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ORIGINAL RESEARCH ARTICLE

Pharmacokinetic Drug–Drug Interactions Between Vonoprazan and Low-Dose Aspirin or Nonsteroidal Anti-inflammatory Drugs: A Phase 2, Open-Label, Study in Healthy Japanese Men

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Abstract

Background Gastroprotective agents are recommended for patients receiving low-dose aspirin (LDA) or nonsteroidal anti-inflammatory drugs (NSAIDs). Vonoprazan is a potassium-competitive acid blocker recently approved for the prevention of peptic ulcer recurrence in patients receiving LDA or NSAIDs.

Methods This phase 2, open-label, single-center study in healthy Japanese males evaluated drug–drug interactions between vonoprazan 40 mg and LDA (100 mg) or NSAIDs [loxoprofen sodium (60 mg), diclofenac sodium (25 mg), or meloxicam (10 mg)] and vice versa. Subjects were allocated to one of eight cohorts and received their orally administered treatment regimen (to assess the effect of vonoprazan vs. NSAID or LDA, or vice versa) once daily. Endpoints were the pharmacokinetics of plasma concentrations of the study drugs alone and in combination (primary), safety (secondary), and vonoprazan effects on aspirin-mediated inhibition of platelet-aggregation.

Results Of 109 subjects screened, 64 were assigned to one of eight cohorts ($n = 8$ per cohort) and received treatment,

one subject discontinued due to a treatment-emergent adverse event (TEAE), and 63 completed the study. There were few differences in the pharmacokinetics of vonoprazan when administered with LDA or NSAIDs, and few differences in the pharmacokinetics of LDA or NSAIDs when administered with vonoprazan. The differences were small and not clinically meaningful. Inhibition of arachidonic-induced platelet aggregation by LDA was not influenced by vonoprazan. Six patients experienced a TEAE, all were mild and were deemed unrelated to study drugs. One subject withdrew due to infection (tonsillitis).

Conclusions No clinically meaningful drug–drug interactions were observed and vonoprazan was well tolerated when administered with LDA or NSAIDs.

Study registration JapicCTI-153100

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Key Points

There were no clinically meaningful differences in the pharmacokinetics of vonoprazan when administered concomitantly with aspirin, loxoprofen sodium, diclofenac sodium, or meloxicam.

There were no clinically meaningful differences in the pharmacokinetics of aspirin, loxoprofen sodium, diclofenac sodium, or meloxicam when administered concomitantly with vonoprazan.

This study shows that vonoprazan is not associated with drug–drug interactions between low-dose aspirin or the nonsteroidal anti-inflammatory drugs loxoprofen sodium, diclofenac sodium, or meloxicam.

△ Adis

1 Introduction

Patients receiving long-term administration of low-dose aspirin (LDA) or nonsteroidal anti-inflammatory drugs (NSAIDs) are at increased risk of developing gastric or duodenal ulcers [1]. Therefore guidelines throughout the world recommend that patients receiving LDA or NSAIDs also receive proton pump inhibitors (PPIs), histamine H_2-receptor antagonists (H2RAs), or prostaglandin analogs to reduce gastric acid levels [2–6]. The efficacy of these agents is variable, but the agents of choice are PPIs [3–5]. In 2010, lansoprazole was the first PPI approved for this indication in Japan. Ulcer recurrence in some patients (12.7 % of patients with NSAID-induced ulcers [7] and 3.7 % with LDA-induced ulcers [8]) occurs despite lansoprazole treatment indicating that secondary prevention is incomplete. Hence, a more effective agent is needed [7, 8].

Vonoprazan, an orally active potassium-competitive acid blocker (P-CAB), effectively reduces gastric acid and has recently been approved in Japan for the treatment of several acid-related disease conditions [9–11]. Vonoprazan is a P-CAB that ionically and reversibly binds to the gastric proton pump [12, 13]. Unlike previously-developed P-CABs, vonoprazan is a different chemotype and therefore avoids the hepatotoxicity seen with previous P-CABs [13–16]. Moreover, unlike PPIs, vonoprazan does not require intermediate complex formation, is stable at low pH, and its bioavailability is unaffected by food [11, 13]. Vonoprazan is rapidly absorbed in healthy adult males, the time to reach the maximum observed plasma concentration (T_{max}) is ≤2 h and the mean elimination half-life is 9 h [17]. *In vitro* studies indicate that vonoprazan is extensively metabolized by multiple metabolizing enzymes in humans including cytochrome P450 (CYP) 3A4/5, CYP2C19, CYP2C9, and the non-CYP enzyme sulfotransferase (SULT)2A1 [18]. CYP3A4 predominantly contributes to the metabolism of vonoprazan to M-I, M-III, and *N*-demethylated vonoprazan, while SULT2A1 contributes to the metabolism of vonoprazan to form vonoprazan *N*-sulfate, and CYP2C9 mediates the formation of M-IV-Sul from vonoprazan *N*-sulfate. Metabolites M-I, M-II, M-III, and M-IV-Sul were quantified in human plasma and none of them are pharmacologically active.

Vonoprazan is effective in promoting healing of erosive esophagitis and gastric/duodenal ulcers, and as an adjunct to *Helicobacter pylori* eradication [9, 10, 11]. Additionally, vonoprazan is useful in preventing recurrence of both erosive esophagitis and of LDA- or NSAID-induced gastric/duodenal ulcers [9, 11].

The objectives of this study were to evaluate the effect of multiple doses of LDA and the most commonly used NSAIDs in Japan (loxoprofen, diclofenac, and meloxicam) on the pharmacokinetics of vonoprazan and, conversely, to evaluate the effects of multiple doses of vonoprazan on the pharmacokinetics of LDA or common NSAIDs. Additionally, the study was designed to evaluate the safety of vonoprazan administered in combination with LDA or NSAIDs, and the effects of vonoprazan on aspirin-mediated inhibition of platelet aggregation.

