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

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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 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.
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The authors confirm that the Principal Investigator for this paper is Robert J. Straka and that he had direct clinical responsibility for patients.

Data availability: Raw 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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Patient consent: Consent was obtained for all the study participants prior to any study related activities.

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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 al\(^19\) 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 allopurinol\(^20-23\) 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, BRCP 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) (clinicaltrial.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. 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. 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 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. 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 (Kfm), apparent clearance (CL/fm) and apparent volume (V/fm) for oxypurinol were estimated, where fm 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:

$$\theta_{i,p} = \theta_{\mu,p} \exp(\eta_{i,p})$$

where $\theta_{i,p}$ is the $p^{th}$ model parameter for the $i^{th}$ individual; $\theta_{\mu,p}$ is the population mean of the $p^{th}$ model parameter; and $\eta_{i,p}$ is a random variable that represents the deviation from the mean of the $p^{th}$ parameter for the $i^{th}$ individual; the collection of $\eta_{i,p}$ are assumed to have a mean of zero and variance $\omega^2$. The variance $\omega^2$ 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. Steady-state oxypurinol concentration was linked to the PD model using a direct effect Emax model was tested, using the following equation:

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

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

where oxypurinol$_{ss}$ 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; $\gamma$ 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 and biological plausibility.

Demographic covariates included gender, total body weight (TBW), adjusted body weight (AJBW), and fat-free mass (FFM). Renal function was tested as standardized CrCl, estimated from the Cockcroft–Gault equation then normalized to a standard CrCl of 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, HMG-CoA reductase inhibitors (particularly, atorvastatin), and calcium channel blockers (CCBs); 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).

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 $\text{CL}/f_{m}$ and $V/f_{m}$ for the PK model, and $\text{BL}_{urate}$, $I_{max}$, and $\text{IC}_{50}$ for the PD model. The significance
of inclusion and elimination of each covariate was tested based on likelihood ratio test that follows the \( \chi^2 \) distribution.

Model selection and qualification

Model selection was dependent on several criteria, including the \( \chi^2 \) (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 Pirana\textsuperscript{44} and R software (version 4.1.0)\textsuperscript{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 publication\textsuperscript{29} 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 \textit{SLC22A12} rs505802 CC, CT, TT genotypes on oxypurinol \( CL/f_m \) and the impact of \textit{PDZK1} rs12129861 GG, GA, and AA genotypes on \( IC_{50} \) were considered (see Result section for the rationale for the selection of these covariates). Simulations were performed using R software (version 4.1.0)\textsuperscript{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).\textsuperscript{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 \textit{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.\textsuperscript{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 \textit{SLC22A12} rs505802C>T as a covariate on \( CL/f_m \), \textit{CARMIL1} rs742132A>G and \textit{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 literature) due to insufficient data to support the parameter estimates and high shrinkage.

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:

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

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

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.

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:

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

$nIC_{50} = 17.6$ for $PDZK1$ rs1219861 GG, 12.8 for GA and 8.1 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 \( \text{CL}/f_m \) 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 (\( \text{BL}_{\text{urate}} \) : 9 mg/dL, \( I_{\text{max}} \) : 7.6 mg/dL, \( IC_{50} \) : 17.6 mg/L) were similar to participants with gout and/or hyperuricemia (\( BL_{\text{urate}} \) : 8.5 mg/dL or 0.511 mmol/L, \( I_{\text{max}} \) : 6.87 mg/dL or 0.409 mmol/L, \( IC_{50} \) : 14.1 mg/L or 83.9 mmol/L)\(^ {28}\) but different from the healthy participants (\( BL_{\text{urate}} \) : 4.6 mg/dL, \( I_{\text{max}} \) : 1 mg/dL, \( IC_{50} \) : 2.59 mg/L).\(^ {31}\) Higher \( I_{\text{max}} \) 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 better\(^ {39}\) 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 \( BL_{\text{urate}} \) in the PKPD model, the overall contribution of renal function is larger in \( BL_{\text{urate}} \). This observation was consistent with previous published PKPD model\(^ {29}\) 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.\textsuperscript{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 observations\textsuperscript{54-57} and in vitro studies\textsuperscript{58-60} by inhibiting urate efflux transporters, such as MRP4 (ABCC4)\textsuperscript{59} and NPT1 (SLC17A1)\textsuperscript{60}, or by increasing urate reabsorption due to extracellular fluid volume deletion from diuresis.\textsuperscript{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.\textsuperscript{51,61} Despite not being statistically significant, we found that patients taking HMG-CoA reductase inhibitors were associated with 52% decrease in oxypurinol $\text{CL/f}_m$. The majority of the participants were taking atorvastatin (4/5, 80%), which suggests the potential impact of atorvastatin on the clearance of oxypurinol.\textsuperscript{41,42}

