T2284

Multiple-Dose Administration of a Free-Fatty Acid Formulation of EPA/DHA Has No Effect on the Pharmacokinetics or Pharmacodynamics of Single-Dose Warfarin

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BACKGROUND

- In patients with severe hypertriglyceridemia (TG ≥ 500 mg/dL), the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III recognized that statins are not powerful triglyceride (TG)-lowering drugs, and therefore recommended the use of specific therapies such as n-3 (omega) fatty acids as an adjunct to diet to lower TG levels.[1]
- Once absorbed, the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins.[1]
- Epanova™ is a complex mixture of omega-3 free-fatty acids, primarily EPA and DHA, being developed as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia, and as an adjunct to statin therapy in patients with persistent hypertriglyceridemia at high risk for cardiovascular disease.
- Warfarin, an anticoagulant administered as a racemic mixture of (R)- and (S)-enantiomers, is prescribed for patients with thrombotic and embolic disorders, and to reduce the risk of thrombosis in high-risk patients. Warfarin acts by inhibiting vitamin K-dependent coagulation factors. Its efficacy can be monitored by measurement of prothrombin time (PT) converted to the standardized parameter of the International Normalized Ratio (INR). Fluctuations in the state of anticoagulation in a patient taking warfarin can have clinical consequences, such as bleeding associated with excessive anticoagulation or thrombosis secondary to subtherapeutic anticoagulation.
- In clinical practice, Epanova™ may be co-administered with warfarin. Since warfarin has a narrow therapeutic index and omega-3 fatty acids may affect the absorption of warfarin and lipid-soluble vitamins such as vitamin K to potentiate the risk of bleeding, the effects of Epanova™ on the pharmacokinetics (PK) and pharmacodynamics (PD) of warfarin were investigated.

OBJECTIVE

To determine the effect of multiple-dose Epanova™ on the PK and PD of a single 25 mg dose of warfarin.

METHODS

Study Design

- Open-label, 2-treatment, fixed-sequence study in 26 healthy male and female participants (18 – 55 yrs of age).
- The duration of the study was approximately 29.5 days (excluding screening).
- Participants were screened for study participation within 28 days of dosing.
- A Therapeutic Lifestyle Changes (TLC, a heart-healthy diet low in saturated fat, trans fat, and cholesterol, created by the National Institutes of Health to help reduce the risk of cardiovascular disease) diet was followed throughout the entire study.
- Beginning on Day -1, the participants were served a daily breakfast containing < 10% fat. Participants were required to fast for a minimum of 10 hours overnight prior to breakfast and continue to fast for at least 4 hours thereafter. Participants were also served lunch and dinner daily.
- On Day 1 following an overnight fast, participants were administered a single 25 mg dose of warfarin with 240 mL of water at Hour 0.
- Blood samples were collected over 168 hours following warfarin dosing on Day 1 to calculate PK and PD parameters of warfarin.
- On Days 8 to 28, participants were administered a 4 g (4 x 1 g capsules) dose of Epanova™ alone, and co-administered with a single 25 mg dose of warfarin on Day 22. All doses of Epanova™ were administered approximately 30 minutes following the start of a low-fat breakfast, with the exception of the Day 22 dose which was co-administered with warfarin following an overnight fast. The breakfast was to be completed prior to Hour 0 dosing of each study day.
- Blood samples were collected over 168 hours following warfarin and Epanova™ co-administration on Day 22 to calculate PK and PD parameters of warfarin.

Pharmacokinetic Blood Sampling

- Blood samples were collected on Days 1 and 22 for the determination of plasma (R)- and (S)-warfarin concentrations at: predose, and 0.5, 1, 2, 3, 4, 5, 6, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose.
- Blood samples were collected on Days 1 and 22 for the determination of the PT INR at: predose, and 0.5, 1, 2, 4, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose.

Bioanalytical Assay

Plasma samples were assayed for (R)- and (S)-warfarin using HPLC/MS-MS with an LLOQ of 12.5 ng/mL.