2 Subjects and Methods

2.1 Study Design

This was a single-site, phase 2, open-label, one-way crossover, clinical pharmacology study (JapicCTI-153100). The pharmacokinetics of vonoprazan were comparatively evaluated in healthy Japanese male subjects when vonoprazan (40 mg) was administered alone or in combination with LDA (100 mg) or NSAIDs [loxoprofen sodium (180 mg), diclofenac sodium (75 mg), or meloxicam (10 mg)]. The pharmacokinetics of aspirin or NSAIDs were evaluated when aspirin or NSAIDs were administered alone and in combination with vonoprazan (Fig. 1).

2.2 Study Population

Healthy Japanese male subjects were screened using pre-defined inclusion and exclusion criteria. Inclusion criteria were: age 20–45 years; body weight ≥50 kg; body mass index between 18.5 and 24.9 kg/m^2; negative for hepatitis B, hepatitis C, human immunodeficiency virus, and syphilis. For subjects in Cohort 5 (measuring pharmacokinetic effect of vonoprazan on aspirin and its metabolite), an additional inclusion criterion was platelet-aggregating activity of ≥70 % induced by collagen or arachidonic acid.

Exclusion criteria were: medical history of hepatic, renal, cardiovascular, hematological, endocrine, metabolic, pulmonary, gastrointestinal, neurological, urological, immunological, or psychiatric disease that would preclude eligibility to participate; allergy or hypersensitivity to any drugs or food; history of drug or alcohol abuse within the past 5 years; poor venous access; history of blood collection of at least 200 ml (within 4 weeks); 400 ml (within 12 weeks), or 800 ml (within 52 weeks); history of blood component collection (within past 2 weeks); use of prescription drugs, vitamins, Chinese herbal remedies, or supplements within the past 4 weeks; ingested food or beverages containing grapefruit, caffeine, or alcohol within the past 72 h; participation in a drug trial in the past 16 weeks; or participation in a previous clinical study of vonoprazan. Subjects were free to withdraw from the study at any time without having to provide a reason.
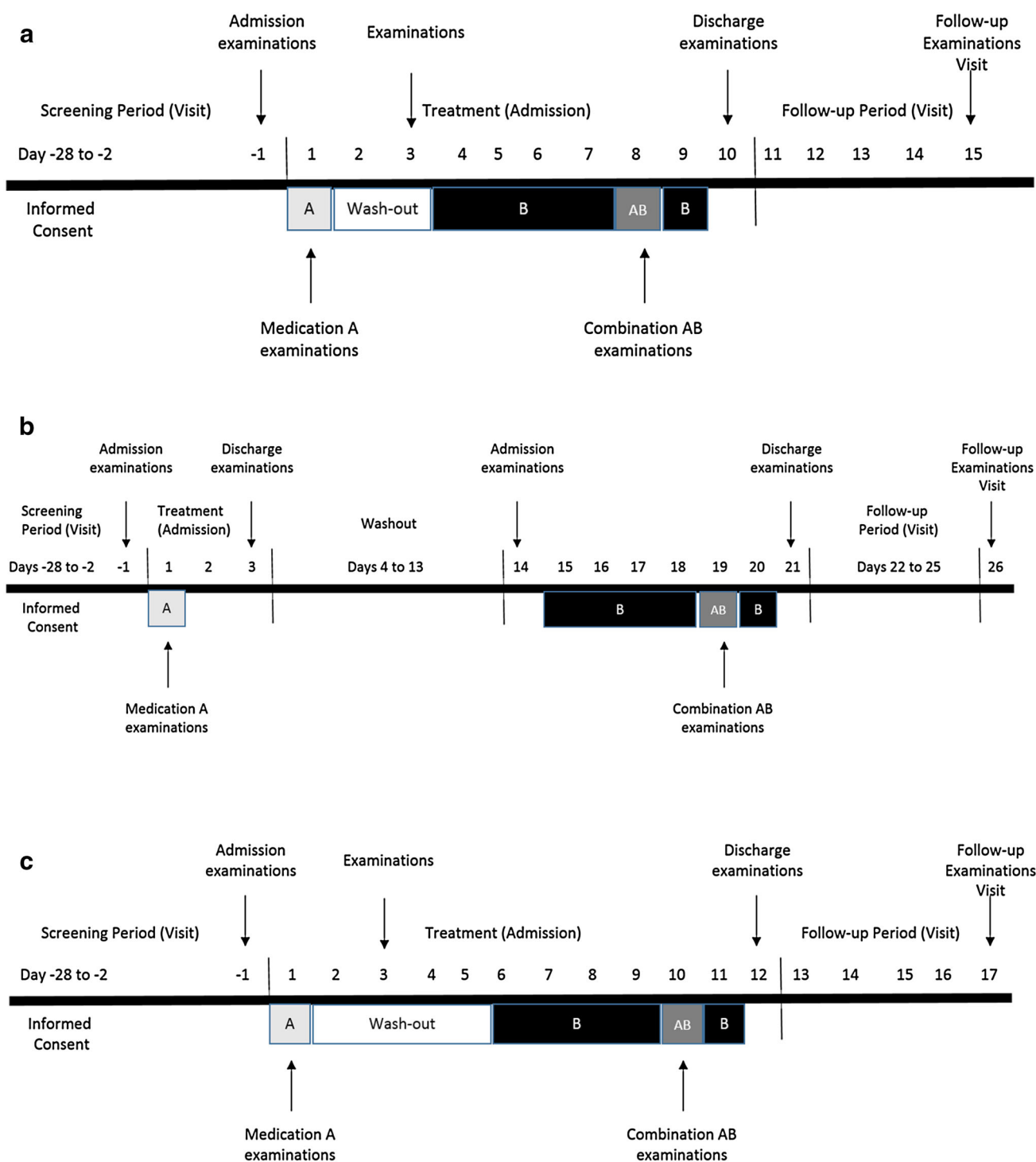
Fig. 1 Study design for Cohorts 1–4, 6, and 7 (**a**), Cohort 5 (**b**), and Cohort 8 (**c**)

