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ORIGINAL RESEARCH ARTICLE

Phase 1 Study of the Effect of Icosapent Ethyl on Warfarin Pharmacokinetic and Anticoagulation Parameters

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Abstract

Background and Objective Icosapent ethyl (IPE) is a high-purity prescription form of eicosapentaenoic acid (EPA) ethyl ester approved to reduce triglyceride levels in patients with severe (≥5.65 mmol/L) hypertriglyceridemia. EPA, the active metabolite of IPE, is mainly metabolized via β-oxidation, and studies suggest that omega-3 fatty acids such as EPA may have antithrombotic effects. The objective of this study was to evaluate the effect of IPE on the pharmacokinetic and anticoagulation pharmacodynamics of warfarin, a substrate of cytochrome P450 2C9-mediated metabolism.

Methods Healthy adults received oral warfarin (25 mg) on day 1, oral IPE (4 g/day) on days 8–35, and co-administration on Day 29. Primary pharmacokinetic end points were area under the concentration-versus-time curve from zero to infinity ($AUC_{0-\infty}$) and maximum plasma concentration (C_{max}) for *R*- and *S*-warfarin; pharmacodynamic end points were area under the international normalized ratio (INR) effect-time curve after the warfarin dose (AUC_{INR}) and maximum INR (INR_{max}).

Results Twenty-five subjects completed the study. $AUC_{0-\infty}$ and C_{max} ratios of geometric means for both *R*- and *S*-warfarin following co-administration of warfarin with versus without IPE were within the 90 % confidence intervals of 0.80–1.25. AUC_{INR}, INR_{max}, and ratios were also similar.

Conclusions IPE 4 g/day did not significantly change the single-dose $AUC_{0-\infty}$ or C_{max} of *R*- and *S*-warfarin or the anticoagulation pharmacodynamics of warfarin when co-administered as racemic warfarin at 25 mg. Co-administration of these drugs was safe and well tolerated in this study of healthy adult subjects.

Key Points

Patients who are candidates for icosapent ethyl therapy may also be receiving warfarin anticoagulation therapy.

Icosapent ethyl 4 g/day did not have an effect on the pharmacokinetics or anticoagulation pharmacodynamics of warfarin.

Co-administration of icosapent ethyl and warfarin was safe and well tolerated.

1 Introduction

Hypertriglyceridemia is common among adults in the United States, yet only a small percentage receive specific treatment [1]. Strategies to lower serum triglyceride levels include lifestyle intervention, statins, fibrates, niacin, ezetimibe, and long-chain omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [2]. Icosapent ethyl (IPE; Vascepa® [formerly AMR101]; Amarin Pharma Inc., Bedminster, NJ, USA) is a high-

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purity prescription form of EPA ethyl ester approved by the United States Food and Drug Administration (FDA) as an adjunct to diet to reduce triglyceride levels in adults with severe (≥5.65 mmol/L) hypertriglyceridemia [3]. In two randomized, placebo-controlled studies, IPE significantly reduced triglyceride levels and improved other lipid parameters without substantially increasing serum low-density lipoprotein cholesterol levels [4, 5].

After oral administration, IPE is de-esterified during the absorption process and the active metabolite EPA is absorbed in the small intestine and enters the systemic circulation mainly via the thoracic duct lymphatic system [3]. EPA is metabolized predominantly by β-oxidation and is not expected to interfere with cytochrome P450 (CYP)-mediated pathways [3]. However, EPA is also known to be metabolized by cyclooxygenases (COX), lipoxygenases, and CYP enzymes, including CYP2C9 [6]. Warfarin, a widely prescribed anticoagulant, is administered as a racemic mixture of the *R*- and *S*-enantiomers [7]. Most of the anticoagulant activity is attributable to *S*-warfarin, which is metabolized by CYP2C9 [8]. Although there was no a priori expectation that EPA would alter the metabolism of warfarin, the possibility of a drug–drug interaction was investigated due to the potential role of CYP2C9 metabolism.

