

Fish Oil, Multivitamin Gave Same Vitamin D Boost

BY JEFF EVANS
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ARLINGTON, VA. — Fish oil capsules and multivitamin tablets that contain 10 mcg of vitamin D₃ provide the same increase in stored levels of the vitamin when taken daily during a 4-week period, Kristin Holvik reported at a conference sponsored by the American Society for Bone and Mineral Research.

Even though many types of vitamin

supplements are available to patients, little is known about whether the bioavailability of vitamin D₃ (cholecalciferol) differs when it is sequestered in fat-containing capsules as opposed to solid tablets, noted Ms. Holvik, a Ph.D. student at the Institute of General Practice and Community Medicine at the University of Oslo.

In a randomized trial, 55 healthy young adults (34 females and 21 males) received 28 days of supplementation with either

fish oil capsules or multivitamin tablets, each of which was taken once daily and contained 10 mcg vitamin D₃ (an amount equivalent to 400 IU).

The participants completed a self-administered questionnaire about diet and sun exposure and had a nonfasting venous blood sample drawn at the beginning and end of the study, which took place in Oslo in late winter 2005, according to Ms. Holvik. She won an ASBMR Young Investigator Award for her research, which

she presented during a poster session at the conference.

Serum 25-hydroxyvitamin D levels in individuals who took fish oil capsules increased from an average of 48.5 nmol/L to 80.4 nmol/L at the end of the study. Multivitamin users had a similar rise in serum 25-hydroxyvitamin D levels from a mean of 40.3 nmol/L to 76.5 nmol/L. On average, the participants were aged about 28 years and had a body mass index of about 24 kg/m². ■

AVANDIA* rosiglitazone maleate tablets

The following is a brief summary only; see full prescribing information for complete product information.

INDICATIONS AND USAGE: AVANDIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. AVANDIA is indicated as monotherapy. AVANDIA is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet, exercise, and a single agent do not result in adequate glycemic control. For patients inadequately controlled with a maximum dose of a sulfonylurea or metformin, AVANDIA should be added to, rather than substituted for, a sulfonylurea or metformin. AVANDIA is also indicated for use in combination with a sulfonylurea plus metformin when diet, exercise, and both agents do not result in adequate glycemic control. Prior to initiation of therapy with AVANDIA, investigate and treat secondary causes of poor glycemic control, e.g., infection.

CONTRAINDICATIONS: AVANDIA is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS: Cardiac Failure and Other Cardiac Effects: AVANDIA, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. In combination with insulin, thiazolidinediones may also increase the risk of other cardiovascular adverse events. AVANDIA should be discontinued if any deterioration in cardiac status occurs. Patients with congestive heart failure (CHF) New York Heart Association (NYHA) Class 1 and 2 treated with AVANDIA have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-controlled echocardiographic study was conducted in 224 patients with type 2 diabetes mellitus and NYHA Class 1 or 2 CHF (ejection fraction \leq 45%) on background antidiabetic and CHF therapy. An independent committee conducted a blinded evaluation of fluid-related events (including congestive heart failure) and cardiovascular hospitalizations according to predefined criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were reported by investigators. Although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed with AVANDIA treatment compared to placebo during the 52-week study.

Table 1. Emergent Cardiovascular Adverse Events in Patients with Congestive Heart Failure (NYHA Class 1 and 2) Treated with AVANDIA or Placebo (in Addition to Background Antidiabetic and CHF Therapy)

	Placebo N=114 n (%)	AVANDIA N=110 n (%)
Events		
Adjudicated		
Cardiovascular Deaths	4 (4)	5 (5)
CHF Worsening	4 (4)	7 (6)
• with overnight hospitalization	4 (4)	5 (5)
• without overnight hospitalization	0 (0)	2 (2)
New or Worsening Edema	10 (9)	28 (25)
New or Worsening Dyspnea	19 (17)	29 (26)
Increases in CHF Medication	20 (18)	36 (33)
Cardiovascular Hospitalization*	15 (13)	21 (19)
Investigator-reported, Non-adjudicated		
Ischemic Adverse Events	5 (4)	10 (9)
• Myocardial Infarction	2 (2)	5 (5)
• Angina	3 (3)	6 (5)

*Includes hospitalization for any cardiovascular reason.

Patients with NYHA Class 3 and 4 cardiac status were not studied during the clinical trials. AVANDIA is not recommended in patients with NYHA Class 3 and 4 cardiac status. In three 26-week trials in patients with type 2 diabetes, 216 received 4 mg of AVANDIA plus insulin, 322 received 8 mg of AVANDIA plus insulin, and 338 received insulin alone. These trials included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. In these clinical studies an increased incidence of edema, cardiac failure, and other cardiovascular adverse events was seen in patients on AVANDIA and insulin combination therapy compared to insulin and placebo. Patients who experienced cardiovascular events were on average older and had a longer duration of diabetes. These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of AVANDIA. In this population, however, it was not possible to determine specific risk factors that could be used to identify all patients at risk of heart failure and other cardiovascular events on combination therapy. Three of 10 patients who developed cardiac failure on combination therapy during the double-blind part of the fixed-dose studies had no known prior evidence of congestive heart failure, or pre-existing cardiac condition. In a double-blind study in type 2 diabetes patients with chronic renal failure (112 received 4 mg or 8 mg of AVANDIA plus insulin and 108 received insulin control), there was no difference in cardiovascular adverse events with AVANDIA in combination with insulin compared to insulin control. Patients treated with combination AVANDIA and insulin should be monitored for cardiovascular adverse events. This combination therapy should be discontinued in patients who do not respond as manifested by a reduction in HbA_{1c} or insulin dose after 4 to 5 months of therapy or who develop any significant adverse events. (See ADVERSE REACTIONS.)

