol 100 mg twice daily for 7 days followed by 150 mg twice daily for 7 days. At the follow-up visit (2 weeks after the baseline visit), participants took the final dose of allopurinol.

Blood samples were collected at the baseline and follow-up visits to measure SU and serum creatinine after overnight fasting for 10 hours. Additionally, blood and urine samples were collected at 0, 2, 4, and 6-hours post-allopurinol dose at the follow-up visit to measure oxypurinol concentrations.

Oxypurinol and urate assay

Urate concentrations were measured using a Roche COBAS 6000 chemistry analyzer (Roche Diagnostics, Indianapolis, IN) using the enzymatic method with a limit detection of 0.2 mg/dL. The inter-assay coefficient of variation was 1.3% at 5.50 mg/dL and 2.0% at 9.67 mg/dL. Oxypurinol concentrations were measured as described in previous publication.²⁵ None of the SU, serum oxypurinol, and urine oxypurinol concentrations were below the limit of quantification.

Pharmacogenetic testing

Genomic DNA was purified and extracted from saliva samples collected using ORAgene DISCOVER kits (OGR-500, DNA Genotek Inc., Ottawa, ON, Canada) with QIAamp DNA Kit (Qiagen Inc., Germantown, MD, USA) per the manufacturer's protocol. Nine SNPs were genotyped using the iPLEX Gold method (iPLEX Application, Agena, San Diego, CA, USA). Functionality of each gene and supporting evidence for inclusion were described previously^{20,24,25,32-34} and are summarized in

Supplementary Table S1.

Population PK model

The population analysis for oxypurinol PK was conducted using the nonlinear mixed effects modeling program, NONMEM version 7.4 (ICON Development Solutions, LC, Ellicott City, MD) with the first order conditional estimation method with interaction. Exploratory analyses and diagnostic plots were performed with R and Perl-speaks-NONMEM (PsN) version 5.2.6.³⁵ One and two compartmental PK models with linear elimination and first-order absorption models with and without a time lag were explored. Model derived values of the combined absorption and formation rate constant (K_{fm}), apparent clearance (CL/f_m) and apparent volume (V/f_m) for oxypurinol were estimated, where f_m represents the fraction of allopurinol dose available as oxypurinol systemically.

The between subject variability (BSV) was assumed to follow a log-normal distribution, described as follow:

$$\theta_{ip} = \theta_{\mu\pi} \exp(\eta_{ip})$$

where θ_{ip} is the p^{th} model parameter θ for the i^{th} individual; $\theta_{\mu\pi}$ is the population mean of the p^{th} model parameter θ ; and η_{ip} is a random variable that represents the deviation from the mean of the p^{th} parameter for the i^{th} individual; the collection of η_{ip} are assumed to have a mean of zero and variance ω^2 . The variance ω^2 of BSV was calculated as a percentage of coefficient of variation (%CV) using the following equation:

$$\text{CV} (\%) = \sqrt{\exp(\omega^2) - 1} \times 100\%$$

The residual unexplained error (RUV) including additive, proportional, and combined errors were tested.

Population PKPD model

After the final PK model was established, the PKPD model was analyzed with a sequential approach using individual pharmacokinetic parameters with the standard error (IPPSE) method.^{36,37} Steady-state oxypurinol concentration was linked to the PD model using a direct effect Emax model was tested, using the following equation:

$$\text{Oxypurinol}_{\text{ss}} (mg/L) = \frac{150 \text{ mg}}{CL/f_m (L/h) \times 12 (h)}$$

$$\text{Post treatment SU} (mg/dL) = \text{BL}_{\text{urate}} (mg/dL) - \frac{I_{\text{max}} (mg/dL) \times \text{oxypurinol}_{\text{ss}}^{\gamma} (mg/L)}{IC_{50}^{\gamma} (mg/L) + \text{oxypurinol}_{\text{ss}}^{\gamma} (mg/L)}$$

where $\text{oxypurinol}_{\text{ss}}$ is the serum oxypurinol concentration at steady-state; BL_{urate} is the baseline SU; I_{max} is the maximum inhibitory effect of oxypurinol on xanthine dehydrogenase to inhibit urate production; IC_{50} is the oxypurinol concentration required to inhibit 50% of the activity of xanthine dehydrogenase; γ is the Hill coefficient for the sigmoid Emax model. The PKPD structural model is depicted in **Figure 1**.

Covariate model development

Demographics, clinical factors, concomitant medications, and genetic variants were evaluated for their influence on the parameters of PK and PD models. The selection of covariates for testing was based on previous significant findings^{26,27,29,31,38} and biological plausibility.