Because warfarin has a narrow therapeutic window, frequent monitoring of prothrombin time (PT), expressed as the international normalized ratio (INR), is required [7]. Various drugs and substances are known to modify warfarin anticoagulant activity, either through interference with its metabolism, protein binding, or via pharmacodynamic interactions wherein the interacting drug impairs coagulation by mechanisms other than warfarin's mechanism (ie, inhibition of the synthesis of vitamin K-dependent clotting factors) [7, 8]. EPA and DHA may affect coagulation through inhibition of COX, inhibition of platelet signaling and function, interactions of platelets with other cell types, effects on inflammatory processes involved in coagulation, and reduction in platelet-mediated thrombin generation [9, 10].

The objective of this study was to investigate the effects of IPE on the pharmacokinetics and anticoagulation pharmacodynamics of warfarin in healthy subjects.

2 Study Subjects and Methods

2.1 Study Population

Healthy men and women between the ages of 19 and 55 years were eligible to participate if they were non-smokers, had a body mass index >18 and ≤35 kg/m^2, and were in good health as determined by medical history, medical examination, and normal test results for serum biochemistry, hematology, and urinalysis. Women who were pregnant, nursing, or planning a pregnancy were excluded; female subjects of childbearing potential were required to use an acceptable method of birth control. Individuals with known hypersensitivity to warfarin or a history or presence of abnormal prolongation of bleeding time or a significant bleeding disorder were ineligible. Subjects were excluded if PT, INR, or plasma protein C and protein S activity (functional) were outside the normal reference range. Antidiabetic therapy, antihypertensive therapy, tamoxifen, estrogen, and progestin were not permitted within 4 weeks prior to screening if the medications were not taken according to the same dose continuously or if dose changes were expected during the study. Individuals receiving thyroid replacement therapy had to be on the same dose continuously for 6 or more weeks prior to screening. Use of medications or dietary supplements with known or potential lipid-altering effects (including statins, niacin >200 mg/day, fibrates, ezetimibe, bile acid sequestrants, or medications or foods enriched with omega-3 fatty acids) was prohibited within 4 weeks prior to the first dose of study medication and until after the end of the study.

2.2 Study Design

This phase I, single-center, open-label study used a crossover design to investigate potential pharmacokinetic and pharmacodynamic drug–drug interactions between warfarin and IPE in healthy subjects. The study consisted of a 28-day screening period to evaluate subject eligibility and a 36-day study period in which subjects received study drugs during planned site visits or via self-administration while away from the study site. Study procedures such as safety evaluations and pharmacokinetic sampling were performed during the planned site visits. Total duration of study participation for each subject was approximately 64 days.

All subjects received the same treatment. Warfarin (25 mg, two 10-mg and one 5-mg tablets, provided as Coumadin®, Bristol-Myers Squibb, Princeton, NJ, USA), was administered as a single dose one half hour prior to breakfast on days 1 and 29. IPE (4 g/day) was administered as twice-daily oral doses (2 liquid-filled, 1 g gelatin capsules per dose) with or following the morning and evening meals on days 8–35. Compliance to the IPE dosing regimen was evaluated at visit 3 (day 28) by counting unused capsules and reconciling the number against entries in the subject's diary. Mean compliance was calculated as actual daily dose/planned daily dose × 100.

Doses selected for the study were based on established pharmacokinetic and safety profiles. For IPE capsules, 4 g/day represents the FDA-approved dose [3]. A single dose of 25 mg warfarin has been used previously to measure

plasma concentrations and anticoagulation effects in drug interaction studies, and is safe to use in healthy subjects with normal INR [11–16]. Warfarin 25 mg typically results in a maximum increase of the INR (INR_{max}) by 60–90 % (INR range, 1.6–1.9) occurring 36–48 h after administration. For comparison, INR of 2.0–3.0 is used in patients for basic anticoagulation therapy.