PRECAUTIONS: General: Due to its mechanism of action, AVANDIA is active only in the presence of endogenous insulin. Therefore, AVANDIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. **Hypoglycemia:** Patients receiving AVANDIA in combination with other hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary. **Edema:** AVANDIA should be used with caution in patients with edema. In a clinical study in healthy volunteers who received AVANDIA 8 mg once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo. Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, AVANDIA should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure (see WARNINGS, Cardiac Failure and Other Cardiac Effects and PRECAUTIONS, Information for Patients). In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with AVANDIA, and may be dose related. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and AVANDIA (see ADVERSE REACTIONS). **Macular Edema:** Macular edema has been reported in postmarketing experience in some diabetic patients who were taking AVANDIA or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. Patients with diabetes should have regular eye exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings. (See ADVERSE REACTIONS, Adult.)

Weight Gain: Dose-related weight gain was seen with AVANDIA alone and in combination with other hypoglycemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

Table 2. Weight Changes (kg) From Baseline During Clinical Trials With AVANDIA

Monotherapy	Duration	Control Group		AVANDIA 4 mg	AVANDIA 8 mg
		Median (25th, 75th percentile) [n]	Median (25th, 75th percentile) [n]	Median (25th, 75th percentile) [n]	Median (25th, 75th percentile) [n]
	26 weeks	placebo	-0.9 (-2.8, 0.9) [210]	1.0 (-0.9, 3.6) [436]	3.1 (1.1, 5.8) [439]
	52 weeks	sulfonylurea	2.0 (0, 4.0) [173]	2.0 (-0.6, 4.0) [150]	2.6 (0, 5.3) [157]
Combination therapy	24-26 weeks	sulfonylurea	0 (-1.0, 1.3) [1155]	2.2 (0.5, 4.0) [613]	3.5 (1.4, 5.9) [841]
		metformin	-1.4 (-3.2, 0.2) [175]	0.8 (-1.0, 2.6) [100]	2.1 (0, 4.3) [184]
	26 weeks	insulin	0.9 (-0.5, 2.7) [162]	4.1 (1.4, 6.3) [164]	5.4 (3.4, 7.3) [150]
		sulfonylurea + metformin	0.2 (-1.2, 1.6) [272]	2.5 (0.8, 4.6) [275]	4.5 (2.4, 7.3) [276]

In a 24-week study in pediatric patients aged 10 to 17 years treated with AVANDIA 4 to 8 mg daily, a median weight gain of 2.8 kg (25th, 75th percentiles: 0.0, 5.8) was reported.

Hematologic: Across all controlled clinical studies in adults, decreases in hemoglobin and hematocrit (mean decreases in individual studies \leq 1.0 g/dL and \leq 3.3%, respectively) were observed for AVANDIA alone and in combination with other hypoglycemic agents. The changes occurred primarily during the first 3 months following initiation of therapy with AVANDIA or following a dose increase in AVANDIA. White blood cell counts also decreased slightly in adult patients treated with AVANDIA. Small decreases in hemoglobin and hematocrit have also been reported in pediatric patients treated with AVANDIA. The observed changes may be related to the increased plasma volume observed with treatment with AVANDIA and may be dose related (see ADVERSE REACTIONS, Laboratory Abnormalities, Hematologic).

Ovulation: Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDIA (see PRECAUTIONS, Pregnancy, Pregnancy Category C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known. Although hormonal imbalance has been seen in preclinical studies (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility), the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with AVANDIA should be reviewed.

Hepatic Effects: Another drug of the thiazolidinedione class, troglitazone, was associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death were reported during clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations in liver enzymes (ALT $>$ 3X upper limit of normal) compared to placebo. Very rare cases of reversible jaundice were also reported. In pre-approval clinical studies in 4598 patients treated with AVANDIA, encompassing approximately 3600 patient years of exposure, there was no signal of drug-induced hepatotoxicity or elevation of ALT levels. In pre-approval controlled trials, 0.2% of patients treated with AVANDIA had elevations in ALT $>$ 3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with AVANDIA were reversible and were not clearly causally related to therapy with AVANDIA. In postmarketing experience with AVANDIA, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established. Rosiglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death during clinical use. Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with AVANDIA undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with AVANDIA in all patients and periodically thereafter per the clinical judgement of the healthcare professional. Therapy with AVANDIA should not be initiated in patients with increased baseline liver enzyme levels (ALT $>$ 2.5X upper limit of normal). Patients with mildly elevated liver enzymes (ALT levels \leq 2.5X upper limit of normal) at baseline or during therapy with AVANDIA should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with AVANDIA in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to $>$ 3X upper limit of normal in patients on therapy with AVANDIA, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain $>$ 3X the upper limit of normal, therapy with AVANDIA should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with AVANDIA should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued. There are no data available from clinical trials to evaluate the safety of AVANDIA in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. AVANDIA should not be used in patients who experienced jaundice while taking troglitazone.