Demographic covariates included gender, total body weight (TBW), adjusted body weight (AJBW), and fat-free mass (FFM).³⁹ Renal function was tested as standardized CrCL, estimated from the Cockcroft–Gault equation then normalized to a standard CrCL of a 70 kg man (calculated as observed CrCL*70/ideal body weight). Concomitant medications were tested based on participants' self-reported information. These included drugs that lower SU: losartan,⁴⁰ HMG-CoA reductase inhibitors (particularly, atorvastatin),^{41,42} and calcium channel blockers (CCBs)⁴³; and drugs that increase SU: angiotensin converting enzyme inhibitors, angiotensin receptor blockers (ARBs, but not including losartan), beta-blockers, diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs).⁴³ In addition to testing the effect of each medication type, two categories were also tested: drugs that lower SU and drugs that increase SU.

Nine SNPs related to SU levels or risks of gout development (**Supplementary Table S1**) were tested. An additive genetic model was assumed for the effect of SNPs on the PKPD parameters.

A stepwise covariant modeling (SCM) approach using the PsN toolkit with the forward and backward thresholds at $p < 0.05$ and $p < 0.01$, respectively was used for selecting covariates that contributed to the CL/f_m and V/f_m for the PK model, and BL_{urate} , I_{max} , and IC_{50} for the PD model. The significance

of inclusion and elimination of each covariate was tested based on likelihood ratio test that follows the χ^2 distribution.

Model selection and qualification

Model selection was dependent on several criteria, including the χ^2 (likelihood ratio) test, goodness of fit (GOF) plots. Visual predictive check (VPC) plots (1000 simulations) stratified for significant covariates was used for model qualification. Non-parametric bootstrap with 1000 simulated bootstrap datasets were used to assess the model stability and precision of the final parameter estimates using PsN. Model development, diagnostics, and graphing were using Pirana⁴⁴ and R software (version 4.1.0)⁴⁵.

Simulations to predict allopurinol maintenance dose

Simulation was performed to examine the impact of important covariates on the serum oxypurinol and urate concentration. Different dosing strategies under a combination of significant covariates in the final PKPD model to achieve target SU of < 6mg/dL were performed for 1000 simulations for a total of 91,584 virtual patients. The distribution of PKPD model parameters were based on the final PKPD model. The model identified maintenance dose was the lowest dose that could achieve the target SU <6mg/dL in at least 75% of the cases. Simulation considerations were based on previous publication²⁹ with a few exceptions. First, the maintenance dose of allopurinol was considered from 50 to 800 mg/day because a maximum of 800 mg/day was approved by the US FDA. Second, creatinine clearance was simulated between 15 to 120 mL/min in 1 mL/min increment then stratified into 15-30 mL/min, 30-60 mL/min, and [?] 60 mL/min categories. Third, FFM between 50 to 100 kg with 10 kg increment was considered. The impact of *SLC22A12* rs505802 CC, CT, TT genotypes on oxypurinol CL/f_m and the impact of *PDZK1* rs12129861 GG, GA, and AA genotypes on *IC50* were considered (see Result section for the rationale for the selection of these covariates). Simulations were performed using R software (version 4.1.0)⁴⁵.

RESULTS

Participant characteristics

The 34 participants' demographics characteristics, clinical features, and self-reported concomitant medications collected at the baseline visit are described in **Table 1**. Notably, there were only 3 women, and only 1 participant with normal weight, based on the World Health Organization's Asian criteria-based body-mass index (BMI).⁴⁶ The dataset included 136 serum oxypurinol, 87 urine oxypurinol, and 102 serum urate concentrations. No genotype information was missing for the 9 SNPs tested. Genotype information and distributions are presented in **Supplemental Table 1**.

Final PK model

A one compartment PK model with first order absorption/conversion and elimination with proportional residual error model provided the best fit to the observed serum oxypurinol-time data. Using a two-compartment PK model or other residual error models provided similar fits, so the simpler model was retained. Covariance between BSV for CL/f_m and V/f_m was tested but this resulted in similar BSV estimates; therefore, the covariance was not included.

Model development steps for the oxypurinol PK model are summarized in **Supplemental Table 2**. The final model included FFM on CL/f_m and V/f_m allometric scaled using the theoretical value (0.75 for CL/f_m and 1 for V/f_m), renal function using estimated CrCL, and *SLC22A12*rs505802C>T. Using TBW as a covariate on CL/f_m improved the model fit but failed to improve the fit when used as covariate on V/f_m . On the other hand, using either AJBW or FFM as a covariate on both CL/f_m and V/f_m improved the fit. The selection of FFM as a covariate instead of AJBW was based on previous findings that FFM was also found to be a significant covariate.^{27,29} HMG-CoA reductase inhibitors and drugs that decrease SU reduced CL/f_m by about 48% and 30%, respectively, but the effect was not statistically significant in the SCM step (**Supplemental Table 2**). In addition to *SLC22A12* rs505802C>T as a covariate on CL/f_m , *CARMIL1* rs742132A>G and *PDZK1* rs12129861G>A were found to be significant during the forward selection step

but were excluded during backward elimination step. The combined absorption and formation rate constant (K_{fm}) and its BSV were fixed to initial estimates (which is similar to the value, 0.92 h^{-1} reported in the literature⁴⁷) due to insufficient data to support the parameter estimates and high shrinkage.⁴⁸