Pharmacokinetic Analysis

The following PK parameters were calculated for plasma (R)- and (S)-warfarin following warfarin alone (Day 1), and warfarin co-administered with Epanova™ (Day 22):

- AUC_{0-t} : Area under the plasma concentration versus time curve from time 0 to the time of the last measurable concentration;
- $AUC_{0-\infty}$: Area under the plasma concentration versus time curve from time 0 to infinity;
- C_{max} : Maximum measured plasma concentration;
- t_{max} : Time at which C_{max} occurred;
- $t_{½}$: Apparent terminal elimination half-life.

Pharmacodynamic Analysis

The following PD parameters were calculated for the INR on Days 1 and 22:

- $INR\ AUC_{0-168}$: Area under the INR versus time curve from time 0 to 168 hours postdose;
- INR_{max} : Maximum measured INR value.

Statistical Analysis

- Analysis of variance was performed on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of plasma (R)- and (S)-warfarin, as well as the ln-transformed INR AUC_{0-168} and INR_{max}.
- No drug interaction was to be claimed if the 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) of the back-transformed AUC_{0-t}, $AUC_{0-\infty}$, and Cmax of plasma (R)- and (S)-warfarin, and the back-transformed INR AUC_{0-168} and INR_{max}, for warfarin co-administered with Epanova™ versus warfarin alone, fell within 80.00% - 125.00%.

RESULTS OVERVIEW

The study enrolled 26 healthy adult male and female participants, and 25 participants (20 males and 5 females) completed the study.

Figures 1 and 2 – Mean plasma (R)-warfarin (Figure 1) and (S)-warfarin (Figure 2) concentrations were similar following a single oral dose of 25 mg warfarin (Day 1), and following a single oral dose of 25 mg warfarin co-administered with multiple-dose Epanova™ (Day 22).

Figure 3 – Mean INR were similar following a single oral dose of 25 mg warfarin (Day 1), and following a single oral dose of 25 mg warfarin co-administered with multiple-dose Epanova™ (Day 22).

Tables 1 and 2 - The geometric mean overall (AUC_{0-t} and $AUC_{0-\infty}$) and peak (C_{max}) exposures to (R)- and (S)-warfarin, as well as the median t_{max} and mean $t_{½}$, were comparable following warfarin alone and warfarin co-administered with Epanova™ (Table 1).
Similarly, the geometric mean INR AUC_{0-168} and INR_{max} were comparable following warfarin alone and warfarin co-administered with Epanova™ (Table 2).

Tables 3 and 4 - The 90% CIs for the GMRs (warfarin + Epanova™ / warfarin alone) of the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for (R)-and (S)-warfarin in plasma were within 80.00% – 125.00% (Table 3).
Similarly, the 90% CIs for the GMRs (warfarin + Epanova™ / warfarin alone) of the ln-transformed INR AUC_{0-168} and INR_{max} were within 80.00% – 125.00% (Table 4).

