Idiosyncratic Valproic Acid–Induced Hepatotoxicity in a Sick Cell Patient

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Abstract

Objective: Suspected idiosyncratic valproic acid–induced hepatotoxicity in a sickle cell patient with chronic migraines is reported. **Case Summary:** A 32-year-old female with a medical history significant for sickle cell anemia and cerebral palsy was admitted to an inpatient medicine service for moderate to severe right flank pain with worsening transaminitis and hyperbilirubinemia. The patient reported taking valproic acid for approximately 6 years for the prevention of chronic migraines. An extensive workup was inconclusive for an etiology of underlying liver disease for the presenting symptoms. Valproic acid was discontinued on hospitalization day 3, resulting in a rapid improvement of the signs and symptoms of hepatotoxicity. **Discussion:** Several mechanisms of idiopathic valproic acid–induced hepatotoxicity have been proposed, including the accumulation of hepatotoxic metabolites, induction of oxidative stress, and deficiency of L-carnitine. Drug-induced hepatotoxicity is typically confirmed following improvement on withdrawal of the suspected agent and exclusion of any underlying etiologies. For this particular patient case, the Council for International Organizations of Medical Sciences scale was also used to evaluate the probability of the hepatotoxicity being drug related. Objective causality assessment with this scale revealed a probable adverse drug event. **Conclusion:** Idiopathic valproic acid–induced hepatotoxicity was suspected in a 32-year-old female with a history of sickle cell anemia and cerebral palsy following improvement of transaminitis and abdominal pain on discontinuation of valproic acid therapy and exclusion of an underlying etiology. This case reveals the clinical significance of prompt pharmacist identification and management of the potential adverse drug event.

Keywords

anticonvulsants, clinical toxicology, drug monitoring, hepatotoxicity, hepatitis, pharmacokinetics, sickle cell anemia, toxicity

Introduction

Valproic acid is a broad spectrum antiepileptic agent indicated as monotherapy or adjuvant therapy for numerous seizure disorders and has more recently adopted indications for the treatment of manic episodes with bipolar disorder and the prophylaxis of migraine headaches. The prescribing information for valproic acid carries a black box warning for nonfatal and fatal hepatotoxicity. Patients taking valproic acid should have liver function tests taken at baseline and monitored at frequent intervals, especially during the first 6 months of therapy.¹ Valproic acid–induced hepatotoxicity is usually dose related and carries an excellent prognosis following cessation of therapy.¹ Although valproic acid has long been associated with hepatotoxicity, idiosyncratic hepatotoxicity is rare, occurring in only 1 in 20 000 patients. Although symptoms of hepatitis usually present within weeks following initial exposure, idiosyncratic hepatotoxicity can present at any time during therapy. Symptoms of this reaction may include abdominal pain, nausea, vomiting, anorexia, jaundice, lethargy, and stupor. This reaction has potential to progress rapidly and be life

threatening. Such reactions often occur at therapeutic levels and typically present with long-term use.² Fatalities resulting from valproic acid–induced hepatotoxicity have been documented in numerous case reports.^{3–6} Furthermore, one case series suggests an increased risk of valproic acid–induced hepatotoxicity in patients with underlying developmental disorders.³ Nonetheless, early drug discontinuation in the setting of suspected hepatotoxicity is essential to avoid the risk of life-threatening progression of liver disease. This report discusses a unique case of suspected idiopathic valproic acid–induced hepatotoxicity in a sickle cell patient with cerebral palsy and chronic migraines, in which multiple comorbidities may have played a role in the pathogenesis of the reaction. The report is also unique in that

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Table 1. Laboratory Findings on Each Day of Hospital Admission.

Date	Day 1: Admission	Day 2	Day 3	Day 4	Day 5	Day 6: Discharge
AST (normal = 0-40 U/L)		205	506	200	106	64
ALT (normal = 0-30 U/L)		191	535	358	250	163
Total bilirubin (normal = <1.2 mg/dL)		2.5	2.9	1.8	2.2	2.1
Direct bilirubin (normal = <0.4 mg/dL)		0.9	1.2	0.6	0.6	0.7
Indirect bilirubin (normal = 0.2-0.7 mg/dL)		1.6	1.7	1.2	1.6	1.4
Alkaline phosphatase (normal = 50-160 U/L)		190	231	200	191	169
INR (normal = 0.8-1.2)		1.0	1.0			

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio.

prompt identification of the drug reaction was made prior to manifestation of fulminant hepatic failure.

