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Original Scientific Article

POPULATION PHARMACOKINETICS OF PANTOPRAZOLE IN PATIENTS ON DUAL ANTIPLATELET THERAPY FOLLOWING ACUTE CORONARY SYNDROME

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Abstract. *This study investigates factors influencing pantoprazole pharmacokinetics (PK) in patients with acute coronary syndrome (ACS) undergoing dual antiplatelet therapy (DAPT) comprising acetylsalicylic acid and clopidogrel, alongside concomitant pantoprazole to mitigate gastrointestinal risks. We conducted a prospective analysis on 93 ACS patients, assessing pantoprazole PK parameters and their correlation with C-reactive protein (CRP) levels, indicative of inflammation. Blood samples for pantoprazole concentration and CRP levels were collected according to a predefined schedule, post-oral pantoprazole administration at steady state. The study highlights a notable influence of CRP levels on pantoprazole clearance, underscoring inflammation's impact on drug metabolism. Elevated CRP was associated with altered pantoprazole pharmacokinetics, suggesting that inflammatory status significantly contributes to metabolic variability in this patient population. Our findings suggest the need for personalized pantoprazole dosing in ACS patients on DAPT, considering the inflammatory status as reflected by CRP levels. This approach could optimize therapeutic efficacy and minimize adverse effects, advancing personalized treatment strategies in the management of ACS.*

Key words: *pantoprazole, acute coronary syndrome, population pharmacokinetics, proton pump inhibitors, NONMEM*

INTRODUCTION

Dual Antiplatelet Therapy (DAPT) is a cornerstone in the management of acute coronary syndrome (ACS), particularly in the setting of percutaneous coronary intervention (PCI). While the standard duration is 12 months, its application is highly individualized. Tailoring DAPT duration based on patient-specific factors, risk assessment, and clinical judgment is crucial to optimizing outcomes and balancing the prevention of ischemic events and the risk of bleeding complications. Gastrointestinal bleeding (GIB) during DAPT is a complex phenomenon influenced by multiple mechanisms. Platelet dysfunction, gastric acid reduction, mucosal vulnerability, drug interactions, individual patient factors, and the direct effects of antiplatelet agents, all contribute to this risk. Proton pump inhibitors (PPIs) have been considered a potential strategy to mitigate this risk [1,2].

The association between chronic PPI use and adverse effects, including increased cardiovascular and cerebrovascular risk, renal deterioration, and the onset of dementia, raises important questions regarding the long-term safety of these medications. While these associations have been noted in epidemiological studies, it is essential to acknowledge that causation has not been definitively established, and the precise mechanisms are still under investigation [3,4].

Pantoprazole stands apart from other proton pump inhibitors (PPIs) due to its selective binding to the ion transport pathway, its stable nature at neutral pH values, and its robust plasma concentration-time curve. The increase in C_{max} (maximum concentration) and AUC (area under the curve) is directly proportional to both oral and intravenous doses ranging from 10 to 80 mg. Notably, pantoprazole does not accumulate, and its pharmacokinetics remain unchanged with multiple daily doses. Following oral or intravenous administration, the serum concentration of pantoprazole undergoes a bi-exponential decline, characterized by a terminal elimination half-life ($t_{1/2}$) of approximately 1 hour [5].