The study protocol was approved by an institutional review board (IntegReview Ethics Review Board, Austin, TX, USA) and was conducted between May 3, 2011 and June 15, 2011 at Frontage Clinical Services (a wholly-owned subsidiary of Frontage Laboratories, Inc., Hackensack, NJ, USA). The study complied with the ethical principles of Good Clinical Practice and in accordance with the Declaration of Helsinki. All subjects provided written informed consent prior to study entry.

2.2.1 Sampling and Bioanalytical Methods

Blood samples (6 mL) for the determination of *R*-warfarin and *S*-warfarin plasma concentrations were obtained on days 1 and 29 at time 0 (prior to dose) and at 0.5, 1, 1.5, 2, 4, 6, 9, 12, 24, 48, 72, 96, 144, and 168 h after the warfarin dose. Given that the elimination half-life of *R*-warfarin ranges from 37–89 h and that of *S*-warfarin ranges from 21–43 h, the 168-h sampling interval was required to adequately characterize the area under the plasma concentration-versus-time curve (AUC). Venous blood samples for measurement of *R*- and *S*-warfarin were collected into pre-chilled glass tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA). Plasma was separated by centrifugation and concentrations of *R*- and *S*-warfarin were measured using a validated liquid chromatography with tandem mass spectrometry (LC–MS/MS) method by Frontage Laboratories, Inc. (Malvern, PA, USA). *R*-warfarin, *S*-warfarin, and the internal standards were extracted from human plasma by solid-phase extraction and separated by reversed-phase high-performance liquid chromatography (HPLC) with a Supelco Astec® Chirobiotic® V column (100 × 4.6 mm, 5 μm; Sigma-Aldrich Corporation, Saint Louis, MO, USA) and Shimadzu HPLC pump and autosampler (Shimadzu, Kyoto, Japan), with a flow rate of 1.0 mL/min at room temperature and elution times of 3.2 min and 4.1 min for *R*-warfarin and *S*-warfarin, respectively. The mobile phase was isocratic with 75 %/25 % A/B; phase A was 5.0 mM ammonium acetate and phase B was 100 % acetonitrile). Warfarin-d_5 was the internal standard and the reference standards were *R*-warfarin and *S*-warfarin. Ions were monitored for *R*- and *S*-warfarin at *m*/*z* 307.1–161.0 and for warfarin-d_5 at 312.1–161.0 in negative ionization mode using the API4000™ mass spectrometer with TurboIonSpray electrospray ion source (AB Sciex, Framingham, MA, USA) at 550 °C and −2,800 V with N_2. The dynamic range was 5–1,500 ng/mL for *R*- and *S*-warfarin with a lower limit of quantitation of 5 ng/mL. The assay accuracy (mean determined concentration/nominal concentration) ranged from 91.2–108.1 % (intra-run) and from 93.0–107.4 % (inter-run). The assay precision (coefficient of variation of the mean determined concentration) ranged from 1.5–6.0 % (intra-run) and from 3.5–4.6 % (inter-run).

For PT and INR assessment, blood samples (4.5 mL) were obtained at screening and on days 1 and 29 at time 0 (prior to dose) and 6, 12, 24, 36, 48, 72, 96, 120, 144, and 168 h after warfarin administration. PT (in seconds) was determined using a validated assay performed at BioReference Laboratories (Elmwood Park, NJ, USA). The INR was calculated as the ratio of the subject's PT test value (PT_{test}) to the PT of a normal control sample (PT_{normal}), raised to the power of the International Sensitivity Index (ISI) assigned to the tissue factor reagent and analytical system used, as follows: $INR = (PT_{test}/PT_{normal})^{ISI}$. All pre-dose samples were collected when subjects were in the fasting state.

