IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Case Report
February 2019 Vol.:14, Issue:3

Mood Stabilisers (Lithium & Valproic Acid) Induced Peripheral Edema

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ISSN 2349-7203
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Submission: 23 January 2019
Accepted: 29 January 2019
Published: 28 February 2019

Keywords: Mood stabilisers, peripheral edema, Bipolar disorder.

ABSTRACT

Mood stabilisers are widely used in psychiatry especially lithium and valproic acid because of their mood stabilising properties. They help to treat and prevent return of both manic and depressive episodes in Bipolar disorder. Valproate is primarily broad-spectrum antiepileptic agent used in the treatment of seizures and referred to as third most common xenobiotic of causing death due to liver injury (in this case study peripheral edema and facial swelling). Lithium is relatively safe but it can lead to uncommon adverse effects. Mood stabilisers induce swelling of ankles, feet and face through abnormal liver function tests and lithium toxicity due to concomitant use of other drugs in given prescription. Here we describing a case of 27 years female patient presented with peripheral edema and facial swelling after one year of taking lithium and valproic acid in view of bipolar disorder. The mortality rate of psychiatry patients increased due to adverse effects of mood stabilisers especially hepatic and renal toxicity despite of their affective disorders. The physicians prescribing valproic acid and lithium should go for careful monitoring of liver function tests and lithium levels throughout the drug course.

INTRODUCTION

Most, if not all, patients with bipolar disorder using mood-stabilizing drugs during acute or maintenance treatment will be confronted with side effects. The literature on the management of various side effects of mood-stabilizing drugs is rather scattered, focusing on either a side effect or on a specific agent, thus leaving the clinician deprived of clear guidance, especially when treating frail patients. Lithium, valproate (VPA), carbamazepine (CBZ), and lamotrigine are among the options recommended in various guidelines for acute mania (lithium and VPA), bipolar depression (lithium, lamotrigine, and VPA), and maintenance treatment for bipolar disorder (lithium, lamotrigine, and VPA). Pedal edema is a rarely reported side effect of lithium and valproate. In fact, after widespread search of literature and of Cochrane and Pubmed databases, we came across only one article mentioning 'peripheral edema' as an uncommon side effect of lithium [1, 2].

We report a patient who developed pedal edema and facial swelling associated with long term mood stabilizer therapy, with absolutely normal plasma lithium levels and increased liver enzymes and decreased albumin. The case demonstrates a rare but significant side effect of lithium and emphasizes that regular clinical assessment of the patient rather than serum lithium levels or laboratory investigation reports, is more relevant as in the absence of any research findings in this aspect, it would be difficult to comment on pathophysiology of lithium-induced pedal edema, but, at the same time, it would be interesting to find out whether this edema involves the cardiovascular, endocrine or the renal system, the three most affected systems of the body by lithium. Long term valproate therapy leads to hepatotoxicity which results in increased liver enzymes and decreased albumin levels [3].

CASE REPORT

A 27-year-old, married female, a known case of bipolar affective disorder, was admitted to the psychiatry ward in manic state presenting with peripheral edema and facial swelling. This was his second admission inward in last three years. Her psychiatric illness began 5 years back with abrupt onset of a manic episode in form of elated mood, pressure of speech, flight of ideas, insomnia, hyperactivity and violence at home. She is on medication like Risperidone, trihexyphenidyl, lithium, valproate and clonazepam since 1 year in view of bipolar disorder. On laboratory, examinations elevated liver SGOT and SGPT levels and decreased albumin levels were found on second day of her admission.

It was decided to stop lithium and valproate altogether and shift the patient onto Quetiapine as maintenance therapy for prophylaxis of bipolar affective disorder. Within 8 days of stopping lithium and valproate, the edema disappeared completely from both his lower legs and face whereas liver enzymes, albumin levels were found to be normal on laboratory investigations.

We analyzed this adverse drug reaction by using WHO, severity, predictability scales.

Sr. No.	Assessment	Result
1	WHO	Probable
2	Severity	Moderately severe
3	Preventability	Probably preventable

DISCUSSION

Lithium, Valproic acid, Carbamazepine, and lamotrigine are recommended in recent guidelines for the acute and prophylactic treatment of bipolar disorder, although each of these drugs has a different efficacy profile across the various phases of the illness. Newer pharmacological options, especially atypical antipsychotics, have a different efficacy and side effect profile and may not be an alternative for patients suffering from side effects from these 'classic' mood stabilizers [4].

In this case, peripheral edema and facial swelling mostly develops due to long term lithium and valproate therapy. Lithium has a narrow therapeutic/ toxic ratio - serum lithium concentrations must be measured regularly. Mild adverse effects can occur even if serum lithium levels are 1mmol/L. Initial post-absorptive symptoms include gastrointestinal discomfort, nausea, vertigo, muscle weakness, which frequently disappear after stabilization of therapy. More common and persistent side effects are fine hand tremors, fatigue, thirst and polyuria. Mild to moderate toxic reactions occur at lithium levels of 1.5 to 2 mmol/L; moderate to severe reactions at levels >2mmol/L [5]. Progressive intoxication may be manifested by confusion, increasing disorientation, muscle twitchings, hyperreflexia, nystagmus, seizures diarrhoea, vomiting, and eventually coma and death. The currently available literature on lithium does not report 'edema' as an adverse effect. No case report pertaining to any type of lithium-induced edema was found by us despite extensive search [6]. In the absence of any research findings in this aspect, it would be difficult to comment on

Pathophysiology of lithium-induced pedal edema, but, at the same time, it would be interesting to find out whether this edema involves the cardiovascular, endocrine or the renal system, the three most affected systems of the body by lithium. The most prevalent renal effect of lithium is impairment of concentrating ability and reduced GFR [7].

Hepatotoxicity due to Valproate appears in two forms. The benign form exists as a mild, dose-related elevation of liver enzymes that disappears with reduction in dosage or discontinuation of the drug. The other form is a less common non-dose related disorder characterized by hepatic failure [8]. The mechanism of valproate hepatotoxicity is thought to be due to mitochondrial toxicity, maybe from inhibition of beta-oxidation and subsequent loss of mitochondrial function. Prospective studies suggest that 5%-10% of persons develop ALT elevations during long term valproate therapy, but it has been said that these abnormalities are usually asymptomatic and can resolve even with continuation of the drug [9]. This hepatotoxicity leads to decrease in albumin level and elevated transaminases eventually results in peripheral edema. The condition was reversible after the offending drugs were stopped. Other measures include administration of IV Carnitine and addition of hepatoprotectives [10].

CONCLUSION

The mortality rate of psychiatry patients increased due to adverse effects of mood stabilisers especially hepatic and renal toxicity despite of their affective disorders. The physicians prescribing valproic acid and lithium should go for careful monitoring of liver function tests and lithium levels throughout the drug course. This case highlights the need for treating doctors to be aware of exact nature and dosage of the drug, its indications, and the nature of adverse side-effects. It also demands paying attention towards uncommon and atypical side effects of commonly used drugs.

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