

# Single-Dose Niacin-Induced Hepatitis

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A 22-year-old man with an unremarkable medical history presented with a 2-week history of intermittent periumbilical abdominal pain.

**N**iacin, also known as vitamin B<sub>3</sub>, is an important cofactor in many metabolic processes necessary to life. Over the past 15 to 20 years, niacin has been prescribed to patients with hyperlipidemia to increase high-density lipoprotein and lower low-density lipoprotein.<sup>1</sup> As a naturally occurring vitamin, niacin is also available over-the-counter (OTC) as a dietary supplement, and is also a common ingredient in energy drinks and multivitamins.<sup>2</sup>

In addition to treating hyperlipidemia and as a nutritional supplement, some anecdotal reports amongst lay-persons suggests that niacin offers other health benefits, such as promoting weight loss and expediting the elimination of alcohol and illicit drugs from one's system (eg, marijuana).<sup>3,4</sup>

The increased use of niacin supplementation in the general population for all of the aforementioned reasons has resulted in an increased incidence of niacin toxicity.

## Formulations

Niacin is available in three formulations: extended-release (ER, also referred to as

intermediate-release), immediate-release (IR), and sustained-release (SR).

The ER formulations of niacin are typically prescribed to treat hyperlipidemia. Patients are usually started on ER niacin at an initial dose of 250 mg once daily. The dose is gradually increased, as tolerated or necessary, to 2 g per day, taken in three doses. It is not uncommon for patients with hyperlipidemia to take more than 1 g of niacin per day after titration by their primary physicians.

## Side Effects

Since niacin increases the release of arachidonic acid from cell membranes that metabolizes into prostaglandins, specifically prostaglandins E<sub>2</sub> and D<sub>2</sub>, many patients taking niacin experience uncomfortable flushing and itching.<sup>5</sup> Nonsteroidal anti-inflammatory drugs (NSAIDs) prevent this side effect by inhibiting the metabolism of arachidonic acid into those vasodilatory prostaglandins. The newer ER and SR formulations of niacin, which are approved for OTC use as a dietary supplement, are less likely to cause flushing.<sup>5</sup>

Extended-release niacin, however, is as-

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**Authors' Disclosure Statement:** The authors report no actual or potential conflict of interest in relation to this article.

DOI: 10.12788/emed.2018.0082

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sociated with a higher incidence of hepatotoxicity than the other prescription formulations of niacin.<sup>6</sup> Toxicity has been well recognized in patients taking niacin chronically for hyperlipidemia, with reports of such cases dating back to the 1980s.<sup>7,8</sup> We report a unique case of niacin toxicity following a single-dose ingestion in a young man.

### Case

A 22-year-old man presented to the ED for evaluation of a 2-week history of intermittent periumbilical abdominal pain. This visit represented the patient's second visit to the ED over the past week for the same complaint.

Upon presentation the patient's vital signs were: blood pressure (BP), 113/64 mm Hg; heart rate, 82 beats/min; respiratory rate, 16 breaths/min; and temperature 36.6°C. Oxygen saturation was 100% on room air. The patient was otherwise healthy and had no significant recent or remote medical history. He denied taking any medications prior to his initial presentation, and reported only occasional alcohol use.

At the patient's initial presentation 1 week earlier, he was diagnosed with acute gastroenteritis and treated with famotidine and ondansetron in the ED. The patient appeared well clinically at this visit, and laboratory values were within normal limits, including normal blood glucose and urinalysis.

The patient was discharged home from this first visit with prescriptions of famotidine and ondansetron, and was advised to follow up with his primary care physician in 1 week. Throughout the week after discharge from the ED, the patient experienced worsening abdominal pain, and he developed frequent nonbloody emesis, prompting his second presentation to the ED. At this second visit, the patient stated that he had taken one dose of ondansetron at home, without effect. He also noted subjective fevers, but had no diarrhea or melena.

Vital signs remained within normal lim-

its with BPs ranging from 115 to 130 mm Hg systolic and 50 to 89 mm Hg diastolic. The patient was never tachycardic, tachypneic, febrile, or hypoxic. Physical examination was remarkable for periumbilical tenderness. The patient had no jaundice. A more thorough laboratory evaluation revealed elevated anion gap and blood urea nitrogen/creatinine values, and leukocytosis. The patient's hepatic enzymes were also elevated, with aspartate aminotransferase (AST) over 2,000 U/L and alanine aminotransferase (ALT) of 1,698 U/L. Lipase, bilirubin, and alkaline phosphatase were all within normal limits. The patient's prothrombin time (PT) was elevated at 14 seconds, and the international normalized ratio (INR) was elevated at 1.28. Laboratory analysis for acetaminophen and alcohol was negative.

A computed tomography (CT) scan of the abdomen/pelvis with intravenous (IV) contrast was unremarkable, demonstrating a liver devoid of any masses, portal or biliary dilation, or cirrhotic changes.

The patient received IV famotidine and ondansetron, and morphine for pain control, and was admitted to the general medical floor for hepatitis of uncertain etiology. A viral hepatitis panel was negative.

On the recommendation of the toxicology service, the patient was given N-acetylcysteine (NAC), and his hepatic enzymes trended down to an AST of 642 U/L and an ALT of 456 U/L by hospital day 2. (The patient essentially completed a positive dechallenge test).<sup>9</sup>

A gastroenterology consult was ordered, during which additional history-taking and chart review noted that the patient admitted to taking one or two tablets of OTC niacin as a dietary supplement the day before his initial presentation. Although the patient could not recall the exact dosage, he stated that he had been taking supplemental niacin approximately once a month over the past several years without any issues. Since OTC niacin is most commonly available in 500-mg tablets, this suggested

the patient's recent one-time ingested dose was approximately 500 to 1,000 mg.