2.3 Statistical Methods

A sample size of 26 subjects, with at least 20 subjects completing the study, was selected as one that would meet study aims based on the number of subjects used in published warfarin drug interaction studies [11–16]. The intent-to-treat (ITT) population included all subjects who signed the informed consent form and were included in the study. The pharmacokinetic population included all subjects who had the primary warfarin pharmacokinetic end point parameters from days 1 and 29 available. The pharmacodynamic population included all subjects who provided the blood samples for the PT/INR analyses required to calculate the primary pharmacodynamic end point parameters for days 1 and 29. Safety was evaluated for all subjects who received at least one dose of study drug.

2.3.1 Pharmacokinetic Evaluations

The primary pharmacokinetic end points were the AUC from time zero to infinity ($AUC_{0-\infty}$) and the maximum observed plasma concentration (C_{max}) for *R*- and *S*-warfarin on day 1 (without IPE) and day 29 (with IPE). Secondary and additional pharmacokinetic end points were the AUC from time zero to the last sampling time with quantifiable concentration (AUC_{last}), time of observed C_{max} (t_{max}), apparent terminal elimination half-life ($t_{½}$), and apparent terminal elimination rate constant (k_{el}) on days 1 and 29 for *R*- and *S*-warfarin. Pharmacokinetic parameters for *R*- and *S*-warfarin were derived by noncompartmental analysis using WinNonlin version 5.01 (Pharsight

Corporation Inc., Mountain View, CA, USA), using actual sampling times for each subject. AUC was calculated using the linear trapezoidal method.

2.3.2 Pharmacodynamic Evaluations

Pharmacodynamic variables were calculated from PT and INR following administration of warfarin without and with IPE using actual sampling times for each subject by non-compartmental methods using WinNonlin Professional (version 5.0.1). Primary pharmacodynamic end points (following warfarin administration without and with IPE on days 1 and 29, respectively) were the area under the INR effect-time curve from time zero to 168 h after the warfarin dose (AUC_{INR}) and the INR_{max}. The time of occurrence of INR_{max} (T_{INRmax}) was a secondary end point. Day 1 pre-dose values were used for determination of change from baseline during days 1–8, and day 29 pre-dose values were used for determination of change from baseline during days 29–35.

2.3.3 Statistical Comparisons

Subjects who had the protocol-defined primary pharmacokinetic parameters available from both pharmacokinetic days were included in statistical comparisons. Evaluations of drug–drug interaction were based on values for $AUC_{0-\infty}$ (primary analysis) and C_{max} of *R*- and *S*-warfarin. Mixed effects analysis of variance (ANOVA) modeling under the crossover design was based on natural log-transformed values with treatment as a fixed effect and subject as a random effect. The estimate of the ratio between the two treatments (warfarin with IPE divided by warfarin alone) and the corresponding 90 % confidence intervals (CI) for the ratio were obtained by exponentiating the mean difference in logarithms. A pharmacokinetic drug–drug interaction was ruled out if the ratios were within the 90 % CI equivalence limits of 0.80–1.25 [17].

R- and *S*-warfarin t_{max} was analyzed without log transformation using nonparametric Wilcoxon signed-rank test. Corresponding 95 % CIs for the difference in medians was reported using the Walsh average and appropriate quantile of the Wilcoxon signed-rank test statistic. Significant differences for the treatment comparison were concluded if the resulting p value was <0.05.

2.4 Safety Assessment

Safety evaluations consisted of monitoring adverse events (AEs), clinical laboratory measurements (chemistry, hematology, urinalysis), vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, oral body temperature), and physical examination findings.

3 Results

3.1 Study Subjects

Twenty-six subjects were enrolled and one withdrew consent on day 6 of the study. A total of 25 (96 %) subjects completed the study and were included in pharmacokinetic and pharmacodynamic analysis populations. All 26 enrolled subjects received at least one dose of study drug and were included in the safety analysis population (Table 1). Mean compliance for IPE dosing (days 8–35) based on capsule counts was 97 %.

