

# Phenytoin-induced chronic liver enzyme elevation and hepatic fibrosis: A case report

Brent Curry, PharmD, BCPP<sup>1</sup>

Lisa Mican, PharmD, BCPP<sup>2</sup>

Tawny L. Smith, PharmD, BCPP<sup>3</sup>

**How to cite:** Curry B, Mican L, Smith TL. Phenytoin-induced chronic liver enzyme elevation and hepatic fibrosis: A case report. *Ment Health Clin* [Internet]. 2018;8(4):184-7. DOI: 10.9740/mhc.2018.07.184.

## Abstract

**Background:** Liver fibrosis results from chronic damage to the liver. Advanced liver fibrosis results in cirrhosis, liver failure, and portal hypertension and may even require liver transplantation. A liver biopsy is considered the “gold standard” method for the assessment of liver fibrosis; however, ultrasonography can also detect changes in the hepatic parenchyma due to fibrosis. Although reports in the literature describe phenytoin-induced hepatic injury, often this rare occurrence is usually accompanied by a hypersensitivity reaction.

**Case report:** Our patient is a 50-year-old female with history of schizoaffective disorder, bipolar type, who had been admitted to a state psychiatric facility. She has a history of seizure disorder, which had been well controlled with phenytoin since 2011. Mild-to-moderate elevations in her liver enzymes were noted during therapy but normalized once phenytoin was discontinued. An ultrasound of the patient’s liver in January 2016 showed changes of fatty infiltration and fibrosis.

**Conclusion:** This case differs from other cases reported in the literature that describe phenytoin-induced hepatic injury. The majority of these cases are accompanied by immune-allergic features. To our knowledge, there have been no reported cases in the literature of prolonged liver enzyme elevation resulting in phenytoin-induced hepatic fibrosis.

**Keywords:** phenytoin, drug-induced, liver fibrosis, hepatic injury

<sup>1</sup> (Corresponding author) Clinical Psychiatric Pharmacist, Central State Hospital, Louisville, Kentucky, [brent.curry@ky.gov](mailto:brent.curry@ky.gov), ORCID: <http://orcid.org/0000-0002-9923-1882>; <sup>2</sup> Assistant Director of Pharmacy, Austin State Hospital, Austin, Texas, ORCID: <http://orcid.org/0000-0002-2852-6632>; <sup>3</sup> Associate Professor of Psychiatry, Dell Medical School, The University of Texas at Austin, Austin, Texas, ORCID: <http://orcid.org/0000-0002-7512-4919>

**Disclosures:** The authors have nothing to disclose concerning possible financial or personal relationships with commercial entities or their competitors that may be referenced in this article.

## Background

Liver fibrosis results from chronic damage to the liver due to the excessive accumulation of extracellular matrix proteins that occurs in most types of chronic liver diseases. Advanced liver fibrosis results in cirrhosis, liver

failure, and portal hypertension and may even require liver transplantation.<sup>1</sup> Liver biopsy is considered the “gold standard” method for the assessment of liver fibrosis.<sup>2</sup> Ultrasonography, computed tomography, and magnetic resonance imaging can also detect changes in the hepatic parenchyma due to moderate-to-severe fibrosis.

Phenytoin is an anticonvulsant that in rare cases can cause acute idiosyncratic drug-induced liver disease that can be severe or even fatal. The liver injury caused by phenytoin appears to be due to a hypersensitivity reaction and resembles cases of immunoallergic hepatotoxicity. This syndrome is more common in African Americans than whites, but few other risk factors have been established. The risk of injury correlates with the presence of HLA-B\*1502. Phenytoin is metabolized to arene oxide, which