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Pantoprazole undergoes extensive hepatic metabolism primarily through the cytochrome P450 isoenzyme 2C19 (CYP2C19) and, to a lesser extent, CYP3A-mediated oxidation. Following this oxidative step, sulfate conjugation occurs, with the primary route of elimination being through the kidneys [6]. Genetic variations in CYP2C19, a crucial enzyme in pantoprazole metabolism, significantly influence drug pharmacokinetics and treatment outcomes [7,8]. The major variant, CYP2C19*2 (rs4244285, c.G681A, p.P227P), is linked to a 'no function' phenotype, resulting in compromised enzyme activity. Approximately 25–35% of individuals of European and African descent and around 60% of Asians carry at least one copy of this nonfunctional allele. Less common variants, including CYP2C193, *4, *5, *6, *7, and *8, further contribute to CYP2C19 variability. Poor metabolizers (PM) with two copies of these nonfunctional alleles constitute a significant proportion of specific populations, such as 2–5% of Europeans and Africans and 15% of Asians. Intermediate metabolizers (IM), with one copy of these alleles, account for 25–35% of Europeans and Africans and 45–50% of Asians. In contrast, an elevated function polymorphism in CYP2C19, specifically 17 (rs12248560), accelerates drug clearance. Approximately 30% of individuals of European and African descent and 2–4% of Asians carry at least one copy of CYP2C1917. This enhanced function allele classifies individuals as rapid metabolizers (RM) or ultra-metabolizers (UM), based on the number of copies of the allele [9].

Given these considerations, the aim of our study is to use a population pharmacokinetic model to investigate the factors influencing the clearance of pantoprazole in patients with ACS. The study explores the complex interplay of drug interactions, patient-specific factors, and their impact on pantoprazole pharmacokinetics in the context of DAPT. This investigation provides valuable insights for optimizing therapeutic strategies in this specific patient population.

METHODS

Patient Data

The investigation was conducted at the Clinic of Cardiology, University Clinical Center Niš, Serbia, over a three-month period from February to May 2016, following approval from the Ethics Committee of the University of Nis Faculty of Medicine (No. 01-2625-10). Prior to inclusion, all patients were provided detailed information about the study protocol and were enrolled upon providing written consent. The inclusion criteria comprised patients of both sexes aged 18 years and older, diagnosed with ACS with or without ST-elevation, as confirmed by cardiologists using electrocardiograms and biochemical tests. Exclusion criteria for the study encompassed pregnant and lactating women, individuals with mental disorders, and patients who declined to participate in the study.

Our study encompassed a population of 93 patients who were treated with pantoprazole, in accordance with the requirements of the Institutional Review Board/Human Subjects Research Committee. All patients received dual antiplatelet therapy, consisting of acetylsalicylic acid and clopidogrel. Additionally, all patients were administered angiotensin-converting enzyme (ACE) inhibitors and other medications as outlined in Table 1. Pantoprazole was administered according to medication recommendations. Clinical and demographic data, including ejection fraction (EF), concomitant diseases, total body weight (TBW), age, and gender, were sourced from medical records. Information regarding patients' lifestyle habits was gathered through conversations with the patients.

Blood sampling and laboratory analysis

The study protocol involved obtaining four blood samples from each patient: two for routine laboratory tests, and two additional blood samples were utilized for genotyping the patients and measuring drug concentrations, respectively. The samples for pantoprazole serum concentrations assessment were obtained at a steady state, 3 days after the medication initiation, 2h after the administration of an oral dose.

Pantoprazole concentrations were measured from the serum using ultrahigh-performance liquid chromatography with diode array detector-mass spectrometry analysis. Analysis was carried out on a Dionex Ultimate 3000 UHPLC system equipped with a DAD-detector and connected to LCQ Fleet Ion Trap Mass Spectrometer (Thermo Fisher Scientific, USA), and separations were performed on a Poroshell 120 EC-C18 column (4.6×50mm, 2.7μm; Agilent technology, USA) at 25◦C. The absorption was recorded on a DAD-detector set at three detection wavelengths of 240, 220, and 300 nm, simultaneously. Mass spectrometric analysis was performed using an LCQ 3D-ion trap mass spectrometer with electrospray ionization in positive ion mode. MS-spectra were acquired by full range acquisition of m/z 300–500. For the fragmentation study (MS/MS), a data-dependent scan was performed by deploying the collision–induced dissociation at 25eV. The range of detection was 0.1-22.5mg/l.

