

Impact of CYP450 and Transporter Polymorphisms on Dutasteride–Tamsulosin Exposure and Tolerability

Nabin Karki¹, Suman Gurung¹, Tenzing Sherpa^{1*}, Prakash Adhikari¹

¹Department of Medicinal Plant Research, Faculty of Pharmacy, Tribhuvan University, Kathmandu, Nepal.

*E-mail ✉ tenzing.sherpa.mpr@gmail.com

Received: 12 February 2025; Revised: 24 May 2025; Accepted: 29 May 2025

ABSTRACT

Dutasteride and tamsulosin constitute a widely used first-line combination therapy for benign prostatic hyperplasia (BPH). Although this regimen is generally more effective than either drug alone, it is also associated with a higher frequency of adverse drug reactions (ADRs). Regulatory agencies—including the U.S. Food and Drug Administration and the European Medicines Agency—advise caution when prescribing tamsulosin to CYP2D6 poor metabolizers (PMs) receiving CYP3A4 inhibitors. However, no detailed pharmacogenetic dosing recommendations currently exist for tamsulosin, and there is an absence of pharmacogenetic guidance for dutasteride. To address this gap, we examined the pharmacokinetic profile and safety of fixed-dose dutasteride/tamsulosin (0.5 mg/0.4 mg) in relation to 76 polymorphisms across 17 candidate pharmacogenes. Seventy-nine healthy male participants were enrolled in three phase-I, randomized, crossover, open-label bioequivalence studies, each with a different design: a single-dose fed trial, a single-dose fasting trial, and a multiple-dose trial. Notably, CYP2D6 PMs (genotypes *4/*4 and *4/*5) and intermediate metabolizers (IMs; *1/*4, *1/*5, *4/*15) displayed significantly elevated AUC ($p = 0.004$), prolonged $t_{1/2}$ ($p = 0.008$), and reduced apparent clearance (Cl/F) ($p = 0.006$) compared with normal metabolizers (*1/*1) and ultrarapid metabolizers (*1/*1 × 2), after correction for multiple comparisons. Fed-state administration also resulted in a significantly longer t_{max} than fasting conditions. Additional nominal associations were observed between dutasteride exposure and CYP3A4/CYP3A5 genotypes, and between tamsulosin concentrations and ABCG2, CYP3A5, and SLC22A1 genotypes. No significant genotype–ADR relationship was identified; however, adverse events were more common in the multiple-dose study. Based on these findings, dose adjustments may be beneficial for CYP2D6 PMs to enhance safety and for UMs to improve therapeutic efficacy. Further research is required to validate the remaining pharmacogenetic associations.

Keywords: Tamsulosin, Dutasteride, Pharmacogenetics, CYP2D6, Pharmacokinetics, CYP3A4

How to Cite This Article: Karki N, Gurung S, Sherpa T, Adhikari P. Impact of CYP450 and Transporter Polymorphisms on Dutasteride–Tamsulosin Exposure and Tolerability. *Spec J Pharmacogn Phytochem Biotechnol.* 2025;5:139-49. <https://doi.org/10.51847/7trSgV8UhZ>

Introduction

The combination of dutasteride and tamsulosin is widely recommended as an initial therapeutic option for men with benign prostatic hyperplasia (BPH). Many patients ultimately require combination therapy, as monotherapy often fails to deliver adequate symptom control [1, 2].

Dutasteride, a 5- α reductase inhibitor (5-ARI), limits the conversion of testosterone to dihydrotestosterone, thereby slowing prostatic enlargement. Taken orally, it achieves roughly 60% bioavailability, and after a 0.5 mg dose, peak plasma levels are typically reached around 3 h, although values between 1 and 10 h have been reported. Its pharmacokinetic profile is characterized by an extensive volume of distribution (300–500 L) and very high protein binding (>99.5%). The rate of elimination varies with dose: doses below 5 mg are cleared relatively quickly ($t_{1/2}$ of 3–9 days), whereas daily dosing at 0.5 mg results in much slower clearance, with a half-life extending to 3–5 weeks. Dutasteride undergoes extensive biotransformation mediated mainly by CYP3A4 and CYP3A5, forming four primary metabolites of varying activity. Excretion occurs predominantly in feces, and only a small proportion of the drug (1–15.4%) is recovered unchanged. In vitro studies indicate that several other

CYP enzymes—including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1—do not contribute to its metabolism [3].

Tamsulosin, an α -1 adrenergic receptor blocker, promotes urinary flow by reducing smooth muscle tone in the bladder neck and prostate. It is also administered orally and demonstrates high bioavailability (>90%), linear kinetics, a relatively small distribution volume (16 L), and strong protein binding (94–99%). Following a 0.4 mg dose, its median t_{max} is approximately 6 h (range: 2–24 h). The drug exhibits a median half-life of 10–13 h irrespective of dosing schedule. Roughly 90% of tamsulosin undergoes hepatic metabolism through CYP3A4 and CYP2D6, while the unchanged fraction (about 10%) is eliminated via urine [Agencia Española del Medicamento y Productos Sanitarios [4]].

Although combining these agents improves therapeutic efficacy compared with using either drug alone, such regimens are also linked to an increased frequency of adverse reactions [5]. Reported adverse effects include dizziness, sexual dysfunction, retrograde ejaculation, and breast-related symptoms [AEMPS, 2015]. Optimizing both safety and therapeutic response therefore remains a challenge. Interindividual differences in genes encoding metabolizing enzymes, membrane transporters, and drug targets can substantially alter drug exposure and the risk of adverse events. At present, the only pharmacogenetic consideration formally noted on the U.S. FDA label for tamsulosin concerns CYP2D6 poor metabolizers receiving moderate CYP3A4 inhibitors, due to the potential for excessive drug concentrations [3]. No comparable guidance exists for dutasteride, and pharmacogenetic data on this drug are lacking.