The BSV in CL/f_m decreased from 42.8% to 28.3%, and V/f_m decreased from 40.7% to 32.4% after including significant covariates. The results of the base and final (including covariate) PK models are summarized in **Table 2**, and the final estimates for CL/f_m and V/f_m for oxypurinol are given by:

$$CL/f_m \text{ (L/h)} = 1.05 \text{ (L/h)} \times \left(\frac{\text{standardized CrCL (mL/min)}}{100 \text{ (mL/min)}} \right)^{0.45} \times \left(\frac{\text{FFM (kg)}}{70 \text{ (kg)}} \right)^{0.75} \times (1 \text{ for } SLC22A12 \text{ rs505802 CC, 1.0 for } CT, 1.1 \text{ for } TT)$$

$$V/f_m \text{ (L)} = 59.3 \text{ (L)} \times \left(\frac{\text{FFM (kg)}}{70 \text{ (kg)}} \right)^1$$

To estimate the renal and non-renal CL/f_m of oxypurinol, a PK model with both serum and urine oxypurinol data was fitted. The renal CL/f_m was 0.77 L/h (77%) and non-renal CL/f_m was 0.23 L/h (23%) (**Supplemental Table 3**). Similar to the PK model with serum oxypurinol, the estimated CrCL and $SLC22A12$ rs505802C>T were found to be significant with renal CL/f_m . NSAIDs, $CARMIL1$ rs742132A>G, and $SLC2A9$ rs1014290C>T were found to be significant in the forward selection step but not in the backward elimination step on renal CL/f_m . No covariates were found to be significant with non-renal CL/f_m .

Final PD model

A direct effect Emax model with BL_{urate} , I_{max} , and IC_{50} with additive residual error model provided an adequate model to the SU data. The Hill coefficient could not be demonstrated to be different from 1.0 and was subsequently fixed to unity. The BSV for I_{max} , and IC_{50} was fixed to estimates from the base model due to insufficient data to estimate the precision of these parameters and high shrinkage in the final model.⁴⁸

Model development steps for the PD model are summarized in **Supplemental Table 4**. The final model included estimated CrCL on BL_{urate} and $PDZK1$ rs12129861G>A on IC_{50} . The results of the base and final (including covariate) PD models are summarized in **Table 2**, and the final estimates for SU response are given by:

$$\text{Serum urate (mg/dL)} = 9 \text{ (mg/dL)} \times \left(\frac{\text{CrCL (mL/min)}}{100 \text{ (mL/min)}} \right)^{-0.175} - \frac{7.6 \text{ (mg/dL)} \times \text{oxypurinol}_{ss} \text{ (mg/L)}}{\text{IC}_{50} \text{ (mg/L)} + \text{oxypurinol}_{ss} \text{ (mg/L)}}$$

$$\setminus n\text{IC}_{50} = 17.6 \text{ for } PDZK1 \text{ rs1219861 GG, } 12.8 \text{ for GA and } 8.1 \text{ for AA}$$

Model evaluation

The median parameter estimates with its 95%CI using 1000 non-parametric bootstrap dataset were comparable to the parameter estimate for the final PKPD models suggesting the PKPD model is stable (**Table 2**). The GOF plots for the final PKPD models also showed no visual or statistical bias for the model prediction (**Figure 2**).

The VPC plot was stratified by $SLC22A12$ rs505802C>T for the PK model and stratified by $PDZK1$ rs12129861G>A for the PD model, presented in **Figure 3A**. The VPC for the serum oxypurinol showed the median, 5th, and 95th percentiles of the model predicted serum oxypurinol concentrations followed the observed data in $SLC22A12$ rs505802 CC and CT genotypes. Due to the small sample size in TT genotype group, the 95%CI of the predicted oxypurinol concentrations overlapped. The VPC plots for the PD model showed some inadequacy in capturing SU at the screening visit (time between -40 to 0 days)

in *PDZK1* rs1219861 GG genotype group. Nonetheless, the predicted SU followed the observed SU data well at the baseline and the follow-up visits in all three genotype groups (**Figure 3B**).

Allopurinol maintenance dose prediction

Table 3 presents the predicted allopurinol daily maintenance dose to achieve serum urate of <6 mg/dL with 75% of success rate. In general, individuals with lower FFM or higher CrCL require lower allopurinol dose. Individuals with *SLC22A12* rs505802 T allele or *PDZK1* rs1219861 G allele require a higher allopurinol dose. Individuals with chronic kidney disease (CrCL <60 mL/min) who carry both *SLC22A12* rs505802 TT and *PDZK1*rs1219861 GG genotypes require a higher than maximum dose, and hence would be candidates for alternative medications.

DISCUSSION

Allopurinol is the first-line ULT; however, many patients fail to achieve target SU on allopurinol. We developed a population PKPD model and identified the importance of clinical variables on the PKPD parameters in Hmong participants with gout and/or hyperuricemia. Body mass (FFM), renal function (estimated CrCL), and *SLC22A12*rs505802C>T are key determinants to the PK of oxypurinol. Baseline SU, estimated CrCL, and *PDZK1* rs1219861G>A are important covariates to the PD of oxypurinol. When determining the minimum allopurinol maintenance dose to achieve target SU, all of the aforementioned clinical factors need to be considered.