The genotyping analysis of patients involved the preliminary step of manually isolating genomic DNA from whole-blood leukocytes. Subsequently, small nuclear polymorphisms (SNPs) were determined using the polymerase chain reaction (PCR) method for specific genetic markers, including *ABCB1 C3435T* (rs1045642), as well as *CYP2C19*2* (rs4244285) and **17* (rs12248560). The commercial mix KAPA2G Readymix (KAPA2G Ready-Mix FastHotStart; Kappa Biosystems, Boston, MA, USA) and a reaction mixture with specific primers were employed for the detection of these SNPs.

For the *ABCB1 C3435T* gene polymorphism, allele-specific primers were used. Other SNPs were determined using forward and reverse primers. Restriction enzymes added to the mixture were as follows: SmaI (*CYP2C19*2*) and LweI (*CYP2C19*17*). Allele determination was performed after vertical electrophoresis on 8%

polyacrylamide gel (*ABCB1 C3435T* and *CYP2C19*2*) or horizontal electrophoresis on 2% agarose gel (*CYP2C19*17*). *CYP2C19* genotypes were classified into four phenotypes: poor metabolizers (PM: homozygotes for *2 or *3), intermediate metabolizers (IM: *wt/*2* or *wt/*3*), extensive metabolizers (EM: *wt/wt*) and ultrarapid metabolizers (homozygotes or heterozygotes for **17*). For PPK analysis, patients were stratified according to metabolism activity: *ABCB1 CC-CT-TT* and *CYP2C19* PM-IM-EM-URM.

Population pharmacokinetics analysis

The population pharmacokinetic (PK) analysis of pantoprazole was conducted through nonlinear mixed-effects modeling (NONMEM (RRID:SCR_016986), version 7.3.0, Icon plc, Dublin, IE). The two-compartment linear mammillary model was used (ADVAN4 TRANS3 subroutine), based on previous knowledge of pantoprazole pharmacokinetics. To effectively capture interindividual and residual variability, various error models were explored, including additive and exponential for interindividual variability and additive, proportional, exponential, or combined for residual variability. Model suitability was evaluated using goodness-of-fit plots, comparing measured concentrations with population-predicted concentrations for the tested drugs. The base models focused on the following PK parameters: apparent clearance (CL), apparent volume of distribution (V), intercompartmental clearance (Q), volume of distribution at steady-state (VSS), and absorption constant (KA). Absolute bioavailability was not assessed since pantoprazole was administered orally to all the patients.

Table 1 Demographic, biochemical and clinical data derived from the study sample

Characterisctics	Index set (mean values ± SD[a])	Range for index set
Number of patients	93	
Number of observations	93	
Sex (male/female)	58/35	
TBW[b] (kg)	77.01±11.08	55-120
Age (years)	61.25±11.59	34-89
Pantoprazole daily dose (mg/day)	40.43±6.58	20-80
Pantoprazole serum concentration (mg/l)	0.3386±0.0381	0.0823-2.3367
ABCB1:	93	
CC	27	
CT	46	
TT	20	
CYP2C19:	93	
poor metabolizers (PM)	2	
intermediate metabolizers (IM)	26	
extensive metabolizers (EM)	39	
ultrarapid metabolizers (URM)	26	
Ejection fraction (%)	49.96±11.07	28-79
Clopidogrel daily dose (mg/day)	81.545±21.14	75-150
AST[c] (U/l)	127.52±169.89	13.4-930
ALT[d] (U/l)	40.99±32.13	1.27-175.5
CRP[e] (mg/l)	17.51±30.66	0.3-200.5
Creatinine clearance (l/h)	4.45±1.51	0.63-9.28
Hypertension	58	
Diabetes mellitus	27	
Smokers	29	
Acyte miocardial infarction:		
STEMI[f]	70	
NONSTEMI[g]	23	
Comedication with:		
Acetylsalicylic acid	93	
ACE inhibitors	66	
Spironolactone	16	
Amiodarone	11	
Digoxin	7	
Sulphonylureas	8	
Trimetazidine	7	
Beta blockers:	69	
Bisoprolol	61	
Carvedilol	7	
Nebivolol	1	
Statin:	88	
Atorvastatine	67	
Rosuvastatine	5	
Simvastatine	16	