2.3 Treatment Protocol

The study consisted of eight cohorts comprising eight subjects each (Table 1). The treatment phase consisted of a single dose of the substrate (Medication A), initially administered alone, followed by a suitable washout period (2 days for Cohort 1–4, 6, and 7, 13 days for Cohort 5, and 4 days for Cohort 8) and then a 6-day period during which multiple doses of the interacting drug (Medication B) were administered. Medication A was concomitantly administered on the fifth day of the 6-day multiple-dose period (Fig. 1a–c).

Table 1 Dosing schedule

Cohort	N	Medication A	Medication B	Analytes evaluated
1	8	Vonoprazan 40 mg	Enteric-coated aspirin 100 mg	Vonoprazan-F and metabolites
2	8	Vonoprazan 40 mg	Loxoprofen sodium 180 mg	Vonoprazan-F and metabolites
3	8	Vonoprazan 40 mg	Diclofenac sodium 75 mg	Vonoprazan-F and metabolites
4	8	Vonoprazan 40 mg	Meloxicam 10 mg	Vonoprazan-F and metabolites
5	8	Aspirin 100 mg	Vonoprazan 40 mg	Aspirin and metabolites
6	8	Loxoprofen sodium 60 mg	Vonoprazan 40 mg	Loxoprofen and metabolites
7	8	Diclofenac sodium 25 mg	Vonoprazan 40 mg	Diclofenac
8	8	Meloxicam 10 mg	Vonoprazan 40 mg	Meloxicam

Washout periods were determined based on the elimination half-life of each study medication, where the minimum wash-out period chosen in each cohort was a minimum of five times the half-life of each medication.

For plasma analysis, blood was collected 0.5 h before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after study drug administration [Day 1, Day 8 (excluding Cohort 5), Day 19 (Cohort 5)], at 9:00 am (Days 2–7), and 16, 24, and 48 h after drug administration (Days 9–10); one blood sample was collected on Day 15 (excluding Cohort 5). For Cohort 5, blood was collected at 9:00 am (Days 15–18) and 16, 24, and 48 h after drug administration (Days 20–21); one blood sample for Cohort 5 was collected on Day 26. Plasma was separated at 4 °C by centrifugation (1500*g* for 10 min) and then stored at −80 °C. Plasma concentrations of analytes were determined using a validated method of liquid chromatography tandem mass spectrometry. The lower limits of quantification (LLOQ) of vonoprazan, M-I, M-II, M-III, and M-IV-Sul were 0.1, 1, 1, 0.1, and 0.1 ng/ml, respectively. The LLOQ of aspirin, salicylic acid, loxoprofen, trans-OH loxoprofen, diclofenac, and meloxicam were 2, 100, 10, 2, 1, and 3 ng/ml, respectively.

2.4 Outcome Measures

2.4.1 Assessment of Pharmacokinetic Variables

Plasma concentrations of the following analytes were determined in order to identify potential drug–drug interactions: vonoprazan free-base (vonoprazan-F) and its metabolites (M-I, M-II, M-III, and M-IV-Sul), unchanged aspirin and its metabolite (salicylic acid), unchanged loxoprofen and its active metabolite (trans-OH metabolite), unchanged diclofenac, and unchanged meloxicam.

Pharmacokinetic measures included the area under the concentration-time curve from time 0 to time of last quantifiable concentration (AUC$_{0-last}$), calculated using the linear trapezoidal rule and the terminal elimination rate constant (λz), calculated as the negative of the slope of the log-linear regression of the natural logarithm

concentration-time curve during the terminal phase. Other pharmacokinetic parameters analyzed included the maximum observed concentration (C_{max}); the time to reach C_{max} (T_{max}); the area under the concentration-time curve from time 0 to infinity, calculated as AUC$_{0-inf}$ = AUC$_{0-last}$ + $C_{last}/\lambda z$, where last is the time of the last quantifiable concentration, and C_{last} is the last quantifiable concentration; the terminal elimination half-life ($T_{1/2}$), calculated as $T_{1/2}$ = ln(2)/λz, and the apparent clearance after extravascular administration (CL/F), calculated as CL/F = Dose/AUC$_{0-inf}$ after a single dose and as CL/F = Dose/AUC$_{0-tau}$ after multiple dosing (at steady state).

2.4.2 Assessment of Pharmacodynamic Effects

The effect of vonoprazan on the platelet-aggregating inhibitory activity of aspirin was evaluated in Cohort 5. A 4.5-ml aliquot of blood was collected to determine platelet-aggregating activity [maximum aggregation (% transmission)] using 1 μg/ml of collagen and 1 mmol/l of arachidonic acid as platelet-aggregation-inducing agents. Platelet aggregation was measured using the P200 aggregometer (Kowa Inc, Nagoya, Japan) according to Ozaki et al. [19]. On Day 1 and Day 19, blood samples were collected 0.5 h before and 1.5, 4, 6, 8, 10, and 12 h after study drug administration. On Days 2, 3, 20, and 21, blood samples were collected at 9:00 am.

2.4.3 Assessment of Safety Variables

Safety variables included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), vital signs, weight, electrocardiogram (ECG) findings, and clinical laboratory tests (hematology, blood chemistry, and urinalysis). An adverse event (AE) was defined as any untoward medical occurrence after administration of a pharmaceutical product; AEs were graded as mild, moderate, or severe. AEs did not necessarily have to have a causal relationship with treatment. A TEAE was defined as an AE with the

date of onset that occurred after receiving study drug through study discharge, or a continuing AE diagnosed before the date of first administration of study drug, which increased in intensity or frequency after the start of dosing. A SAE was defined as any occurrence that was life threatening, or resulted in death, hospitalization, significant disability or incapacity, or a congenital anomaly or birth defect.