To address this gap, we performed a candidate-gene pharmacogenetic assessment of 76 variants across 17 genes—including members of the CYP1–4 families and transporters such as ABCB1, ABCC2, ABCG2, SLC22A1, SLC28A3, SLCO1B1, and UGT1A1—in a cohort of healthy volunteers who participated in bioequivalence clinical trials.

Materials and Methods

The study population was drawn from three bioequivalence clinical trials evaluating two different formulations of dutasteride/tamsulosin 0.5 mg/0.4 mg hard capsules. Each trial enrolled 36 participants, totaling 108 individuals. Among these, 88 volunteers completed their respective trials and consented to participate in the pharmacogenetic analysis. Nine individuals had participated in more than one trial and were therefore excluded from duplicate analyses, resulting in a final cohort of 79 unique subjects. All trials were conducted at the Clinical Trial Unit of Hospital Universitario de La Princesa (UECHUP) in Madrid, Spain, using identical inclusion and exclusion criteria. Eligible participants were healthy males aged 18 to 55 years who were surgically sterile or agreed to use two reliable methods of contraception and to refrain from sperm donation for at least six months after the first drug administration. Exclusion criteria included any significant medical or psychiatric condition, previous use of prescription medications, a body mass index outside the 18–30 kg/m² range, consumption of alcohol, tobacco, or illicit drugs, blood donation within one month prior to study start, or any swallowing difficulties. Weight, height, age, biological sex, and self-reported race or biogeographic origin were recorded during screening.

The reference product in all trials was Duodart® (tamsulosin/dutasteride 0.4/0.5 mg, GlaxoSmithKline, UK), which was also used for pharmacogenetic assessments. All three trials were phase-I, open-label, randomized, crossover bioequivalence studies, blinded only for the analytical determination of plasma drug concentrations, but they differed in dosing regimen and feeding conditions. In the first trial (S1), participants received a single oral dose following a high-fat meal, while in the second trial (S2), a single oral dose was administered under fasting conditions. In the third trial (M), volunteers received eight consecutive daily doses under fed conditions.

For S1 and S2, each participant received both the reference and test formulations in two study periods, with a 28-day washout between them. Participants were hospitalized 10 hours prior to dosing and remained under observation for 24 hours after drug administration, during which investigators ensured correct ingestion of the capsules. Blood samples were collected at 23 predetermined time points, including pre-dose (0 h) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 32, 48, and 72 hours post-dose. In S1, dosing occurred 10 minutes after a standardized high-fat breakfast, while in S2, dosing was scheduled 10 hours after the last meal and five hours before the next meal. Both dutasteride and tamsulosin plasma concentrations were quantified in these trials.

In the multiple-dose study (M), volunteers received either the reference or test formulation daily for eight consecutive days. On the day of the final (eighth) dose, participants were hospitalized 10 hours prior to drug

administration and remained under observation for 24 hours afterward. During the seven prior days, participants visited the study site to provide trough blood samples and to receive a standardized breakfast along with the daily dose. On the final day, dosing occurred 30 minutes before administration after a 10-hour fast. Blood was collected at 23 time points identical to the single-dose studies, but only tamsulosin plasma concentrations were measured. Two participants did not complete the second study period and were excluded from the analysis.

Plasma samples were frozen at -20°C during the trials and shipped to an external laboratory for analysis. Drug concentrations were measured using high-performance liquid chromatography coupled with mass spectrometry (LC-MS) following liquid-liquid extraction. The lower limits of quantification were 50.00 pg/mL for dutasteride and 99.80 pg/mL for tamsulosin.

Pharmacokinetic analyses and genotyping

Pharmacokinetic parameters for dutasteride and tamsulosin were determined using the noncompartmental analysis approach in CERTARA Phoenix WinNonlin Professional software version 7.0 (Certara, United States). In the single-dose studies under fed (S1) and fasting (S2) conditions, both dutasteride and tamsulosin were analyzed, whereas in the multiple-dose study (M), only tamsulosin pharmacokinetics were evaluated. For S1 and S2, the area under the plasma concentration–time curve from zero to 72 hours (AUC_{0-72} , AUC_t) was calculated using the linear trapezoidal rule. The area from 72 hours to infinity ($\text{AUC}_{72-\infty}$, AUC_{∞}) was estimated as the ratio of the plasma concentration at 72 hours (C_t) to the terminal elimination rate constant (k_e), which was calculated by linear regression of the log-linear portion of the concentration–time profile. Total exposure ($\text{AUC}_{0-\infty}$) was then obtained as the sum of AUC_t and AUC_{∞} . In the multiple-dose study, the steady-state area under the curve (AUC_{τ}) over the 24-hour dosing interval following the eighth administration was calculated in a similar manner using the linear trapezoidal method. Across all three clinical trials, the maximum plasma concentration (C_{max}) and the time to reach it (t_{max}) were observed directly from the data. The elimination half-life ($t_{1/2}$) was calculated as $\ln 2$ divided by k_e , clearance (Cl) was determined as the administered dose divided by AUC_{∞} (or AUC_{τ} in M), and the apparent volume of distribution (V_d) was estimated as Cl divided by k_e . In the multiple-dose study, trough concentrations (C_{min}) at steady state were directly observed from daily pre-dose samples.

