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Pharmacy Column



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Vitamin D dosing considerations in COVID-19

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I commonly share my bi-monthly pharmacy columns with friends and colleagues after I submit them to Geriatric Nursing for publication. The most recent article, which appeared in the May/June, 2020 issue reviewed the role of Vitamin D in COVID-19 infections, generated a number of questions about the vitamin, especially with respect to dosing.¹ I decided to address some of these questions in this issue's column. As always, space limitation prevents an in-depth review so the reader is referred to a Vitamin D Fact Sheet for Health Professionals for those who would like more detailed information as well as the other references that I cite below.^{2,3–8}

Should elderly persons take a vitamin D supplement?

To answer this question, we need to reflect on what is probably the most important principal of drug therapy which is, "the possible risks of therapy must outweigh its possible benefits."

In the case of vitamin D this risk/benefit ratio is skewed far in favor of benefits. Vitamin D has many therapeutic benefits ranging from maintaining bone metabolism and strength to reducing the prevalence of colon cancer.²

Toxicity can include non-specific symptoms such as anorexia, weight loss, polyuria and heart arrhythmias. The primary toxicity concern is elevated serum calcium concentration which can lead to vascular and tissue calcification with subsequent damage to kidneys, blood vessels and the heart. Risks are minimal, especially at

recommended doses and most reports suggest a toxicity threshold for vitamin D of 10,000 to 40,000 International Units per day (IU/d) and serum concentrations of 200–240 ng/mL for that severe toxicity to occur.² Those doses and concentrations are not recommended but highlight the fact that at more reasonable doses and concentrations discussed below toxicity is not a big concern for most patients.

So, with possible benefits being great, and possible risk minimal, many elderly people are appropriate candidates for vitamin D supplementation.

What is the difference between vitamin D-2 and D-3 and is one better than the other?

There are two forms of vitamin D. Vitamin D-2 or ergocalciferol and vitamin D-3, cholecalciferol. Both forms are biologically inert and must undergo two hydroxylations in the body for activation. The first occurs in the liver which converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. The second occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as calcitriol.²

There are a limited number of foods that are sources of these compounds. Vitamin D-2 is found mostly in mushrooms and fortified foods such as cereal. Vitamin D-3 is found primarily in animal-based foods such as fish, liver, eggs and America's old favorite, cod-liver oil.

While both versions are effective in increasing vitamin D concentration in the body, vitamin D-3 is thought by many to be more effective in raising vitamin D levels. It is widely available as an inexpensive over-the-counter supplement in a variety of dosage forms and dosages.

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Vitamin D is referred to as the “sunlight vitamin.” How much sunlight exposure do I need to receive an adequate amounts of vitamin D?

When skin is exposed to sunlight cutaneous 7-dehydrocholesterol is converted to previtamin D-3 which is then metabolized in the body to the active form. However, relying on sunlight to meet our vitamin D requirements is controversial due to the well-known skin damage that results from even small amounts of exposure to sunlight. It has been suggested by some vitamin D researchers that approximately 5–30 min of sun exposure between 10 AM and 3 PM at least twice a week to the face, arms, legs, or back without sunscreen usually leads to sufficient vitamin D synthesis.² However, numerous factors can reduce the skin's ability to convert vitamin D including time of day, inclement weather or dark skin color. As well, conversion is less efficient in the skin of older persons and some individuals, such as those who are home-bound and get little to no sun exposure.³ Sunlight exposure through glass is ineffective in producing vitamin D because glass filters out the ultraviolet light necessary for that conversion.²

Sunscreens with a sun protection factor (SPF-8) or higher may block vitamin D-producing ultraviolet waves. However, people generally do not apply sufficient amounts of sunscreen to all sun-exposed skin and/or do not reapply it regularly so skin likely synthesizes some vitamin D even when it is protected by sunscreen as typically applied.²

What is the recommended daily dose of vitamin D?

The recommended daily allowance (RDA), which is the amount that will meet the nutritional requirements of 97%–98% of healthy individuals, for vitamin D in persons over 70 years of age is 800 International Units (IU).² This RDA was calculated under the assumption that a person's vitamin D would be obtained primarily through diet and supplements and not sun exposure.

This RDA is consistent with 25-Hydroxyvitamin D [25(OH)D] serum concentrations of approximately 20 ng/mL which is at the low end of the range of concentration generally considered to be adequate for bone health and overall health in healthy adults.

The National Health and Nutrition Examination Survey (NHANES) has estimated that women in the US >70 years of age have an average total vitamin D intake from food of only 156 IU per day.²

These data indicate that insufficient vitamin D intake may be common. But, keep in mind that there is no consensus about what vitamin D concentrations should be maintained when used in COVID-19. The 25(OH)D serum concentration assay, which best reflects the body's vitamin D status, is readily available and can be used to help individuals decide whether a vitamin D supplement is appropriate for them.

Vitamin D's Tolerable Upper Intake Level (UL), which is the maximum daily intake unlikely to cause adverse health effects, is 4,000 IU per day. Some health groups recommend taking from 800 to 2,000 IU per day but some clinicians recommend higher doses such as a 5,000 IU OTC capsule or even 10,000 IU per day without symptoms of toxicity.^{3,4}

Frequent monitoring of concentration is not recommended but it might be prudent to have this test performed, especially if doses much higher than the RDA are routinely taken. The US Institute of Medicine currently recommends 25(OH)D concentration 20 ng/mL or higher to be generally considered to be adequate for bone health and overall health in healthy individuals. They further state that levels exceeding 50 ng/mL, and particularly greater than 60 ng/mL are linked to potential adverse effects. However, these recommendations were made long-before the emergence of COVID-19. As I noted in my previous

column, to the best of my knowledge the optimal 25(OH)D concentration for combatting COVID-19 is not known.¹ One of the references I cited in my recent column recommends that the goal should be 25 (OH)D concentrations above 40–60 ng/mL or perhaps even higher in people who become infected with COVID-19 but they further clarify that “randomized controlled trials and large population studies should be conducted to evaluate these recommendations.”⁵

Is a vitamin D loading dose necessary?

An initial loading dose, perhaps administered all at one time or distributed over a series of administrations, is a common principle of drug therapy. Vitamin D is no exception and is actually a good model because it may take a matter of months to reach a “steady state” serum concentration if vitamin D-3 is administered at standard daily doses. Various loading dosage protocols have been published. For example, one protocol studied the administration of 100,000 IU doses of vitamin D-3 to be administered every 2 weeks for a total of 4 doses. Seven days after the fourth dose all subjects who were initially found to be vitamin D deficient were found to have reached sufficient 25(OH)D concentration.⁶ Note that it took two months to achieve sufficient serum concentration with this bi-weekly loading dose so, how well this would benefit COVID-19 prevention or treatment is uncertain especially in light of a study finding noted in my recent column that vitamin D's ability to protect the risk of acute respiratory infection was seen in patients taking daily or weekly vitamin D but not in those who had dosage regimens consisting of large vitamin D bolus doses.⁷

Another study demonstrated that administration of a vitamin D loading dose can achieve desired steady-state serum concentration within 5 weeks by administering a weekly loading dose calculated for each patient by using a dosage algorithm that incorporated patient weight, initial 25(OH)D concentration and target concentration.⁸

Summary

I must again remind the reader that we are only beginning to appreciate the role of vitamin D in helping to prevent and/or ameliorate COVID-19 infection.¹ Based on that evidence it would seem prudent to initiate therapy to achieve sufficient 25(OH)D concentrations in order to benefit from whatever therapeutic advantage it might provide in COVID-19.

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