

## Phenytoin Toxicity with High Dose, Concomitant Ascorbic Acid Dosing

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### Abstract

High dose ascorbic acid may increase risk of phenytoin toxicity. This case report demonstrates high phenytoin levels resulting in adverse drug reactions subsequent to dosing concomitantly with high dose vitamin C, or ascorbic acid (AA), as a precaution against acquiring corona virus (COVID) infection. This patient suffered from a major seizure when he ran out of his phenytoin prescription. Subsequent initiation of phenytoin and later addition of high dose AA resulted in truncal ataxia and falls with bilateral wrist and finger extension weakness. Phenytoin and AA were discontinued, and the patient returned to baseline on a new medication regimen of lacosamide and gabapentin without any other major seizures one year later.

**Keywords:** phenytoin toxicity, vitamin C, ascorbic acid

### Background

Vitamin C, or ascorbic acid (AA), is a water-soluble vitamin needed for the maintenance of connective tissue and the immune system. The recommended daily allowance for ascorbic acid is 75-90 mg.<sup>1</sup>

Since AA is a weak acid and chelates ferric iron at acidic pH, it may help in the absorption of minerals such as iron when dosed with it.<sup>2</sup> AA has also shown evidence of increasing phenytoin exposure. This increasing exposure was demonstrated in animals when AA was added to phenytoin at multiple doses, augmenting urethane-induced loss of righting reflex at every dose, more than what was expected just by increasing the phenytoin dose alone.<sup>3</sup> High doses of AA are taken by patients to assist in the prevention of common colds or other viral and bacterial infections.<sup>4</sup> High dose vitamin C could be defined as any dose higher than the RDA. When patients take AA, it can be significantly more than the RDA, as in this case. Evidence of AA in prevention of infectious disease when taken at high doses has been lacking.<sup>4</sup>

Phenytoin is an effective antiepileptic drug (AED) used to treat a wide variety of seizures, including tonic-clonic, partial and absence seizures.<sup>5</sup> As a monitored medication, total phenytoin levels are periodically drawn to keep the preferred therapeutic range between 10 and 20 mcg/mL (free phenytoin, 1 to 2 mcg/mL). Usual dosing is 300 to 400 mg per day in divided doses.<sup>5</sup>

This is a case where a patient with epilepsy, stable on phenytoin, started taking 1600 mg of AA with his phenytoin to help prevent corona virus disease (COVID) infection. He subsequently developed truncal ataxia resulting in falls with bilateral wrist and finger extension weakness. Spinal cord dysfunction and polyradiculopathy were ruled out.

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### Case Summary

Patient is a 38-year-old male with a medical history of hydrocephalus, spastic quadriplegia and seizure onset at the hospital manifested as several minutes of whole-body stiffening and rhythmic shaking. This event occurred secondary to a seizure that hospitalized him in which he fell out of his wheelchair and was found by his father. He was found face down with associated tongue biting. Patient stated that he had a similar episode when he was 18 years old but never this severe. An abnormal electroencephalogram (EEG) revealed two brief focal impaired awareness seizures of the right hemisphere, temporally predominant with subsequent nocturnal convulsive status epilepticus manifested as three focal to bilateral tonic-clonic seizures. Diagnosis was focal epilepsy arising from the right frontal temporal head region. The seizure was a result running out of the phenytoin prescription he was taking for seizure control.

He again started taking phenytoin 200 mg per day, dosed as one, 100mg capsule by mouth twice daily in early February, a lower dose than the normal 300 to 400mg daily. After 3 months, phenytoin levels spiked above the therapeutic level of 10 to 20 mcg/mL to 39 mcg/mL in May and the patient was experiencing truncal ataxia resulting in falls with bilateral wrist and finger extension weakness. At the same dose and same frequency, the patient was therapeutic when on phenytoin during prior visits per lab draws at 19.5 mg/L in early February and prior at another facility. The difference was the patient started taking excessive AA supplementation to bolster his immune system amidst the COVID virus pandemic in late February after his last phenytoin in-range level. The patient began to take 1,600 mg of ascorbic acid daily with his evening dose of phenytoin in late February. The only other variables between February and May were albumin that decreased from 4.2 to 3.7 g/dL and alkaline phosphatase that increased from 94 to 138 U/L. It was determined neither of these factors could account for the difference in phenytoin levels since the alkaline phosphatase levels was taken post tonic-clonic seizure activity and albumin remained within the normal range. After having toxic levels in May, patient was placed on lacosamide and gabapentin with

increasing dosage while phenytoin was tapered down to discontinue after the AA was stopped. On the new medication regimen of lacosamide and gabapentin, the patient returned to baseline with no other major seizures one year later.

### Discussion

There was a close correlation with start of the high dose AA and the elevation of phenytoin levels with seemingly no other significant variables that could be identified for this elevation. However, the mechanism of action is unclear.