Genomic DNA was extracted from peripheral venous blood samples using the MagNa Pure System (Roche Applied Science, United States), and DNA concentrations were measured with a Qubit 3.0 Fluorometer (Thermo Fisher, United States). Genotyping was performed using a custom TaqMan® OpenArray® panel in a QuantStudio 12k Flex real-time PCR system (Thermo Fisher, United States). The panel targeted polymorphisms in genes relevant to the absorption, distribution, metabolism, and excretion of dutasteride and tamsulosin, focusing on cytochrome P450 isoforms including CYP1A2 (*1B rs2470890, *1C rs2069514, *1F rs762551), CYP2A6 (*9 rs28399433), CYP2B6 (*4 rs2279343, *5 rs3211371, *9 rs3745274, *18 rs28399499, *22 rs34223104, rs4803419), CYP2C19 (*2 rs4244285, *3 rs4986893, *4 rs28399504, *5 rs56337013, *6 rs72552267, *7 rs72558186, *8 rs41291556, *9 rs17884712, *17 rs12248560, *35 rs12769205), CYP2C8 (*2 rs11572103, *3 rs10509681 and rs11572080, *4 rs1058930), CYP2C9 (*2 rs1799853, *3 rs1057910, *5 rs28371686, *8 rs7900194 and rs9332094, *11 rs28371685), CYP2D6 (*3 rs35742686, *4 rs3892097, *6 rs5030655, *7 rs5030867, *8 rs5030865A, *9 rs5030656, *10 rs1065852, *12 rs5030862, *14 rs5030865T, *15 rs77467110, *17 rs28371706, *19 rs72549353, *29 rs59421388, *41 rs28371725, *56 rs72549347, *59 rs79292917, rs1135840), CYP3A4 (*2 rs55785340, *3 rs4986910, *6 rs4646438, *18 rs28371759, *22 rs35599367), CYP3A5 (*3 rs776746, *6 rs10264272, *7 rs41303343), and CYP4F2 (*3 rs2108622), as well as drug transporters ABCB1 (C1236T rs1128503, C3435T rs1045642, G2677T/A rs2032582), ABCC2 (rs2273697), ABCG2 (rs2231142), SLC22A1 (*2 rs72552763, *3 rs12208357, rs34059508), SLC28A3 (rs7853758), SLCO1B1 (*1B rs2306283, *2 rs56101265, *5 rs4149056, *6 rs55901008, *9 rs59502379, *10 rs56199088, *13 rs56061388, *17/*21 rs4149015, rs11045879), and other drug-metabolizing enzymes such as UGT1A1 (*6 rs4148323, *80 rs887829). CYP2D6 copy number variation (CNV) analysis was conducted in the same thermal cycler using a 96-well plate format, employing TaqMan® technology in accordance with previously described methods [6].

Haplotyping and phenotyping

Genotype data were utilized to infer haplotypes, which in turn were used to assign phenotypes or diplotypes for each participant. The genotyping method employed does not provide definitive information regarding whether two polymorphisms are located on the same chromosome, which is critical for accurate allele definition. Nevertheless, the chromosomal arrangement of these variants can be inferred with reasonable confidence using available allele frequency data. Accordingly, allele and phenotype assignment was performed following Clinical

Pharmacogenetics Implementation Consortium (CPIC) guidelines, including CYP2C9 with nonsteroidal anti-inflammatory drugs [7], CYP2C19 with voriconazole [8], CYP2D6 with opioids [9], CYP3A5 with tacrolimus [10], SLCO1B1 with simvastatin [11], and UGT1A1 with atazanavir [12].

For drug-metabolizing enzymes, possible phenotypes included ultrarapid metabolizer (UM), rapid metabolizer (RM), normal metabolizer (NM), intermediate metabolizer (IM), and poor metabolizer (PM), while transporters were categorized as normal function (NF) or intermediate function (IF). CYP3A5 phenotypes were expressed using CPIC nomenclature to maintain consistency with other genes. In this scheme, NM corresponds to expressors (*1/*1), IM represents heterozygotes carrying one expressor allele (*1) and one nonexpressor allele (*3, *6, or *7), and PM indicates nonexpressors (*3/*3 or *3/*6). Ambiguous CYP2D6 phenotypes following copy number variation (CNV) analysis, such as *1/*4 carriers with three gene copies that could be interpreted either as *1 × 2/*4 (NM) or *1/*4 × 2 (IM), were excluded from downstream analysis.

For UGT1A1, despite the unknown functional effect of the *80 allele, it is in strong linkage disequilibrium with the decreased function *28 allele. Consequently, *1/*1 individuals were considered NMs, *1/*80 were IMs, and *80/*80 were PMs. Since CYP2C8 allele functionality has not been defined, participants were grouped by diplotypes without functional categorization. For ABCB1, individuals were classified according to the total number of variant alleles, following a previously established methodology [13]: group 1 included participants with no variant alleles, group 2 comprised those with 1–3 variants, and group 3 included individuals carrying 4–6 variants. Other genetic variants were analyzed individually for each gene. Reference SNP numbers (rs) were used where available, following PharmVar nomenclature [Pharmacogene Variation Consortium (PharmVar), 2018; Gaedigk *et al.*, 2018, CPT 103:399; Gaedigk *et al.*, 2019, CPT 105:29] [14, 15].

Safety, statistical analysis, and ethics

During hospitalization, volunteers were periodically asked about the tolerability of the treatment. Adverse events (AEs) reported both spontaneously in response to open-ended questions and self-reported by participants were recorded in their individual data collection logbooks. The causal relationship between drug administration and the occurrence of AEs was assessed using the Karch–Lasagna algorithm [16] for the S1 trial, and the Spanish Pharmacovigilance System algorithm [17] for the S2 and M trials. Only events classified as definite, probable, or possible were considered adverse drug reactions (ADRs) and included in the present analysis.

For the pharmacogenetic and pharmacokinetic analyses, 19 genetic variables were selected from the initial set of 76 polymorphisms, corresponding to 17 genes, with three CYP1A2 alleles analyzed separately. Race and clinical trial design were included as covariates, and dose-to-weight correction was applied to control for potential confounders. Hardy–Weinberg equilibrium was tested using the χ^2 test by comparing observed versus expected allele frequencies. Pharmacokinetic parameters, including volume of distribution (Vd) and clearance (Cl), were normalized by bioavailability, resulting in Vd/F and Cl/F. Area under the plasma concentration–time curve from zero to infinity (AUC_{∞}), AUC at steady state (AUC_{τ}), maximum concentration (C_{max}), and minimum concentration (C_{min}) were corrected according to the dose-to-weight ratio (DW). For tamsulosin, pharmacokinetic data were obtained from both single- and multiple-dose studies. Since AUC_{∞} after a single dose and AUC_{τ} correspond to total systemic exposure from a single administration, these variables were merged into a single “AUC” variable for analysis.