2.4.4 Assessment of Helicobacter pylori Status

Participants were screened for *H. pylori* antibody using a serum antibody test. Values <10 U/ml were considered negative and those ≥10 U/ml were considered positive.

2.5 Ethics

The institutional review board for SOUSEIKAI Hakata Clinic was responsible for the initial and continuing review and approval of the clinical study in accordance with the requirements of Good Clinical Practice. The protocol and the subject informed consent form for this study were approved in writing before commencement of the study.

2.6 Statistical Analysis

No sample size calculation was performed. The sample sizes were determined after considering the feasibility of the study. A statistical analysis plan was prepared and finalized before database lock. The pharmacokinetic analysis set comprised subjects who received the study drug, had no significant protocol deviations, completed the minimum required study procedures, and had sufficient drug concentration data. The safety analysis set was defined as all subjects who received at least one dose of study drug.

Concentrations below the quantification limit were treated as 0 in the computation of summary statistics. Missing values due to discontinuation or lack of measurement were not interpolated and were excluded from the summary statistics.

Pharmacokinetic parameters were derived for single- and combination-dose periods from concentrations of each analyte of Medication A up to 48 h after dosing by non-compartmental analysis using WinNonlin V5.3 (Pharsight—A Certara Company, Princeton, NJ, USA).

Summary statistics (number of subjects, mean, standard deviation, standard error, maximum, minimum and quartile value) were used to summarize concentrations of each analyte at each time point and the pharmacokinetic parameters. Analysis of variance was performed on the natural logarithms of AUC_{0-inf}, AUC_{0-48}, and C_{max} of Medication A as dependent variables; dosing conditions (combination dose period or single dose period) were fixed effects, in order to examine the drug–drug interaction. A point estimate and 90 and 95 % confidence intervals (CIs) of the least squares (LS) means ratios between dosing conditions (combination dose period–single dose period) were provided. The 90 % CIs were compared with the standard bioequivalence criteria of 0.8 to 1.25 [20]. Non-transformed parameters were also analyzed for reference.

Summary tables were generated for TEAEs by preferred term for each treatment period (single dose period, multiple dose period, combination dose period).

3 Results

3.1 Demographic and Baseline Clinical Characteristics

A total of 109 subjects were screened. Of these, 64 subjects were entered into the study (Fig. 2). The reasons for screening failure were voluntary withdrawal or did not meet entrance criteria. Sixty-three subjects completed the study. No clinically relevant differences were observed among the cohorts for any demographic characteristics at baseline (Table 2). Subjects had a mean age of 24.2 years, most (79.7 %) were negative for *H. pylori* antibody.

3.2 Pharmacokinetic Measures

Of the 64 patients enrolled, 61 comprised the pharmacokinetic analysis set. Three patients were excluded (one each in Cohorts 1, 4, and 7) due to lack of samples for pharmacokinetic evaluation.
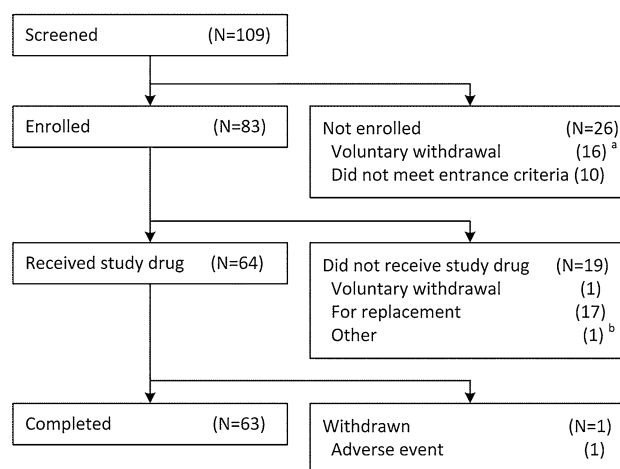
Fig. 2 Patient disposition. [a]Including four subjects who were judged "eligible" at screening. [b]One subject was replaced before administration because a more appropriate subject was identified