The final estimated population oxypurinol clearance [CL/f_m of 1.05 L/h (95%CI 0.88-1.31)] was similar to a previous study (1.32 L/h)²⁹ where the study participants had similarly estimated CrCL (70 mL/min versus 87 mL/min in GOUT-H). The final estimated population oxypurinol volume of distribution [V/f_m of 59.3 L (95%CI 51.3-71.9)] was higher than the aforementioned study (41.6 L), possibly due to the older mean age of participants in their study (60-year-old versus 43-year-old in GOUT-H) and their approach to adjust for body mass (TBW versus FFM in GOUT-H). Given that the plasma protein binding for oxypurinol is negligible, the distribution of oxypurinol is similar to water content.⁴⁹ Since elderly typically have 10-15% less total body water compared to younger individuals,⁵⁰ the higher observed volume of oxypurinol (V/f_m) in our population is expected.

The final estimated population parameters for the PD model (BL_{urate} : 9 mg/dL, I_{max} : 7.6 mg/dL, IC_{50} : 17.6 mg/L) were similar to participants with gout and/or hyperuricemia (BL_{urate} : 8.5 mg/dL or 0.511 mmol/L, I_{max} : 6.87 mg/dL or 0.409 mmol/L, IC_{50} : 14.1 mg/L or 83.9 μ mol/L)²⁹ but different from the healthy participants (BL_{urate} : 4.6 mg/dL, I_{max} : 1 mg/dL, IC_{50} : 2.59 mg/L).³¹ Higher I_{max} value observed in patients with hyperuricemia suggests the maximum SU lowering effect of allopurinol depends on the baseline SU level. The considerably higher IC_{50} in patients with gout and/or hyperuricemia indicates that the potency of allopurinol is much lower and thus requires a higher dose of allopurinol to achieve the same effect compared to non-hyperuricemic adults.

Similar to previous findings^{27,29}, we found that FFM predicts oxypurinol clearance and volume of distribution better than TBW. Since the majority of our study participants were either overweight or obese, FFM approximates the lean body weight better³⁹ and better reflects the true volume of distribution of oxypurinol. Renal function also plays a critical role in both PK and PD of oxypurinol, which has been demonstrated in previous population PKPD analyses and clinical studies.⁵¹⁻⁵³ Contrary to a clinical observation that a lower allopurinol dose is needed to achieve target SU in patients with renal impairment (CrCl[?]60 ml/min) compared with patients with CrCl >60 ml/min,⁵¹ we predicted that a higher allopurinol dose is required in patients with renal impairment. Although estimated CrCL is positively associated with both CL/f_m and BL_{urate} in the PKPD model, the overall contribution of renal function is larger in BL_{urate} . This observation was consistent with previous published PKPD model²⁹ where a higher allopurinol dose was required in patients with renal impairment compared to those without renal impairment if patients were taking diuretics. This relationship, which would appear to be counterintuitive, is likely under-appreciated by clinicians and clinical pharmacologists.

Drugs that may impact SU were not important factors in the final PKPD model. This contrasts with other studies that clearly demonstrated that people taking diuretics have a 25-30% lower oxypurinol clearance compared to those not taking diuretics.^{26,27,29} We did not observe this relationship in our study, likely due to our modest count of participants (n=4) who were taking various diuretics (hydrochlorothiazide, triamterene/hydrochlorothiazide, furosemide, and bumetanide). The association of loop, thiazide, and thiazide-like (but not potassium-sparing) diuretics with the increased SU and the higher incidence of gout are well demonstrated from clinical observations⁵⁴⁻⁵⁷ and *in vitro* studies⁵⁸⁻⁶⁰ by inhibiting urate efflux transporters, such as MRP4 (*ABCC4*)⁵⁹ and NPT1 (*SLC17A1*)⁶⁰, or by increasing urate reabsorption due to extracellular fluid volume deletion from diuresis.⁵⁸ On the other hand, the evidence of how diuretics impact the PK of oxypurinol is less clear, although previous studies showed loop diuretics, particularly furosemide, to be associated with increased plasma oxypurinol concentration.^{51,61} Despite not being statistically significant, we found that patients taking HMG-CoA reductase inhibitors were associated with 52% decrease in oxypurinol CL/f_m . The majority of the participants were taking atorvastatin (4/5, 80%), which suggests the potential impact of atorvastatin on the clearance of oxypurinol.^{41,42}

SLC22A12 rs505802C>T was found to be a key determinant of oxypurinol clearance CL/f_m . This association is plausible because oxypurinol undergoes extensive reabsorption through URAT1 encoded by *SLC22A12*,⁶² such that URAT1 dysfunction would impact the disposition of oxypurinol. Although the association between *ABCG2* rs2231142C>A and SU-lowering response to allopurinol has been established in GWAS and replicated in other observational studies,²⁰⁻²³ no studies have shown a clear association between this SNP (rs2231142) and the PK parameters of allopurinol or oxypurinol. However, we cannot rule out the importance of *ABCG2* rs2231142C>A, particularly in patients with extrarenal underexcretion hyperuricemia. Since a larger portion of the GOUT-H Hmong participants were overproduction hyperuricemia, instead of extrarenal underexcretion hyperuricemia,²⁵ the impact of *ABCG2* rs2231142C>A may be diminished in our study population.

