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ORIGINAL RESEARCH ARTICLE

Evaluation of CYP2C19-Mediated Pharmacokinetic Drug Interaction of Tegoprazan, Compared with Vonoprazan or Esomeprazole

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Abstract

Background and Objective CYP2C19-mediated drug interactions of acid-reducing agents are clinically important given the high possibility of concomitant administration with CYP2C19 substrates. This study aimed to evaluate the effect of tegoprazan on the pharmacokinetics (PK) of a CYP2C19 substrate, proguanil, compared with vonoprazan or esomeprazole.

Methods A two-part, randomized, open-label, two-sequence, three-period crossover study was conducted in 16 healthy CYP2C19 extensive metabolizers (eight subjects per part). In each period, a single oral dose of atovaquone/proguanil 250/100 mg was administered alone or co-administered with tegoprazan 50 mg, esomeprazole 40 mg (Part 1 only) or vonoprazan 20 mg (Part 2 only). The plasma and urine concentrations of proguanil and its metabolite, cycloguanil, were measured up to 48 h post-dose. PK parameters were calculated using a non-compartmental method and compared between administered alone and co-administered with tegoprazan, vonoprazan or esomeprazole.

Results Co-administration of tegoprazan did not significantly affect the systemic exposure of proguanil and cycloguanil. In contrast, co-administration of vonoprazan or esomeprazole increased proguanil systemic exposure and decreased cycloguanil systemic exposure, and the magnitude of the corresponding change was greater with esomeprazole co-administration than vonoprazan co-administration.

Conclusion Tegoprazan, unlike vonoprazan and esomeprazole, exhibited negligible CYP2C19-mediated PK interaction. It suggests that as an alternative to other acid-reducing agents, tegoprazan can be used concomitantly with CYP2C19 substrates in clinical settings.

Trial Registration Clinicaltrials.gov identifier: NCT04568772 (Registered on September 29, 2020).

1 Introduction

Acid-reducing agents, especially proton pump inhibitors (PPIs), are widely used to control gastric acid-related disorders and prevent drug-induced gastrointestinal complications [1, 2]. Because most PPIs are predominantly metabolized by cytochrome P450 (CYP) 2C19 and have CYP2C19 inhibitory effects, the intake of PPIs in combination with CYP2C19 substrates requires caution regarding pharmacokinetic (PK) drug interactions and, by extension, their clinical relevance [2, 3]. Notably, concomitant PPI administration is recommended as a gastroprotective agent in patients who receive antiplatelet therapy with clopidogrel, which is a well-known CYP2C19 substrate [1, 4]. Accordingly, the CYP2C19-mediated drug interactions of PPIs are clinically important issues given the high possibility of concomitant use with CYP2C19 substrates.

CYP2C19-mediated drug interactions of PPIs may result in unwarranted clinical outcomes. PPIs, including esomeprazole, exhibit PK interactions with CYP2C19 substrates, such as diazepam, phenytoin, warfarin, and clopidogrel, most of which are of clinical significance [5–7]. In particular, clopidogrel, which is often used in combination with PPIs in clinical practice, requires the formation of an active metabolite by CYP2C19 to exert its antiplatelet activity [4], and it was reported that concomitant PPI administration reduced the antiplatelet effect of clopidogrel and ultimately increased the cardiovascular events of patients [8, 9]. Therefore, alternative acid-reducing agents to PPIs that can be

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Key Points

Tegoprazan, a novel potassium-competitive acid blocker, is expected to exert negligible cytochrome P450 (CYP) 2C19 interaction based on in vitro studies. Considering the clinical importance of CYP2C19-mediated drug interactions of acid-reducing agents, this study evaluated the effect of tegoprazan on CYP2C19 activity, compared with vonoprazan or esomeprazole, using proguanil as a CYP2C19 substrate.

Tegoprazan had no meaningful effect on proguanil pharmacokinetics, which indicates that tegoprazan is neither an inhibitor nor an inducer of CYP2C19. In contrast to tegoprazan, vonoprazan and esomeprazole both decreased the CYP2C19-mediated metabolism of proguanil.

Tegoprazan exhibited insignificant CYP2C19-mediated pharmacokinetic interaction. Our findings suggest that as an alternative to other acid-reducing agents, tegoprazan can be used concomitantly with CYP2C19 substrates in clinical practice without any dose adjustment.

used concomitantly with CYP2C19 substrates without caution are needed.

Potassium-competitive acid blockers (P-CABs) are a novel class of acid-reducing agents that overcome several limitations of PPIs, such as nocturnal acid breakthrough [10]. It is noteworthy that the concomitant administration of P-CABs is likely not restricted by CYP2C19-mediated drug interactions considering their elimination pathways are mainly via CYP3A4, not CYP2C19, and because of their relatively low in vitro CYP2C19 inhibition potential [10, 11].

