Multiple Doses of Omega-3 PUFAs Do Not Alter the Pharmacokinetics of Simvastatin or the Antiplatelet Effect of ASA

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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]

Omthera Pharmaceuticals is developing a complex mixture of omega-3 polyunsaturated fatty acids, primarily EPA and DHA (n-3 PUFAs), as an adjunct to diet to reduce TG 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.

Simvastatin, a lipid-lowering agent, and omega-3 fatty acid lipid-regulating agents such as Omthera Pharmaceuticals' n-3 PUFAs (which also have effects on hemostatic factors, blood viscosity, and platelet function), may be prescribed and taken concomitantly in patients with cardiovascular disease. Therefore, this study was intended to examine the potential influence of multiple dose n-3 PUFAs on the PK of multiple-dose simvastatin.

Drug interactions may cause aspirin resistance, i.e., the inability of aspirin to reduce platelet production of thromboxane A2 (TXA_2) and to inhibit platelet activation. Patients with cardiovascular disease are frequently prescribed low-dose aspirin, therefore this study was also aimed at assessing the effect of n-3 PUFAs on the antiplatelet action of low-dose aspirin.

OBJECTIVE

To determine the effect of multiple-dose n-3 PUFAs on the pharmacokinetics (PK) of multiple-dose simvastatin, and on the antiplatelet action of low-dose aspirin.

METHODS

Study Design

- Open-label, 2-way crossover study in 52 healthy male and female participants (18 - 55 years of age).
- On Days 1 to 14 of each period, participants were administered 40 mg simvastatin, 81 mg aspirin and 4 g n-3 PUFAs (Treatment A) or 40 mg simvastatin and 81 mg aspirin (Treatment B).
- Participants were confined from Day -1 to Day 15 of each period, and each period was separated by a washout of 14 days between the last dose in Period 1 and the first dose in Period 2.

Pharmacokinetic Blood Sampling and Assay

- Predose blood samples were obtained on Days 12, 13 and 14 of each period, and serial blood samples were collected at the following times on Day 14 of each period, to determine plasma concentrations of simvastatin and β–hydroxysimvastatin acid: 0.333, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, and 24 hours postdose.
- Simvastatin and β-hydroxysimvastatin acid in plasma were assayed using high performance liquid chromatography with mass spectrometric detection, with an analytical range of 0.100 – 20.0 ng/mL.

Platelet Activation Samples and Assays

- In each period, blood samples were collected at check-in (baseline) and check-out (Day 15) for use in the VerifyNow® Aspirin assay, a whole blood assay to aid in the detection of platelet inhibition due to aspirin therapy. The results of this assay are expressed in Aspirin Reaction Units (ARUs), which indicate the amount of TXA_2-mediated activation of platelet glycoprotein (GP) IIb/IIIa receptors involved in platelet aggregation. ARU is calculated as a function of the rate and extent of platelet aggregation. Expected values are in the range of 350 – 700 ARU. ARU values < 550 are indicative of the therapeutic benefit of aspirin, i.e., platelet inhibition.[2]
- In each period, a urine sample was collected at check-out for use with the AspirinWorks® test kit. The AspirinWorks® test kit is an enzyme-linked immunoassay (ELISA) to determine levels of 11-dehydrothromboxane B_2 (11-dTXB_2), a stable metabolite of TXA_2, in human urine, which aids in the qualitative detection of aspirin effect in apparently healthy individuals post-ingestion. TXA_2 is generated from arachidonic acid by the COX-1 enzyme (which is inhibited by aspirin) in active platelets, hydrolyzed by the liver into a number of metabolites, including 11-dTXB_2, and filtered from the blood through the kidneys into the urine. An 11-dTXB_2 urine level > 1500 pg/mg creatinine is expected in healthy, aspirin-free individuals, but in patients receiving low-dose aspirin therapy, such levels suggest insufficient inhibition of the patient's COX-1 pathway. A level ≤ 1500 pg/mg creatinine in individuals taking aspirin indicates complete inhibition of the COX-1 pathway, and is consistent with response to aspirin therapy.[3]

Pharmacokinetic Analysis

The following PK parameters were calculated for plasma simvastatin and β-hydroxysimvastatin acid on Day 14:

- $AUC_{0\text{-}t}$: Area under the plasma concentration versus time curve, from time 0 to the time of the last measurable concentration.
- C_{max}: Maximum measured plasma concentration.
- T_{max}: Time of the maximum measured plasma concentration.