Table 2 Baseline subject characteristics of the safety analysis set

| Variable	Cohort 1 (n = 8)	Cohort 2 (n = 8)	Cohort 3 (n = 8)	Cohort 4 (n = 8)	Cohort 5 (n = 8)	Cohort 6 (n = 8)	Cohort 7 (n = 8)	Cohort 8 (n = 8)	Total (n = 64)
Age, years, mean (SD)	26.9 (3.00)	24.6 (1.92)	22.8 (3.20)	22.4 (2.33)	24.9 (3.09)	27.0 (2.00)	21.6 (1.19)	23.4 (3.02)	24.2 (3.07)
Height, cm, mean (SD)	171.4 (7.74)	177.3 (6.30)	172.3 (6.96)	170.1 (4.29)	172.5 (4.78)	173.6 (7.21)	169.3 (5.23)	175.8 (5.78)	172.8 (6.33)
Weight, kg, mean (SD)	61.44 (3.737)	68.59 (10.328)	61.21 (6.687)	60.93 (6.678)	65.60 (6.197)	63.09 (6.485)	61.49 (6.627)	66.64 (4.067)	63.62 (6.830)
Body mass index, kg/m², mean (SD)	20.98 (1.642)	21.73 (2.091)	20.65 (2.087)	21.04 (1.929)	22.06 (2.028)	20.91 (1.574)	21.46 (1.794)	21.63 (1.542)	21.31 (1.802)
Helicobacter pylori antibody negative, n (%)	5 (62.5)	8 (100.0)	7 (87.5)	6 (75.0)	7 (87.5)	4 (50.0)	7 (87.5)	7 (87.5)	51 (79.7)
Alcohol consumption, n (%)									
Drinks few days per week	–	1 (12.5)	1 (12.5)	3 (37.5)	2 (25.0)	1 (12.5)	–	3 (37.5)	11 (17.2)
Drinks few days per month	5 (62.5)	4 (50.0)	5 (62.5)	4 (50.0)	4 (50.0)	4 (50.0)	5 (62.5)	4 (50.0)	35 (54.7)
Non-drinker	3 (37.5)	3 (37.5)	2 (25.0)	1 (12.5)	2 (25.0)	3 (37.5)	3 (37.5)	1 (12.5)	18 (28.1)
Consumes caffeine, n (%)	3 (37.5)	2 (25.0)	4 (50.0)	2 (25.0)	2 (25.0)	1 (12.5)	2 (25.0)	4 (50.0)	20 (31.3)
Smoking, n (%)									
Never smoker	2 (25.0)	3 (37.5)	1 (12.5)	4 (50.0)	3 (37.5)	3 (37.5)	2 (25.0)	2 (25.0)	20 (31.3)
Current/ex-smoker	6 (75.0)	5 (62.5)	7 (87.5)	4 (50.0)	5 (62.5)	5 (62.5)	6 (75.0)	6 (75.0)	44 (68.8)

cm centimetre, *kg* kilogram, *m* meter, *SD* standard deviation

3.2.1 Vonoprazan-F and its Metabolites (Cohorts 1–4)

Few or no differences were observed in the pharmacokinetics of vonoprazan-F or its metabolites when vonoprazan was administered alone or concomitantly with aspirin (Fig. 3, Supplementary Table 1). The 90 % CIs of the ratio of LS means for C_{max} and AUCs of vonoprazan-F were within the range (0.8, 1.25), except that the upper bound for C_{max} was 1.257, marginally above 1.25. Slight increases (approximately 13–24 %) were observed in C_{max} and AUCs of M-II when vonoprazan was administered concomitantly with aspirin. The 90 % CIs of the ratios of LS means for C_{max} and AUCs of M-II were not within the range (0.8, 1.25).

No differences were observed in C_{max} and AUCs of M-I, M-III, and M-IV-Sul when vonoprazan was administered alone or concomitantly with aspirin. The 90 % CIs of the ratios of LS means for C_{max} and AUCs for the three metabolites were within the range (0.8, 1.25).

Few or no differences were observed in the pharmacokinetics of vonoprazan-F or its metabolites when vonoprazan was administered alone or concomitantly with loxoprofen (Fig. 3, Supplementary Table 2). The 90 % CIs of the ratios of LS means for C_{max} and AUCs of vonoprazan-F were within the range (0.8, 1.25), except that the lower bound for C_{max} was 0.695, marginally below 0.80. Few or no differences in M-I, M-II, and M-IV-Sul were observed in C_{max} and AUCs when vonoprazan was
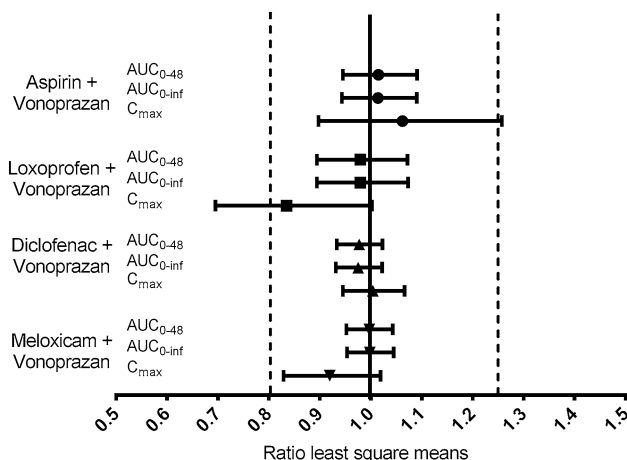
Fig. 3 Effect of aspirin, loxoprofen sodium, diclofenac sodium, or meloxicam on the pharmacokinetics of vonoprazan-F when coadministered. Ratio of least square means and 90 % confidence intervals (CIs) are presented. *Dotted lines* represent the standard equivalence criterion of 0.80 to 1.25 rate limits for the 90 % CIs. *AUC* area under the plasma concentration-time curve, $AUC_{0–48}$ AUC from time 0–48 h, calculated using the linear trapezoid rule, $AUC_{0–inf}$ AUC from time 0 to infinity, C_{max} maximum observed plasma concentration

administered alone or concomitantly with loxoprofen sodium. The 90 % CIs of the ratios of LS means for C_{max} and AUCs were within the range (0.8, 1.25), except that the lower bounds for the C_{max} of M-I and M-IV-Sul were 0.787 and 0.772, respectively, marginally below 0.80, and the upper bound for $AUC_{0–inf}$ of M-II was 1.258, marginally

above 1.25. No differences were observed in C_{max} and AUCs of M-III when vonoprazan was administered alone or concomitantly with loxoprofen sodium. The 90 % CIs of the ratios of LS means for C_{max} and AUCs of M-III were within the range (0.8, 1.25).

