A Rare Case of Drug-Induced Liver Injury (DILI) Due to Valproate Hepatocellular Injury

Hope Baldwin BS, Ahmed Elbanna DO, Syed-Mohammed Jafri MD

Henry Ford Hospital, Detroit, MI, USA.

Henry Ford Health System

Henry Ford Transplant Institute

Introduction

Valproate is a widely-used antiepileptic drug which works by increasing inhibitory gamma-aminobutyric acid (GABA) levels in the brain. We present a unique form of drug-induced liver injury (DILI) in a patient prescribed valproate for trigeminal neuralgia pain.

Case Description

A 45-year old African American female with a history of hypertension and trigeminal neuralgia was prescribed divalproex for trigeminal neuralgia pain after trials of duloxetine, gabapentin, baclofen, oxcarbazepine, carbamazepine, topiramate, amitriptyline, and tizanidine failed to provide durable relief. Six weeks later she presented with a two-week history of worsening nausea, diarrhea, fever, facial rash, production of dark phlegm, and grade 1 encephalopathy.

Lab results showed acute liver failure (ALF) with total bilirubin 15.6 mg/dL, ALP 180 U/L, AST 937 U/L, ALT 943 U/L, and INR 2.8. Exam findings included scleral icterus, hepatomegaly, small volume ascites, and some small liver cysts. A diagnosis of DILI was made, with possible drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.

Divalproex was discontinued and the patient was admitted for two weeks of stabilizing treatment including N-acetylcysteine, lactulose, rifaximin, Vitamin K, and L-carnitine transfusion (Figure 1). The patient was evaluated for liver transplant but it was ultimately not indicated given liver function improvement. An acute kidney injury developed but was resolved before patient discharge.

Case Description

Two weeks later the patient presented with signs of acute kidney injury, elevated liver function tests, and pancreatitis. Upon readmission, complications including hepatic encephalopathy, macrocytic anemia, spontaneous bacterial peritonitis, and acute respiratory failure developed over the course of several weeks. All stabilizing treatment efforts were made but the patient ultimately developed septic shock and died.

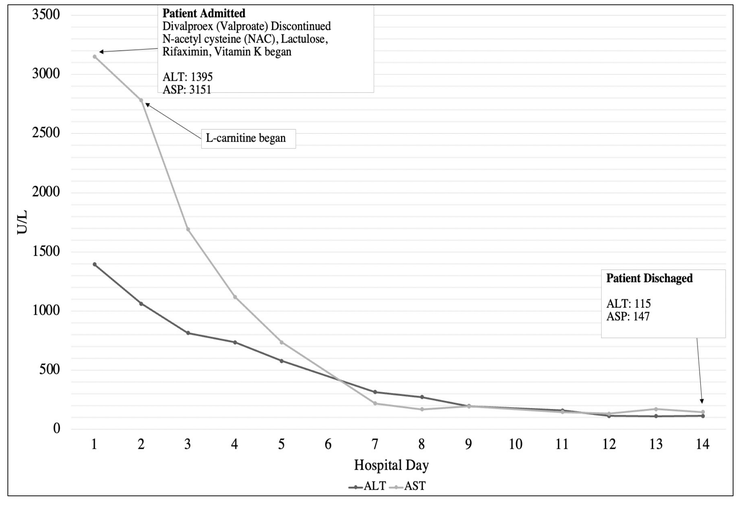

Figure 1A: Patient's AST and ALT values over the course of her hospital admission.

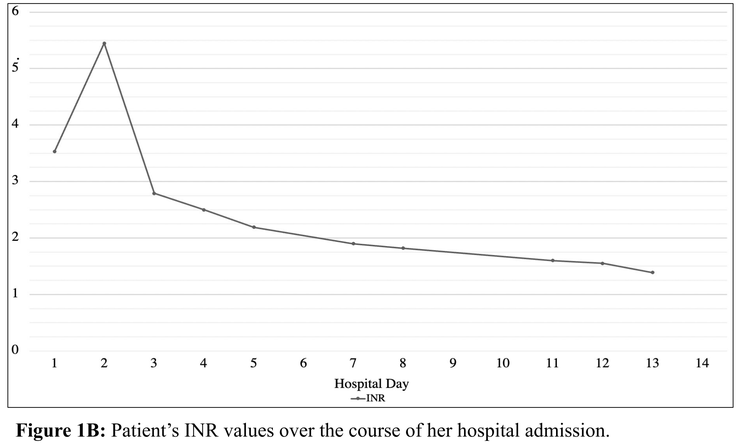

Figure 1B: Patient's INR values over the course of her hospital admission.

The authors have no conflicts of interest to report.

Discussion

DILI is the most common cause of ALF in the United States. There are a wide range of presenting symptoms, but patients commonly display nausea, jaundice, fever, and abdominal pain.

It is known that drug-induced hepatotoxicity is a possible adverse effect of valproate use, and 5-10% of patients report some form of liver dysfunction (although less than .02% experience hepatic failure). Valproate-induced hepatotoxicity is thought to be a result of mitochondrial injury from impaired beta-oxidation and decreased tissue carnitine levels, which may result in microvesicular steatosis. Such hepatocellular injury typically shows very elevated AST and ALT levels with a smaller elevation in ALP.

Early diagnosis of DILI is crucial to promptly discontinue use of the causative agent and begin optimal treatment. In the case of valproate, it is recommended that patients receive intravenous (IV) carnitine until symptoms improve. Additionally, liver transplant evaluation is crucial for ALF patients given morality risks.

References

Fisher K, Vuppalanchi R, Saxena R. Drug-Induced Liver Injury. *Arch Pathol Lab Med*. 2015;139(7):876-887. doi:10.5858/arpa.2014-0214-RA

Katarey D, Verma S. Drug-induced liver injury. *Clin Med (Lond)*. 2016;16(Suppl 6):s104-s109. doi:10.7861/clinmedicine.16-6-s104

Lheureux PE, Hantson P. Carnitine in the treatment of valproic acid-induced toxicity. *Clin Toxicol (Phila)*. 2009;47(2):101-111. doi:10.1080/15563650902752376

Nanau RM, Neuman MG. Adverse drug reactions induced by valproic acid. *Clin Biochem*. 2013;46(15):1323-1338. doi:10.1016/j.clinbiochem.2013.06.012

Patel AR, Nagalli S. Valproate Toxicity. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; July 19, 2022.

Valproate. In: *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury.* Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; July 31, 2020.