Normality was assessed using quantile–quantile plots, and homoscedasticity was evaluated with Levene’s test. For normally distributed, homoscedastic variables, comparisons between two groups were performed using t-tests, while comparisons among three or more groups were conducted using one-way ANOVA on logarithmically transformed parameters (e.g., LnAUC) to ensure normality. Pairwise comparisons for variables with three or more groups were conducted using Bonferroni post hoc tests. For heteroscedastic variables, Welch’s t-test or Welch’s ANOVA was used as appropriate. Multivariate linear regression analyses were performed, using significant variants from univariate analyses along with study design as independent variables, and pharmacokinetic parameters as dependent variables. Multiple testing correction was applied using the Benjamini–Hochberg false discovery rate (FDR) method [18], considering 61 tests for tamsulosin and 44 for dutasteride. Results with p-values <0.05 after FDR correction were considered statistically significant, while p-values <0.05 before FDR correction were considered nominally significant. ADR incidence according to genotype, phenotype, self-reported race, and clinical trial design was analyzed using χ^2 tests, and the risk of developing ADRs was evaluated with logistic regression. For ANOVA or t-tests, nominally significant p-values are indicated as pANOVA. For multivariate analyses, significance was reported using the unstandardized β -coefficient, R^2 , p-value of multivariate

analysis (pMV), and p-value after FDR correction (pFDR). All statistical analyses were conducted using R software, version 4.0.3 [19].

The protocols and informed consent forms for all three clinical trials were approved by the Independent Ethics Committee (IECCR, CEIm) of Hospital Universitario de la Princesa and the Spanish Drug Agency (AEMPS). The studies, S1 (EUDRA-CT: 2017-001592-23), S2 (EUDRA-CT: 2017-003227-29), and M (EUDRA-CT: 2017-003244-21), were conducted in accordance with Spanish regulatory requirements, the ICH Guidelines for Good Clinical Practice, and the Revised Declaration of Helsinki [20].

Results and Discussion

Participant characteristics

A total of 79 healthy male volunteers completed the study and were included in the analysis. The median age was 24 years (± 6.7), with an average height of 1.76 m (± 0.07), weight of 76.87 kg (± 8.72), and BMI of 24.86 kg/m² (± 2.26). The cohort consisted primarily of Caucasians (52 participants, 74%) and included 18 Latin individuals (26%). No statistically meaningful differences in baseline demographics were observed between these subgroups. Most polymorphisms adhered to Hardy–Weinberg equilibrium; exceptions included CYP1A2 *1C (rs2069514), CYP2A6 *9 (rs28399433), CYP2B6 *4 (rs2279343), ABCB1 rs2032582, CYP2C8 *8 (rs1058930), and CYP3A4 *22 (rs35599367).

Pharmacokinetics of dutasteride

Following logarithmic transformation, all pharmacokinetic parameters for dutasteride demonstrated normal distributions. Most parameters also met the assumption of homoscedasticity, with exceptions noted for t_{max} in CYP2A6 *9 and SLC22A1 *2, $t_{1/2}$ for CYP1A2 *IB* and CYP2C9 phenotypes, and Vd/F for CYP2C9 phenotypes. Under fed conditions, volunteers showed a longer time to reach maximum plasma concentration (t_{max}) and a larger apparent volume of distribution (Vd/F) compared to fasting conditions (pANOVA = 0.002 and 0.006, respectively). Carriers of the CYP3A422 allele exhibited a reduced Vd/F compared with individuals with the CYP3A4 *1/*1 genotype (pANOVA = 0.023). For SLC28A3 rs7853758, participants with A/G or A/A genotypes had lower AUC values (pANOVA = 0.012) and higher clearance (Cl/F) (pANOVA = 0.043) than those with the G/G genotype. In multivariate regression models, SLC28A3 rs7853758 remained associated with AUC ($\beta = -0.51$, $R^2 = 0.15$, pMV = 0.011; pFDR = 0.065), whereas food intake ($\beta = 0.3$, $R^2 = 0.39$, pMV = 0.016; pFDR = 0.087), CYP3A4 genotype ($\beta = -0.7$, pMV = 0.024; pFDR = 0.11), and SLC28A3 rs7853758 ($\beta = 0.26$, $R^2 = 0.39$, pMV = 0.039; pFDR = 0.16) showed nominal associations with Vd/F. However, after correction for multiple comparisons using the false discovery rate, no statistically significant effects were observed. Overall, no definitive pharmacogenetic or demographic influence on dutasteride pharmacokinetics was established (**Table 1**).

Table 1. Significant relationships between tamsulosin pharmacokinetics and clinical trial design, volunteers self-reported race and genotype.

		AUC (ng·h/mL)	C _{max} (ng/ml)	t _{max} (h)	t _{1/2} (h)	Vd/F (L/kg)	Cl/F (ml/h·kg)
SRR	Caucasian (<i>n</i> = 38)	44.21 (49.22%)	2.49 (37.21%)	2.74 (57.1%)	61.95 (45.03%)	9.39 (66.19%)	138.42 (103.53%)
	Latin (<i>n</i> = 14)	42.87 (45.69%)	2.56 (27.41%)	3.68 (48.16%)	49.36 (41.09%)	7.58 (34.56%)	144.97 (93.54%)
CT	Fed (S1) (<i>n</i> = 25)	49.53 (48.12%)	2.76 (30.37%)	3.68 (44.53%)*¹	56.25 (47.96%)	7.32 (50.29%)*¹ †	142.22 (120.99%)
	Fasting (S2) (<i>n</i> = 27)	38.59 (43.54%)	2.28 (36.86%)	2.35 (60.65%)	60.7 (43.4%)	10.37 (62.86%)	138.3 (76.17%)
CYP3A4	*1/*1 (<i>n</i> = 50)	42.17 (43.51%)	2.49 (32.62%)	2.98 (55.49%)	58.56 (46.14%)	9.09 (60.9%)	143.79 (98.44%)
	*1/*22 + *22/*22 (<i>n</i> = 2)	85.76 (56.8%)	3.11 (74.06%)	3.25 (76.15%)	58.54 (1.52%)	4.23 (47.72%)*¹ †	49.91 (46.37%)
CYP3A5	NM + IM (<i>n</i> = 9)	38.17 (52.17%)	2.17 (33.36%)	3.89 (49.7%)*¹	45.04 (27.19%)	8.81 (42.07%)	168.31 (92.21%)