3.2 Pharmacokinetic Parameters

Mean plasma concentration-versus-time curves for *R*- and *S*-warfarin were comparable for subjects administered racemic warfarin alone or with concomitant IPE at steady state (Fig. 1). Pharmacokinetic parameters obtained for *R*- and *S*-warfarin were similar when subjects received warfarin alone versus co-administration of warfarin and IPE (Table 2). Based on p values of 0.209 and 0.195 for *R*- and *S*-warfarin, respectively, there was no significant difference in t_{max} of warfarin when administered without or with IPE.

3.3 Pharmacodynamic Parameters

Mean INR following warfarin administration without and with IPE throughout the 168-h sampling period is shown in Fig. 2. Corresponding median values for AUC_{INR} and

Table 1 Subject demographics and baseline characteristics (safety population)

Characteristic	Value
Number of patients	26
Age, years	37.7 ± 10.6
Sex, *n* (%)	
Men	20 (77)
Women	6 (23)
Race, *n* (%)	
Black/African American	17 (65)
White	6 (23)
Other	3 (12)
Ethnicity, *n* (%)	
Hispanic or Latino	9 (35)
Weight, kg	80.6 ± 16.6
Body mass index, kg/m^2	26.7 ± 4.1

Values are expressed as mean ± SD unless specified otherwise

SD standard deviation

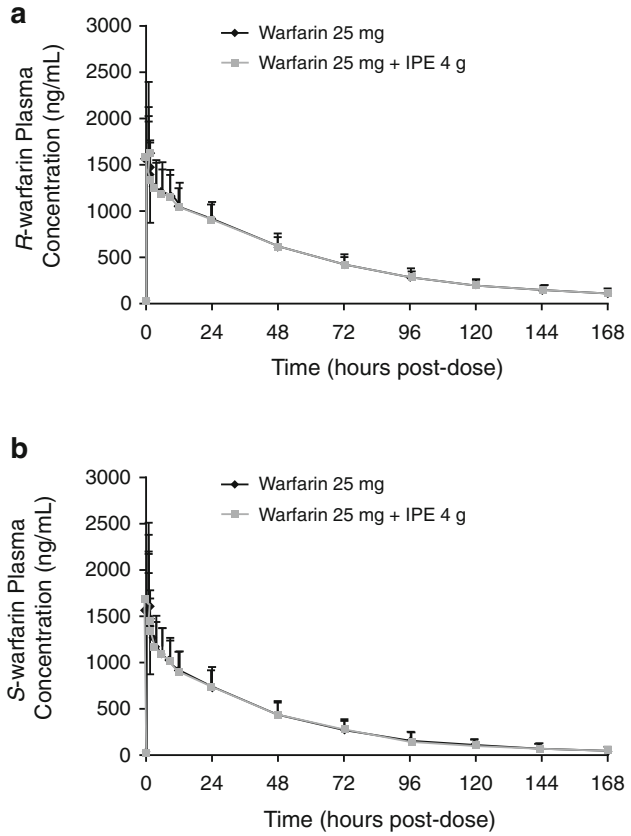

Fig. 1 Mean (standard deviation [SD]) plasma concentrations of **a** *R*-warfarin and **b** *S*-warfarin following oral administration of 25 mg warfarin without and with 4 g/day icosapent ethyl (IPE) at steady state (pharmacokinetic and pharmacodynamic population)

INR_{max} were similar when warfarin was given alone or with IPE (Table 3). Based on a p value of 0.026, there was a significant reduction in the median time to T_{INRmax} with concomitant administration of warfarin and IPE compared with warfarin alone. However, this difference (a reduction from 48 to 36 h) may have been influenced by the sparse sampling. No differences were observed in the change from baseline (pre-dose) in the INR or PT values when warfarin was administered without or with IPE.

