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Prevention and Management of Vitamin D Deficiency in Children: Part II. Vitamin D Supplementation Marcia L. Buck, Pharm.D., FCCP

The previous issue of *Pediatric Pharmacotherapy* reviewed recent studies documenting the prevalence of vitamin D deficiency and the need to increase dietary vitamin D intake. Several papers published within the last five years have highlighted the growing incidence of vitamin D deficiency, defined as a serum hydroxyvitamin D [25(OH)D] level less than 20 ng/mL, in infants, children, and adolescents world-wide.^{1,2} As a result of these epidemiologic studies and new information on the role of vitamin D in preventing autoimmune diseases, cardiovascular disease, and cancer, the American Academy of Pediatrics (AAP) and the Lawson Wilkins Pediatric Endocrine Society have published updated guidelines which recommend increasing the daily intake of vitamin D to 400 International Units for infants and children.^{3,4} Vitamin D supplements may be necessary for those patients unable to meet this standard with dietary intake alone, including breast-fed infants. This issue of the newsletter will review the pharmacology of oral vitamin D supplements and provide recommendations for dosing and monitoring.

Vitamin D Supplements

Exogenous vitamin D is available as a dietary supplement in two forms: ergocalciferol (vitamin D₂), derived from the irradiation of ergosterol in yeast, and cholecalciferol (vitamin D₃), obtained from animal sources. The two forms are regarded as equivalent in most dosing resources, with 1 mcg of either providing 40 International Units of vitamin D activity. Several recent sources, however, suggest that cholecalciferol is better absorbed and may raise serum 25(OH)D levels up to three-fold higher than ergocalciferol in adults, producing more long-lasting physiologic results.³⁻⁷

Pharmacokinetics

Oral vitamin D supplements are well-absorbed from the small intestine. The presence of bile is necessary for absorption. Cholecalciferol appears to be more rapidly and completely absorbed than ergocalciferol. Circulating vitamin D is bound to serum proteins and is widely distributed throughout the body. It is stored primarily in the liver and fat.⁵⁻⁷

Both forms of vitamin D are inactive and must undergo conversion in the liver and kidneys to form biologically active compounds. Ergocalciferol and cholecalciferol are hydroxylated by hepatic microsomal enzymes to 25(OH)D, also referred to as calcifediol. Further conversion of this intermediate form in the kidneys produces the physiologically active form, 1,25-dihydroxyvitamin D, or calcitriol. Vitamin D products are primarily eliminated through excretion in the bile. The mean elimination half-life of 1,25-dihydroxyvitamin D is 5 to 8 hours in adults.⁵⁻⁷

Although it is not the biologically active form, the intermediate form, 25(OH)D, is used to assess vitamin D status since 1,25-dihydroxyvitamin D levels do not typically decrease until clinical symptoms of vitamin D deficiency have become severe. The intermediate 25(OH)D form also has a longer half-life (approximately 15 days) and is less affected by parathyroid hormone, calcium, or phosphate levels. There is a lag time of 10 to 24 hours after administration of exogenous vitamin D₂ or D₃ until the biologically active forms have been produced. Maximum clinical response typically occurs approximately a month after therapy has been initiated. Pharmacologic effects may continue for more than 2 months after vitamin D administration.⁵⁻⁷

Warnings and Precautions

Vitamin D supplements are contraindicated in patients with hypercalcemia or a known hypersensitivity to any component of the product. Some vitamin D supplements contain tartrazine (FD&C yellow dye no. 5) and may produce a hypersensitivity reaction in susceptible individuals. Patients taking vitamin D supplements in doses above the recommended daily dietary intake should be monitored for hypercalcemia, impaired renal function, or other evidence of vitamin D toxicity.⁵⁻⁷

Adverse Effects

Excessive administration of vitamin D may result in weakness, headache, somnolence, nausea, vomiting, dry mouth, a metallic taste, constipation, muscle or bone pain. With continued high-dose vitamin D intake (> 10,000 International Units/day) or overdose (serum 25(OH)D levels > 100 ng/mL), patients may develop polyuria, polydipsia, anorexia, irritability, mild acidosis, hypercalciuria, anemia, azotemia, nephrocalcinosis, vascular calcifications, pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, cardiovascular instability, bone demineralization, and hepatic or renal dysfunction. These symptoms may persist for several months after discontinuing therapy.⁵⁻⁸