Meanwhile, it was recently reported that vonoprazan, one of the P-CABs, acts as a clinically relevant CYP2C19 inhibitor at therapeutic doses although its CYP2C19 half-maximum inhibitory concentration (IC_{50}) value (13 μM) was sufficiently higher than its unbound maximum plasma concentration (C_{max}) (approximately 0.01 μM) at the therapeutic dose [12]. This result may partially explain the previously reported attenuation of the antiplatelet function of clopidogrel by vonoprazan [13]. These unexpected findings suggest the need for clinical evaluations of the CYP2C19-mediated PK interactions of other P-CABs for use in combination with CYP2C19 substrates in clinical settings.

Tegoprazan is a newly approved P-CAB for the treatment of acid-related diseases in several countries, including the Republic of Korea. Given its sufficient acid suppression, tegoprazan also has potential for combination therapy with various drugs including CYP2C19 substrates, as a gastroprotective agent in addition to an acid suppressant [14]. Even though tegoprazan is expected to exert negligible CYP2C19 interaction based on in vitro studies (IC_{50} >30 μM), the CYP2C19-mediated PK interaction of tegoprazan has not been clinically evaluated. Indeed, like vonoprazan, the unbound C_{max} of tegoprazan (approximately 1.3 μM) at the therapeutic dose is much lower than the aforementioned IC_{50} value [15].

This study was aimed to evaluate the effect of tegoprazan on the PK of a CYP2C19 substrate, proguanil, compared with vonoprazan or esomeprazole. Proguanil was chosen as the CYP2C19 substrate in this study because it is primarily metabolized to cycloguanil by CYP2C19, and approximately 40–60% of the dose is renally excreted [16].

2 Methods

The Institutional Review Board of Seoul National University Hospital and the Korean Ministry of Food and Drug Safety approved the study protocol and informed consent form. This study was conducted in accordance with the Korean Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The study was registered in the public clinical trial registry on September 29, 2020 (ClinicalTrials.gov identifier: NCT04568772). Eligible subjects were recruited through a recruitment notice at the Seoul National University Hospital Clinical Trials Center, including the website (https://ctcr.snuh.org/). Prior to any study-related procedures, written informed consent was obtained from all individual subjects.

2.1 Study Population

Eligible subjects were healthy CYP2C19 extensive metabolizers carrying the *CYP2C19 *1/*1* diplotype who were 19–50 years old with a body mass index (BMI) of 19.0–30.0 kg/m^2. Subjects who had evidence or a history of gastrointestinal disorders likely to influence drug absorption and/or who ingested drug metabolizing inducers (e.g., barbiturates) or inhibitors (e.g., clarithromycin) within 4 weeks prior to the first administration and/or other medications within 2 weeks prior to the first administration were excluded from the study. The exclusion criteria also included aspartate aminotransferase or alanine aminotransferase values 1.5 times greater than the upper normal limit or Modification of Diet in Renal Disease (MDRD) glomerular filtration ratio (GFR) values < 80 mL/min. The enrolled subjects were prohibited from

intake of any medication without the prior permission of the investigators and the consumption of grapefruit products, caffeine, or alcohol throughout the study. The sample size was determined empirically based on the exploratory and descriptive characteristics of the study without calculating study power for any statistical hypothesis.

2.2 Study Design

This study had a two-part, randomized, open-label, two-sequence, three-period crossover design (Fig. 1). Each sequence consisted of the following three treatments (i.e., one control treatment and two co-administration treatments): a single oral administration of atovaquone/proguanil 250/100 mg alone [control], 6-day pretreatment with once-daily oral doses of tegoprazan 50 mg, followed by a single oral administration of atovaquone/proguanil 250/100 mg concomitant with tegoprazan 50 mg [co-administration], and 6-day pretreatment with once-daily oral doses of esomeprazole 40 mg, followed by a single oral administration of atovaquone/proguanil 250/100 mg concomitant with esomeprazole 40 mg (Part 1) or 6-day pretreatment with once-daily oral doses of vonoprazan 20 mg, followed by a single oral administration of atovaquone/proguanil 250/100 mg concomitant with vonoprazan 20 mg (Part 2) [co-administration]. In accordance with the guideline for clinical drug interaction studies, the dose of each study drug was set to the therapeutic dose for a substrate, proguanil, and to the approved maximum dose for perpetrators, tegoprazan, vonoprazan, and esomeprazole, respectively [17]. The following drug products were used: atovaquone/proguanil 250/100 mg (Malarone® Tab., GlaxoSmithKline Inc., Seoul, Republic of Korea), tegoprazan 50 mg (K-CAB® Tab. 50 mg, HK inno.N Corp., Seoul, Republic of Korea), esomeprazole 40 mg (Nexium® Tab. 40 mg, AstraZeneca Pharmaceutical Co., Ltd., Seoul, Republic of Korea), or vonoprazan 20 mg (Takecab® Tab. 20 mg, Takeda Pharmaceutical Co., Ltd., Tokyo, Japan).

The enrolled subjects were randomly assigned to one of two sequences in each part and received their respective treatment with 150 mL of water after at least 10 h of overnight fasting. The respective treatment was separated by a 7-day washout period, which was set based on the turnover half-life ($t_{½}$) of CYP2C19 and the $t_{½}$ of the study drugs [14, 16, 18–20].