[a] standard deviation; [b] total body weight; [c] aspartate transaminase; [d] alanine transaminase; [e] C-reactive protein; [f] acute myocardial infarction with ST elevation; [g] acute myocardial infarction without ST elevation

The impact of 25 covariates on the PKs of pantoprazole was assessed (Table 1). Creatinine clearance in patients was calculated using the Cockcroft-Gault equation. Full model development involved examining each covariate for inclusion through a forward selection process based on an additive regression using linear or exponential functions. A full population PK model for drug clearance was created by simultaneous inclusion of covariates with a difference in the minimum of the objective function (MOF) value higher than 3.84 ($p<0.05$, df=1) and low interindividual and residual variability. Subsequently, the included covariates underwent backward elimination following the same order as introduced in the model, with a more restrictive criterion, i.e., deletion of each covariate except when the MOF increase after elimination was higher than 6.63 ($p<0.01$, df=1), in which case the covariate was considered significant. As a result, the final population PK models contained only covariates fulfilling both requirements of stepwise regressions. The final and basal models were validated by bootstrap analyses with 200 samples each.

RESULTS

Ninety-three patients of both sexes were engaged to determine the population values of pantoprazole clearance. Their mean values of age and total body weight were 61 years and 77kg, respectively. Pantoprazole was administered orally as tablets of 20mg or 40mg registered in Serbia. A wide range of HPLC - measured concentrations of the drug in steady-state was noted in our target population. Its values were from 0.0823 to 2.3367mg per liter after usage of the average pantoprazole dose of 40mg. Our analysis included several different covariates such as: patient age, weight and sex, clinical data (ejection fraction, STEMI or NONSTEMI myocardial infarction, presence of hypertension and diabetes mellitus) biochemical (alanine and aspartate transaminase, C reactive protein, creatinine clearance) and genetic parameters (ABCB1 and CYP2C19 genotype), life habits, as well as dose of pantoprazole and co-administered drugs or their dosage (from ten different drug groups). To examine their influence on the value of pantoprazole clearance in the population the ADVAN4 TRANS3 subroutine from the NONMEM software was used, reflecting the two-compartment linear mammillary model.

Table 2 MOF values for the basic and univariate regression models of investigated covariates obtained in the process of building full PK model of pantoprazole clearance

Clearance models	Minimum objective function	P-value*
Base Model		
$CL^{a}= \theta_1{}^{b}\times EXP(ETA(1)^{c})$	1182.883	
Univariate Regression Models		
$CL= \theta_1\times EXP(ETA(1)) + \theta_2{}^{d}\times AGE$	1180.123	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_3\times TBW^{e}$	1181.964	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_4\times SEX^{f}$	1182.883	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_5\times DD^{g}$ of pantoprazole	1182.832	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_6\times ABCB1^{h}$	1181.005	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_7\times$ CYP2C19 phenotype^{i}	1181.888	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_8\times EF^{j}$	1182.844	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_9\times$ DD of clopidogrel	1182.882	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{10}\times AST^{k}$	1182.854	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{11}\times ALT^{l}$	1182.833	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{12}\times CRP^{m}$	1176.471	<0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{13}\times CLcr^{n}$	1181.966	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{14}\times HTA^{o}$	1182.883	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{15}\times DM^{p}$	1182.883	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{16}\times TOB^{q}$	1182.004	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{17}\times MI^{r}$	1182.883	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{18}\times ASK^{s}$	1182.883	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{19}\times ACEi^{t}$	1182.881	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{20}\times SPI^{u}$	1182.883	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{21}\times AMI^{v}$	1182.883	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{22}\times DIG^{w}$	1182.452	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{23}\times SUL^{x}$	1182.770	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{24}\times TRIM^{y}$	1182.883	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{25}\times BB^{z}$	1182.836	>0.05
$CL= \theta_1\times EXP(ETA(1)) + \theta_{26}\times STAT^{aa}$	1173.605	<0.05
Full Model		
$CL= \theta_1\times EXP(ETA(1)) + 0.0000488\times CRP + 0.00237\times STAT$	1165.832	