**SLC22A12 rs505802C>T** was found to be a key determinant of oxypurinol clearance $\text{CL/f}_m$. This association is plausible because oxypurinol undergoes extensive reabsorption through URAT1 encoded by SLC22A12,\textsuperscript{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,\textsuperscript{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,\textsuperscript{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 $I_{C50}$ in the inhibitory $E_{\text{max}}$ model of oxypurinol. PDZK1 is a key component of urate-transporting molecular complex for URAT1 and OAT4.\textsuperscript{63,64} The PDZK1 rs12129861 A allele was also associated with a lower SU level\textsuperscript{24} and a decrease risk of gout.\textsuperscript{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\textsuperscript{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/fm 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.\cite{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.

**Acknowledgment**

The authors wish to thank the support from all the Hmong participants, the Hmong GOUT-H Research Board, and Minnesota Community Care.

**Conflict of interest**

All listed authors declare no conflicts of interest.

**Funding Information**

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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.

**References**


55. Savage PJ, Pressel SL, Curb JD, et al. Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic


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<thead>
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<th>Characteristicsa</th>
<th>N = 34b</th>
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<tr>
<td>Age (years)b</td>
<td>43 ± 13 (24-68)</td>
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<td>Gender, malec</td>
<td>31 (91%)</td>
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<tr>
<td>Height (cm)b</td>
<td>160 ± 7 (146-179)</td>
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Characteristics

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<tr>
<td>Weight (kg)b</td>
<td>84 ± 17 (54-134)</td>
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<tr>
<td>BMI (kg/m²)b,d</td>
<td>32.5 ± 5.5 (21.6-47.0)</td>
</tr>
<tr>
<td>Normal c</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Overweight c,d</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>Obesity c</td>
<td>29 (85%)</td>
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<tr>
<td>Estimated CrCL (mL/min)b,e</td>
<td>87 ± 31 (25-165)</td>
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</tr>
<tr>
<td>30 [?] Estimated CrCL &lt; 60</td>
<td>8 (24%)</td>
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<tr>
<td>Estimated CrCL [?] 60</td>
<td>25 (74%)</td>
</tr>
<tr>
<td>Baseline serum urate (mg/dL)b</td>
<td>9.61 ± 1.67 (5.8-13.0)</td>
</tr>
<tr>
<td>Post-treatment serum urate (mg/dL)b</td>
<td>5.4 ± 1.1 (3.1 – 7)</td>
</tr>
</tbody>
</table>

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 BMI 46.

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
**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**

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

BLurate, baseline serum urate; fₘ, fraction of the allopurinol systemically available as oxypurinol; CL/fₘ, apparent clearance of oxypurinol; V/fₘ, apparent volume of distribution of oxypurinol; Kₘ, combined absorption and formation rate constant; Iₘₜₐₓ, 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; Cssoxy, 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.
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*PDZK1 rs1219861 AA is a genetic marker associated with fat-free mass (FFM) in different age groups.*
Fat Free Mass (FFM)

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“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}, \text{baseline serum urate; } C, \text{serum oxypurinol concentration; CL, apparent oxypurinol clearance; } f_m, \text{fraction of the allopurinol dose systemically converts to oxypurinol; } K_{fm}, \text{combined absorption and formation rate constant; } I_{max}, \text{maximum inhibitory effect of oxypurinol on xanthine dehydrogenase to inhibit urate production; } IC_{50}, \text{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 SLCL22A12 rs505802 genotypes. B, serum urate concentration stratified by SLCL22A12 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.
Sequential fit with IPPSE
Effect = \( f(\text{Oxypurinol}_{SS}) \)
\[ f = E_{max} \text{ model (with} \]
\[ BL_{urate}, I_{max}, IC_{50} \]

Allopurinol

\[ f_m \]

GI depot

Central C, V

CL/V

Serum urate

\[ K_{fm} \]
A  Stratify by SLC22A12 rs505802

B  Stratify by PDZK1 rs12129861