Laboratory Tests: Periodic fasting blood glucose and HbA_{1c} measurements should be performed to monitor therapeutic response. Liver enzyme monitoring is recommended prior to initiation of therapy with AVANDIA in all patients and periodically thereafter (see PRECAUTIONS, Hepatic Effects and ADVERSE REACTIONS, Serum Transaminase Levels).

Information for Patients: Patients should be informed of the following. It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. Patients should be advised that it can take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see full effect. Patients should be informed that blood will be drawn to check their liver function prior to the start of therapy and periodically thereafter per the clinical judgement of the healthcare professional. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician. Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on AVANDIA should immediately report these symptoms to their physician.

Drug Interactions: Drugs Metabolized by Cytochrome P450: An inhibitor of CYP2C8 (such as gemfibrozil) may increase the AUC of rosiglitazone and an inducer of CYP2C8 (such as rifampin) may decrease the AUC of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response. (See CLINICAL PHARMACOLOGY, Drug Interactions in the full prescribing information.)

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses \geq 1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses \geq 0.3 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in vivo micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic activation.

Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose). In juvenile rats dosed from 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in females (approximately 68 times human AUC at the maximum recommended daily dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

Animal Toxicology: Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose, respectively). Effects in juvenile rats were consistent with those seen in adults. Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

Pregnancy: Pregnancy Category C. Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible. Rosiglitazone has been reported to cross the human placenta and be detectable in fetal tissue. The clinical significance of these findings is unknown. There are no adequate and well-controlled studies in pregnant women. AVANDIA should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. **Animal Studies:** There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced the number of uterine implantations and live offspring when juvenile female rats were treated at 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day (approximately 4 times human AUC at the maximum recommended daily dose). There was no effect on pre- or post-natal survival or growth.

Labor and Delivery: The effect of rosiglitazone on labor and delivery in humans is not known.

Nursing Mothers: Drug-related material was detected in milk from lactating rats. It is not known whether AVANDIA is excreted in human milk. Because many drugs are excreted in human milk, AVANDIA should not be administered to a nursing woman.

Pediatric Use: After placebo run-in including diet counseling, children with type 2 diabetes mellitus, aged 10 to 17 years and with a baseline mean body mass index (BMI) of 33 kg/m², were randomized to treatment with 2 mg twice daily of AVANDIA (n=99) or 500 mg twice daily of metformin (n=101) in a 24-week, double-blind clinical trial. As expected, fasting plasma glucose (FPG) decreased in patients naive to diabetes medication (n=104) and increased in patients withdrawn from prior medication (usually metformin) (n=90) during the run-in period. After at least 8 weeks of treatment, 49% of AVANDIA-treated patients and 55% of metformin-treated patients had their dose doubled if FPG $>$ 126 mg/dL. For the overall intent-to-treat population, at week 24, the mean change from baseline in HbA_{1c} was -0.14% with AVANDIA and -0.49% with metformin. There was an insufficient number of patients in this study to establish statistically whether these observed mean treatment effects were similar or different. Treatment effects differed for patients naive to therapy with antidiabetic drugs and for patients previously treated with antidiabetic therapy (Table 3).

Table 3. Week 24 FPG and HbA_{1c} Change from Baseline Last-Observation-Carried Forward in Children with Baseline HbA_{1c} $>$ 6.5%

N	Naïve Patients		Previously-Treated Patients	
	Metformin	Rosiglitazone	Metformin	Rosiglitazone
	40	45	43	32
FPG (mg/dL)				
Baseline (mean)	170	165	221	205
Change from baseline (mean)	-21	-11	-33	-5
Adjusted Treatment Difference* (rosiglitazone-metformin) [†] (95% CI)		8 (-15, 30)		21 (-9, 51)
% of patients with \geq 30 mg/dL decrease from baseline	43%	27%	44%	28%
HbA _{1c} (%)				
Baseline (mean)	8.3	8.2	8.8	8.5
Change from baseline (mean)	-0.7	-0.5	-0.4	0.1
Adjusted Treatment Difference* (rosiglitazone-metformin) [†] (95% CI)		0.2 (-0.6, 0.9)		0.5 (-0.2, 1.3)
% of patients with \geq 0.7% decrease from baseline	63%	52%	54%	31%

*Change from baseline means are least squares means adjusting for baseline HbA_{1c}, gender, and region.

[†]Positive values for the difference favor metformin.