[a] pantoprazole clearance (l/h); [b] typical value of CL; [c] interindividual variability in CL; [d] θ_2 to θ_{26} slopes of the covariate effects; [e] patient´s body weight (kg); [f] takes the value 1 for male and 0 for female; [g] daily dose of pantprazole or clopidogrel (mg/day); [h] ABCB1 (CC=1, CT=2, TT=3), [i] CYP2C19 (PM=1, IM=2, EM=3, URM=4); [j] ejection fraction; [k] aspartate transaminase; [l] alanine transaminase; [m] C raective protien; [n] creatinine clearance (l/h); [o] presence of hypertension; [p] presence of diabetes mellitus; [q] takes the value 1 for smokers and 0 for non-smokers; [r] type of miocardial infarction; co-medication with ASK[s] (acetylsalicylic acid), ACEi[t] (angiotensing-converting-enzyme inibitors), SPI[u] (spironolactone), AMI[v] (amiodarone), DIG[w] (digoxin), SUL[x] (sulphonylureas), TRIM[y] (trimetazidine), BB[z] (beta blockers), STAT[aa] (statine) takes the value 1 if the patient received co-medication and 0 otherwise.
*P-value for the MOF difference between the base and tested models

The estimated values of apparent pantoprazole clearance and apparent volume of distribution were 0.019 liters per hour and 3.81 liters, respectively. These values were obtained using initial literal and the collected data from the study sample and referred to the base model. The next step of the analysis was the testing effect of each covariate on drug clearance. The difference in the minimum objective function between the base and each univariate model was carefully recorded. This value was the main statistical criterion for assessing the significance of covariates and had to be greater than 3.84 ($p < 0.05$, df=1). Although we investigated the effects of twenty-five covariates, only two fulfilled the required statistical requirements and were included in the full model of pantoprazole clearance: C reactive protein and co-medication with a statin (Table 2). After backward deletion both covariates from the full model remained in the final model, since their independent elimination had increased the MOF by more than 6.62 ($p<0.01$, df=1) (Table 3). Based on the final model, the population clearance of pantoprazole in the target population could be described by the following equation:

$$CL = 0.009 + 0.0000488 \times CRP + 0.00237 \times STATIN$$

Parameter estimates of the final model were confirmed by the results of the bootstrapping analysis (Table 4) which indicated its stability and precision. Furthermore, the graphic layout of points connecting individual predicted and measured pantoprazole concentrations (ng/ml) in Figure 1, as well as the reduction of interindividual and residual variability (expressed as coefficient of variation) between the base and the final model for 20.18% and 11.46%, respectively, both suggest the good predictive ability of the final population model of pantoprazole clearance in the target population.

Table 3 The process of deletion of significant covariates from the full PK model of pantoprazole clearance.

Covariate	Increase in MOF value	P-value
C reactive protein	10.904	<0.01
Statine	8.02	<0.01

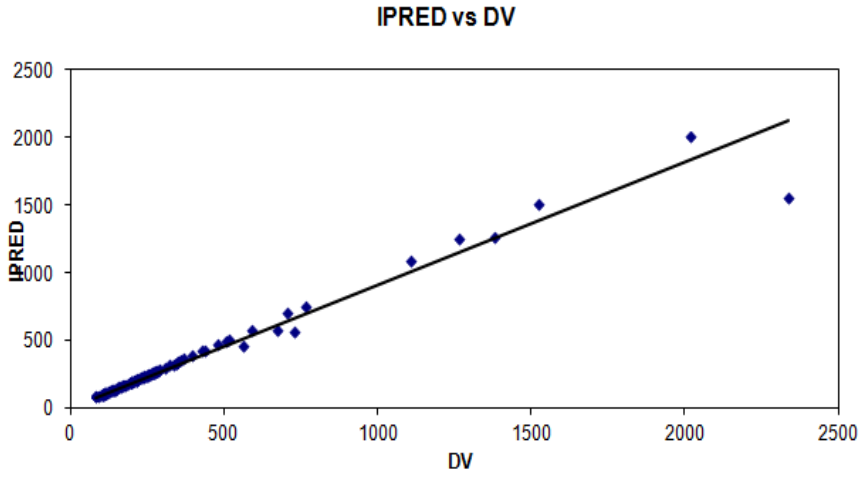

Fig 1 Scatterplot of individual pantoprazole concentrations (IPRED) predicted by the final model versus its measured concentrations (DV) in ng/ml.