3.4 Statistical Analyses of Pharmacokinetic and Pharmacodynamic Drug–Drug Interaction

In the primary pharmacokinetic analysis, the 90 % CIs for the least squares geometric mean (LSGM) ratios for *R*- and *S*-warfarin $AUC_{0-\infty}$ and C_{max} were found to lie within the 0.80–1.25 bounds (Table 4). The 90 % CIs obtained for the LSGM ratios for the pharmacodynamic parameters AUC_{INR} and INR_{max} were also contained within the 0.80–1.25 bounds (Table 4).

3.5 Safety

A total of 26 subjects were exposed to at least one dose of study drug. Nine (35 %) subjects reported at least one AE during the study. Two (8 %) subjects reported at least one AE during days 1–8 (i.e., during warfarin administration without IPE), and 8 (32 %) subjects reported at least one

Table 2 Pharmacokinetic parameters for *R*- and *S*-warfarin in plasma following a single 25-mg dose of warfarin without and with icosapent ethyl 4 g/day at steady state (pharmacokinetic and pharmacodynamic population)

Analyte	Parameter (unit)	Treatment[a]	
		Warfarin 25 mg ($n = 25$)	Warfarin 25 mg + IPE 4 g ($n = 25$)
R-warfarin	$AUC_{0-\infty}$, ng·h/mL	82,620 (19,725)	82,460 (22,798)
	C_{max}, ng/mL	1,766 (673)	1,865 (592)
	AUC_{last}, ng·h/mL	77,539 (17,374)	77,117 (19,505)
	t_{max}, h	1.0 (0.5–9.0)	1.0 (0.5–1.5)
	$t_{½}$, h	46.4 (8.4)	46.8 (8.3)
	k_{el}, 1/h	0.015 (0.005)	0.016 (0.005)
S-warfarin	$AUC_{0-\infty}$, ng·h/mL	60,216 (15,009)	60,253 (16,204)
	C_{max}, ng/mL	1,836 (729)	1,973 (616)
	AUC_{last}, ng·h/mL	59,253 (15,429)	59,134 (16,451)
	t_{max}, h	1.0 (0.5–9.0)	1.0 (0.5–1.5)
	$t_{½}$, h	36.7 (8.2)	37.7 (9.1)
	k_{el}, 1/h	0.020 (0.005)	0.020 (0.005)

$AUC_{0-\infty}$ area under the plasma concentration-versus-time curve from time zero to infinity, AUC_{last} area under the plasma concentration-versus-time curve from time zero to the last sampling time with quantifiable concentration, C_{max} maximum observed concentration, *IPE* icosapent ethyl, k_{el} apparent terminal rate constant, $t_{½}$ apparent terminal half-life, t_{max} time of observed C_{max}

[a] Mean (SD) displayed for all pharmacokinetic parameters except t_{max}, which is displayed as median (range)

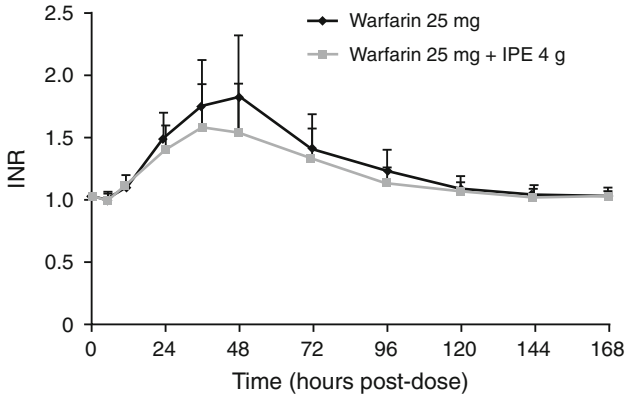

Fig. 2 Mean (standard deviation [SD]) international normalized ratio (INR) following administration of racemic warfarin 25 mg without and with icosapent ethyl (IPE) 4 g/day at steady state (pharmacokinetic and pharmacodynamic population)