Statistical Analysis

Drug-Drug Interaction Assessment

- The drug-drug interaction was assessed by analyzing the natural log (ln)-transformed PK parameters $AUC_{0\text{-}t}$ and C_{max} of simvastatin and β-hydroxysimvastatin acid using a linear mixed-effects model.
- No interaction was to be claimed if the 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) of the back-transformed PK parameters $AUC_{0\text{-}t}$ and C_{max} for simvastatin and β-hydroxysimvastatin acid fell within 80% - 125%.

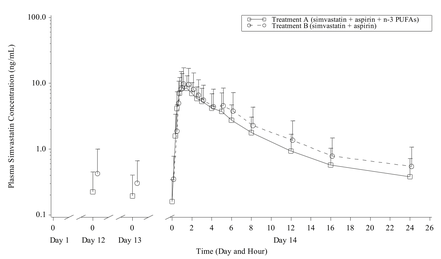
Platelet Activation Assessments

- The VerifyNow® Aspirin assay data at check-in (baseline) prior to treatment, check-out (Day 15) post-treatment, and change from baseline (post-treatment – baseline), and the 11-dTXB_2 concentrations at check-out (Day 15) post-treatment, were compared between treatments using a linear mixed-effects model.

RESULTS

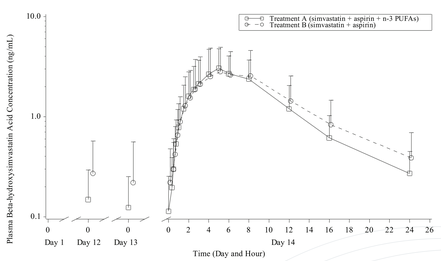
Mean (SD) plasma simvastatin and β-hydroxysimvastatin acid concentrations following the administration of 40 mg simvastatin + 81 mg aspirin with or without 4 g n-3 PUFAs, once-daily for 14 days, are presented in Figures 1 and 2, respectively.

Figure 1: Mean (SD) Plasma Simvastatin Concentrations



Treatment B is shifted to the right for ease of reading

Figure 2: Mean (SD) Plasma β-Hydroxysimvastatin Acid Concentrations



Treatment B is shifted to the right for ease of reading

The summary of plasma simvastatin and β-hydroxysimvastatin acid PK parameters is presented in Table 1. The geometric mean overall ($AUC_{0\text{-}t}$) and peak (C_{max}) exposures to plasma simvastatin and β-hydroxysimvastatin acid, as well as the median T_{max} values, were comparable following simvastatin + aspirin + n-3 PUFAs, and following simvastatin + aspirin.

Table 1: Summary of Plasma Simvastatin and β-Hydroxysimvastatin Acid Pharmacokinetic Parameters

	Simvastatin + Aspirin + n-3 PUFAs	Simvastatin + Aspirin
Simvastatin		
$AUC_{0\text{-}t}$ (ng•hr/mL)	40.3 (60.7) (n=52)	45.9 (75.7) (n=51)
C_{max} (ng/mL)	9.27 (62.1) (n=52)	9.98 (71.9) (n=51)
T_{max} (hr)	1.50 (0.748, 5.00) (n=52)	1.00 (0.500, 6.00) (n=51)
β-Hydroxysimvastatin Acid		
$AUC_{0\text{-}t}$ (ng•hr/mL)	26.9 (56.1) (n=52)	28.1 (61.4) (n=50)
C_{max} (ng/mL)	2.94 (61.6) (n=52)	2.63 (63.0) (n=51)
T_{max} (hr)	5.00 (2.00, 8.00) (n=52)	5.00 (3.01, 12.0) (n=51)

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

The statistical comparisons of plasma simvastatin and β-hydroxysimvastatin acid PK parameters are summarized in Table 2. The 90% CIs of the ln-transformed ($AUC_{0\text{-}t}$) and (C_{max}) for plasma simvastatin and β-hydroxysimvastatin acid for simvastatin + aspirin + n-3 PUFAs versus simvastatin + aspirin, were within 80% – 125%.

