Low Vitamin D Levels in Rheum Clinic Patients

BY SUSAN LONDON

FROM THE ANNUAL MEETING OF THE PEDIATRIC ACADEMIC SOCIETIES

VANCOUVER, B.C. — Vitamin D deficiency and insufficiency are highly prevalent in the pediatric rheumatology population, according to the findings of a retrospective chart review. Slightly more than half of patients who were seen in a pediatric rheumatology clinic at Tufts Medical Center in Boston during an 11-month period had levels of vitamin D that were in the deficient or insufficient range, with no significant difference in prevalence between children with autoimmune conditions and children with nonautoimmune conditions.

“The bottom line is there’s no magic number. My sense is to look for it, no matter what their baseline condition,” lead researcher Dr. Christina F. Pelajo recommended.

“And I would look even more carefully in children with the risk factors”—namely, overweight status, black race/ethnicity, older age, and nonsummer season of the visit, she added.

The investigators reviewed the medical records of consecutive children visiting the center’s pediatric rheumatology clinic between November 2008 and September 2009, and assessed associations between mean levels of vitamin D (serum 25-hydroxyvitamin D) and various factors. Study results were based on 169 children with autoimmune conditions (predominantly juvenile idiopathic arthritis and juvenile systemic lupus erythematosus) and 85 children with nonautoimmune conditions (Lyme disease, autoimmune hemolytic anemia, Kawasaki disease, and others). Two-thirds were girls, and the average age was 12 years.

“The mean level of vitamin D was 28.1

<table>
<thead>
<tr>
<th>ADVERSE EVENTS</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
</tr>
<tr>
<td>Flushing</td>
<td>6</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>3</td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>3</td>
</tr>
<tr>
<td>Pain in leg</td>
<td>3</td>
</tr>
<tr>
<td>Pain in abdomen</td>
<td>3</td>
</tr>
</tbody>
</table>

Adverse events were generally transient and mild to moderate in nature.

Table 1: Adverse Allergy Adverse Events in ≥ 3% of Patients and More Frequent (> 1% than Placebo)

In patients taking sildenafil, the risk of priapism was slightly higher with sildenafil 20 mg TID (1.4%) than placebo (0%); for all sildenafil doses studied was 1.9% versus 0% placebo. The incidence of retinal hemorrhage at the recommended sildenafil 20 mg TID dose was 1.4% versus 0% placebo and for all sildenafil doses studied was 1.5% versus 0% placebo. The incidence of eye hemorrhage at both the recommended dose and at the co-administered dose of 20 mg TID was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these events had risk factors for hemorrhage including concurrent anticoagulant therapy.

INDICATIONS AND USAGE:

REVATIO® (SILDENAFIL)

Sildenafil is marketed as VIAGRA. The safety and efficacy of combinations of REVATIO with VIGA or other PDE5 inhibitors have not been studied. Inform patients taking REVATIO not to take TADALAFIL or other PDE5 inhibitors.

Prolonged Erection

Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, Peyronie’s disease) or in patients who have conditions which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists for more than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hypotension (see Warnings and Precautions)
- Vision loss (see Warnings and Precautions)
- Hearing loss (see Warnings and Precautions)
- Priapism (see Warnings and Precautions)

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

SAFETY INFORMATION

No cases of syncope or fainting were reported in the sildenafil interaction studies with alpha-blockers, cases of symptomatic hypotension consisting of dizziness and lightheadedness were reported [see Drug Interactions]. No cases of syncope or fainting were reported during these interaction studies. The safety of combined use of PDE5 inhibitors, including sildenafil, and alpha-adrenergic blocking agents are both associated with the increased risk of NAION with patients who have already experienced NAION in one eye. The incidence of NAION was 0.03% in patients taking Alpha Blockers and 0.04% in patients taking Sildenafil. The incidence of NAION in patients taking sildenafil was 0.02% in patients taking Alpha Blockers and 0.05% in patients taking Sildenafil.

The overall frequency of disconnection in REVATIO-treated patients at the recommended dose of 20 mg TID was 3% and was the same for the placebo group.