may represent the toxic or immunogenic intermediate.<sup>3</sup> The typical case of liver injury due to phenytoin arises after 2 to 8 weeks of therapy with initial onset of fever, rash, facial edema, and lymphadenopathy, followed in a few days by jaundice and dark urine. Eosinophilia, increased white blood cell counts, and atypical lymphocytosis can also occur.<sup>3</sup> Almost all cases of phenytoin hepatotoxicity occur in the context of a systemic hypersensitivity syndrome, and it is therefore referred to often as the anticonvulsant hypersensitivity syndrome or drug rash with eosinophilia and systemic symptoms syndrome. Other manifestations can be Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anemia, thrombocytopenia, neutropenia, nephritis, and pneumonitis.<sup>4</sup> Most cases of liver injury are self-limiting and resolve within 1 to 2 months of stopping phenytoin. Patients on phenytoin may have transient serum aminotransferase elevations. These elevations are usually benign, not associated with liver histological abnormalities, and usually resolve even with phenytoin continuation.<sup>3</sup> Marked aminotransferase elevations, greater than 3-fold elevations, rarely occur. Chronic injury due to phenytoin hepatotoxicity is often rare or nonexistent.

## Case Report

A 50-year-old African American female with a 35-year history of schizoaffective disorder, bipolar type, with a history of frequent and sometimes prolonged admissions to a state psychiatric facility has a history of seizure disorder, which had been controlled with phenytoin since the first documented seizure event in late June 2011. Prior to initiation of phenytoin, she had no known history of elevations in liver enzymes. She has a remote history of alcohol and cocaine use with reported 13-year sobriety. Prior to phenytoin initiation, her liver enzymes were all within normal limits from labs obtained just a few days as well as 6 weeks prior to initiation. Her aspartate aminotransferase (AST) ranged from 14 to 27 U/L (reference range 10 to 42 U/L), alanine aminotransferase (ALT) ranged from 11 to 15 U/L (reference range 10 to 60 U/L), and alkaline phosphatase ranged from 37 to 40 U/L (reference range 38 to 126 U/L). Since phenytoin initiation in 2011 and onward, she had elevations in AST and ALT and periodic elevations in alkaline phosphatase. The highest reported AST and ALT occurred in mid-January 2016 with AST = 94 U/L and ALT = 139 U/L. This corresponded with a reported phenytoin level of 22 mcg/mL, above the therapeutic range of 10 to 20 mcg/mL. While the patient was on phenytoin, the usual range of her AST was approximately 40 to 60 U/L and ALT from approximately 80 to 110 U/L. The highest reported alkaline phosphatase of 180 U/L occurred in late January 2016. The usual range of alkaline phosphate was on the upper end of normal of approximately 90 to 120 U/L. The Table states the patient's daily scheduled medication regimen in mid-January 2016.

**TABLE:** Patient's daily scheduled medication regimen in mid-January 2016

Medication	Dose	Frequency	Route
Atorvastatin	10 mg	At bedtime	Oral
Benzotropine	1 mg	Twice daily	Oral
Haloperidol decanoate	300 mg	Monthly	Intramuscular injection
Lithium carbonate extended-release	900 mg	At bedtime	Oral
Nicotine	7 mg	Daily	Transdermal patch
Phenytoin	200 mg	Twice daily	Oral

The patient did not have significant abnormalities in other hepatic markers, such as bilirubin, total protein, or albumin. A November 2015 fasting lipid profile and complete blood cell count with differential including platelets and eosinophils were within normal limits. In addition to the elevations in liver enzymes, her ammonia levels had also been elevated while on phenytoin therapy. Ammonia levels ranged from 49 to 73 mcg/dL (reference range 11 to 35 mcg/dL). An ultrasound of the patient's liver performed in mid-January 2016 showed changes of fatty infiltration and fibrosis. After these findings and due to the long history of liver enzyme elevations, divalproex and atorvastatin were discontinued. Despite discontinuation of these medications, elevations in liver enzymes and ammonia continued. Tests for possible viral hepatitis infection were negative. The patient's phenytoin was ultimately discontinued in early October 2016, and the patient was transitioned to lacosamide for control of her seizure disorder. Two weeks after the discontinuation of the patient's phenytoin, her liver enzymes normalized with an AST = 22 U/L, ALT = 19 U/L, and alkaline phosphatase = 96 U/L and have remained within normal limits since that time.