Table 4 Estimates of the final model parameters.

Parameter	NONMEM		Bootstrap Analysis	
	Estimate	95% CI*	Estimate	95% CI**
CL/F[a] (l/h)	0.009	0.0039–0.0141	0.0087	0.0042–0.0132
Vd/F[b] (l)	2.47	1.974–2.966	2.51	2.01–3.01
VSS/F[c] (l	21400	18852–23948	21732	19432–24032
Q/F[d] (l h^{-1})	0.205	0.159–0.251	0.211	0.138–0.284
ω^2_{CL}[e]	0.104	0.067–0.141	0.107	0.056–0.158
σ^2 (exponential)[f]	0.05	0.0272–0.0728	0.049	0.0291–0.0697

[a] apparent clearance; [b] apparent volume of distribution; [c] apparent volume of distribution in the steady-state; [d] intercompartmental clearance; [e] interindividual variance of CL; [f] residual variance

* (Estimate)±1.96 × (standard error of the estimate); ** 2.5th and 97.5th percentile of the ranked bootstrap parameter estimates

DISCUSSION

The objective of the present study was to establish and apply a population pharmacokinetic model for pantoprazole clearance in routinely treated ACS patients. In the absence of prior studies measuring pantoprazole clearance in ACS patients, our investigation represents a pioneering effort, limiting our ability to contextualize the observed results. According to our base model, without incorporating covariates, the average values for pantoprazole clearance and apparent volume of distribution in our population were 0.019 l/h and 3.81 liters, respectively. In our final model, constructed to elucidate the factors influencing pantoprazole clearance, C-reactive protein (CRP) levels and co-medication with statins emerged as the sole significant covariates, forming the foundation of a comprehensive pharmacokinetic model for pantoprazole clearance in this patient population.

Several studies have delved into the relatively understudied impact of inflammation on drug pharmacokinetics. They underscore the significance of inflammation as an intrinsic factor capable of influencing an individual's metabolic phenotype, thereby potentially affecting drug metabolism. This emphasizes that, beyond external factors like drug-drug interactions and food-drug interactions, inflammation can play a substantial role in what is termed "metabolic phenoconversion" [10]. To support the concept that inflammation significantly impacts individual metabolic capacity, a study conducted controlled laboratory experiments using liver and intestinal cell lines [11]. The exposure of these cells to various cytokines led to a notable decrease in CYP mRNA, accompanied by simultaneous reductions in protein production and a corresponding decline in metabolic activity. Particularly, interleukin-6 (IL-6) was identified as a key contributor to these observed effects [12]. Moreover, the study employed pharmacokinetic modelling utilizing physiology-based pharmacokinetics (PBPK) [13]. This approach was utilized to investigate the impact of inflammation on the activities of cytochrome P450 enzymes, specifically CYP3A4 and CYP2C19. The selected probe drugs for the study were midazolam, voriconazole, and omeprazole, all known to interact with both CYP3A4 and CYP2C19. CRP levels were selected as a marker for inflammation. The results demonstrated that integrating PBPK models with routinely measured CRP levels effectively predicted how inflammation influences the pharmacokinetics of substrates metabolized by CYP2C19 and CYP3A4. In the absence of specific data on inflammatory cytokine concentrations, CRP levels proved valuable as indicators of inflammatory status. Inflammatory cytokines are recognized for stimulating the production of acute-phase proteins, with CRP exhibiting rapid fluctuations in response to changes in a patient's inflammatory status. Consequently, CRP concentrations are widely employed in routine clinical practice as reliable markers of inflammation [14]. The standpoint endorsed by the French Society of Pharmacology and Therapeutics aligns with the notion that inflammation biomarkers, such as CRP, should be regarded as potential covariates in population pharmacokinetic studies. This recommendation is particularly emphasized for drugs that undergo extensive metabolism [10].