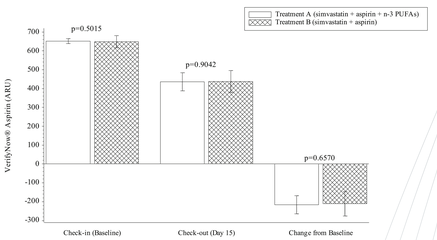
Table 2: Summary of the Statistical Comparisons of Plasma Simvastatin and β-Hydroxysimvastatin Acid Pharmacokinetic Parameters

Pharmacokinetic Parameter	Geometric Least-Squares Means: Simvastatin + Aspirin + n-3 PUFAs (Test)	Geometric Least-Squares Means: Simvastatin + Aspirin (Reference)	Test/Reference Ratio (%)	90% Confidence Intervals
Simvastatin				
$AUC_{0\text{-}t}$ (ng•hr/mL)	40.27 (n=52)	46.04 (n=51)	87.47	80.19 - 95.41
C_{max} (ng/mL)	9.27 (n=52)	10.12 (n=51)	91.61	82.82 - 101.33
β-Hydroxysimvastatin Acid				
$AUC_{0\text{-}t}$ (ng•hr/mL)	26.86 (n=52)	28.01 (n=50)	95.90	89.27 - 103.02
C_{max} (ng/mL)	2.94 (n=52)	2.61 (n=51)	112.56	103.48 - 122.43

Parameters were ln-transformed prior to analysis.
Geometric Mean values for Test and Reference are the exponentiated (back-transformed) least-squares means from the ANOVA.
Geometric Mean Ratio = 100*(Test/Reference)

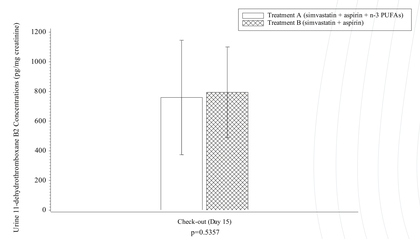
Mean (SD) VerifyNow® Aspirin assay results at check-in (baseline) prior to treatment, check-out (Day 15) post-treatment, and change from baseline following simvastatin + aspirin + n-3 PUFAs, and following simvastatin + aspirin, are presented in Figure 3. The mean of 435 ARU observed at check-out (Day 15) following simvastatin + aspirin + n-3 PUFAs, was comparable to the mean of 437 ARU observed at check-out (Day 15) following simvastatin + aspirin. The values following both treatments are consistent with those from patients receiving the antiplatelet effect of aspirin, i.e., ARU < 550. The post-treatment decreases, with respect to baseline, of 216 ARU and 211 ARU following simvastatin + aspirin + n-3 PUFAs and following simvastatin + aspirin, respectively, were comparable (p > 0.05).

Figure 3: Mean (SD) VerifyNow® Aspirin Assay Results



Mean (SD) urine 11-dTXB_2 concentrations at check-out (Day 15) following simvastatin + aspirin + n-3 PUFAs, and following simvastatin + aspirin, are presented in Figure 4. The mean urine 11-dTXB_2 concentration of 759 pg/mg creatinine observed at check-out (Day 15) following simvastatin + aspirin + n-3 PUFAs was comparable (p>0.05) to the mean of 794 pg/mg creatinine observed at check-out (Day 15) following simvastatin + aspirin. The levels following both treatments were consistent with response to aspirin therapy, i.e., ≤ 1500 pg/mg creatinine.

Figure 4: Mean (SD) Urine 11-dehydrothromboxane B_2 Concentrations



CONCLUSIONS

- Co-administration of 4 g n-3 PUFAs, 40 mg simvastatin, and 81 mg aspirin, once-daily for 14 days, does not alter the PK of simvastatin nor β-hydroxysimvastatin acid.
- The anti-platelet effect of low-dose aspirin is not altered by the concomitant administration of n-3 PUFAs.
- Co-administration of 4 g n-3 PUFAs, 40 mg simvastatin, and 81 mg aspirin is well-tolerated.

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.

2 VerifyNow® Aspirin Test Information Sheet. Accumetrics, Inc., San Diego, California, USA.

3 Aspirin Resistance (11-Dehydrothromboxane B_2) Test Summary: http://www.questdiagnostics.com/testcenter/testguide.action?fn=Cardiovascular/TS_Aspirin_Resistance.htm.

www.celerion.com