INTRODUCTION

Epilepsy is a chronic neurological condition in which patients experience recurrent seizures.\(^1,2\) It is characterized by sudden, recurrent excessive electrical neuronal stimulation in the brain, leading to seizures. It can occur in populations of any age.

According to the Centers for Disease Control and Prevention (CDC), approximately 2.5 million people in the U.S. have epilepsy.\(^3\) The National Institute of Neurological Disorders and Stroke indicates that approximately 20% of patients with epilepsy have seizures even while they are receiving treatment.\(^4\) The very young and elderly age groups are most likely to experience epilepsy.

Seizures can be classified into two essential types: generalized and partial.\(^5\) These classifications are based on the location of the electrical neuronal stimulation. Generalized seizures are characterized by a disturbance in neuronal electrical activity, and they are present in both hemispheres of the brain at once. A loss of consciousness is the key clinical manifestation.

Partial seizures are identified by disturbed neuronal electrical activity observed in one part of the brain. Consciousness is not usually lost; however, in rare cases, it might be impaired. Partial seizures can affect other areas of the brain and become "secondarily generalized" seizures.

Generalized seizures are divided into six subtypes:\(^5\)

- absence
- atypical absence
- atonic
- clonic
- myoclonic
- tonic–clonic or grand mal

Partial seizures are divided into three subtypes:\(^5\)

- simple partial: the patient does not lose consciousness
- complex partial: the patient’s consciousness is impaired
- secondarily generalized

The anti-epileptic drug phenytoin (Dilantin, Pfizer) is used to control several types of seizures. Phenytoin is indicated for generalized tonic-clonic (grand mal) seizures and complex partial (psychomotor, temporal lobe) seizures. It is also used to prevent or control seizures occurring during and after neurosurgery.\(^6\)

Phenytoin, like all drugs, is associated with a number of side effects that must be considered when it is prescribed to patients. A number of articles have been published on the subject of phenytoin and its effects on bone structure, all suggesting that prolonged exposure to this medication may result in osteomalacia (softening of the bones) and bone demineralization.\(^7,8\)

This article discusses possible mechanisms by which phenytoin affects the calcium levels in the body and explores appropriate strategies when calcium loss results from this medication.

CALCIUM AND VITAMIN D

Phenytoin and other anticonvulsants can lead to a vitamin D deficiency in the body. Other anticonvulsants that can have this effect include carbamazepine (e.g., Tegretol, Novartis) and barbiturates, which decrease calcium absorption and cause medication-induced hyperparathyroidism.

Scientific research cites the following mechanisms as a possible explanation for phenytoin-associated calcium effects:

- decreased intestinal absorption of calcium (a theoretical approach to the drug’s effects on ion exchange)
- interference with renal activation and metabolism of vitamin D\(^9\)–\(^11\)
- drug-induced secondary hyperparathyroidism resulting from the phenytoin-associated low calcium level in the blood, leading to bone demineralization\(^12\)

Decreased Intestinal Calcium Absorption

In theory, calcium ions are absorbed in the intestine by two processes.

The first process involves the paracellular pathway, a passive transport, down a chemical gradient, located in the small intestine, most frequently in the ileum. The second process, the transcellular pathway, is an active transport, located in the upper duodenum. Transcellular transport provides the entry of calcium ions from the lumen into the cytoplasm, the movement of calcium through the cytoplasm, and the exit through the pumps in the endothelial (intestinal) cell. The principal process by which calcium enters the bloodstream is mediated primarily by calcium adenosine triphosphatase (Ca\(^{2+}\) ATPase) and, to a minor degree, by the calcium/sodium (Ca\(^{2+}/Na^+\)) ion exchanger.

Phenytoin is a sodium-channel inhibitor in the central nervous system. As a result of the similarity of the genetic origin of the Na\(^+/Ca^{2+}\) exchanger in brain and intestine,\(^13\) it is possible that phenytoin disturbs the normal exchange of these ions, thus leading to decreased calcium absorption in the intestine.\(^14\)

Vitamin D is important in the intestinal absorption of calcium. This nutrient increases the number of pumps in the endothelial cell and plays a role in the biosynthesis of calbindin D9k (intestinal calcium-binding protein, or 9-kD cholecalcin),

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which augments the intracellular diffusion rate of the calcium ion.\textsuperscript{15}

Vitamin D becomes available in the body through various mechanisms. One way is through the skin’s dermal and epidermal layers, which contain 7-dehydrocholesterol. After 7-dehydrocholesterol is exposed to sunlight, the skin absorbs ultraviolet B photons, leading to the formation of vitamin D\textsubscript{3} (cholecalciferol).