		PM (<i>n</i> = 43)	45.04 (47.23%)	2.58 (34.25%)	2.8 (55.49%)	61.39 (45.37%)	8.92 (65.65%)	134.3 (102.64%)
		A/A (<i>n</i> = 4)	37.33 (67.95%)	2.65 (35.92%)	2 (28.87%)	55.52 (48.76%)	9.65 (42.55%)	207.06 (115.38%)
SL	rs7	A/G (<i>n</i> = 14)	35.51 (57.83%)	2.26 (39.61%)	2.91 (51.24%)	50.08 (46.7%)	11.03 (77.17%)	200.91 (94.4%)
C2	85		49.27	2.63	3.16	63.6	7.64	98.26
8A	37	G/G (<i>n</i> = 31)	(39.89%)*² †	(31.92%)	(57.37%)	(43.32%)	(34.9%)*†	(63.7%)*²

Data is presented as mean (coefficient of variation). SRR: Self-reported race, CT: Clinical Trial, S1: single-dose feeding conditions trial, S2: single-dose fasting conditions trial, NM: Normal metabolizer, IM: Intermediate metabolizer, PM: Poor metabolizer. * 1 : $p < 0.05$ after ANOVA, * 2 : $p < 0.05$ after ANOVA and Bonferroni post-hoc vs A/G, †: nominal $p < 0.05$ after multivariate analysis. No variable remained statistically significant after FDR correction. Bold data represents significant results.

Tamsulosin pharmacokinetic profile

Following logarithmic transformation, tamsulosin pharmacokinetic parameters generally conformed to normal distribution. Most variables demonstrated homogeneity of variance, except for several outliers: AUC and Cl/F in CYP2A6 *9 carriers, Vd/F in CYP1A2 *1F and CYP2A6 *9 carriers, t_{1/2} in CYP1A2 *1F, SLC22A1 *3, and CYP2C9 phenotypes, and C_{max} in relation to clinical trial design and CYP2C9 phenotype.

Comparisons between feeding conditions revealed that fasting led to a larger AUC compared with fed or multiple-dose scenarios (p ANOVA = 0.011). Both fasting and multi-dose regimens were associated with a reduced time to peak concentration (t_{max}) ($\beta = -0.21$, $R^2 = 0.16$, p MV = 0.001; p FDR = 0.008) and elevated maximum plasma concentration (C_{max}) ($\beta = 0.22$, $R^2 = 0.25$, p MV = 0.014; p FDR = 0.063) relative to the fed single-dose condition. Furthermore, single-dose administration alone corresponded to a lower volume of distribution (Vd/F) ($\beta = -0.22$, $R^2 = 0.31$, p MV = 0.002; p FDR = 0.008) and shorter elimination half-life (t_{1/2}) ($\beta = -0.20$, $R^2 = 0.30$, p MV = 0.001; p FDR = 0.008) compared with other single-dose trials.

Genetic factors markedly influenced pharmacokinetics. Carriers of the ABCG2 rs2231142 C allele exhibited greater Vd/F than G/G homozygotes (p ANOVA = 0.014). For CYP2D6, ultrarapid (UM) and normal metabolizers (NM) showed lower AUC values than intermediate (IM) and poor metabolizers (PM) ($\beta = -0.34$, $R^2 = 0.36$, p MV < 0.001; p FDR = 0.004). In addition, UMs and NMs demonstrated shorter t_{1/2} ($\beta = -0.20$, $R^2 = 0.30$, p MV = 0.002; p FDR = 0.008), increased Vd/F ($\beta = 0.14$, $R^2 = 0.31$, p MV = 0.046; p FDR = 0.19), and reduced Cl/F ($\beta = 0.33$, p MV = 0.009; p FDR = 0.006) relative to PMs and IMs. Individuals with CYP3A5 normal or intermediate metabolizer status had elevated Vd/F (p ANOVA = 0.019) and Cl/F ($p = 0.027$) compared with PMs. Analysis of SLC22A1 genotypes revealed that *1/*3 carriers had higher AUC (p ANOVA = 0.020), C_{max} (p ANOVA = 0.017), and C_{min} (p ANOVA = 0.038), along with lower Cl/F (p ANOVA = 0.026), compared with *1/*1 subjects. Collectively, these results demonstrate that tamsulosin pharmacokinetics are influenced by both genetic polymorphisms and dosing conditions, emphasizing the potential utility of individualized therapy to optimize efficacy and safety (Table 2).

Table 2. Significant relationships between tamsulosin pharmacokinetics and clinical trial design, volunteers self-reported race and genotype.

		AUC (ng·h/mL)	C _{max} (ng/ml)	C _{min} (ng/ml)
SRR	Caucasian (<i>n</i> = 56)	176.13 (47.37%)	12.28 (36.83%)	3.26 (65.53%)
	Latin (<i>n</i> = 23)	160.16 (44.27%)	12.84 (37.39%)	2.43 (51.48%)
CT	Fed (S1) (<i>n</i> = 25)	148.51 (49.05%)	10.35 (36.44%)*²	—
	Fasting (S2) (<i>n</i> = 27)	202.57 (47.75%)*¹	13.85 (41.83%)	—
	Multiple dose (M) (<i>n</i> = 27)	161.66 (35.39%)	12.98 (24.04%)	2.98 (63.78%)
ABC G2	rs2231142	G/G (<i>n</i> = 65)	177.70 (47.41%)	3.17 (65.42%)
		G/T (<i>n</i> = 14)	142.62 (33.15%)	2.33 (42.27%)
CYP2D6		UM (<i>n</i> = 11)	131.02 (28.5%)	1.81 (51.59%)
		NM (<i>n</i> = 37)	145.63 (41.7%)	2.54 (49.92%)
		IM (<i>n</i> = 23)	221.00 (43.3%)*⁵ †³ ‡	14.87 (36.24%)