Few or no differences were observed in the pharmacokinetics of vonoprazan-F when vonoprazan was administered alone or concomitantly with diclofenac sodium (Fig. 3, Supplementary Table 3). The 90 % CIs of the ratios of LS means for C_{max} and AUCs of vonoprazan-F were within the range (0.8, 1.25). A slight decrease (approximately 13 %) was observed in the C_{max} of M-I when vonoprazan was administered concomitantly with diclofenac sodium. The 90 % CIs of the ratios of LS means for C_{max} and AUCs for M-I were within the range (0.8, 1.25), except that the lower bound for C_{max} was 0.759, below 0.80. A slight decrease (approximately 12 %) was observed in AUC_{0-inf} of M-II when vonoprazan was administered concomitantly with diclofenac sodium. The 90 % CIs of the ratios of LS means for C_{max} and AUCs for M-II were within the range (0.8, 1.25), except that the lower bound for AUC_{0-inf} was 0.682, below 0.80. No differences in M-III and M-IV-Sul were observed in C_{max} and AUCs when vonoprazan was administered alone or concomitantly with diclofenac sodium. The 90 % CIs of the ratios of LS means for C_{max} and AUCs were within the range (0.8, 1.25).

No differences were observed in the pharmacokinetics of vonoprazan-F when vonoprazan was administered alone or concomitantly with meloxicam (Fig. 3, Supplementary Table 4). The 90 % CIs of the ratios of LS means for C_{max} and AUCs of vonoprazan-F were within the range (0.8, 1.25). A slight increase (approximately 12 %) was observed in AUC_{0-inf} of M-II, when vonoprazan was administered concomitantly with meloxicam. The 90 % CIs of the ratios of LS means for C_{max} and AUCs were within the range (0.8, 1.25), except that the upper bound for AUC_{0-inf} was 1.255, slightly above 1.25. No differences in M-I, M-III, and M-IV-Sul were observed in C_{max} and AUCs when vonoprazan was administered alone or concomitantly with meloxicam. The 90 % CIs of the ratios of LS means for C_{max} and AUCs for these three metabolites were within the range (0.8, 1.25).

3.2.2 Aspirin and its Metabolites (Cohort 5)

An 83 % increase was observed in C_{max} and a slight increase (approximately 18 %) was observed in AUC_{0-48} of aspirin, when aspirin was administered concomitantly with vonoprazan (Fig. 4, Supplementary Table 5). The 90 % CIs of the ratios of the LS means for C_{max} and AUCs were not within the range (0.80, 1.25). One subject exhibited very slow absorption (T_{max} was 24 h); additional analyses excluding this patient were performed. After exclusion of this subject, an approximately 56 % increase
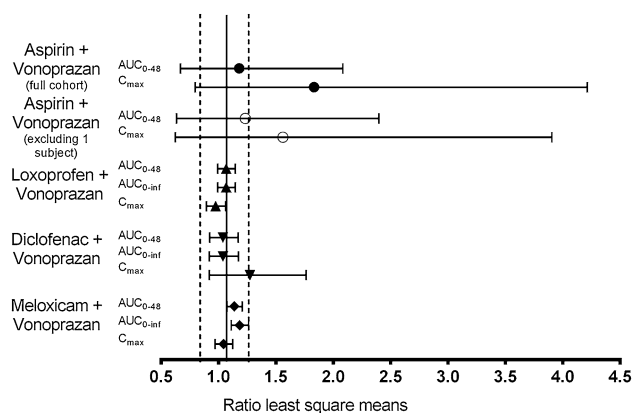
Fig. 4 Effect of vonoprazan on the pharmacokinetics of aspirin (full cohort and cohort excluding one patient who exhibited very slow absorption), loxoprofen sodium, diclofenac sodium, or meloxicam when coadministered. Ratio of least square means and 90 % confidence intervals (CIs) are presented. *Dotted lines* represent the standard equivalence criterion of 0.80 to 1.25 rate limits for the 90 % CIs. AUC_{0-inf} for aspirin + vonoprazan is not shown because it was not possible to estimate the elimination rate constant for five subjects in the single-dose period and three subjects in the combination dose period due to insufficient data in the elimination phase. *AUC* area under the plasma concentration-time curve, AUC_{0-48} AUC from time 0–48 h, calculated using the linear trapezoid rule, AUC_{0-inf} AUC from time 0 to infinity, C_{max} maximum observed plasma concentration