Based on the patient's admission to niacin use, additional studies were ordered, including an abdominal ultrasound and a urine drug screen. Ultrasound findings were unremarkable for portal venous thrombosis. The urine drug screen, however, was positive for marijuana and opiates. While the patient denied any history of opioid use, the positive opiate assay could have been attributed to the morphine given in the ED.

Throughout the patient's hospital course, he remained normotensive and had no change in mental status. His liver enzymes, PT, and INR continued to normalize, and he was discharged home after 3 days, with instructions to follow up with the gastrointestinal clinic within 11 days. An appointment was made for him, which he did not attend.

Given the patient's negative autoimmune and viral workup, and rapid resolution of symptoms after discontinuing niacin use, it is believed that he had an acute drug-induced hepatitis due to niacin ingestion. Regarding any coingestants that could have contributed to the hepatitis, the patient denied taking other common coingestants such as alcohol and acetaminophen; this assertion was supported by laboratory results.

Since we were unable to attain a qualitative measurement of the patient's niacin concentration, our diagnosis was primarily based on the patient's reported history.<sup>10</sup> It is possible the patient had been taking more niacin than that to which he admitted, or that he was taking another hepatotoxic substance not detected on our toxicology workup. As previously noted, there are many medications and/or dietary supplements that could cause or contribute to a synergistic effect of drug-induced hepatitis for which the patient was not tested at his initial presentation. The patient could have co-ingested this large dose of niacin with acetaminophen and/or other supple-

ments, energy drinks, or alcohol. A combination such as this could have contributed to his hepatitis, and the metabolites of these other substances would have been eliminated by the time of his second ED presentation.

### Discussion

There are over 900 different drugs, toxins, and supplements known to cause hepatic injury.<sup>11,12</sup> Clinical manifestations of toxicity range from asymptomatic incidental elevations in transaminases to fulminant liver failure causing mortality. Ingestion of commonly used medications such as statins (although not in overdose quantities) can cause transient asymptomatic transaminitis.<sup>13</sup> These elevations are usually mild—ie, less than twice the upper limit of normal. Patients who experience such elevations can usually continue to take the medications with frequent and vigilant monitoring of hepatic function.

### Signs and Symptoms

**Acute Liver Injury.** Acute liver injury is diagnosed when AST and ALT levels are greater than twice the upper limit of normal. Patients also typically have mild-to-moderate abdominal findings, such as pain, nausea, and vomiting—as was experienced by our patient. Along with niacin, angiotensin-converting enzyme inhibitors, NSAIDs, and antifungal medications are examples of other medications that can cause this degree of drug-induced hepatitis.

**Severe Liver Injury.** Severe liver injury features elevations in not only AST and ALT, but also alkaline phosphate and bilirubin. Patients with severe hepatic injury appear clinically ill and may exhibit altered mental status and jaundice. This type of subfulminant hepatic failure commonly results from acetaminophen toxicity, anesthetic gases, iron toxicity, phosphorus toxicity, and cocaine toxicity. Examples of drugs that result in massive liver necrosis and fulminant hepatitis are acetaminophen, isoniazid, phenelzine, phenytoin, propyl-

thiouracil, and sertraline. Patients with massive hepatic necrosis and hepatitis may require liver transplantation.

### Etiology

Identifying the etiology of liver injury is made largely through the patient's history because there are simply too many possible hepatotoxic agents to test for them all. Diagnostic suspicion of hepatic toxicity should be increased with signs of more serious disease; however, drug-induced liver injury should be included in the differential diagnosis for all cases of abdominal pain.

With respect to the patient in our case, obtaining a more complete history involving supplement and vitamin use would have allowed us to make the diagnosis in the ED. Unfortunately, these subtle aspects of a patient's history are often overlooked in the emergent care setting.

### Treatment

The treatment of niacin-induced liver injury is similar to the guidelines for treating most other drug-induced pathology.<sup>14</sup> Removal of the offending agent and providing supportive care is the primary treatment modality.<sup>15</sup> In addition, it is important that the clinician exclude and rule-out other causes of hepatitis such as those of viral, autoimmune, or ischemic etiology.

**N-acetylcysteine.** A medication classically used in patients with acetaminophen overdose, NAC is a safe and effective treatment for non-acetaminophen-induced liver injury, and was given to treat our patient.<sup>16</sup>

**L-carnitine.** L-carnitine has been shown to be effective in cases of chronic steatosis from hepatitis C and in valproic acid induced hepatitis.<sup>17</sup> Since L-carnitine is not included on our hospital's formulary, it was not a treatment option for our patient.

**Glucocorticoid Therapy.** Although glucocorticoids are occasionally given to patients with systemic symptoms of drug reactions, its effectiveness has not been adequately studied.<sup>18</sup>

### Prognosis

The prognosis of patients with acute drug-induced hepatitis is generally good, and most patients fully recover once the offending agent is removed. Poor prognostic factors include the presence of jaundice, requirement for dialysis, underlying chronic liver conditions, or elevated serum creatinine. While most patients will experience a complete recovery, approximately 5% to 10% will develop chronic hepatitis and/or cirrhosis.

### Conclusion

Niacin is now available as prescription and OTC formulations and is a potentially hepatotoxic medication and dietary supplement. Niacin can cause an acute hepatitis, especially when taken in conjunction with other hepatotoxic substances. Drug-induced liver injury from niacin ingestion will improve quickly following removal, and the prognosis in otherwise healthy individuals is good.

Patients, especially young, healthy patients who present with symptoms concerning for hepatitis, should be asked specifically about any nutritional, herbal, or other supplement usage. During the history intake, many patients do not consider vitamins or other nutritional or herbal supplements as "medication" or as being significant, and only report prescription and OTC medications.

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