For PK analyses of proguanil and cycloguanil, blood samples were obtained at pre-dose and 1, 2, 3, 4, 6, 8, 10, 24, and 48 h after atovaquone/proguanil dosing, and urine samples were collected at pre-dose and 0–8, 8–24, and 24–48 h after atovaquone/proguanil dosing. At each blood sampling point, approximately 8 mL of blood was collected in a sodium heparin tube and then centrifuged at 4 °C and 3000 rpm for 10 min, and the supernatant was separated in Eppendorf tubes® and stored at −70 °C until analysis. At each urine collection interval, the collected urine was gently mixed, and separated and stored in the same manner as the blood samples.

2.3 CYP2C19 Genotyping

To identify CYP2C19 extensive metabolizers, DNA was extracted from whole blood using a Maxwell® CSC Blood DNA Kit and Maxwell® CSC Instrument (Promega, Madison, WI, USA), and TaqMan allelic discrimination assays were performed in a real-time polymerase chain reaction (PCR) System (Applied Biosystems, Foster City, CA, USA). A 10-µL PCR mixture was prepared with 5 µL of 2× TaqMan Universal Master Mix II, 0.5 µL of 20× Drug Metabolism Genotyping Assay Mix, 3.5 µL of DNase-free water, and 1 µL of DNA. Genotyping for the *CYP2C19*2* allele (rs4244285, assay ID: C__25986767_70) and *CYP2C19*3* allele (rs4986893, assay ID: C__27861809_10)

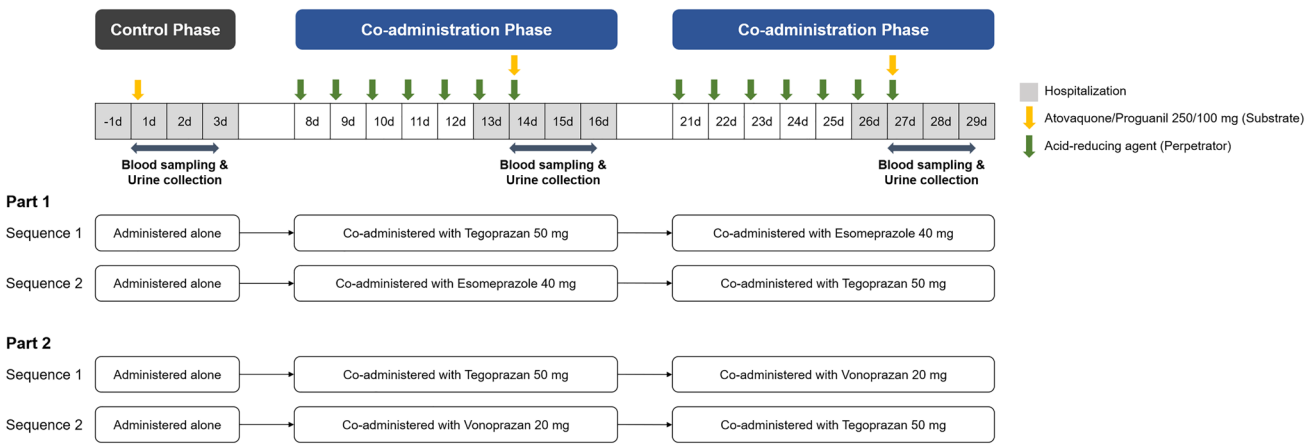

Fig. 1 Study design

was performed using validated TaqMan Genotyping Assays. The PCRs were carried out in the order of initial denaturation at 95 °C for 10 min followed by 40 cycles of denaturation at 95 °C for 15 seconds and annealing/extension at 60 °C for 1 minute. The allelic discrimination results were determined using 7500 Real-Time PCR System software version 2.0.6 (Applied Biosystems, Foster City, CA, USA). Based on the genotyping results, only CYP2C19 extensive metabolizers carrying the *CYP2C19 *1/*1* diplotype were included in the study.

2.4 Determination of Plasma and Urine Proguanil and Cycloguanil Concentrations

The plasma and urine concentrations of proguanil and cycloguanil were determined using validated high-performance liquid chromatography (HPLC; Agilent 1260/1290 Infinity system, Agilent Technologies) coupled with tandem mass spectrometry (MS/MS; API4000, AB Sciex for plasma samples and Agilent 6460, Agilent Technologies for urine samples). For plasma specimens, 50 µL of plasma was mixed with 10 µL of internal standard solution (0.2 µg/L proguanil-d_4 in 50% acetonitrile and 0.1 µg/L cycloguanil-d_4 in 50% acetonitrile, respectively), followed by 1 mL of 100% acetonitrile. Mixed solutions were centrifuged at 4 °C and 14,000 rpm for 5 min. The supernatant was dried at 40 °C and dissolved with 100 µL of 30% acetonitrile, followed by centrifugation at 4 °C and 14,000 rpm for 5 min. Then, 5 µL of the supernatant was subjected to HPLC-MS/MS analysis. For urine specimens, 50 µL of urine was mixed with 10 µL of internal standard solution (proguanil-d_4 12.5 µg/L in 50% acetonitrile and cycloguanil-d_4 10 µg/L in 50% acetonitrile, respectively), followed by 930 µL of 100% acetonitrile. Mixed solutions were centrifuged at 4 °C and 14,000 rpm for 5 min. The supernatant was dried at 40 °C and dissolved with 500 µL of 0.1% formic acid in 20% acetonitrile, followed by centrifugation at 4 °C and 14,000 rpm for 5 min. Then, 5 µL of the supernatant was subjected to HPLC-MS/MS analysis.