An interesting finding was the impact of *PDZK1* rs12129861G>A on IC_{50} in the inhibitory E_{max} model of oxypurinol. *PDZK1* is a key component of urate-transporting molecular complex for URAT1 and OAT4.^{63,64} The *PDZK1* rs12129861 A allele was also associated with a lower SU level²⁴ and a decrease risk of gout.^{65,66} We found individuals with AA genotype have almost half of the IC_{50} as GG genotype (8.1 versus 17.6 mg/L) suggesting a higher affinity of oxypurinol with individuals with AA genotype. However, since this SNP is in the upstream region of *PDZK1*, a causal SNP has yet to be determined; a mechanistic study needs to be performed to elucidate the impact of *PDZK1* on oxypurinol SU-lowering effect.

Limitations

A number of limitations should be noted. First, the small sample size (n=34) limits the ability to identify important covariates that could further explain the BSV in PKPD parameters of oxypurinol. However, the significant association between *SLC22A12* rs505802 genotype and oxypurinol clearance, and *PDZK1* rs1219861 genotype with IC_{50} in this population but not in other populations highlight the importance of including diverse populations in clinical studies. In other words, these observations may be unique to the Hmong population studied. Secondly, PK sampling scheme only covered half of the dosing interval that may negatively impact the accuracy of oxypurinol PK parameters estimate. This was a design feature suggested by the Hmong Genomics Board based on respecting the practical limitations of our participants. Given oxypurinol likely exhibits one compartmental PK behavior that is in concordance with previous studies^{26,27,29,31} and the maximum oxypurinol concentration observed in our study was at 2 hours, these provide confidence in our estimates. In addition, although we identified *SLC22A12* rs505802 and *PDZK1* rs1219861 are key determinants for PKPD response of oxypurinol, these SNPs are in the non-coding region, thus the causal SNPs for the differences observed in CL/f_m and IC_{50} among individuals with different genotypes require further investigation. As this was a pilot study in this unique population, the proposed allopurinol maintenance dose to achieved target SU requires validation in a prospective clinical study in a larger Hmong population.

CONCLUSION

In summary, we developed a population PKPD model for oxypurinol in Hmong participants with gout and/or hyperuricemia who take allopurinol. Body mass and renal function are key determinants for oxypurinol clearance and baseline SU, which aligns with previous findings. We also identified SNPs that can impact the oxypurinol clearance and its SU-lowering effect, which could have clinical importance. Considering all the important covariates, we propose a maintenance dose scheme of allopurinol to achieve target SU in the Hmong population that could help to better manage gout in this population, which exhibits a high prevalence of gout.^{67,68} The validity of this dosing scheme will require further study. However, we believe this study represents an important step in demonstrating the value of clinical trials including unique, under-represented populations who are at high risk for clinical consequences from hyperuricemia and gout and could benefit from effective ULT.

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Conflict of interest

All listed authors declare no conflicts of interest.

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Data availability statement

Data is not available to the public due to lack of patient consent for data sharing. NONMEM control files for pharmacokinetics and pharmacodynamics modeling and R script for allopurinol dose simulation are available in the supplemental text 1-4.

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Table 1. GOUT-H participants characteristics

Characteristics ^a	N = 34 ^b
Age (years) ^b	43 ± 13 (24-68)
Gender, male ^c	31 (91%)
Height (cm) ^b	160 ± 7 (146-179)

Characteristics ^a	N = 34 ^b
Weight (kg) ^b	84 ± 17 (54-134)
BMI (kg/m ²) ^{b,d}	32.5 ± 5.5 (21.6-47.0)
Normal ^c	1 (2.9%)
Overweight ^{c,d}	4 (12%)
Obesity ^c	29 (85%)
Estimated CrCL (mL/min) ^{b,e}	87 ± 31 (25-165)
15 [?] Estimated CrCL < 30	1 (3%)
30 [?] Estimated CrCL < 60	8 (24%)
Estimated CrCL [?] 60	25 (74%)
Baseline serum urate (mg/dL) ^b	9.61 ± 1.67 (5.8-13.0)
Post-treatment serum urate (mg/dL) ^b	5.4 ± 1.1 (3.1 – 7)
Self-reported medications related to SU/gout^{c,f}	
Drugs that lower serum urate	10 (29%)
Losartan	1 (2.9%)
HMG-CoA inhibitors	5 (15%)
Calcium channel blockers	5 (15%)
Drugs that increase serum urate	22 (65%)
Angiotensin converting enzyme inhibitors	5 (15%)
Angiotensin receptor blockers (not losartan)	1 (2.9%)
Beta-blockers	6 (18%)
Diuretics	4 (12%)
Non-steroidal anti-inflammatory drugs	16 (47%)

BMI, body mass index; CrCL, creatinine clearance; SU, serum urate

^a Characteristics were assessed at the baseline study visit after 10 days washout period.