## Discussion

This case demonstrates possible phenytoin-induced hepatic fibrosis after chronic mild-to-moderate liver enzyme elevations. Based on the timeline of events and resolution of liver enzyme elevations after the discontinuation of phenytoin, the drug-induced hepatic fibrosis may likely be attributed to phenytoin therapy. A score of 6 on the Naranjo Adverse Drug Reaction Probability Scale indicates phenytoin as a probable cause for the hepatic injury.<sup>5</sup> Although minor dose-related elevations in liver function tests can occur with divalproex<sup>6</sup> and atorvastatin,<sup>7</sup> in this patient, divalproex was discontinued weeks prior to the highest reported AST and ALT that occurred in mid-January 2016. Atorvastatin was discontinued shortly thereafter with continued liver function test elevations. The patient had been on divalproex for mood stabilization

since 2011. The patient had only been recently initiated on atorvastatin and had not been prescribed any similar lipid-lowering medications prior. Elevations in liver enzymes were first reported after initiation of phenytoin, and liver enzymes then normalized after its discontinuation. The literature on phenytoin causing hepatic injury is limited. According to the product labeling, there are rare cases of acute hepatotoxicity being reported with phenytoin.<sup>8</sup> It can cause benign transient elevations in hepatic enzymes that generally remit with continued use and, less commonly, more serious manifestations, such as focal hepatic necrosis, hepatomegaly, and acute hepatitis or hepatic failure. However, almost all cases of phenytoin hepatotoxicity occur in the context of a systemic hypersensitivity syndrome, which was not observed in this case.

The published literature of phenytoin-induced hepatic injury is limited to that of case reports. In one case<sup>9</sup> of phenytoin causing hepatitis, the hepatotoxicity was a component of a severe hypersensitivity reaction. Another case<sup>10</sup> describes a 25-year-old male started on phenytoin for new-onset seizures and subsequently developed fever, morbilliform pruritic rash, and fatigue 3 weeks after initiation. Another 2 weeks of being maintained on the anticonvulsant, he was hospitalized for worsening rash and jaundice. Phenytoin was discontinued, and a liver biopsy that was later performed did show changes of acute hepatitis. Similar to our case, the patient in this case also did not have other medical illnesses, had no history of liver disease, and drank little alcohol. But unlike our case, the patient in this case report<sup>10</sup> had a pattern of onset and association with immunoallergic manifestations that is typical of phenytoin hepatic injury. The hepatic injury was also severe but rapidly reversible once phenytoin was discontinued.

Additional literature available on phenytoin hepatotoxicity supports it as part of a hypersensitivity reaction. The guidelines from the American College of Gastroenterology on the Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury<sup>11</sup> state that phenytoin-induced hepatic injury is often accompanied by immune-allergic features. Additional literature<sup>12</sup> available also reports that elevations in liver enzymes are dose dependent. This was true in our case as the highest reported elevations in her liver enzymes did occur when her phenytoin level was reported to be slightly above the therapeutic range in mid-January 2016.

There is an additional case in the literature<sup>13</sup> that does report phenytoin-induced chronic hepatitis. In that case report, an asymptomatic 52-year-old female who received phenytoin for 11 years was found to have elevated serum aminotransferases. A liver biopsy was performed and showed chronic persistent hepatitis. This documentation

of phenytoin-induced chronic persistent hepatitis was proven by histology and its etiology confirmed by drug withdrawal and by rechallenge. This case is similar to our case as several years of phenytoin did result in chronically elevated serum aminotransferases. Additionally, there were no immune-allergic features or a hypersensitivity reaction. However, in our case, the hepatitis was not able to be confirmed by biopsy or confirmed by rechallenge. It is important to note the limitation that the phenytoin-induced fatty infiltration and liver fibrosis in our patient was only confirmed by ultrasound.

## Conclusion

Despite the limitation of confirming fatty infiltration and fibrosis by only a liver ultrasound, this case demonstrates possible phenytoin-induced hepatic fibrosis after chronic mild-to-moderate liver enzyme elevations. A 50-year-old female who had seizure disorder controlled with phenytoin for many years had mild-to-moderate elevations in her liver enzymes noted during therapy, which only normalized after phenytoin was discontinued. Our case differs from other cases reported in the literature that describe phenytoin-induced hepatic injury accompanied by immune-allergic features and a hypersensitivity reaction. To our knowledge, there have been no reported cases in the literature of phenytoin-induced fatty liver infiltration and fibrosis, such as this one.

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