Figure 1 Mean Plasma (R)-warfarin Concentrations Versus Time

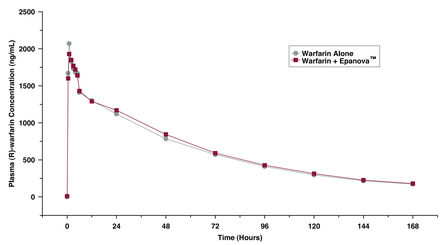

Figure 2 Mean Plasma (S)-warfarin Concentrations Versus Time

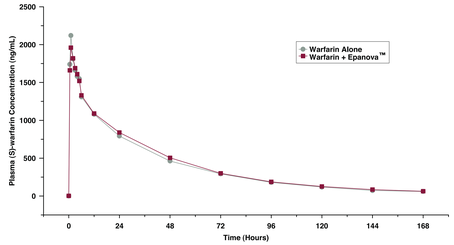

Figure 3 Mean INR Versus Time

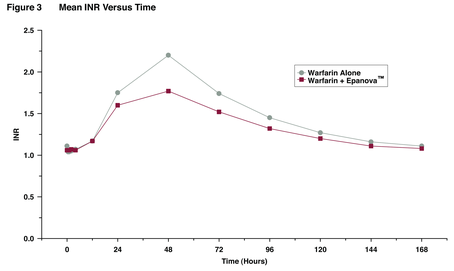

Table 1 Summary of the Pharmacokinetic Parameters of Warfarin in Plasma

Pharmacokinetic Parameter	Warfarin Alone (n=25)	Warfarin + Epanova™ (n=25)
(R)-warfarin		
AUC_{0-t} (ng·hr/mL)	101000 (19.0)	105000 (20.5)
$AUC_{0-\infty}$ (ng·hr/mL)	115000 (21.1)	119000 (22.8)
C_{max} (ng/mL)	2240 (22.7)	2050 (21.7)
t_{max} (hr)	0.999 (0.499, 5.00)	1.00 (0.494, 5.00)
$t_{½}$ (hr)	55.0 (19.6)	55.1 (17.7)
(S)-warfarin		
AUC_{0-t} (ng·hr/mL)	62800 (28.7)	64800 (31.1)
$AUC_{0-\infty}$ (ng·hr/mL)	66100 (32.1)	68300 (34.7)
C_{max} (ng/mL)	2300 (23.4)	2080 (23.5)
t_{max} (hr)	0.999 (0.499, 2.01)	0.999 (0.494, 5.00)
$t_{½}$ (hr)	42.1 (20.1)	42.6 (23.0)

AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} are presented as Geometric Mean (Geometric CV%).
t_{max} is presented as Median (Minimum, Maximum).
$t_{½}$ is presented as Arithmetic Mean (Arithmetic CV%).

Table 2 Summary of the Pharmacodynamic Parameters of Warfarin

Pharmacodynamic Parameter	Warfarin Alone (n=26)	Warfarin + Epanova™ (n=25)
$INR\ AUC_{0-168}$	247 (20.2)	225 (14.6)
INR_{max}	2.14 (31.5)	1.77 (23.2)

$INR\ AUC_{0-168}$ and INR_{max} are presented as Geometric Mean (Geometric CV%).

Table 3 Summary of the Statistical Comparisons of the Pharmacokinetic Parameters of Plasma Warfarin

Pharmacokinetic Parameter	Geometric Least-Squares Means		Geometric Mean Ratio	90% Confidence Interval
	Warfarin + Epanova™	Warfarin Alone		
(R)-warfarin				
AUC_{0-t} (ng·hr/mL)	104659.28	101257.14	103.36	100.81 - 105.97
$AUC_{0-\infty}$ (ng·hr/mL)	119006.62	114785.21	103.68	100.61 - 106.84
C_{max} (ng/mL)	2052.48	2240.29	91.62	87.44 - 96.00
(S)-warfarin				
AUC_{0-t} (ng·hr/mL)	64810.54	62845.55	103.13	100.32 - 106.01
$AUC_{0-\infty}$ (ng·hr/mL)	68346.95	66141.98	103.33	100.27 - 106.49
C_{max} (ng/mL)	2081.49	2302.04	90.42	85.28 - 95.86

Table 4 Summary of the Statistical Comparisons of the Pharmacodynamic Parameters of Warfarin

Pharmacodynamic Parameter	Geometric Least-Squares Means		Geometric Mean Ratio	90% Confidence Interval
	Warfarin + Epanova™	Warfarin Alone		
$INR\ AUC_{0-168}$	224.91	244.87	91.85	89.85 - 93.90
INR_{max}	1.77	2.11	84.02	80.96 - 87.19

CONCLUSIONS

- Once-daily 4 g doses of Epanova™ for 21 days had no effect on the PK nor PD of a single 25 mg dose of warfarin, in that the systemic exposure to plasma (R)- and (S)-warfarin, and the PT INR, were comparable following warfarin alone and warfarin co-administered with Epanova™.
- There were no serious adverse events in this study and no participant was discontinued due to an adverse event.

REFERENCES

1. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation. 2002; 106:3143-421.

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