Drug Interactions

The absorption of vitamin D supplements may be decreased by administration with mineral oil, cholestyramine, colestipol, or orlistat. Use of magnesium-containing antacids during vitamin D supplementation may result in hypermagnesemia, especially in renal dialysis patients.⁵⁻⁷

Administration of vitamin D supplements in patients with hypoparathyroidism who are also taking thiazide diuretics may produce hypercalcemia. Use of vitamin D and calcium supplements may antagonize the effects of calcium channel blockers. This combination may also increase the risk of toxicity in patients taking digoxin. Administration of phenobarbital or phenytoin may increase the rate of hepatic metabolism of vitamin D to inactive compounds and reduce calcium absorption.⁵⁻⁷

Dosing Recommendations

The current recommendation from both the AAP and the Lawson Wilkins Pediatric Endocrine Society is a minimum dietary intake of 400 International Units/day (10 mcg/day) for neonates, children, and adolescents.^{3,4} If this amount cannot be achieved through their normal diet, a vitamin D supplement should be administered. Exclusively breastfed infants and

those consuming less than 1 L of infant formula/day should receive 400 International Units/day of an oral liquid vitamin D product.^{3,4} The Lawson Wilkins Pediatric Endocrine Society recommends that preterm infants should receive 400 to 800 International Units of vitamin D (10 to 20 mcg) per day to compensate for decreased placental transfer in utero and decreased gastrointestinal absorption after birth.⁴

For treatment of documented vitamin D deficiency, infants may be given 1,000 to 2,000 International Units/day (25 to 50 mcg) and older children may be given up to 5,000 International Units/day (125 mcg) for 2 to 3 months.^{4,8} A variety of alternative dosing regimens have been published over the past decade. A high-dose short-course regimen providing a total of 100,000 to 600,000 International Units (2.5 to 15 mg) over 1 to 5 days has been suggested for patients who might not adhere to longer regimens.⁴

Vitamin D dosing in children with kidney disease or other chronic illnesses should be based on serum 25(OH)D levels. Table 1 provides general recommendations for these patients. Table 2 lists dosing recommendations for children with severe or chronic deficiency states.³⁻⁷

Table 1. Examples of Vitamin D Dosing Based on Serum 25(OH)D Levels

<u>25(OH)D</u>	<u>Dose</u>
16-30 ng/mL	2,000 International Units/day (50 mcg) or 50,000 International Units (1.25 mg) monthly for 3 months
5-15 ng/mL	4,000 International Units/day (100 mcg) or 50,000 International Units (1.25 mg) every other week for 3 months
< 5 ng/mL	8,000 International Units/day (200 mcg) or 50,000 International Units (1.25 mg) weekly for 1 month followed by 4,000 International Units/day or 50,000 International Units every other week for a total of 3 months

Table 2. Examples of Vitamin D Dosing Based on Diagnosis

<u>Diagnosis</u>	<u>Dose</u>
Rickets	1,000-10,000 International Units/day (25 to 250 mcg/day) for 2 to 3 months, followed by

	maintenance treatment with 400 to 1,000 International Units/day
Malabsorption syndromes	25,000 International Units/day (625 mcg/day)
Familial hypophosphatemia	40,000-80,000 International Units/day (1 to 2 mg/day)
Hypoparathyroidism	200,000 International Units/day (5 mg/day), titrated to maintain optimal levels

Vitamin D supplements may be taken with or without food. Administration with food may be useful to reduce stomach upset. Calcium supplementation (30 to 75 mg/kg/day oral elemental calcium) is often necessary to maximize response in patients with vitamin D deficiency. Patients receiving vitamin D supplementation beyond the recommended daily dietary intake should undergo periodic monitoring of serum 25(OH)D levels, using an assay for both 25(OH)D₂ and 25(OH)D₃, as well as serum calcium, phosphorus, and alkaline phosphatase at one and three months or until stabilized, followed by annual reassessment. Parathyroid and bone mineralization studies should be conducted as needed.³⁻⁷

Availability and Cost

Ergocalciferol (Drisdol[®] or others) is available by prescription in 25,000 and 50,000 International Units (0.625 and 1.25 mg) capsules. It is also available without a prescription in an 8,000 International Units/mL (200 mcg/mL) liquid.^{5,6} The liquid product contains propylene glycol as a vehicle and should not be used for high-dose therapy.⁴ The average wholesale price (AWP) for a bottle of 50 capsules ranges from \$75 to \$100. A 60 mL bottle of Drisdol[®] liquid, which would provide 20 doses, has an AWP of \$149.13.⁹