^b Mean ± standard deviation (range)^c n (%)

^d Overweight was defined as BMI 23.0-27.5 kg/m²; obesity was defined as BMI > 27.5 kg/m² based on World Health Organization Asian criteria-based BMI⁴⁶.

^e Estimated CrCL was calculated using Cockcroft-Gault Equation with adjusted body weight.

^f Only medications that may impact serum urate are listed.

Table 2 . Parameter estimates for the population pharmacokinetic/pharmacodynamic models using sequential fit

Parameter	Base model (RSE%)	Final model (RSE%)	Bootstrap, median (95%CI)
Fixed parameters	Fixed parameters	Fixed parameters	Fixed parameters
<i>CL/f_m</i> (L/h)	1 (7)	1.05 (10)	1.04 (0.88, 1.31)
<i>V/f_m</i> (L)	47.7 (12)	59.3 (9)	59.1 (51.3, 71.9)
<i>K_{fm}</i> (/h)	1.1 (fixed)	1.1 (fixed)	1.1 (fixed)
<i>BL_{urate}</i> (mg/dL)	9.3 (3)	9.0 (4)	9.0 (8.3, 9.6)
<i>Imax</i> (mg/dL)	6.1 (18)	7.6 (25)	7.3 (4.9, 14.4)
<i>IC₅₀</i> (mg/L)	8.0 (53)	17.6 (48)	16.5 (6.0, 50.4)
Effects of covariates on <i>CL/f_m</i>			

Parameter	Base model (RSE%)	Final model (RSE%)	Bootstrap, median (95%CI)
Standardized creatinine clearance (power)	-	0.45 (31)	0.46 (0.14, 0.77)
<i>SLC22A12</i> rs505802 T allele	-	1.32 (36)	1.32 (1.1, 1.57)
Effects of covariates on baseline SU	Effects of covariates on baseline SU	Effects of covariates on baseline SU	Effects of covariates on baseline SU
Standardized creatinine clearance (power)	-	-0.18 (66)	-0.18 (-0.42, 0.05)
<i>PDZK1</i> rs1219861 A allele on <i>IC₅₀</i>	-	0.73 (32)	0.73 (0.50, 1.03)
Random effect parameters, CV% (RSE%) [shrinkage]	Random effect parameters, CV% (RSE%) [shrinkage]	Random effect parameters, CV% (RSE%) [shrinkage]	Random effect parameters, CV% (RSE%) [shrinkage]
BSV <i>CL/f_m</i>	42.8 (9) [0%]	28.3 (14) [0%]	26.5 (19.5, 34.4)
BSV <i>V/f_m</i>	40.7 (22) [25%]	32.4 (21) [30%]	31.5 (16.0, 46.3)
BSV <i>K_{fm}</i>	27.9 (fixed)	27.9 (fixed)	27.9 (fixed)
BSV <i>BL_{urate}</i>	11.1 (30) [11%]	13.7 (18) [6]	13.3 (8.6, 19.5)
BSV <i>I_{max}</i>	32.4 (fixed)	32.4 (fixed)	32.4 (fixed)
BSV <i>IC₅₀</i>	71.8 (fixed)	71.8 (fixed)	71.8 (fixed)
Residual error	Residual error	Residual error	Residual error
Serum oxypurinol, proportional (CV%) [shrinkage]	5.2 (33.3) [23.2%]	5.2 (17.9) [21.3%]	5.2 (4.2, 6.1)
Serum urate, additive (mg/dL) [shrinkage]	0.90 (53) [16%]	0.69 (33) [18%]	0.59 (0.25, 1.08)

BL_{urate} , baseline serum urate; *f_m* , fraction of the allopurinol systemically available as oxypurinol; *CL/f_m* , apparent clearance of oxypurinol; *V/f_m* , apparent volume of distribution of oxypurinol; *K_{fm}* , combined absorption and formation rate constant; *I_{max}* , maximum inhibitory effect of oxypurinol on xanthine dehydrogenase to inhibit urate production; *IC₅₀* , oxypurinol concentration at half maximum inhibitory effect; *CrCL* , creatinine clearance calculated using ideal body weight; FFM, fat free mass; *C_{ss_{oxy}}* , steady-state plasma oxypurinol concentration

Table 3. Predicted allopurinol daily maintenance dose to achieve serum urate of <6 mg/dL with 75% of success rate, considering genetic variants of *SLC22A12* rs505802 and *PDZK1* rs1219861

		Fat Free Mass (FFM)					
		50 kg	60 kg	70 kg	80 kg	90 kg	100 kg
<i>PDZK1</i> rs1219861 GG	CrCL (mL/min)						
	<i>SLC22A12</i> rs505802						
	CC						
	[?]15 and <30	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	[?]30 and <60	500	650	700	700	800	Alternative