The lower limits of quantification for proguanil and cycloguanil were 1 µg/L and 0.5 µg/L, respectively, in plasma and 200 µg/L and 100 µg/L, respectively, in urine. The accuracies for proguanil and cycloguanil were 92.87–100.19% and 96.10–98.68%, respectively, in plasma samples and 96.65–99.75% and 99.28–100.95%, respectively, in urine samples. The precision coefficients of variation for proguanil and cycloguanil were ≤ 5.65% and ≤ 6.49%, respectively, in plasma samples and ≤ 2.32% and ≤ 2.69%, respectively, in urine samples.

2.5 Pharmacokinetic Analysis

The PK parameters of proguanil and cycloguanil were derived using a non-compartmental method in Phoenix® WinNonlin® version 8.2 (Certara, St. Louis, MO, USA). The area under the concentration–time curve (AUC) from 0 to last measurable time point (AUC_{last}) was calculated using the linear-up and log-down trapezoidal rule and extrapolated to infinity (AUC_{inf}) using the terminal elimination rate constant (λ_z). C_{max} and the time to reach C_{max} (T_{max}) were determined directly from the observed plasma concentration–time profiles. The elimination $t_{½}$ was calculated as ln(2) divided by λ_z, and the apparent clearance (CL/F) was calculated as the dose divided by AUC_{inf}. The fraction excreted unchanged in the urine (f_e) was calculated as the cumulative amount of proguanil in urine up to 48 h post-dose divided by the dose. The metabolic ratio was calculated as the AUC_{inf} ratio of cycloguanil to proguanil, and the apparent formation clearance (CL_F/F) was calculated as the cumulative amount of cycloguanil in urine up to 48 h post-dose divided by AUC_{last} of proguanil.

2.6 Safety Evaluation

Safety was evaluated based on adverse event (AE) monitoring, clinical laboratory tests, vital signs, physical examination, and 12-lead electrocardiogram (ECG) throughout the study. Each finding from the safety evaluation was assessed regarding its clinical significance and relationship with the treatment by the investigators.

2.7 Statistical Analysis

Statistical analyses were performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA). The demographic characteristics were compared between parts and sequences in each part using Wilcoxon's rank sum test. For control and tegoprazan co-administration treatments, the PK data from Part 1 and Part 2 were pooled. The PK parameters of proguanil and cycloguanil were summarized by treatment and compared between administered alone and co-administered with tegoprazan, vonoprazan, or esomeprazole. Analysis of variance was performed for log-transformed AUC and C_{max}, and the effects on the PK of proguanil and cycloguanil were compared by estimating the geometric mean ratios of each co-administration to control and the corresponding confidence intervals. Additionally, CYP2C19 metabolism-related PK parameters, the metabolic ratio and CL_F/F of cycloguanil were evaluated using Dunnett's t test.

3 Results

3.1 Study Population

A total of 19 healthy Korean male subjects, eight in Part 1 and 11 in Part 2, were enrolled in this study. Of those, three subjects involved in Part 2 discontinued the study before the second administration due to the practical issues of the site, and in consequence, 16 subjects, eight in each part, completed the study. All of the enrolled subjects were CYP2C19 extensive metabolizers. PK was analyzed in 16 subjects who had completed the study as planned, and safety was evaluated in 19 subjects who had taken the treatment at least once.

The arithmetic mean (± standard deviation) values of age, height, weight, and BMI of the enrolled subjects were 32.63 (± 7.70) years, 172.30 (± 6.29) cm, 73.57 (± 9.59) kg, and 24.79 (± 3.04) kg/m^2, respectively. The demographic characteristics of the enrolled subjects were not significantly different between parts or sequences in each part. Furthermore, the enrolled subjects did not take any medications other than the study drugs throughout the study.

3.2 Effect of Tegoprazan on the Pharmacokinetics of Proguanil and Cycloguanil

Co-administration of tegoprazan did not significantly affect the PK of proguanil and cycloguanil. When co-administered with tegoprazan, the plasma concentrations and the degree of urinary excretion of proguanil and cycloguanil were marginally higher or comparable to when administered alone (Figs 2 and 3). The systemic exposure of proguanil and cycloguanil was not significantly changed by concomitant tegoprazan administration, showing comparable AUC_{last} and C_{max} values (Fig. 4, Table 1). In addition, the metabolic ratio and CL_F/F of cycloguanil were similar regardless of tegoprazan co-administration (Fig. 5, Table 1), which indicated that tegoprazan had a negligible effect on the CYP2C19-mediated metabolism of proguanil to cycloguanil.