"Phenoconversion" refers to the disparity between a patient's genetically predicted drug-metabolizing phenotype and their actual metabolizer status. This phenomenon can be triggered by various factors, including concomitant drug use and patient- or disease-related factors [15]. The frequent association of concomitant medication use with phenoconversion is well-documented, reflecting the influence of drug-drug interactions on drug pharmacokinetics. Simultaneous administration of potent CYP2C19 inhibitors typically induces phenoconversion in most subjects. However, individuals with genotypic intermediate metabolizer (IM) status may be particularly susceptible to phenoconversion induced by CYP2C19 inhibitors compared to other metabolizer statuses. The expected frequency of CYP2C19 poor metabolizers (PMs) based on genotype was initially 2.7%, but phenoconversion increased this frequency to 17%, a 5.7-fold rise attributed to the impact of drugs acting as moderate or potent CYP2C19 inhibitors [16]. In summary, in pathological conditions, inflammatory cytokines have the potential to down-regulate the expression of the CYP2C19 gene. However, the precise regulatory mechanisms governing this process are not fully understood. Taking these observations into account, it can be deduced that the importance of CYP2C19 in our pharmacokinetic study was blundered by phenoconversion.

The primary metabolic pathway of pantoprazole involves demethylation by CYP2C19, followed by sulfation. Furthermore, an alternative metabolic route involves oxidation facilitated by CYP3A4. In situations where the primary metabolic pathway of pantoprazole mediated by CYP2C19 is down-regulated, an alternative pathway involving CYP3A4 takes precedence. The increased involvement of CYP3A4, known for its high capacity, serves as a protective mechanism against elevated concentrations of pantoprazole [17]. This protective function is particularly crucial in instances where the activity of CYP2C19 is diminished due to inflammation-induced conditions.

In vitro investigations have demonstrated that statins possess the ability to augment the expression of CYP3A [18]. This phenomenon is ascribed to the role of statins as ligands for nuclear receptors, specifically the pregnane X receptor and the constitutive androsterone receptor. These nuclear receptors form heterodimers with retinoid X receptors, binding to responsive elements situated in the promoter regions of CYP3A4 and CYP3A5. Moreover, the correlation between the mRNA level, protein expression, and metabolic activity of this isoenzyme has been verified [19]. Statins such as atorvastatin, simvastatin, and lovastatin are metabolized primarily via CYP3A4 and CYP2C9, with the former two also acting as prodrugs. These statins, particularly atorvastatin, can also inhibit

CYP3A4, adding complexity to their potential for drug-drug interactions. This variability in metabolism and interaction potential necessitates careful statin selection to optimize patient care [20].

Considering the factors discussed earlier, such as the inflammation-mediated regulation of CYP2C19 activity, the predominant involvement of CYP3A4 in these conditions, and the potential induction of CYP3A4 by statins, these elements collectively provide an explanatory framework for incorporating CRP levels and concurrent statin use as pivotal variables in our final pharmacokinetic model.

Our study presents certain noteworthy limitations. Firstly, the small sample size may introduce some degree of result variability. Additionally, the study's scope was confined to a limited set of variables, which cannot comprehensively account for all the factors contributing to individual pharmacokinetic variations of pantoprazole.

Our findings on the significant influence of CRP levels and statin co-medication on pantoprazole clearance underscore the broader clinical and pharmacological principle that inflammation, as indicated by elevated CRP levels, can significantly impact drug metabolism. This aligns with broader research highlighting the role of inflammation in metabolic phenoconversion, further emphasizing the need for personalized treatment strategies that account for the inflammatory status of patients, particularly in those with ACS undergoing dual antiplatelet therapy.

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