In the placebo-controlled trial in pulmonary arterial hypertension, adverse drug reactions that were reported by at least 3% of REVATIO patients treated at the recommended dosage (20 mg TID) and were more frequent in REVATIO patients than placebo patients are shown in Table 1. Adverse events were generally transient and mild to moderate in nature.
ng/mL in the group with autoimmunity conditions and 29.7 ng/mL in the group with nonautoimmune conditions, a nonsignificant difference, reported by Dr. LeMay, who was a research fellow at the center. Overall, 55% of children had levels of vitamin D in the range for deficiency (less than 20 ng/mL) or insufficiency (20-29 ng/mL), with no significant difference between the two groups. The prevalence of deficiency was 23% in the children with autoimmune conditions and 14% in the children without; the prevalence of insufficiency was 33% and 38%, respectively. Vitamin D levels did differ by race/ethnicity: Mean values were highest among white children (30.7 ng/mL), lowest among black children (17.9 ng/mL), and intermediate among children who were Hispanic (21.3 ng/mL), Asian Indian (20.2 ng/mL), and Asian (21.1 ng/mL). Levels were lower in overweight children, compared with their counterparts who had a normal body mass index (24.1 vs. 25.1 kg/m², respectively), and they decreased with increasing age.

Finally, levels varied by season of visit, with the highest values seen in sum-
mer (36.0 ng/mL) and considerably lower ones seen in fall (27.9 ng/mL), winter (25.7 ng/mL), and spring (26.3 ng/mL).

Children who took supplements had higher vitamin D levels than those who did not; however, the supplement group was stratified by dose, the difference relative to the nonsupplemented group was significant only for children who took supplements containing more than 400 IU of vitamin D.

"Taking 400 IU is the same as not taking anything because it’s such a low dose," commented Dr. LeMay.

In a placebo-controlled fixed dose titration study of REVATIO (starting with recommended dose of 20 mg tid and increased to 40 mg tid and then 80 mg tid) as an adjunct to intravenous epoprostenol in pulmonary arterial hypertension, the adverse events that were reported were more frequent than in the placebo arm (<6% differences are shown in Table 2).

**Table 2. REVATIO-Epoprostenol Adverse Events More Frequent (>6%) than Placebo

<table>
<thead>
<tr>
<th>ADVERSE EVENTS</th>
<th>Placebo Epoprostenol</th>
<th>Revatio Epoprostenol</th>
<th>Placebo-Subtracted %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>34</td>
<td>57 23</td>
<td>23</td>
</tr>
<tr>
<td>Edema</td>
<td>29</td>
<td>13 7</td>
<td>6</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19</td>
<td>16 4</td>
<td>5</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>17 10</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>25 7</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>25 7</td>
<td>8</td>
</tr>
<tr>
<td>Congestion</td>
<td>2</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

Includes peripheral edema

REVATIO injection was studied in a 66-patient, placebo-controlled study at doses targeting plasma concentrations between 10 and 50 ng/mL, up to 9 times the exposure of the recommended dose. Adverse events in PDE5 patients were similar to those seen with oral tablets.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sildenafil (see Warnings and Precautions).

Cardiovascular Events

In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhage have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient’s underlying cardiovascular disease, or to a combination of these or other factors.

Decreases in and Loss of Vision

When used for erectile dysfunction, non-articular anterolateral optic neuropathy (NAON), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of PDE5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of PDE5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. (See Warnings and Precautions.)

Other Events

The following list includes other adverse events that have been identified during postmarketing use of REVATIO. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system: seizure, seizure recurrence

Drug Interactions

Nitrates

Concomitant use of REVATIO with nitrates in any form is contraindicated [see Contraindications].

Ribavirin and other Potent CYP3A4 Inhibitors

Concomitant use of ribavirin and other potent CYP3A4 inhibitors is not recommended [see Warnings and Precautions].

Alpha-blockers

Use caution when co-administering alpha-blockers with REVATIO because of additive blood pressure-lowering effects [see Warnings and Precautions].

In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) on placebo or on doxazosin therapy. In these studies, patients were randomized to receive placebo, doxazosin 4 mg or 8 mg combined with placebo or REVATIO 20 mg TID. In a study of BPH patients with postvoid residual volume ≥75 mL, patients were randomized to receive placebo, doxazosin 8 mg BID, or REVATIO 20 mg TID in combination with doxazosin 8 mg BID.