3.3 Effect of Vonoprazan or Esomeprazole on the Pharmacokinetics of Proguanil and Cycloguanil

Co-administration of vonoprazan or esomeprazole considerably changed the PK of proguanil and cycloguanil. When co-administered with vonoprazan or esomeprazole compared with when administered alone, the plasma concentrations and the degree of urinary excretion of proguanil were higher, and the corresponding profiles of cycloguanil were lower (Figs. 2 and 3). With each concomitant vonoprazan and esomeprazole administration, the systemic exposure of proguanil increased 18% and 32% in AUC_{last}, respectively, and the systemic exposure of cycloguanil decreased 25% and 51% in AUC_{last}, respectively, showing greater changes in esomeprazole co-administration than in vonoprazan co-administration (Fig. 4, Table 1). Correspondingly, the metabolic ratio and CL_F/F of cycloguanil were reduced with the co-administration of vonoprazan or esomeprazole (Fig. 5, Table 1), which indicated that vonoprazan and esomeprazole had meaningful effects on the CYP2C19-mediated metabolism of proguanil to cycloguanil.

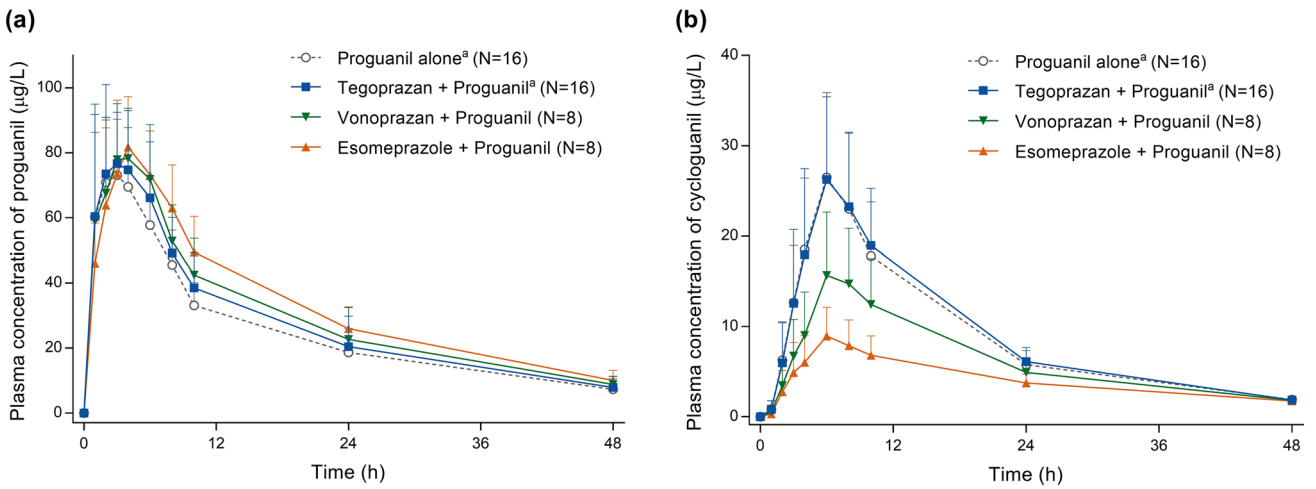

Fig. 2 Mean plasma concentration–time profiles of **a** proguanil and **b** cycloguanil following a single oral administration of atovaquone/proguanil 250/100 mg alone or co-administered with tegoprazan 50 mg, vonoprazan 20 mg or esomeprazole 40 mg in linear scale. The error bars represent the standard deviations. [a]The data from Part 1 and Part 2 were pooled