Another way is through food consumption, although the vitamin D originally enters the body in the form of vitamin D\textsubscript{2} (ergocalciferol). Upon entering the body, both types of vitamin D are inactive and must be converted into its active form (1,25-(OH)\textsubscript{2}D\textsubscript{3}); the conversion occurs with the help of the liver and kidneys. In the liver, with the help of 25-hydroxylase systems, vitamin D changes and is converted to the 25-hydroxyvitamin D\textsubscript{3} or 25(OH)D\textsubscript{3}. Its active form (1,25-(OH)\textsubscript{2}D\textsubscript{3}) then becomes available with the action of 1-alpha-hydroxylase in the kidney.\textsuperscript{10,17}

Renal Activation
Phenytoin interferes with the renal activation of vitamin D. Studies have shown that patients taking phenytoin have low serum levels of 1,25-(OH)\textsubscript{2}D\textsubscript{3} even when their serum levels of 25(OH)D\textsubscript{3} are normal, thus suggesting that phenytoin might affect the performance of 1-alpha-hydroxylase in the kidney.\textsuperscript{6} Furthermore, phenytoin increases the catabolism of activated vitamin D.

To avoid vitamin D toxicity and to maintain calcium homeostasis, a feedback mechanism is initiated by cytochrome CYP 24,\textsuperscript{13} which belongs to the mitochondrial P450 family of enzymes. CYP 24 initiates the process of decomposition of 1,25-(OH)\textsubscript{2}D\textsubscript{3} to the inactive product, calciotropic acid (1-alpha-hydroxy-23 carboxy-24,25,26,27-tetranorvitamin D\textsubscript{3}).\textsuperscript{18} Phenytoin activates nuclear receptor pregnane X, which in turn leads to the up-regulation of CYP 24’s gene expression.\textsuperscript{19} This increases the tendency to elevate the decomposition of 1,25(OH)\textsubscript{2}D\textsubscript{3} by the hydroxylation reaction on its side chain.

Some extensive studies have been conducted on phenytoin’s effects on vitamin D. Collective outcomes of several studies lead to the following observations:

1. Phenytoin induces the microsomal enzyme system in the liver, thus increasing 25-hydroxylase production and biliary excretion.\textsuperscript{10}

2. Phenytoin’s induction of microsomal mixed oxidase system elevates the conversion of active vitamin D, making it more polar and less active—thus leading to the gastrointestinal loss of vitamin D.

3. Unlike the first two processes, which are directly caused by phenytoin, the third process is secondary and is caused by the first two. The effects of phenytoin, described earlier, lead to the unfavorable outcome of poor calcium absorption. If that happens, the parathyroid gland reacts by releasing parathyroid hormone, which in its turn raises the calcium level in the blood by releasing calcium from bones. This step results in the conservation of calcium excretion from the kidneys and leads to the increased absorption of calcium from ingested food.\textsuperscript{20}

In the end, these processes result in bone demineralization, kidney stones, and hypertension. Basically, one can observe signs of phenytoin-induced hyperparathyroidism.

Bone Remodeling and Demineralization
Continuous bone remodeling preserves bone homeostasis. Remodeling is a normal cellular process that involves well-balanced bone resorption and bone-formation mechanisms coupled with osteoclasts and osteoblasts, respectively. Phenytoin speeds up bone remodeling,\textsuperscript{21} and it affects bone cells directly: at therapeutic doses, phenytoin appears to inhibit the maturation rate of human osteoblast-like cells,\textsuperscript{10} ultimately delaying the process of the bone mineralization.

In vitro studies have shown the following:\textsuperscript{10}

- With phenytoin at subtherapeutic levels (below 1 mcg/ml), a direct relationship is observed between the phenytoin concentration and the proliferation of human osteoblast-like cells.
- With phenytoin at levels above 1 mcg/ml and at therapeutic levels (10–20 mcg/ml), the relationship between the phenytoin concentration and the proliferation of human osteoblast-like cells is inverted.

BONE DENSITY
Phenytoin’s effects on calcium and bone homeostasis lead to the important question of the drug’s effects on bone mass density. In fact, in several studies, the use of phenytoin led to decreased bone density in the sites most susceptible to fractures, such as the femoral neck and lumbar spine, in both men and women.\textsuperscript{10,21}

Measuring Bone Density
To measure the bone mineral density (BMD) of skeletal bones in the studies, scientists use noninvasive, dual-energy x-ray absorptiometry (DXA).\textsuperscript{22} This instrument functions according to the theory that bones absorb radiation; as such, the equipment generates a radiation dose, which is smaller than that from a standard chest x-ray, and sends the dose through the bone tissue. The bone absorbs some of the radiation, and the rest of the rays travel through the bone to the radiation detector in the equipment. The higher the bone density, the more radiation is absorbed.