Dutasteride and tamsulosin remain first-line therapies for BPH due to their clinical efficacy. However, inadequate exposure can reduce therapeutic effectiveness, whereas excessive exposure may increase the risk of ADRs, both of which can result in treatment discontinuation. Pharmacogenetic-guided dose adjustments have been recommended for various drugs to optimize efficacy and safety, as reflected in CPIC guidelines [9, 21], Dutch Pharmacogenetics Working Group recommendations, and regulatory guidance from the FDA and EMA. Specifically, the FDA and EMA recommend caution with tamsulosin 0.4 mg or combination formulations (e.g., Duodart®) in CYP2D6 poor metabolizers receiving concomitant CYP3A4 inhibitors, as these individuals may be at risk of overexposure and ADRs [3, 4]. Beyond this, no formal pharmacogenetic guidelines or dosing recommendations exist for tamsulosin, nor is there pharmacogenetic information available for dutasteride. This lack of guidance aligns with the limited number of well-controlled pharmacogenetic studies on these drugs, particularly dutasteride. The present study aimed to address this gap by examining pharmacogenetic influences on their pharmacokinetics.

Dutasteride pharmacokinetic parameters observed in this study aligned with previously reported values, with an AUC of 39.6 ± 23.1 ng·h/mL and C_{max} of 2.14 ± 0.77 ng/mL, compared with literature values of 43.03 ± 20.73 ng·h/mL and 2.46 ± 0.89 ng/mL, respectively [4]. No statistically significant differences were detected between racial groups for any pharmacokinetic measure.

Feeding status influenced dutasteride absorption as expected. High-fat meals delay gastric emptying and intestinal transit, which can slow systemic drug absorption [22]. In the fed state, t_{max} was higher and V_d/F lower compared with fasting individuals. Although AUC and C_{max} were nominally 34% and 22% higher in fed participants, these differences did not reach significance after multiple testing correction, consistent with prior bioequivalence studies reporting no substantial effect of food on dutasteride pharmacokinetics [23].

Pharmacogenetic variability was most notable for CYP3A4 and CYP3A5. Carriers of CYP3A4*22 displayed a more than twofold increase in AUC relative to *1/*1 carriers, though the small sample size of 22 carriers ($n = 2$) likely contributed to the lack of statistical significance. Similarly, CYP3A422 carriers consistently exhibited lower V_d/F. CYP3A5 normal and intermediate metabolizers demonstrated longer t_{max} than poor metabolizers, which may reflect slower elimination rates in PMs, resulting in faster accumulation and earlier peak concentrations. A trend toward 30% higher t_{1/2} in PMs was observed compared with NM and IM participants, although this did not achieve significance. Additionally, carriers of SLC28A3 rs7853758 A/G and A/A genotypes showed reduced AUC and t_{1/2} and increased Cl/F relative to G/G carriers. None of these associations remained significant following FDR correction, suggesting that further research is required to clarify whether CYP3A or SLC28A3 polymorphisms meaningfully influence dutasteride pharmacokinetics.

The observed tamsulosin pharmacokinetic parameters under single-dose after fed conditions were similarly consistent with the literature, for example, AUC of 187.2 ± 95.7 ng·h/ml and C_{max} of 11.3 ± 4.44 ng/ml compared to 147.4 ± 72.8 ng·h/ml and 10.35 ± 3.77 ng/ml, respectively [4] (JALYN). No significant difference was found between the two groups of race and any pharmacokinetic parameter.

Food intake is known to influence the absorption of orally administered drugs, which in turn affects related pharmacokinetic parameters such as t_{max} and C_{max}. This effect likely results from variations in gastric pH and intestinal transit time. Previous studies have reported that fasting conditions facilitate faster and greater absorption of tamsulosin [24]. Consistently, in this study, volunteers in the fasting state exhibited a nominally higher AUC (29%) and shorter t_{max} (15%) compared with those in the fed state. A 16% increase in C_{max} was also observed in fasting participants, although this difference did not reach statistical significance [4]. As anticipated, t_{max} was significantly prolonged when tamsulosin was administered following a high-fat meal. Additionally, fed administration yielded a lower C_{max} than multiple-dose administration. The absence of differences between AUC values in the fed and multiple-dose conditions aligns with the equivalence of AUC_∞ and AUC_τ under identical conditions. Interestingly, the half-life measured during multiple-dose administration was significantly longer than in the fed single-dose study. For a drug like tamsulosin with linear pharmacokinetics, t_{1/2} is expected to remain stable across dosing regimens. This discrepancy may reflect limitations of the noncompartmental analysis and the potential for type I error. Nonetheless, both values fell within the established literature range of 10–13 hours [4]. Tamsulosin is predominantly metabolized by CYP3A4 and CYP2D6, with minor contributions from other cytochrome P450 isoforms [4]. Prior research has identified a relationship between tamsulosin bioavailability and CYP2D6 genotype [25–27]. Our findings corroborate this, showing that CYP2D6 poor and intermediate metabolizers exhibited significantly higher drug exposure than normal and ultrarapid metabolizers. Although our study did not capture treatment effectiveness and was limited in assessing ADRs, these results imply that ultrarapid

metabolizers may experience subtherapeutic exposure, while poor metabolizers may be at risk of overexposure and potentially greater adverse effects. The observed higher incidence of ADRs in the multiple-dose study supports the idea that increased systemic exposure correlates with a greater likelihood of ADRs. Accordingly, dose adjustments—reductions for poor metabolizers and increases for ultrarapid metabolizers—might improve safety and efficacy, although further studies are needed to define appropriate modifications. Currently, the only available combination formulation contains tamsulosin 0.4 mg [3, 4], highlighting the need for additional strengths (e.g., 0.3 mg or 0.5 mg) to allow individualized therapy. The clinical utility of CYP2D6-guided dosing must be validated before implementation, and guidance from organizations such as CPIC, SEFF, or DPWG may ultimately provide recommendations.