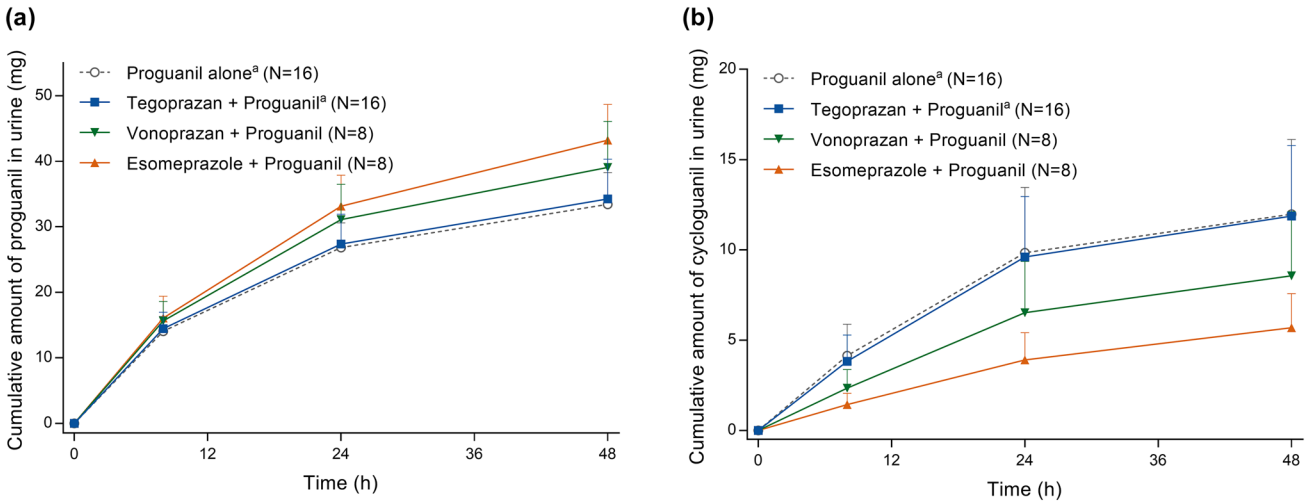

Fig. 3 Mean cumulative urinary excretion–time profiles of **a** proguanil and **b** cycloguanil following a single oral administration of atovaquone/proguanil 250/100 mg alone or co-administered with tegoprazan 50 mg, vonoprazan 20 mg or esomeprazole 40 mg in linear scale. The error bars represent the standard deviations. [a]The data from Part 1 and Part 2 were pooled

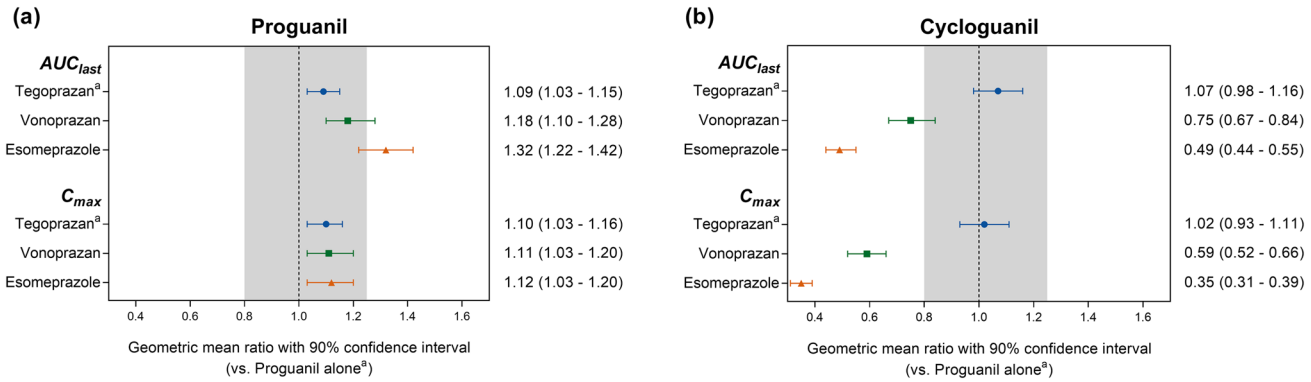

Fig. 4 Effect of tegoprazan, vonoprazan or esomeprazole on the pharmacokinetics of **a** proguanil and **b** cycloguanil. The symbols and error bars represent the geometric mean ratios and 90% confidence intervals, respectively. The shadowed region represents the conventional bioequivalence range (0.80–1.25). [a]The data from Part 1 and Part 2 were pooled. AUC_{last} area under the plasma concentration–time curve from 0 to last measurable time point, C_{max} maximum plasma concentration, *Esomeprazole* a single oral administration of atovaquone/proguanil 250/100 mg co-administered with esomeprazole 40 mg, *Proguanil alone* a single oral administration of atovaquone/proguanil 250/100 mg alone, *Tegoprazan* a single oral administration of atovaquone/proguanil 250/100 mg co-administered with tegoprazan 50 mg, *Vonoprazan* a single oral administration of atovaquone/proguanil 250/100 mg co-administered with vonoprazan 20 mg

3.4 Safety

A total of three treatment-emergent AEs, two in Part 1 and one in Part 2, were reported in two subjects throughout the study. All cases occurred after the administration of control treatment and were mild in intensity, and no serious AEs occurred. Moreover, no clinically significant changes or issues in clinical laboratory tests, vital signs, physical examination, and 12-lead ECG were observed.

4 Discussion

Considering the clinical importance of CYP2C19-mediated drug interactions of acid-reducing agents, the current study investigated the effect of tegoprazan on CYP2C19 activity, compared with vonoprazan or esomeprazole, using proguanil as a CYP2C19 substrate. It is worth noting that we evaluated the potential of acid-reducing agents for not only CYP2C19 inhibition but also CYP2C19 induction by administering the corresponding drugs for 7 days [21, 22].