		Fat Free Mass (FFM)					
	[?]60	400	450	450	550	550	600
	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>
	rs505802	rs505802	rs505802	rs505802	rs505802	rs505802	rs505802
	CT	CT	CT	CT	CT	CT	CT
	[?]15 and <30	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	[?]30 and <60	700	750	Alternative	Alternative	Alternative	Alternative
	[?]60	500	550	600	650	750	800
	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>
	rs505802	rs505802	rs505802	rs505802	rs505802	rs505802	rs505802
	TT	TT	TT	TT	TT	TT	TT
	[?]15 and <30	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	[?]30 and <60	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	[?]60	600	650	750	Alternative	Alternative	Alternative
<i>PDZK1</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>
rs1219861	rs505802	rs505802	rs505802	rs505802	rs505802	rs505802	rs505802
GA	CC	CC	CC	CC	CC	CC	CC
	[?]15 and <30	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	[?]30 and <60	400	450	500	600	600	650
	[?]60	250	300	350	400	450	450
	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>
	rs505802	rs505802	rs505802	rs505802	rs505802	rs505802	rs505802
	CT	CT	CT	CT	CT	CT	CT
	[?]15 and <30	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	[?]30 and <60	550	600	650	750	800	Alternative
	[?]60	350	400	450	500	550	550
	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>
	rs505802	rs505802	rs505802	rs505802	rs505802	rs505802	rs505802
	TT	TT	TT	TT	TT	TT	TT
	[?]15 and <30	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	[?]30 and <60	650	750	Alternative	Alternative	Alternative	Alternative
	[?]60	450	500	550	650	700	750
<i>PDZK1</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>
rs1219861	rs505802	rs505802	rs505802	rs505802	rs505802	rs505802	rs505802
AA	CC	CC	CC	CC	CC	CC	CC
	[?]15 and <30	550	600	700	800	800	Alternative
	[?]30 and <60	250	300	350	400	400	450

	Fat Free Mass (FFM)					
[?]60	200	200	250	250	300	300
<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>
rs505802	rs505802	rs505802	rs505802	rs505802	rs505802	rs505802
CT	CT	CT	CT	CT	CT	CT
[?]15 and <30	750	800	Alternative	Alternative	Alternative	Alternative
[?]30 and <60	350	400	400	450	500	550
[?]60	250	250	300	350	350	350
<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>	<i>SLC22A12</i>
rs505802	rs505802	rs505802	rs505802	rs505802	rs505802	rs505802
TT	TT	TT	TT	TT	TT	TT
[?]15 and <30	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
[?]30 and <60	400	500	500	600	650	700
[?]60	300	350	350	400	450	450

“Alternative” indicates an alternative medicine is preferred over allopurinol, given that the target serum urate was not achieved despite the maximum dose of allopurinol (800 mg/day). CrCL, creatinine clearance.

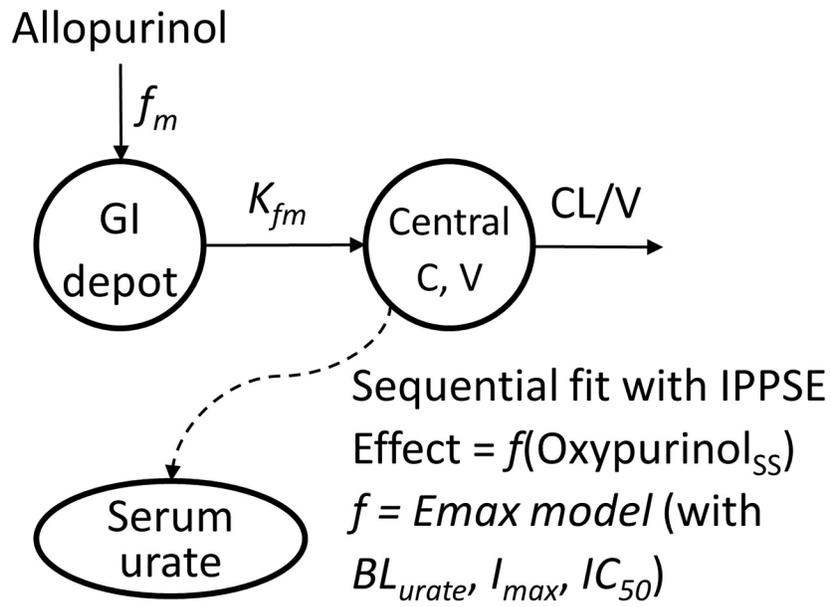
Figure 1. The structural model of the pharmacokinetics and pharmacodynamics effect of allopurinol