Case Report

A 32-year old African American female was admitted to an inpatient medicine service with a chief complaint of moderate to severe right flank pain. The patient described the pain as radiating to the right abdomen during and after urination. The patient had not experienced these symptoms in the past but does suffer from frequent urinary tract infections. The patient did not report any precipitating or alleviating factors. She did complain of bilateral leg and arm pain consistent with her symptoms of sickle cell anemia. Her past medical history is significant for sickle cell anemia, cerebral palsy, general anxiety disorder, asthma, endometriosis, and chronic migraines. Medications prior to admission included delayed-release valproic acid 500 mg twice daily, baclofen 20 mg 3 times daily, meclizine 25 mg every 8 hours as needed for vertigo, diphenhydramine 50 mg as needed, folic acid 1 mg daily, cholecalciferol 1000 units daily, docusate sodium 100 mg as needed for constipation, gabapentin 100 mg 3 times daily, methadone 10 mg 3 times daily, immediate-release morphine sulfate 15 mg every 4 to 6 hours, budesonide-formoterol oral inhalation 2 puffs twice daily, duloxetine 20 mg daily, omeprazole 40 mg daily, and melatonin 6 mg daily. The patient reported taking delayed-release valproic acid for approximately 6 years for migraine prophylaxis. On hospitalization day 1, the patient's basic metabolic panel was found to be unremarkable, and the complete blood count was only significant for a white blood cell count of 22 000 cells/mm³. The patient was afebrile on admission and a urinalysis taken on hospitalization day 1 showed no evidence for infection. Liver function tests were not taken on hospitalization day 1. However, on hospitalization day 2, the patient was found to have transaminitis with aspartate aminotransferase (AST) of 205 U/L and alanine aminotransferase (ALT) of 191 U/L and hyperbilirubinemia with total bilirubin of 2.5 mg/dL (see Table 1). Baseline liver function tests during previous hospital admissions ranged from 23 to 163 U/L for AST and from 19 to

135 U/L for ALT. Although not ordered during this admission, an elevated ammonia level of 82 μ mol/L was documented during a previous admission 2 months earlier.

On hospitalization day 3, delayed-release valproic acid was discontinued due to a concern for drug-induced hepatotoxicity. The patient underwent several imaging studies during her stay in order to rule out an underlying cause of abdominal pain. A retroperitoneal ultrasound (US) showed a normal urinary bladder and no evidence of hydronephrosis or nephrolithiasis. There was evidence of an echogenic lesion in the right kidney with indeterminate significance. Magnetic resonance imaging (MRI) of the abdomen also showed no evidence of hydronephrosis or nephrolithiasis. The liver, spleen, and pancreas were unremarkable on MRI. Computed tomography (CT) scan of the abdomen revealed a stable right renal cyst but no findings to explain the symptoms on presentation. Hepatitis serologies on hospitalization day 4 were found to be negative for hepatitis B and hepatitis C infection. Hepatotoxicity was not found to be a well-documented adverse event associated with the patient's other home medications. An extensive workup for moderate to severe abdominal pain showed no underlying etiologies to explain the symptoms on presentation. The patient's liver function tests and abdominal pain improved following cessation of valproic acid on hospitalization day 3. A valproic acid level of 35 μ g/mL was taken on hospitalization day 4, one day after drug discontinuation. A trend of the patient's pertinent laboratory values from admission to discharge is listed in Table 1.

Discussion

Multiple syndromes of valproic acid-induced liver injury have been described in great detail.^{2,7-9} Valproic acid hepatotoxicity can be classified as either a type A or type B adverse event. Type A reactions are typically dose-dependent and account for the majority of adverse drug events. Dose-dependent valproic acid-induced hepatotoxicity typically manifests as a mild transaminitis and hyperbilirubinemia with or without systemic symptoms.² This occurs in up to 44% of patients initiated on valproic acid and usually presents within the first 6 months of therapy.⁹

Type B reactions are idiosyncratic adverse events that are not related to the dose or known mechanism of action. These events are rare, unpredictable, and often very serious. Idiosyncratic valproic acid-induced hepatotoxicity can occur at any point in therapy, although symptoms of hepatitis typically present within days to weeks following exposure. Symptoms may include abdominal pain, nausea, vomiting, jaundice, anorexia, lethargy, and stupor. Evidence of liver damage and/or liver dysfunction is typically apparent. Idiosyncratic hepatotoxicity from valproic acid can be rapidly progressive and life threatening. A recent pharmacovigilance study reported 34 published cases of fatal valproic acid-induced hepatotoxicity.⁴

This patient reported moderate to severe abdominal pain with evidence of worsening transaminitis and hyperbilirubinemia, but no signs of overt hepatic dysfunction or mental status changes. Nonetheless, early drug discontinuation is essential in the setting of suspected hepatotoxicity. In this unique patient case, the drug reaction was identified prior to any manifestation of fulminant hepatic failure, such as impaired synthetic function or encephalopathy. The intervention to discontinue valproic acid in this patient may have prevented life-threatening hepatotoxicity.