Table 1 Pharmacokinetic parameters of proguanil and cycloguanil following a single oral administration of atovaquone/proguanil 250/100 mg alone or co-administered with tegoprazan 50 mg, vonoprazan 20 mg or esomeprazole 40 mg

	Proguanil alone[a] ($N = 16$)	Proguanil + tegoprazan[a] ($N = 16$)	Proguanil + vonoprazan ($N = 8$)	Proguanil + esomeprazole ($N = 8$)
Proguanil				
AUC_{last} (h*µg/L)	1186.73 ± 335.70	1301.84 ± 402.93	1400.80 ± 400.32	1535.69 ± 283.70
AUC_{inf} (h*µg/L)	1376.77 ± 447.14	1496.81 ± 490.43	1614.87 ± 450.64	1785.62 ± 355.65
C_{max} (µg/L)	77.56 ± 17.30	84.46 ± 15.85	85.78 ± 18.11	86.29 ± 15.49
T_{max} (h)	3.00 [1.00–6.00]	2.50 [1.00–6.00]	3.00 [1.00–6.00]	4.00 [3.00–10.02]
$t_{½}$ (h)	16.81 ± 3.14	16.28 ± 2.80	16.37 ± 2.87	16.56 ± 3.41
CL/F (L/h)	79.13 ± 21.93	73.44 ± 22.15	65.90 ± 16.74	58.07 ± 11.98
f_e (%)	33.43 ± 4.84	34.25 ± 6.08	39.05 ± 7.05	43.21 ± 5.46
Cycloguanil				
AUC_{last} (h*µg/L)	393.16 ± 123.15	407.12 ± 121.68	284.66 ± 101.79	191.32 ± 57.29
AUC_{inf} (h*µg/L)	424.21 ± 124.83	438.10 ± 123.24	321.60 ± 105.54	247.24 ± 72.90
C_{max} (µg/L)	26.50 ± 9.38	26.51 ± 9.04	16.17 ± 6.85	8.92 ± 3.20
Metabolic ratio[b]	0.35 ± 0.16	0.34 ± 0.15	0.22 ± 0.11	0.14 ± 0.05
CL_F/F (L/h)[c]	11.45 ± 5.75	10.48 ± 5.19	6.84 ± 3.87	3.93 ± 1.80

Data are expressed as the arithmetic mean ± standard deviation, except for T_{max} which is expressed as the median [minimum–maximum]

AUC_{inf} area under the plasma concentration–time curve (AUC) from 0 to infinity, *AUC_{last}* AUC from 0 to last measurable time point, *CL/F* apparent clearance, *CL_F/F* apparent formation clearance, *C_{max}* maximum plasma concentration, *f_e* fraction excreted unchanged in the urine, *$t_{½}$* elimination half-life, *T_{max}* time to reach maximum plasma concentration

[a]The data from Part 1 and Part 2 were pooled

[b]Ratio of AUC_{inf} of cycloguanil to AUC_{inf} of proguanil

[c]Cumulative amount of cycloguanil in urine up to 48 h post-dose divided by AUC_{last} of proguanil

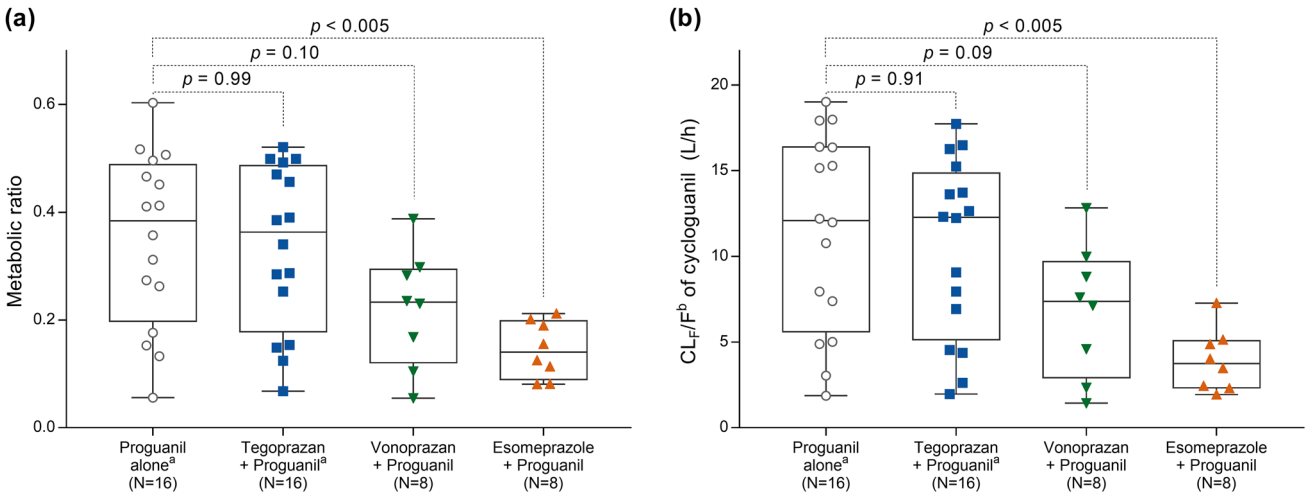

Fig. 5 Comparison of **a** metabolic ratio and **b** CL_F/F of cycloguanil following a single oral administration of atovaquone/proguanil 250/100 mg alone and co-administered with tegoprazan 50 mg, vonoprazan 20 mg or esomeprazole 40 mg. The horizontal lines, boxes, vertical lines and symbols represent the median, interquartile range, minimum to maximum and individual values, respectively. The significance was evaluated by Dunnett's *t*-test. [a]The data from Part 1 and Part 2 were pooled. [b]Cumulative amount of cycloguanil in urine up to 48 h post-dose divided by AUC_{last} of proguanil. *AUC_{last}* area under the plasma concentration–time curve from 0 to last measurable time point, *CL_F/F* apparent formation clearance

