Case Report

Dangers of Rapid Dosing: A Case of Dose-Dependent Drug-Induced Liver Injury From Duloxetine

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Duloxetine[1] is a commonly used antidepressant, with over 10 million prescriptions written per month in 2014 according to IMS Health.[2] The medication acts by inhibiting the reuptake of serotonin and norepinephrine, increasing the concentration of these neurotransmitters in the brain. This dual mechanism enables duloxetine to be efficacious in the treatment of many disease states. It is approved by the US Food and Drug Administration for major depressive disorder as well as generalized anxiety disorder, diabetic neuropathy, fibromyalgia, and chronic musculoskeletal pain. Duloxetine is generally well tolerated, but can potentially elevate liver enzymes and in rare cases cause liver damage. While cases of hepatotoxicity associated with duloxetine use have been documented by Vuppalanchi et al,[3] no studies have demonstrated this relationship to be dose-dependent.

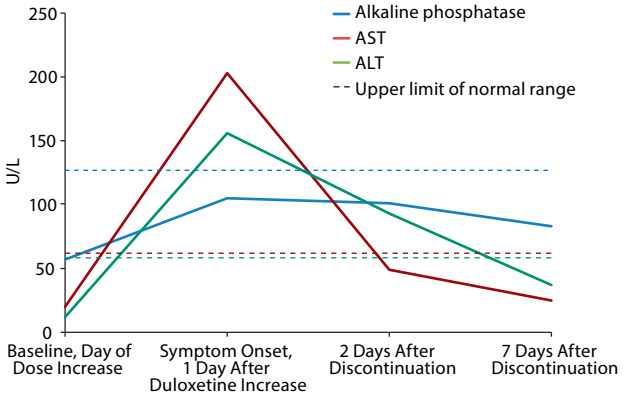
Case Report

We present the case of a 37-year-old woman with a known history of major depressive disorder, unspecified anxiety disorder, alcohol use disorder, and opioid use disorder. She initially presented with depressive symptoms, including suicidal ideation, and was admitted to the inpatient psychiatric unit for acute stabilization. Given her uncontrolled symptoms of depression and anxiety and history of chronic pain, the patient was started on duloxetine 40 mg daily (9 AM). She had no other significant comorbidities, and duloxetine was the only scheduled medication she was receiving while an inpatient. She tolerated the medication well and reported an improvement in depressive symptoms. After 3 doses of duloxetine 40 mg, her dose was subsequently increased from 40 mg to 60 daily (day 4 at 9 AM) to target residual depressive symptoms. Twenty-four hours after the dose increase, the patient presented with significant anxiety, bilateral tremor, hyperthermia, diaphoresis, and autonomic instability. Her physical examination was remarkable for a mild right upper quadrant tenderness. A comprehensive inpatient cardiac evaluation identified no evidence of myocardial ischemia or dysfunction. Tests results for viral hepatitis and autoantibodies were negative.

Laboratory markers of liver function were measured before, during, and after duloxetine-induced liver injury. A rise and fall of alkaline phosphatase, AST (aspartate transaminase), and ALT (alanine transaminase) correlated with an increase in duloxetine dose and subsequent discontinuation.

The patient's initial laboratory work revealed normal liver function tests upon admission (see the table in the Figure). Repeated laboratory tests performed at the time of symptom onset revealed significant increases in alkaline phosphatase, AST, and ALT over baseline. All medications were held, and the patient was given a 1-liter bolus of normal saline.

Figure. Time Course of Duloxetine-Induced Liver Injury[a]



Time of Test	Total Bilirubin (mg/dL)	Alkaline Phosphatase (U/L)	AST (U/L)	ALT (U/L)
Reference range	0.1–1.2	38–126	17–59	11–58
Baseline, day of dose increase	0.4	57	20	12
Symptom onset, 1 day after dose increase	0.4	105	203	156
2 days after discontinuation	0.2	101	49	93
7 days after discontinuation	0.3	83	25	37

[a]Laboratory markers of liver function were measured before, during, and after duloxetine-induced liver injury. A rise and fall of alkaline phosphatase, aspartate transaminase (AST), and alanine transaminase (ALT) correlated with an increase in duloxetine dose and subsequent discontinuation. At no time did the patient fall below values in the reference range, and total bilirubin was never elevated.

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Forty-eight hours after the cessation of medication and fluids, the patient showed improvement of physical symptoms, and hepatic enzymes began to normalize. Symptoms fully resolved and laboratory markers returned to baseline within 1 week of duloxetine discontinuation (see Figure).

Discussion

This case offers an example of acute drug-induced liver injury occurring after a dosage increase of duloxetine. Risk of hepatotoxicity with duloxetine has been reported in case reports before[3]; however, this case is important because the injury appears after the patient did well initially on duloxetine. A dose increase appears to have resulted in rapid autonomic dysfunction and liver injury. The mechanism by which duloxetine causes hepatotoxicity remains unknown. Some case studies identified by Vuppalanchi et al[3] have noted that biopsies indicate primary hepatocellular pattern of injury versus cholestatic. These lesions are quite likely caused by a metabolite of duloxetine, though further research is needed in this area. Until such time, the mechanism remains idiosyncratic in nature. Our patient possessed significant risk factors for hepatic dysfunction including female sex and alcohol consumption; however, no underlying disease process was identified in this case. It further should be noted that providers should have a heightened level of cognizance in individuals with several risk factors for liver injury. Also, she did not present with jaundice or elevated bilirubin. The onset of symptoms 24 hours after a duloxetine dose increase and a corresponding significant elevation in hepatic enzymes support the etiology of a dose-dependent drug-induced liver injury in this patient.

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