Table 3 Pharmacodynamic parameters following a single 25-mg dose of warfarin without and with icosapent ethyl 4 g/day at steady state (pharmacokinetic and pharmacodynamic population)

Parameter	Statistic	Treatment	
		Warfarin 25 mg ($n = 25$)	Warfarin 25 mg + IPE 4 g ($n = 25$)
AUC_{INR}	Mean (SD)	217.8 (27.7)	204.8 (24.7)
	Median	213.4	200.1
	Range	177.5–275.4	172.4–267.3
INR_{max}	Mean (SD)	1.86 (0.48)	1.60 (0.39)
	Median	1.74	1.54
	Range	1.25–2.90	1.12–2.64
T_{INRmax}, h	Median	48.0	36.0
	Min, Max	24.0, 96.0	24.0, 48.0

AUC_{INR} area under the effect-time curve from time zero to 168 h after the warfarin dose, *INR_{max}* maximum observed international normalized ratio (INR) value, *IPE* icosapent ethyl, *T_{INRmax}* time of occurrence of INR_{max}

AE on all other days. All AEs were mild or moderate in intensity.

Somnolence occurred in 2 of the 25 subjects (8 %) who received co-administration of warfarin and IPE; headache was reported by 2 subjects (1 subject each in the groups where warfarin was given alone or with IPE). Sinus headache and insomnia were reported by 1 subject each in the warfarin alone group, and palpitations, diarrhea, flatulence, fatigue, arthralgia, depressed mood (considered moderate in intensity), dysmenorrhea, and rash were reported by 1 subject each in the warfarin plus IPE group. There were no discontinuations due to an AE and no serious AEs or bleeding events were reported. No clinically significant changes in laboratory test results, vital sign assessments, or physical examination findings were observed in this study.

4 Discussion

Patients with elevated serum triglycerides who may be candidates for IPE treatment may also have cardiovascular and/or metabolic conditions and be receiving multiple therapies, such as anticoagulation with warfarin. This study in healthy adults demonstrated that IPE 4 g/day at steady state did not significantly alter the exposure ($AUC_{0-\infty}$), peak plasma concentration (C_{max}) or the anticoagulation pharmacodynamics of *R*- and *S*-warfarin when co-administered at 25 mg. It is expected that steady state was reached for plasma levels of IPE in the present study following 28 days of treatment with IPE because a previous pharmacokinetic study of IPE found that steady state was reached in plasma by 14 days [18]. The 90 % CIs for C_{max} and $AUC_{0-\infty}$ LSGM ratios for *R*- and *S*-warfarin were within the 0.80–1.25 bounds, indicating no clinically relevant pharmacokinetic effects with co-administration. Anticoagulation parameters (AUC_{INR}, INR_{max}, PT) of a 25-mg dose of warfarin were also unaffected by IPE at steady state concentrations. IPE 4 g/day and the single dose of warfarin were well tolerated in this group of healthy men and women.

The active metabolite of IPE is EPA and although after oral administration in humans, EPA is metabolized predominantly via β-oxidation rather than CYP-mediated processes, a significant effect on CYP2C9-mediated metabolism was not expected but was possible because EPA is also known to be metabolized at least in part by CYP enzymes, including CYP2C9 [6]. Evaluation of *S*-warfarin is recommended by the United States FDA for use as a sensitive CYP2C9 substrate for study of potential drug–drug interactions in humans [17]. Comparisons of pharmacokinetic parameters and LSGM ratio 90 % CIs for *S*-warfarin without and with IPE support that IPE 4 g/day does not alter the pharmacokinetics of this CYP2C9 substrate.