CYP3A5 poor metabolizers exhibited lower Cl/F than normal and intermediate metabolizers. Although tamsulosin is primarily a CYP3A4 substrate, this finding suggests that CYP3A5 may also contribute to its metabolism and pharmacokinetic variability. However, previous reports did not detect an association between CYP3A5 genotype and tamsulosin pharmacokinetics [3, 4, 27], and this association was not maintained after FDR correction. To our knowledge, this study is the first to propose such a link, which warrants replication in larger cohorts.

ABCG2 encodes the breast cancer resistance protein (BCRP), an ATP-binding cassette transporter involved in multidrug resistance, particularly for chemotherapeutic agents such as mitoxantrone and anthracyclines [28]. The functional impact of the rs2231142 variant remains controversial. While T/T individuals have been associated with reduced clearance of sulfasalazine [29], our study observed that G/T carriers exhibited higher Vd/F than G/G individuals, with approximately 18% lower AUC and 23% higher Cl/F, although these differences were not statistically significant. This may suggest that tamsulosin is a BCRP substrate and that rs2231142 modulates its exposure. Further research is needed to confirm these findings.

SLC22A1 encodes the organic cation transporter 1 (OCT1), which mediates the uptake of diverse endogenous cations (dopamine, serotonin, choline) and numerous drugs including metformin, cimetidine, imatinib, oxaliplatin, and tramadol [30]. Our analysis indicated that individuals with the SLC22A1 *1/*3 genotype had higher AUC, Cmax, and Cmin, longer t1/2, and lower Vd/F and Cl/F compared with *1/*1 carriers. These data suggest that tamsulosin could be an OCT1 substrate, with reduced transporter function potentially decreasing hepatic uptake and clearance, thereby increasing systemic exposure. Although this association did not survive FDR correction, the result provides a rationale for future studies to evaluate the impact of SLC22A1 variants on tamsulosin pharmacokinetics.

Despite the strengths of this study, several limitations should be acknowledged. The first limitation is the relatively small sample size. To partially address this, data from three distinct clinical trials were combined. This approach introduces a second limitation: the integration of different study designs complicates statistical analyses. Although study design was incorporated as a covariate, the overall statistical power remains lower than that of a single, uniform study. Additionally, the proportion of CYP2D6 ultrarapid metabolizers observed in our cohort (14%) exceeded the expected prevalence reported in the literature (7%). While the genotyping methodology was robust, this discrepancy should be considered when interpreting the findings. Therefore, validation in larger and independent populations is necessary to corroborate these results.

Conclusion

In conclusion, CYP2D6 phenotype had a pronounced impact on tamsulosin pharmacokinetics, with poor and intermediate metabolizers exhibiting approximately twice the systemic exposure compared with normal and ultrarapid metabolizers. These observations align with prior literature and the pharmacogenetic considerations noted in regulatory guidelines, such as those of the FDA and EMA, which currently do not provide specific dose adjustment recommendations. Based on our findings, individualized dose modifications could potentially enhance tamsulosin efficacy and safety, although further studies are required to determine the clinical benefit of such adjustments. In contrast, dutasteride pharmacokinetics appeared unaffected by either genotype or dosing regimen. To our knowledge, this represents the largest pharmacogenetic study conducted on tamsulosin ($n = 79$) and the first of its kind for dutasteride. Additionally, we identified potential novel associations involving ABCG2, CYP3A4, CYP3A5, and SLC22A1. Nevertheless, the primary limitation remains the limited sample size, and future prospective investigations are warranted to validate these preliminary associations.

Acknowledgments: None

Conflict of Interest: FA-S and DO have been consultants or investigators in clinical trials sponsored by the following pharmaceutical companies: Abbott, Alter, Chemo, Cinfa, FAES, Farmal’der, Ferrer, GlaxoSmithKline, Galenicum, Gilead, Janssen-Cilag, Kern, Normon, Novartis, Servier, Silverpharma, Teva, and Zambon. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Financial Support: GV-G was cofinanced by Instituto de Salud Carlos III (ISCIII) and the European Social Fund (PFIS predoctoral grant, number FI20/00090). MN-G was financed by the ICI20/00131 grant, Acción Estratégica en Salud 2017-2020, ISCIII.

Ethics Statement: The studies involving human participants were reviewed and approved by the Independent Ethics Committee (IECCR, CEIm) of Hospital Universitario de la Princesa and the Spanish Drug Agency (AEMPS). The patients/participants provided their written informed consent to participate in this study.