Several mechanisms for idiopathic valproic acid hepatotoxicity have been proposed, although the exact mechanism has not been fully elucidated. Valproic acid is extensively metabolized by cytochrome P450 glucuronic conjugation and oxidation pathways.^{1,2} The accumulation of toxic metabolites may play a role in the pathogenesis of hepatotoxicity. The metabolite 4-ene-VPA is associated with a reversible hepatotoxicity, while 2-ene-VPA and propionic acid derivatives are associated with cerebral edema and hyperammonemia, respectively.^{2,8} Hyperammonemia results from disruption of the urea cycle and subsequently the impairment of nitrogen metabolism.⁹ Evidence suggests that valproic acid metabolism also results in oxidative stress from impaired free radical scavenging secondary to glutathione depletion and increased production of reactive oxygen species.⁸ Toxicology data of valproic acid have also suggested a mechanism of hepatotoxicity secondary to a deficiency of carnitine.^{2,8} A depletion of carnitine has been associated with high-dose or long-term use of valproic acid.⁹ Carnitine is an important cofactor in the β -oxidation of fatty acids. The accumulation of fatty acids in the liver can result in hepatic steatosis, a histological finding associated with valproic acid-induced hepatotoxicity.¹⁰ β -Oxidation metabolism may also play an important role in the detoxification of reactive valproic acid metabolites.⁸

It should be noted that sickle cell anemia is often characterized by a state of oxidative stress and chronic inflammation.¹¹ Thus, the patient's medical history may have played a role in precipitating an idiosyncratic drug reaction. Furthermore, genetics, comorbidities, and duration of treatment may all

play a role in the pathogenesis of hepatotoxicity. Because valproic acid levels do not correlate with idiosyncratic hepatotoxicity, the mechanism of toxicity may involve abnormal metabolism secondary to genetic or congenital errors in mitochondrial function. A report of valproic acid hepatic fatalities suggests that patients with developmental disorders may be at an increased risk of hepatotoxicity.³ Other risk factors for valproic acid-induced hepatotoxicity described in the literature include polypharmacy and metabolic abnormalities.⁵ Indeed, idiosyncratic reactions to valproic acid have been described as a mosaic of genetic and acquired factors.² It is interesting to note the medical history of cerebral palsy in this patient, although it is still unclear exactly what role the developmental disorder played in the suspected hepatotoxicity.

Unfortunately, drug-induced hepatotoxicity is difficult to diagnose based on low incidence and unspecific signs and symptoms. Valproic acid-induced hepatotoxicity can be confirmed on improvement following discontinuation of therapy and exclusion of underlying etiologies.² In addition, an objective causality assessment may be used to evaluate the probability of an adverse drug reaction. In this patient case, the Council for International Organizations of Medical Sciences scale was used to evaluate the likelihood of the hepatotoxicity being drug related.¹² This algorithm was chosen based on its simplicity, ease of use, discriminative power, and evidence of reproducibility in terms of scoring.¹³ The reaction was awarded a score of 8, corresponding to a probable adverse drug event.

Initial management of suspected hepatotoxicity should include immediate drug cessation and supportive care. Electrolyte abnormalities, acid-base disorders, and coagulopathies should be monitored and corrected if present. Furthermore, L-carnitine supplementation has been shown to be safe and effective in the management of severe valproic acid-induced hepatotoxicity, although the evidence is limited.¹⁴ At present there is a lack of durable data on clinical outcomes following L-carnitine administration. The suspected mechanism of action of L-carnitine involves the detoxification of valproic acid by acting as an acceptor of acyl groups, namely, valproyl-CoA.¹⁵ This agent should be considered in the setting of hepatic dysfunction, hyperammonemia, and central nervous system depression. A dosing regimen of L-carnitine for adult patients that has been replicated in multiple studies for treatment of valproic acid toxicity is 100 mg/kg intravenously, followed by 250 mg intravenously every 8 hours for 4 days.¹⁶⁻¹⁸ However, success with alternative dosing regimens has also been reported.¹⁵

Conclusion

Idiopathic valproic acid-induced hepatotoxicity was suspected in a 32-year-old female with a history of sickle cell anemia and cerebral palsy following improvement of transaminitis and abdominal pain on discontinuation of valproic

acid therapy and exclusion of an underlying etiology. The timely identification and management of the adverse drug event underscores the role and value of prospective and direct pharmacist involvement in patient care. The case also highlights the importance of evaluating a patient for the presence of potential drug-induced toxicity in the setting of an acute disease state. Prompt pharmacist identification of the adverse drug event and intervention may have prevented a progression to life-threatening hepatic failure in this patient.

Declaration of Conflicting Interests

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