The mean decreases in systolic and diastolic pressure were significantly greater with the combination of doxazosin 8 mg BID and REVATIO 20 mg TID (9/5 mmHg and 8/4 mmHg, respectively) than with either drug alone (2/1 and 1/0 mmHg, respectively). The mean decreases in postvoid residual volume were significantly greater with the combination therapy (55 mL) compared to either doxazosin (20 mL) or REVATIO alone (23 mL).

During the 12-week treatment period, the mean changes from baseline in hemoglobin and hematocrit were significantly greater with doxazosin 8 mg BID alone and with the combination therapy compared to REVATIO alone.

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Carcinogenesis, Mutagenesis, Impairment of Fertility

Sildenafil was not carcinogenic when administered to rats for up to 24 months at doses of 25, 250, and 2500 mg/kg/day. In a two-year study in mice, the no-observed-adverse-effect level was 500 mg/kg/day. In the mouse bone marrow micronucleus assay, the no-observed-adverse-effect level was 500 mg/kg/day.

In studies with healthy volunteers of single doses up to 800 mg, adverse events were generally mild to moderate, with no apparent dose relationship. In studies in which sildenafil was administered to a nursing woman, there was no evidence of adverse events in her breastfed infant, and it is not known whether sildenafil or its major metabolite is detected in human milk.

It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to nursing women.

Pediatric Use

REVATIO was not studied in children. Postmarketing experience with sildenafil includes reports of use in children aged 6-17 years. The efficacy and safety of sildenafil in children aged 6-17 years who have pulmonary arterial hypertension was studied in a randomized controlled trial.

In all, 42 patients were randomized to receive codeine and ibuprofen, whereas 41 patients in the control group received ibuprofen and placebo. The children’s pain levels were measured at triage, then at the 60-, 90-, and 120-minute marks afterward.

Children in the experimental group had a mean score of 5.9VAS at triage, then 4.2, 4.0, and 3.5, respectively; those in the control group had mean scores of 5.7, 4.9, 4.1, and 3.8, respectively.

Dr. LeMay explained that she underlined the study because, in her experience as a nurse, children “with this kind of pain [from limb trauma] need to receive an opioid. That’s the standard, but physicians are really not using it.”

Dr. LeMay said that her 2005-2007 study of 150 charts of children presenting to EDs with severe sprains, fractures, burns, deep lacerations, and abdominal pain found that only 3% of children received an opioid for their pain.

"Taking 400 IU is the same as not taking anything because it’s such a low dose,” commented Dr. LeMay.

Disclosures: Dr. LeMay reported having no conflicts of interest.

For Kids’ Pain, Opioid Combo Equals Ibuprofen

From the American Pain Society annual meeting

Baltimore — Opioid combined with ibuprofen did not relieve pain from pediatric acute musculoskeletal injuries any more effectively than ibuprofen alone; however, the combination therapy was associated with fewer side effects, according to findings from a small, randomized controlled trial.

Pain management in children generally tends to be poor, and children presenting with a limb trauma need to receive an opioid, and possibly one that’s stronger than codeine, “to better relieve their pain and bring it down to below a [Visual Analog Scale score of] 4,” Sylvie Le May, Ph.D., said.

The study involved 83 children (aged 6-17 years) who presented to the emergency department at CHU Sainte-Justine University Hospital Center, Montreal, with limb fractures, sprains, and contusions between March 2008 and October 2009. At baseline, the children reported having moderate to severe pain (4-10 on the VAS).

In all, 42 patients were randomized to receive codeine and ibuprofen, whereas 41 patients in the control group received ibuprofen and placebo. The children’s pain levels were measured at triage, then at the 60-, 90-, and 120-minute marks afterward.

Children in the experimental group had a mean score of 5.9 VAS at triage, then 4.2, 4.0, and 3.5, respectively; those in the control group had mean scores of 5.7, 4.9, 4.1, and 3.8, respectively.

Dr. LeMay explained that she undertook the study because, in her experience as a nurse, children “with this kind of pain [from limb trauma] need to receive an opioid. That’s the standard, but physicians are really not using it.”

Dr. LeMay said that her 2005-2007 study of 150 charts of children presenting to EDs with severe sprains, fractures, burns, deep lacerations and abdominal pain found that only 3% of children received an opioid for their pain.

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