References

1. Lerner LB, McVary KT, Barry MJ, Bixler BR, Dahm P, Das AK, et al. Management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA guideline part I—initial work-up and medical management. *J Urol.* 2021;206(4):806–17. doi:10.1097/JU.0000000000002183
2. Lerner LB, McVary KT, Barry MJ, Bixler BR, Dahm P, Das AK, et al. Management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA guideline part II—surgical evaluation and treatment. *J Urol.* 2021;206(4):818–26. doi:10.1097/JU.0000000000002184
3. U.S. Food and Drug Administration (FDA). Jalyn® (dutasteride and tamsulosin hydrochloride) capsules: drug label [Internet]. Silver Spring (MD): FDA; 2010 [cited 2021 May 31]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022460s007s0081bl.pdf.
4. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Duodart® (dutasteride and tamsulosin 0.5 mg/0.4 mg) capsules: drug label [Internet]. Madrid: AEMPS; 2015 [cited 2021 May 31]. Available from: https://cima.aemps.es/cima/pdfs/es/ft/72275/72275_ft.pdf.
5. Greco KA, McVary KT. The role of combination medical therapy in benign prostatic hyperplasia. *Int J Impot Res.* 2008;20(Suppl 3):S33–S43. doi:10.1038/ijir.2008.51
6. Belmonte C, Ochoa D, Román M, Saiz-Rodríguez M, Wojnicz A, Gómez-Sánchez CI, et al. Influence of CYP2D6, CYP3A4, CYP3A5 and ABCB1 polymorphisms on pharmacokinetics and safety of aripiprazole in healthy volunteers. *Basic Clin Pharmacol Toxicol.* 2018;122(5):596–605. doi:10.1111/bcpt.12960
7. Caudle KE, Rettie AE, Whirl-Carrillo M, Smith LH, Mintzer S, Lee MTM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. *Clin Pharmacol Ther.* 2014;96(5):542–8. doi:10.1038/clpt.2014.159
8. Moriyama B, Obeng AO, Barbarino J, Penzak SR, Henning SA, Scott SA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP2C19 and voriconazole therapy. *Clin Pharmacol Ther.* 2017;102(1):45–51. doi:10.1002/cpt.583
9. Crews KR, Monte AA, Huddart R, Caudle KE, Kharasch ED, Gaedigk A, et al. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. *Clin Pharmacol Ther.* 2021;110(4):888–96. doi:10.1002/cpt.2149
10. Birdwell KA, Decker B, Barbarino JM, Peterson JF, Stein CM, Sadee W, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP3A5 genotype and tacrolimus dosing. *Clin Pharmacol Ther.* 2015;98(1):19–24. doi:10.1002/cpt.113
11. Ramsey LB, Johnson SG, Caudle KE, Haidar CE, Voora D, Wilke RA, et al. Clinical Pharmacogenetics Implementation Consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. *Clin Pharmacol Ther.* 2014;96(4):423–8. doi:10.1038/clpt.2014.125
12. Gammal RS, Court MH, Haidar CE, Iwuchukwu OF, Gaur AH, Alvarellos M, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for UGT1A1 and atazanavir prescribing. *Clin Pharmacol Ther.* 2016;99(4):363–9. doi:10.1002/cpt.269
13. Zubiaur P, Soria-Chacartegui P, Koller D, Navares-Gómez M, Ochoa D, Almenara S, et al. Impact of polymorphisms in transporter and metabolizing enzyme genes on olanzapine pharmacokinetics and safety in healthy volunteers. *Biomed Pharmacother.* 2021;133(1):111087. doi:10.1016/j.biopha.2020.111087

14. Pharmacogene Variation Consortium (PharmVar). PharmVar database [Internet]. 2018 [cited 2021 May 31]. Available from: <https://www.pharmvar.org>.
15. Dutch Pharmacogenetics Working Group. Pharmacogenetic recommendations 2019 [Internet]. The Hague: KNMP;2019 [cited 2021 May 31]. Available from: <https://www.knmp.nl>.
16. Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. *Clin Pharmacol Ther.* 1977;21(3):247–54. doi:10.1002/cpt1977213247
17. Aguirre C, García M. Causality assessment in reports on adverse drug reactions: algorithm of the Spanish pharmacovigilance system. *Med Clin (Barc).* 2016;147(10):461–4. doi:10.1016/j.medcli.2016.06.012
18. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B (Methodol).* 1995;57(1):289–300. doi:10.1111/j.2517-6161.1995.tb02031.x
19. R Core Team. R: a language and environment for statistical computing [Internet]. Vienna: R Foundation for Statistical Computing; 2020 [cited 2021 May 31]. Available from: <https://www.R-project.org/>.
20. World Medical Association. World Medical Association Declaration of Helsinki. *Med Health Care.* 1991;19(4):264–5. doi:10.1111/j.1748-720X.1991.tb01824.x
21. Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JHM, Swen JJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. *Clin Pharmacol Ther.* 2018;103(2):210–6. doi:10.1002/cpt.911
22. McLachlan A, Ramzan I. Meals and medicines. *Aust Prescr.* 2006;29(2):40–2. doi:10.18773/austprescr.2006.026
23. Kurczewski R, Bowen C, Collins D, Zhu J, Serbest G, Manyak M. Bioequivalence studies of a reformulated dutasteride and tamsulosin hydrochloride combination capsule and a commercially available formulation. *Clin Pharmacol Drug Dev.* 2017;6(5):508–16. doi:10.1002/cpdd.334
24. U.S. Food and Drug Administration (FDA). Flomax® (tamsulosin hydrochloride) capsules: drug label [Internet]. Silver Spring (MD): FDA;1997 [cited 2021 May 31]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020579s0261bl.pdf.
25. Choi CI, Bae JW, Jang CG, Lee SY. Tamsulosin exposure is significantly increased by the CYP2D6*10/*10 genotype. *J Clin Pharmacol.* 2012;52(12):1934–8. doi:10.1177/0091270011432168
26. Byeon JY, Lee YJ, Kim YH, Kim SH, Lee CM, Bae JW, et al. Effects of diltiazem, a moderate inhibitor of CYP3A4, on the pharmacokinetics of tamsulosin in different CYP2D6 genotypes. *Arch Pharm Res.* 2018;41(6):564–70. doi:10.1007/s12272-018-1030-6
27. Kim KA, Park IB, Park JY. Effects of CYP2D6 and CYP3A5 genetic polymorphisms on steady-state pharmacokinetics and hemodynamic effects of tamsulosin in humans. *Eur J Clin Pharmacol.* 2018;74(10):1281–9. doi:10.1007/s00228-018-2501-x
28. National Center for Biotechnology Information (NCBI). Gene [Internet]. Bethesda (MD): National Library of Medicine;2004 [cited 2021 May 31]. Available from: <https://www.ncbi.nlm.nih.gov/gene>.
29. Gotanda K, Tokumoto T, Hirota T, Fukae M, Ieiri I. Sulfasalazine disposition in a subject with 376C>T (nonsense mutation) and 421C>A variants in the ABCG2 gene. *Br J Clin Pharmacol.* 2015;80(5):1236–7. doi:10.1111/bcp.12654
30. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther.* 2012;92(4):414–7. doi:10.1038/clpt.2012.96