was observed in C_{max} and a slight increase (approximately 23 %) was observed in the AUC_{0-48} of aspirin when aspirin was administered concomitantly with vonoprazan (Fig. 4). The 90 % CIs of the ratios of LS means for C_{max} and AUCs were not within the range (0.80, 1.25).
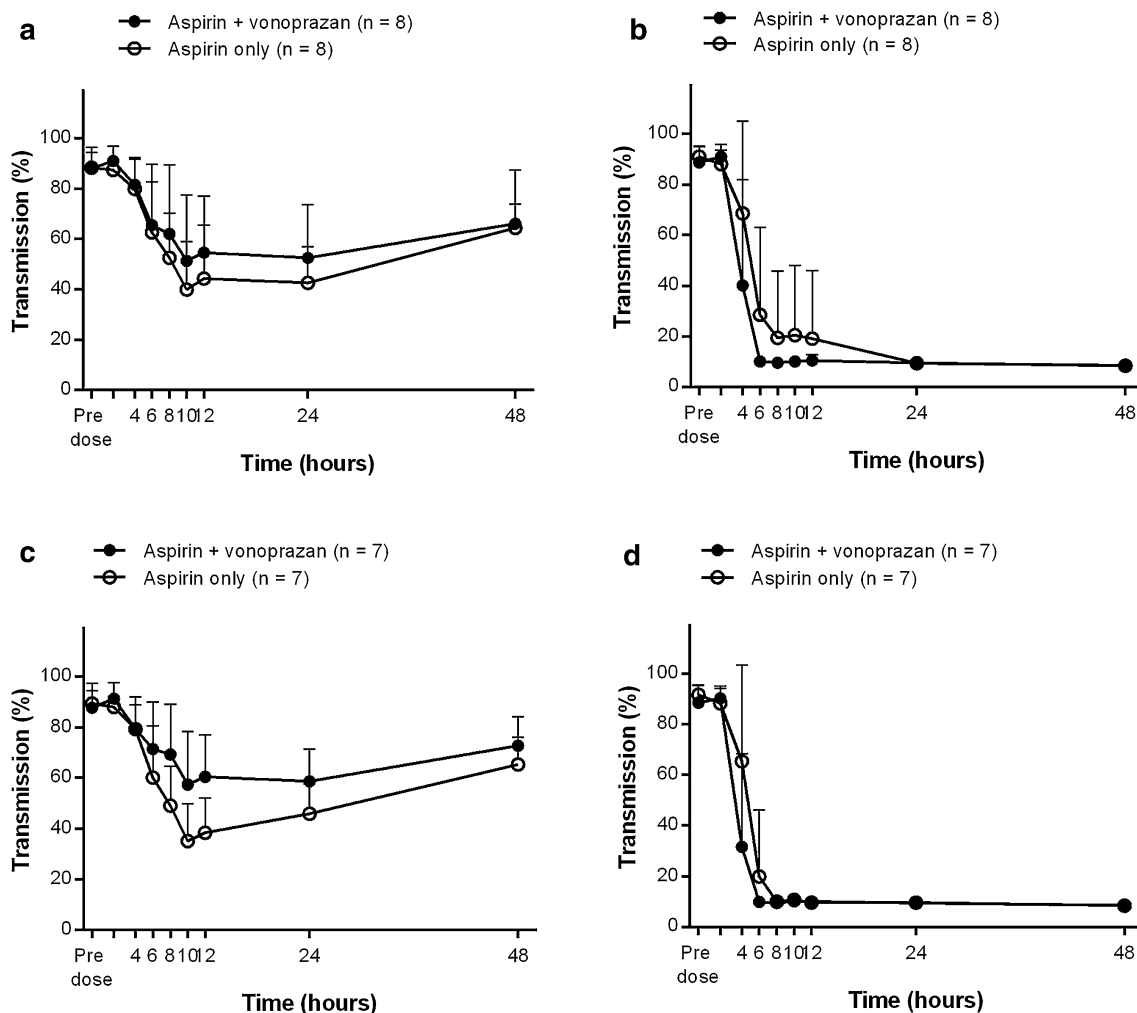
Few differences were observed in the pharmacokinetics of salicylic acid, when aspirin was administered alone or concomitantly with vonoprazan (Supplementary Table 5). Though the 90 % CIs of the ratios of LS means for C_{max} and AUCs were not within the range (0.80, 1.25), the point estimate for C_{max} was around 1, and the lower bounds of AUCs were 0.765 to 0.783, marginally below 0.80. This small difference was not clinically meaningful.

3.2.3 Loxoprofen and its Metabolites (Cohort 6)

No differences were observed in the pharmacokinetics of loxoprofen or its trans-OH metabolite when loxoprofen sodium was administered alone or concomitantly with vonoprazan (Fig. 4, Supplementary Table 6). The 90 % CIs of the ratios of LS means for C_{max} and AUCs were within the range (0.80, 1.25) for both loxoprofen and its trans-OH metabolite.

3.2.4 Diclofenac Sodium (Cohort 7)

A slight increase (approximately 27 %) was observed in the C_{max} of diclofenac when diclofenac sodium was

Fig. 5 Pharmacodynamic effects of vonoprazan on **a** collagen-induced or **b** arachidonic acid-induced platelet-aggregation activity during coadministration in the full cohort. Pharmacodynamic effects of vonoprazan on **c** collagen-induced or **d** arachidonic acid-induced platelet-aggregation activity during coadministration in the cohort excluding one patient who exhibited very slow absorption. Means and standard deviations are shown

administered alone or concomitantly with vonoprazan (Fig. 4, Supplementary Table 7). However, few or no differences were observed in other pharmacokinetic parameters. The 90 % CIs of the ratios of LS means for C_{max} and AUCs were within the range (0.80, 1.25), except that the upper bound for C_{max} was 1.764, above 1.25. This significant difference was not clinically meaningful, because the point estimate for C_{max} was 1.274 and the lower bound for C_{max} was 0.920.

3.2.5 Meloxicam (Cohort 8)

Although a slight increase (approximately 18 %) was observed in the AUC_{0-inf} of meloxicam, few or no differences were observed in other pharmacokinetic parameters when meloxicam was administered alone or administered concomitantly with vonoprazan (Fig. 4, Supplementary Table 8). The 90 % CIs of the ratios of LS means for C_{max}

and AUCs were within the range (0.80, 1.25), except that the upper bound for AUC_{0-inf} was 1.263, marginally above 1.25. This small difference was not clinically meaningful.

3.3 Pharmacodynamic Measures

No differences were observed in arachidonic acid-induced platelet-aggregating activity when aspirin was administered alone or concomitantly with vonoprazan (Fig. 5b, d). Concomitant vonoprazan slightly reduced the collagen-induced platelet-aggregating inhibitory activity of aspirin (Fig. 5a, c).

3.4 Safety and Tolerability Measures

Among 64 subjects, a total of six subjects experienced TEAEs during this study (Table 3). All TEAEs were mild in intensity and not related to study drugs. The TEAEs