Cholecalciferol (Delta D3[®] or others) is available without a prescription in 400, 1,000, 2,000, and 10,000 International Units tablets or capsules.⁵ The cost of a bottle of 500 tablets/capsules ranges from \$2.50 to \$10.00. Cholecalciferol is also available in a liquid formulation (Just D[®] infant drops, D-Drops[®], and others) with 400, 1,000, or 2,000 International Units of vitamin D per drop or per mL, depending on the product. The liquid formulations range in price from \$8.00 to \$25.00. While cholecalciferol preparations are less expensive than ergocalciferol, some patients will require multiple tablets/capsules or a larger liquid volume to achieve the desired dose.^{9,10}

Summary

Vitamin D supplementation for children has been the focus of a number of publications within the last year. New demographic data have identified a growing number of children with vitamin D deficiency at risk for rickets or impaired bone growth and mineralization. In addition, there is growing evidence of the role of vitamin D in the prevention of autoimmune and cardiovascular diseases, as well as cancer. The AAP and the Lawson Wilkins Pediatric Endocrine Society have recently adopted new standards for daily vitamin D requirements. As a result, more children will need vitamin D supplementation. The choice of supplement, as well as dose and dosing frequency, vary among references. Additional research is needed to identify the optimal dosing strategy for vitamin D supplementation in pediatric patients.

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Pharmacology Literature Update

Effects of Valproate and Quetiapine on White Blood Cell Count

After observing several cases of neutropenia and leukopenia in children receiving valproate and quetiapine, the authors of this paper conducted a

retrospective study of this drug combination. A total of 131 patients who received either drug or the combination were evaluated. The incidence of neutropenia and/or leukopenia was 44% in the patients receiving both drugs, 26% in the patients receiving just valproate, and 6% in those taking only quetiapine. The combination therapy group had a significantly higher incidence of moderate-to-severe neutropenia (14 cases) compared to the valproate and quetiapine groups (5 and 0 cases, respectively). Based on their findings, the authors recommend that patients receiving valproate or the combination of valproate and quetiapine be monitored for leukopenia or neutropenia and that additional studies be conducted to evaluate a potential drug interaction between the two agents. Rahman A, Mican LM, Fischer C, et al. Evaluating the incidence of leukopenia and neutropenia with valproate, quetiapine, or the combination in children and adolescents. **Ann Pharmacother** 2009;43:822-30.

Off-labeling Prescribing

While recent changes in Food and Drug Administration (FDA) policies have been made to facilitate the approval process, many drugs needed by children are still not approved for pediatric use. Bazzano and colleagues have examined the frequency of off-label prescribing for children in the outpatient setting. The authors used data from the 2001-2004 National Ambulatory Medical Care Surveys, which included a sample of 7,901 outpatient visits by children under 18 years of age. A total of 62% of the pediatric clinic visits included off-label prescribing.

The most frequent therapeutic classes included were cardiovascular drugs (96% of prescriptions were written off-label), analgesics (86%), gastrointestinal agents (80%), and pulmonary drugs or medications for dermatologic conditions (each 67%). Children < 6 years of age had a significantly higher probability of receiving a drug off-label ($p<0.01$) and visits to a subspecialist were more likely to result in off-label prescribing ($p<0.01$). The authors suggest that current measures to increase FDA approval for pediatric drugs have not yet made a significant impact in reducing off-label prescribing and that additional measures are needed. Bazzano AFT, Mangione-Smith R, Schonlau M, et al. Off-label prescribing to children in the United States outpatient setting. **Academic Pediatr** 2009;9:81-8.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 5/22/09:

1. Lacosamide (Vimpat[®]) was added for the treatment of partial-onset seizures in patients 17 years of age and older. This agent is available in oral tablets (restricted to Neurology) and an injection (restricted to use in patients previously stabilized on oral therapy). Both forms were approved for the Inpatient Formulary. The tablets were approved for addition to the Outpatient Formulary.
2. 6% hydroxyethyl starch 130/0.4 (Voluven[®]), a colloid solution for management of hypovolemia was also added to the Inpatient Formulary.
3. Imiglucerase (Cerezyme[®]), an analogue of human enzyme β -glucocerebrosidase, was added to the Outpatient Formulary for the treatment of patients with Type 1 Gaucher disease. Doses typically range from 2.5 units/kg three times weekly to 60 units/kg every 2 weeks. Imiglucerase is administered as a 1-2 hour infusion. The drug will not be routinely stocked, but will be ordered as needed.
4. All propoxyphene-containing products were deleted from the Outpatient Formulary.

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