

Many Diabetic, Endocrine Patients Lack Vitamin D

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ORLANDO — A deficiency of vitamin D is extremely common among patients with diabetes and other endocrine conditions, according to findings from two recent studies.

In one study, Dr. Kanakasabai Narasimhan and Dr. Ali A. Rizvi of the University of South Carolina, Columbia, looked at 97 patients who were seen at

their institution's diabetes unit. The group comprised 39 men and 58 women, with an average age of 55 years. Two-thirds of the patients were white and one-third were black. The researchers presented their findings in a poster at the annual meeting of the American Association of Clinical Endocrinologists.

The mean serum calcium for the study group was 9.46 mg/dL (reference range, 8.6-10.2), mean serum creatinine was 1.06 mg/dL (range, 0.5-1.3), average hemo-

globin A_{1c} (HbA_{1c}) was 7.52%, and most of the patients had estimated glomerular filtration rate values greater than 60 mL/min per 1.73 m².

The average serum 25-hydroxyvitamin D (25[OH]D) level for the group was 23.3 ng/mL (range, 7-68 ng/mL). "Deficient" or "extremely low" 25(OH)D values less than or equal to 20 ng/mL were found in 49 patients (50.5%), whereas 23 patients (23.7%) had "relatively insufficient" levels in the 21- to 29-ng/mL range. Only 25 pa-

tients (25.8%) had 25(OH)D levels of 30 ng/mL or greater, which is considered "sufficient" or normal, Dr. Narasimhan and Dr. Rizvi reported.

The mean 25(OH)D values were slightly lower in women (22.6 ng/mL) than in men (24.4 ng/mL). Younger patients tended to have lower mean 25(OH)D values, with 22.9 ng/mL among those younger than 50 years, 25.8 ng/mL in those aged 50-59 years, and 23.5 ng/mL among those aged 60 years and older. The mean 25(OH)D value was also slightly lower among those with poorer diabetes control (22.54 ng/mL for the patients with HbA_{1c} levels above 7%, compared with 24.3 ng/mL for those who had HbA_{1c} levels of 7% or lower).

Although none of these correlations was statistically significant, the findings may still be clinically important in a selected population such as this one. Alternatively, "the lack of a clear-cut association with any single parameter may be due to the general risk that the presence of diabetes imparts, or may simply reflect the high prevalence of vitamin D deficiency in the general population," Dr. Narasimhan and Dr. Rizvi said.

Regardless, until the data are confirmed, "consideration may be given to recommendations for screening for vitamin D deficiency in the diabetic population," they concluded.

In the other study, which was also presented in a poster at the meeting, Dr. Syeda Zaidi and Dr. Thomas A. Hughes of the University of Tennessee, Memphis, reviewed the charts of 262 patients seen over a 6-year period at a private endocrinology-lipid clinic. The "relatively healthy, affluent" group had a mean age of 59.9 years (range, 21-88 years); 89% were white, 7% were black, and 46% were male. Their mean serum calcium level was 9.6 mg/dL (range, 7.8-11.0 mg/dL) and serum creatinine was 1.0 mg/dL (range, 0.5-2.0 mg/dL). One-fourth had known osteopenia or osteoporosis. Other diagnoses included hyperlipidemia (92%), type 2 diabetes (60%), and thyroid disease (28%).

Severe 25(OH)D deficiency (below 10 ng/mL) was present in 6% of the patients, moderate deficiency (10-20 ng/mL) in 32%, and mild deficiency (20-32 ng/mL) in 35%. Only 11% had levels considered satisfactory (above 40 ng/mL). These patients were typically younger and/or on low-dose vitamin D supplements. However, 23% of the patients with 25(OH)D levels below 32 ng/mL were taking low-dose vitamin D supplements, and 58% were taking multivitamin supplements.

Moreover, only one of the 18 black patients in the group had 25(OH)D levels above 32 ng/mL, noted Dr. Zaidi and Dr. Hughes. They also pointed out that their institution is located in the Sunbelt, where one might expect to see higher 25(OH)D levels than elsewhere in the country.

"Vitamin D deficiency and secondary hyperparathyroidism are associated with metabolic bone disease, myopathy, cardiomyopathy, vasculopathy, and carcinogenesis. Therefore, this high incidence of deficit could have widespread clinical consequences," they commented. ■

Drugs Metabolized by CYP2D6—Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg BID) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold [see *Warnings and Precautions*].

Drugs Metabolized by CYP2C9—Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP3A—Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP2C19—Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

Monoamine Oxidase Inhibitors—Switching Patients to or from a Monoamine Oxidase Inhibitor—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI [see *Contraindications and Warnings and Precautions*].

Serotonergic Drugs—Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta, and the potential for serotonin syndrome, caution is advised when Cymbalta is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort. The concomitant use of Cymbalta with other SSRIs, SNRIs or tryptophan is not recommended [see *Warnings and Precautions*].

Triptans—There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [see *Warnings and Precautions*].

Alcohol—When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol.

In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen [see *Warnings and Precautions*].

CNS Drugs—[see *Warnings and Precautions*].

Drugs Highly Bound to Plasma Protein—Because duloxetine is highly bound to plasma protein, administration of Cymbalta to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse reactions.

USE IN SPECIFIC POPULATIONS: Pregnancy—Teratogenic Effects, Pregnancy Category C—In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m² basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m² basis in rabbit). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m² basis in rat; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis in rabbits).

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

There are no adequate and well-controlled studies in pregnant women; therefore, duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects—Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see *Warnings and Precautions*].

When treating pregnant women with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cymbalta in the third trimester.

Labor and Delivery—The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. However, if the physician determines that the benefit of duloxetine

therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics.

Pediatric Use—Safety and effectiveness in the pediatric population have not been established [see *Boxed Warning and Warnings and Precautions*]. Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use—Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPNP premarketing studies, 33% (357) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD and DPNP studies, no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Cymbalta have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see *Warnings and Precautions*].

Gender—Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

Smoking Status—Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Race—No specific pharmacokinetic study was conducted to investigate the effects of race.

Hepatic Insufficiency—[see *Warnings and Precautions*].

Severe Renal Impairment—[see *Warnings and Precautions*].

DRUG ABUSE AND DEPENDENCE: Abuse—In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential.

While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Dependence—In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

OVERDOSAGE: Signs and Symptoms—In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.

Management of Overdose—There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, and Impairment of Fertility—Carcinogenesis—Duloxetine was administered in the diet to mice and rats for 2 years.

In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m² basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m² basis).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m² basis) did not increase the incidence of tumors.

Mutagenesis—Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility—Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m² basis) did not alter mating or fertility.

PATIENT COUNSELING INFORMATION: See FDA-approved Medication Guide and Patient Counseling Information section of full PI.

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