The pharmacodynamic component of the present clinical study adds important safety evidence regarding the potential use of IPE in patients receiving warfarin as antithrombotic therapy. Long-chain omega-3 fatty acid products derived from fish oils have been reported to decrease platelet aggregation and reduce production of platelet-derived growth factor, which could potentially contribute to a decrease in clinical atherothrombosis and the possibility of increased bleeding risk [19–26]. However, clinical studies have demonstrated that omega-3 fatty acid supplementation did not affect bleeding time [27] or cause significant changes in INR or increased bleeding episodes in patients receiving chronic anticoagulation therapy [28]. An evidence-based review concluded that fish oils rich in omega-3 fatty acids do not increase the risk of bleeding and are not contraindicated in patients treated

Table 4 Statistical analysis of drug–drug interaction (pharmacokinetic and pharmacodynamic population; $n = 25$)

Parameter	Statistic[a]	*R*-warfarin		*S*-warfarin	
		Warfarin 25 mg	Warfarin 25 mg + IPE 4 g	Warfarin 25 mg	Warfarin 25 mg + IPE 4 g
Pharmacokinetic parameters					
$AUC_{0-\infty}$ (ng·h/mL)	LSGM	80,486	79,873	58,344	58,236
	LSGM ratio (90 % CI)	0.99 (0.96–1.03)		1.00 (0.97–1.03)	
C_{max}, ng/mL	LSGM	1,659.6	1,789.6	1,715.9	1,897.0
	LSGM ratio (90 % CI)	1.08 (0.99–1.17)		1.11 (1.01–1.21)	

		Warfarin 25 mg	Warfarin 25 mg + IPE 4 g
Pharmacodynamic parameters			
AUC_{INR}	LSGM	216.2	203.4
	LSGM ratio (90 % CI)	0.94 (0.93–0.96)	
INR_{max}	LSGM	1.80	1.56
	LSGM ratio (90 % CI)	0.87 (0.84–0.90)	

$AUC_{0-\infty}$ area under the plasma concentration-versus-time curve from time zero to infinity, AUC_{INR} area under the effect-time curve from time zero to 168 h after the warfarin dose, C_{max} maximum observed concentration, INR_{max} maximum observed international normalized ratio (INR) value, *IPE* icosapent ethyl, *LSGM* least squares geometric means

[a] LSGM derived from mixed models; LSGM ratios are provided for IPE plus warfarin/warfarin alone

with antiplatelet and anticoagulation therapies [9]. Furthermore, a review of available studies in which patients undergoing major vascular surgery also received omega-3 fatty acids at doses of 1–4 g/day and higher found that omega-3 fatty acids do not increase the risk for clinically significant bleeding, even in patients receiving antiplatelet or antithrombotic medications [29]. A recent review omega-3 fatty acids and bleeding spanning multiple clinical settings (including randomized controlled studies, epidemiological studies, and evidence from investigations in neurology, nephrology, critical care, surgery, cardiology, hematology, obstetrics, and dentistry) found no increase in the risk of clinically significant bleeding with omega-3 fatty acid monotherapy or combination therapy in nearly all of the studies discussed [10]. In the present study, the lack of effect of IPE on warfarin anticoagulation pharmacodynamic parameters supports previous findings that omega-3 fatty acids do not increase bleeding risk. However, patients receiving anticoagulation therapy and prescription omega-3 fatty acid therapies such as IPE or omega-3 acid ethyl esters should be monitored periodically [3, 30].

Limitations of this study include sparse sampling for T_{INRmax} and thus it is difficult to determine definitively whether IPE affected this parameter. Although the use of a single-dose design for warfarin may be considered a potential limitation of this study, use of a large, single loading dose of 25 mg warfarin is a typical approach to investigating the effects of concomitant drug administration on the pharmacokinetics and anticoagulation pharmacodynamics of warfarin [11–16].

5 Conclusions

At steady-state concentrations, IPE at the approved dose of 4 g/day did not have an effect on the single dose pharmacokinetics or anticoagulation pharmacodynamics of 25-mg racemic warfarin in healthy adults. Co-administration of these drugs was safe and well-tolerated in this study of healthy adult subjects.

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