Table 3 Adverse events

Variable	Cohort 1 (n = 8)	Cohort 2 (n = 8)	Cohort 3 (n = 8)	Cohort 4 (n = 8)	Cohort 5 (n = 8)	Cohort 6 (n = 8)	Cohort 7 (n = 8)	Cohort 8 (n = 8)	Total (n = 64)
Summary of AEs, event (subject [%])									
Drug related AEs	–	–	–	–	–	–	–	–	
Non-drug related AEs	–	1 (1 [12.5%])	–	–	1 (1 [12.5%])	2 (2 [25.0%])	2 (2 [25.0%])	–	6 (6 [9.4%])
Mild AEs	–	1 (1 [12.5%])	–	–	1 (1 [12.5%])	2 (2 [25.0%])	2 (2 [25.0%])	–	6 (6 [9.4%])
Moderate AEs	–	–	–	–	–	–	–	–	
Severe AES	–	–	–	–	–	–	–	–	
Leading to discontinuations	–	–	–	–	1 (1 [12.5%])	–	–	–	
Serious AEs	–	–	–	–	–	–	–	–	
Deaths	–	–	–	–	–	–	–	–	
Preferred term[a] AEs, subject (%)									
Pharyngitis	–	1 (12.5%)[b]	–	–	–	–	–	–	1 (1 [1.6%])
Tonsillitis	–	–	–	–	1 (12.5%)[c]	–	–	–	1 (1 [1.6%])
Epistaxis	–	–	–	–	–	–	1 (12.5%)[b]	–	1 (1 [1.6%])
Blood creatine phosphokinase increased	–	–	–	–	–	2 (25.0%)[c]	–	–	2 (2 [3.1%])
ALT increased	–	–	–	–	–	–	1 (12.5%)[c]	–	1 (1 [1.6%])

AEs adverse events, *ALT* alanine aminotransferase

[a] AEs were coded by MedDRA Version 13

[b] AE occurred during single dose period

[c] AE occurred during combination dose period

were observed in Cohorts 2, 5, 6, and 7. In Cohort 2, pharyngitis occurred in one subject when vonoprazan was administered alone. In Cohort 5, tonsillitis that led to discontinuation occurred in one subject when aspirin was administered concomitantly with vonoprazan. In Cohort 6, blood creatine phosphokinase increased occurred in two subjects when loxoprofen sodium was administered concomitantly with vonoprazan. In Cohort 7, epistaxis occurred in one subject when diclofenac sodium was administered alone and alanine aminotransferase increase occurred in one subject when diclofenac sodium was administered concomitantly with vonoprazan.

No serious TEAEs were reported and no deaths occurred during the study period. No instances of serious liver dysfunction were reported during the study. All of the TEAEs occurred during the combination dose period (i.e., loxoprofen sodium with vonoprazan in Cohort 6 and diclofenac sodium with vonoprazan in Cohort 7). No hematology or urinalysis result or ECG finding was assessed by the investigator or subinvestigator to be clinically significant or a TEAE.

4 Discussion

This study is the first to examine the potential risk for drug–drug interactions between vonoprazan and LDA or vonoprazan and NSAIDs. The results of this study showed that there were no clinically significant effects of LDA or the NSAIDs loxoprofen sodium, diclofenac sodium, and meloxicam on the pharmacokinetics of vonoprazan, and no clinically significant effects of vonoprazan on the pharmacokinetics of LDA or the NSAIDs.

Long-term LDA or NSAIDs have been associated with increased risk of upper gastrointestinal events such as ulcers and bleeding [21]. Therefore, acid-suppressive agents are concomitantly administered to provide gastroprotection [21]. Hence, it was important to assess whether

vonoprazan was associated with drug–drug interactions with LDA or commonly prescribed NSAIDs. Loxoprofen sodium, diclofenac sodium, and meloxicam are the most commonly prescribed NSAIDs in Japan for the management of pain in patients with osteoarthritis or rheumatoid arthritis [22]. The results of this study support the lack of drug–drug interactions between vonoprazan and LDA or these NSAIDs.

Low-dose aspirin is a key component of thromboprophylaxis in patients at risk of adverse cardiovascular events such as myocardial infarction, angina pectoris, or atrial fibrillation (approved indication outside Japan). Therefore, it was important to confirm the lack of pharmacokinetic and pharmacodynamic effects of vonoprazan on aspirin. The effects of vonoprazan on LDA and salicylic acid pharmacokinetics were difficult to determine because of the large inter-subject variability observed. Although the AUCs of aspirin increased when concomitantly administered with vonoprazan, few differences were observed in the pharmacokinetics of salicylic acid. Similarly, variability in the pharmacodynamic effects of aspirin were also observed in that vonoprazan slightly reduced the collagen-induced platelet-aggregating inhibitory activity of aspirin during concomitant administration. However, the arachidonic acid-induced platelet-aggregating inhibitory activity of aspirin was not influenced by vonoprazan administration. In addition, this study used a low dose of aspirin which is within the range commonly used to prevent thromboembolism (100 mg), whereas the maximum dose is 324 mg. Previous studies have reported that an increased concentration of salicylic acid has no meaningful effect on platelet aggregation [23, 24]. Overall, vonoprazan was considered to have no significant effect on the pharmacokinetics or pharmacodynamics of aspirin and salicylic acid and therefore can be considered to have no clinically relevant drug–drug interactions when taken in combination with LDA. In addition, concomitant administration of vonoprazan with LDA or NSAIDs was well tolerated. Few AEs were noted during the study.

The strengths of this study include the prospective design and the high study completion rate. However, because this was a clinical pharmacology study, the sample size was small and there was a limited duration of follow-up. The subjects enrolled in the study were relatively young whereas patients with osteoarthritis or rheumatoid arthritis are likely to be older. In addition, the study was conducted only in healthy male volunteers in order to compare the results with other pharmacokinetic studies of vonoprazan. Although caution is advised when extrapolating to women, gender-related disparities in pharmacokinetics are largely inconsequential [25]. Therefore, the potential for drug–drug interactions cannot be ruled out in females or in an older population who may be taking other concomitant medications.

5 Conclusion

In conclusion, despite some small differences, no clinically meaningful drug–drug interactions were observed in healthy male volunteers between vonoprazan and either LDA or commonly prescribed NSAIDs. The results suggest that vonoprazan at the dose evaluated in this study can be concomitantly administered with LDA or NSAIDs such as loxoprofen sodium, diclofenac sodium, or meloxicam.

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