In the present study, tegoprazan had no meaningful effect on the PK of the CYP2C19 substrate, indicating that tegoprazan is neither an inhibitor nor an inducer of CYP2C19. Our findings align with the results of in vitro studies using human liver microsomes, in which tegoprazan showed limited inhibition of CYP2C19 (IC_{50} >30 μM). In contrast to tegoprazan, vonoprazan and esomeprazole both decreased the CYP2C19-mediated metabolism of the CYP2C19 substrate, indicating that vonoprazan and esomeprazole are CYP2C19 inhibitors, and esomeprazole exhibited greater CYP2C19 inhibition than vonoprazan. Taken together, these results suggest favorable properties of tegoprazan in comparison with other anti-reducing agents when used concomitantly with CYP2C19 substrates in clinical settings.

Compared with a previous vonoprazan–proguanil study, the current study showed a consistent tendency in the effect of both vonoprazan and esomeprazole on proguanil PK, but the cycloguanil-to-proguanil ratio was lower overall in all treatments (e.g., metabolic ratio for 'proguanil alone': 0.35 in this study vs 0.84 in the previous study) [12]. A recent study found that hepatic uptake by OCT1 played a rate-limiting role in the hepatic metabolism of proguanil to cycloguanil [23]. Therefore, the observed phenomenon may be attributed to the resulting OCT1 deficiency in the enrolled subjects given the high frequency of *OCT1*-deficient alleles in Koreans [24]. However, it does not appear to have affected the interaction results observed in this study because we used a crossover design.

CYP2C19 is highly genetically polymorphic with resulting differences in drug metabolic capacity between phenotypes, and the frequency of CYP2C19 genetic polymorphism is particularly higher in Asian populations than in other races [25–27]. A previous study reported that the metabolic degree of proguanil to cycloguanil varied significantly between CYP2C19 phenotypes [28]. Accordingly, only CYP2C19 extensive metabolizers were recruited in the present study to exclude gene-related confounding factors. Our findings represent the metabolism-specific interaction by tegoprazan.

The US Food and Drug Administration recommends lansoprazole and omeprazole as CYP2C19-sensitive index substrates for clinical drug interaction studies [29]. However, these drugs increase gastric pH by themselves and this increase in gastric pH likely affects their absorption due to their physicochemical properties, classified as Biopharmaceutical Classification System (BCS) class II [30, 31]. Therefore, lansoprazole and omeprazole are considered inappropriate for use in drug metabolism-mediated interaction studies of acid-reducing agents. Based on these points, the present drug interaction study utilized proguanil, which belongs to BCS class III [32], as a CYP2C19 substrate to exclude the possibility of absorption-related drug interaction owing to gastric pH elevation by acid-reducing agents.

This study used the drug product of a fixed-dose combination of atovaquone/proguanil 250/100 mg, which is the only formulation commercially available in the Republic of Korea. Atovaquone, an antiprotozoal agent, is excreted mostly unchanged in the feces (≥94%) and is rarely metabolized by CYP2C19 as well as not affecting CYP2C19 activity [16, 33, 34], implying no CYP2C19-mediated PK interaction with proguanil. Indeed, the concomitant administration of atovaquone did not have a meaningful effect on proguanil PK [35]. Although atovaquone has in vitro CYP3A4 inhibition potential (IC_{50} of 4.7 μM), it does not appear to influence in vivo CYP3A4 activity at clinically relevant concentrations due to its high protein binding [16, 34]. Thus, it seems that atovaquone did not influence the achievement of steady states of the acid-reducing agents used in this study though the PK of these drugs was not evaluated.

Overall, our well controlled study provided robust results on CYP2C19-mediated PK interaction by tegoprazan in comparison with other acid-reducing agents, which may be generalized to other CYP2C19 substrates.

5 Conclusion

Tegoprazan, unlike vonoprazan and esomeprazole, exhibited negligible CYP2C19-mediated PK interaction. Our findings suggest that as an alternative to other acid-reducing agents, tegoprazan can be used concomitantly with CYP2C19 substrates in clinical settings without any dose adjustment.

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Declarations

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Conflict of Interest The authors declare no conflicts of interest in this work.

Ethics Approval The protocol and informed consent form of this study were reviewed and approved by the Ministry of Food and Drug Safety of Korea and by the Institutional Review Board at Seoul National University Hospital. This study was performed in accordance with the Korean Good Clinical Practice guidelines and the Declaration of Helsinki.

Consent to Participate Written consent was obtained from each subject prior to any study-related procedures.

Consent for Publication Not applicable.

Availability of Data and Material The individual de-identified participant data supporting published results are available with approval

from the corresponding author on reasonable request, at any time after publication.

Code Availability Not applicable.

Author Contributions YE and LS wrote the manuscript. YE and LS designed the research. YE, SCJ, I-JJ, and LS performed the research. YE and LS analyzed the data. All the authors reviewed and revised the paper. All the authors approved the final version of the manuscript.

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