The benefit of DXA is that clinicians can identify bone and soft tissue, and this information leads to more accurate results. DXA can reveal that BMD might be low enough to cause bones to become fragile later in life.\textsuperscript{10}

After the DXA results are received, physicians identify two basic score values:

- The T-score represents a patient’s BMD, as compared with the mean value of that of healthy young adults. For every standard deviation below the mean, a patient’s risk of fracture increases by a factor of two.
- The Z-score is the patient’s BMD, as compared with the value estimated for that patient’s age group.\textsuperscript{23}

Stages of Bone Loss
On the basis of T-scores, the World Health Organization has defined criteria for varying stages of bone loss: normal, osteopenia, osteoporosis, and severe osteoporosis.\textsuperscript{21} These values are helpful for physicians who treat patients taking phenytoin, because they can determine the bone status of a particular patient.
FRACTURES
Bone mass density is inversely related to the risk of fracture. As bone mass density decreases, the risk of fracture increases. The increase in the fracture rate in patients with epilepsy during phenytoin treatment has been observed in several studies. Fractures lead to a number of clinical complications, especially in elderly populations. It is important to identify the patients who are prone to fractures while they are taking phenytoin.

TREATMENT
The goal of treatment for patients who take phenytoin and experience low BMD is to delay the process of accelerated bone turnover. Calcium and vitamin D supplements are options that may delay bone turnover. In 1994, the National Institutes of Health prepared guidelines for the optimal calcium requirements for patients based on age, sex, and reproductive status (Figure 1).

Patients who are at high risk for osteoporosis should take 800 IU of vitamin D and 1,500 mg of elemental calcium daily. The high-risk population includes immobile patients, the elderly, and postmenopausal women. Scientists have concluded that doses of vitamin D can range from 400 to 4,000 IU/day to maintain normal serum 25-hydroxyvitamin D levels in patients who are at risk of developing antiepileptic drug-induced osteomalacia.

In addition to a daily vitamin supplement, physical activity, if possible, is recommended. For patients with low bone density, exercise is as important as taking calcium and vitamin D supplements. Weight-bearing physical activities, such as dancing, walking, and stair climbing, can increase bone density. The usual recommendation is to spend 45 minutes on each activity three to five times per week.

Patients who are taking phenytoin should undergo monitoring to detect any changes in bone density and structure, and they should take supplements if needed. Epileptic patients with decreased bone mass benefit from taking supplements of vitamin D₂ (ergocalciferol), but not vitamin D₃ (calcitriol, cholecalciferol), because vitamin D₃ supplementation does not appear to have an effect on bone mass.

![Figure 1 Optimal calcium intake. (Based on data from National Institutes of Health, 1994.27)](image-url)
Because it is possible that phenytoin delays the process of the bone mineralization by inhibiting the maturation rate of osteoblasts, it would be wise to thoroughly investigate the use of medications that inhibit the bone-resorption process. Bisphosphonate compounds and calcitonin might be helpful, and each of these medications inhibits bone resorption.

After a calcium supplement is taken, pharmacists should also consider this important point: calcium ions decrease the absorption process of phenytoin, possibly by the mechanism of chelation. Therefore, the administration of calcium supplements and phenytoin should be separated by at least two hours; otherwise, their concurrent use may lead to poor seizure control in the patient.

While patients are taking calcium supplements, pharmacists should recommend that physicians monitor other laboratory values, such as magnesium and albumin levels, in addition to Ca\(^{2+}\) and phosphorus. Because calcium is a highly albumin-bound ion, changes in the albumin level—specifically a decrease—can give false readings of calcium levels. In such cases, the following formula should be used:

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\text{corrected calcium} = \frac{\text{observed serum calcium}}{1 + 0.8 \times (4 - \text{serum albumin})}
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Similarly, low levels of magnesium can interfere with calcium absorption. An inadequate magnesium level also prevents calcium from being deposited into the bones and, likewise, cannot prevent the harmful calcium deposition in the kidneys and soft tissue.

CONCLUSION

Phenytoin lowers calcium levels in the body by various mechanisms. Careful monitoring and collaborative efforts between physicians and pharmacists can reduce the risk of osteomalacia and bone demineralization in patients undergoing anticonvulsant therapy.

REFERENCES