Phenytoin is a weak acid so is better absorbed in an acidic environment.<sup>6</sup> Phenytoin is initially excreted in the bile as inactive metabolites but then reabsorbed from the intestinal tract for elimination in the urine. Liver hydroxylation of phenytoin is saturable, so a small increase in exposure may disproportionately increase levels of phenytoin, resulting in high plasma levels and toxicity.<sup>6</sup> Ascorbic acid effects on hydroxylation could not be elucidated.

In relatively high dosages, AA supplementation is unlikely to be harmful, largely causing nausea, vomiting, diarrhea, or heartburn.<sup>7</sup> Being water-soluble, excess AA can be filtered and excreted renally. However, when in the stomach AA as a weak acid may affect stomach acidity.<sup>7</sup> It is postulated a change in stomach acidity, increased urinary acidity, both or other contributing factors may have contributed to the increased phenytoin exposure, leading to the patient's toxic phenytoin levels.<sup>7-8</sup> Phenytoin has a dissociation constant ( $pK_a$ ) of 8, AA has a  $pK_a$  of 4.2 and the  $pK_a$  of hydrochloric acid (HCl) in the stomach is -8. The lower or more negative the number, the more acidic the substance. Phenytoin and AA with higher  $K_a$  values would theoretically increase the overall  $K_a$  of the mixture.<sup>6-8</sup> However, other studies point to ascorbic acid overall increasing acid output, thus lowering pH.<sup>9</sup>

Phenytoin metabolism is multifactorial, being affected by protein binding, oral formulation, pharmacogenomics (CYP2C9, CYP2C19) and possibly altered pH in the stomach and/or small intestine.<sup>6, 10-11</sup> Altered pH from AA affecting absorption and/or phenytoin metabolism could have been contributory to the patient's elevated phenytoin levels.<sup>3,9</sup> The patient was taking 1,600 mg of ascorbic acid with his phenytoin dose. 1,600 mg of ascorbic acid in the stomach likely temporarily changes the acidity of the stomach and possibly the proximal small intestine. It should be noted that phenytoin sodium in the stomach, once dissolved, changes to phenytoin acid which precipitates after it dissolves.<sup>6</sup> This precipitate must then reach the small intestine where the drug can then distribute into the body. With regard to decreased stomach acid effect on drug absorption of phenytoin, omeprazole was associated with a 10% reduction in systemic clearance of phenytoin.<sup>6,12-13</sup> The modified acidity of the stomach acid and possibly the duodenum may have led to downstream consequences of phenytoin's clearance. It may also be possible the AA present in the small intestine alters pH enough to alter phenytoin absorption there to affect levels.

90% of phenytoin is bound to albumin while the other 10% remains unbound and free, this 10% is the pharmacologically active phenytoin.<sup>6</sup> Paradoxically, at high concentrations, phenytoin can induce seizures.<sup>6</sup> The patient's phenytoin levels were at 39 mcg/mL so not at the >50 mcg/mL threshold for seizures, coma, or death.<sup>14</sup> Pharmacogenetics also play a role in the balance of getting phenytoin levels therapeutic. Phenytoin primarily metabolized by CYP2C9 (90%) and CYP2C19 (10%).<sup>10-11</sup> Intermediate and poor metabolizers of CYP2C9 substrates may exhibit increased phenytoin serum concentrations compared to patients who are normal metabolizers. Intermediate or poor metabolizers may require lower doses of phenytoin to maintain similar steady-state concentrations.<sup>5,10-11</sup> The patient did not have Pharmacogenomics (PGx) testing.

A patient's level of neurotoxicity depends on serum concentration. When serum concentrations are <10 mg/L, there are minimally reported side effects. In the 10 - 20 mcg/mL range there can be mild nystagmus on lateral gaze. In the 20 - 30 mcg/mL range, nystagmus is often reported. In the 30 - 40 mcg/mL range slurred speech, tremor, nausea, vomiting and ataxia may occur. In the 40 - 50 mcg/mL patients may experience lethargy, confusion, often with associated hyperactivity. For serum concentrations >50 mcg/mL coma and seizures have been reported.<sup>14</sup> The patient in this case only had phenytoin levels up to 39 mcg/mL; however, if left unchecked the patient could be at greater risk of harm. At this time, we would recommend to separate AA administration from phenytoin dosages as they may be linked to increasing phenytoin levels.

Since the patient was taking AA for COVID prevention, value for prevention of COVID with AA was investigated. There was no clear evidence found AA helps prevent COVID infection.<sup>15-16</sup>

Not having the patient's genotype and resulting pharmacogenomic phenotype may be a weakness of this case study analysis. Ideally, in this type of patient case study we would like to have the patient's genotype to fully assess the patient's ability to metabolize phenytoin as an additional factor in determining cause for elevated phenytoin levels. More research will need to be done to determine the exact mechanism of AA's effect on phenytoin levels. In the meantime, patients taking phenytoin can be counseled on avoidance of over supplementation with AA since phenytoin toxicity can be an unwarranted side effect.

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The opinions expressed in this paper are those of the authors.

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