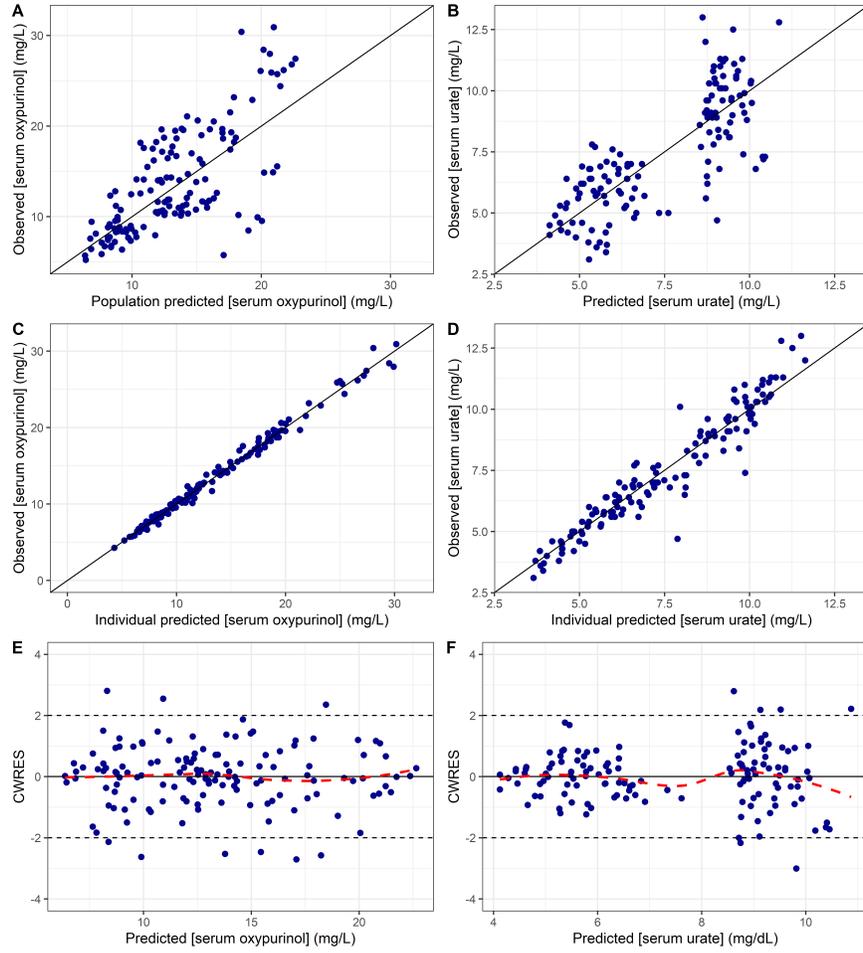
BL_{urate} , baseline serum urate; C, serum oxypurinol concentration; CL, apparent oxypurinol clearance; f_m , fraction of the allopurinol dose systemically converts to oxypurinol; K_{fm} , combined absorption and formation rate constant; I_{max} , maximum inhibitory effect of oxypurinol on xanthine dehydrogenase to inhibit urate production; IC_{50} , oxypurinol concentration required to inhibit 50% of the activity of xanthine dehydrogenase; IPPSE, individual pharmacokinetic parameters with standard error; V, apparent oxypurinol volume of distribution

Figure 2. Goodness-of-fit plots of the final PKPD models for oxypurinol.

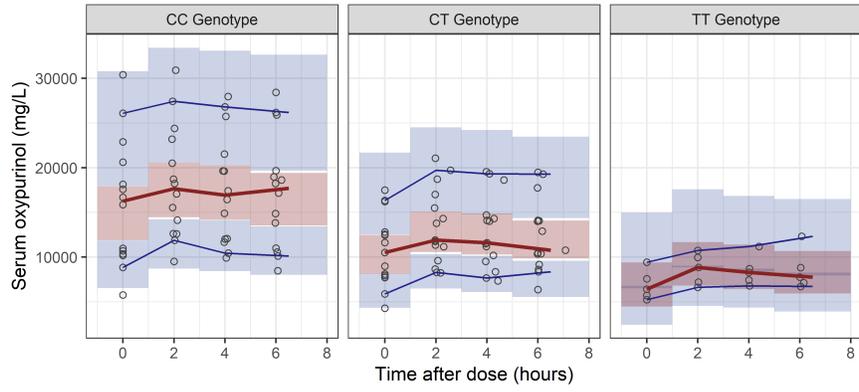
A and B, observed versus population-predicted concentration for serum oxypurinol and serum urate. C and D, observed versus individual-predicted concentration for serum oxypurinol and serum urate. E and F, conditional weighted residuals versus population-predicted concentration for serum oxypurinol and serum urate. CWRES = conditional weighted residuals.

Figure 3. Visual predictive checks of the final PKPD models for oxypurinol. A, serum oxypurinol concentration stratified by *SLC22A12* rs505802 genotypes. B, serum urate concentration stratified by *SLC22A12* rs505802 genotypes. The open circles represent the observed data, and the blue and red lines represent the 5, 50, and 95th percentiles of the observed data. The blue and shaded areas are the 95% confidence intervals of the simulated concentrations for the corresponding percentile values.





A Stratify by *SLC22A12* rs505802



B Stratify by *PDZK1* rs12129861

