CASE REPORTS

SEROTONIN SYNDROME AND LIVER FAILURE WITH DULOXETINE OVERDOSE

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ABSTRACT

We present a unique case of serotonin syndrome and acute liver failure associated with Duloxetine overdose in a young female. This pathological combination has not been reported previously with this medication and in our opinion deserves attention of medical community. Duloxetine use has increased exponentially over the years, putting significant patient population at risk of side effects from this drug.

Keywords: Duloxetine toxicity, Liver failure, Serotonin syndrome.

INTRODUCTION

Duloxetine is a serotonin/norepinephrine reuptake inhibitor (SNRI) which has been in market since 2004; its indications include both depression and pain syndromes. Serotonin syndrome is a potentially life threatening condition associated with increased serotonergic activity in the central nervous system (CNS). It can be seen with therapeutic dose, overdose or as an interaction with other drugs[1]. Serotonin syndrome may involve a spectrum of clinical findings, which often include mental status changes, autonomic hyperactivity, and neuromuscular abnormalities. Selective serotonin reuptake inhibitors (SSRIs) are perhaps the most commonly implicated group of medications associated with serotonin syndrome[2]. Serotonin syndrome has been reported with solo use of duloxetine as well[3-5] which is very rare, although many cases in poly-pharmacy situations have been reported.

There is an association between duloxetine use and liver injury[6]. In most cases it's been found to be transient and self-limiting[7]. There has been at least one case report of fulminant liver failure with duloxetine as well[8]. As far as we have searched there has been no reported case of liver failure and serotonin syndrome combined with duloxetine overdose in literature.

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Received: 15 Jun 2017; revised received: 15 Aug 2017; accepted: 17 Aug 2017

CASE REPORT

A 37 year old lady with past medical history of depression was brought to hospital because of agitation, talking fast and intractable vomiting. She had admitted to taking 600mg her prescription duloxetine intentionally with a suicidal intent, and was last seen normal the night before. She was not on any other prescription medications, and there was no history of reported drug abuse. Review of system could only be obtained from family and was otherwise unremarkable. In the emergency department, she was found to have temperature of 104.6˚F, heart rate was 140/minute, respiratory rate 35/minute, labile BP ranging from 170/95 to 80/40 mmHg but mostly on higher side. Unlike her reportedly hyperactive state at home, in the ER she was poorly responsive. Her body was stiff with frequent clonus, her were pupils dilated but reactive; she was found to have shallow tachypnea and sinus tachycardia. She was intubated for airway protection and was transferred to ICU for further management.

Laboratory work and radiological testing revealed the following significant findings: WBC $12.3X10^9$/L, HCO_3 9mmol/L, AG 29mmol/L, creatinine 3.05mg/dl, AST 581 U/L, ALT 132

U/L, total bilirubin 2.0mg/dl, lactate 18.9 mg/dl, ammonia 419 umol/L, CPK 14000U/L, INR 2.67, acetaminophen <2.0 ug/ml and alcohol level <3mg/dl. Urine drug screening was unremarkable. ABGs revealed, PH 7.28, HCO_3 9mmol/L and CO_2 20kPa. CT C/A/P without contrast suggested bilateral aspiration pneumonia.

Over next few days, AST and ALT continued to climb and peaked at 2500 U/L and 2200 U/L respectively; INR peaked at 3.97. Platelets dropped to as low as $13X10^9$/L with elevated LDH, and low fibrinogen. Hepatitis profile, HIV and pan-cultures turned out to be negative. Patient's liver profile and hematological profile eventually stabilized over next 4-5 days.

Patient was kept on IV fluids, cyproheptadine protocol for serotonin syndrome, benzodiazepines were initiated to counter hyperadrenergic effects. Patient was oliguric in setting of acute kidney injury and high anion gap metabolic acidosis, so hemodialysis had to be initiated immediately. She continued to get supportive care for other hematologic and metabolic derangements. Patient was eventually extubated and improved significantly; all her metabolic and hematological derangements resolved with exception of renal failure for which she continued to require hemodialysis at the time of discharge.

DISCUSSION

Duloxetine is a SNRI. Its indications include chronic musculoskeletal pain, diabetic peripheral neuropathic pain, generalized anxiety disorder, major depression and fibromyalgia and it is generally this patient population with depression and chronic pains who are at risk of polypharmacy; which can lead to interactions, increasing risk of serotonin syndrome. Our patient presented with serotonin syndrome due to duloxetine over dose, without any other interacting drug intake, which is a rare presentation. In our research we found only three such case reports in which serotonin syndrome was purely due to duloxetine[3-5]. So our case adds to this still germinal body of evidence which links duloxetine to serotonin syndrome; as opposed to SSRIs which already have strong established relation.

Many studies have evaluated association of liver toxicity with duloxetine. Some suggest, liver injury incidence in duloxetine appears to be more common as compared to venlafaxine (SNRI) and SSRIs[6], but the jury is still out there[9]. When liver injury does occur it is mostly self-limiting and transient[7]. So acute liver failure with duloxetine is certainly a very rare occurrence. It needs to be pointed out that our patient did have a transient drop in her blood pressure; but the liver injury pattern she had didn't represent an ischemic event. In our case, elevated transaminases were present even before she had a hypotension and the pattern of deranged metabolic and synthetic functions of liver seen in our patient in the form of elevated INR and profound hyperammonaemia, is not typical of ischemic liver injury. As rest of the work up including viral hepatitis profile and acetaminophen level was unremarkable, and the fact that she was not on any other medications besides duloxetine, the evidence suggests that liver failure was most likely due to duloxetine. This reveals a link to yet another life-threatening condition associated with duloxetine toxicity in addition to serotonin syndrome.

In our literature review we didn't find any case report of liver failure and serotonin syndrome combined in a patient with duloxetine overdose, which makes this case unique and worth presenting to our colleagues.

CONCLUSION

Doluxetine use has increased in recent years due to its efficacy in both depression and pain syndromes. Patients with chronic pain also tend to be on other medications e.g. tramadol, cyclobenzaprine; which can increase risk of serotonin syndrome. Similarly, liver injury with duloxetine can present with different levels of severity, and monitoring liver enzymes has been recommended by some experts. Clinicians should

keep high index of suspicion while caring for patients on this medication.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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