Case Report

Successful treatment of endoxifen overdose: A case report

Nahid Dave[1], Sagar Karia[2]

From [1]Consultant Psychiatrist, [2]Assistant Professor, Department of Psychiatry, LTMMC and GH, Mumbai, Maharashtra, India

ABSTRACT

Endoxifen is a direct protein kinase C inhibitor available in India for the management of bipolar disorder since 2021. Clinical studies show that endoxifen is as effective as divalproex sodium and has a good tolerability profile. Clinical data related to overdosage of endoxifen has not yet been reported. We hereby report the case of a 37-year-old female presenting with suicidal ingestion of 56 mg of endoxifen, leading to mild mania. No changes were observed in vital signs, laboratory parameters, electrocardiogram, or ophthalmic examination. This case report suggests a good tolerability profile of endoxifen.

Key words: Bipolar disorder, Endoxifen, Overdosage

Endoxifen is a direct protein kinase C (PKC) inhibitor [1] that plays an important role in the pathophysiology of bipolar disorder [2]. Endoxifen is currently approved for the management of manic and mixed episodes related to bipolar I disorder in 2019 in India [3]. Doses of 4 mg and 8 mg/day of endoxifen have been studied in clinical trials, ultimately leading to the approval of 8 mg dose [4,5]. During clinical development, endoxifen has shown similar efficacy and fewer side effects as compared to divalproex sodium. It was also reported that endoxifen induces faster remission as early as day 4 [4,5].

Endoxifen is an active metabolite of tamoxifen and has 4 times more potency for inhibiting PKC [1]. The primary tamoxifen metabolite, N-desmethyltamoxifen, undergoes biotransformation due to CYP2D and results in endoxifen, which is a secondary metabolite [6]. Endoxifen provides substantial drug exposure unaffected by CYP2D6 metabolism, unlike tamoxifen, and showed an acceptable toxicity profile [7]. Endoxifen follows the linear kinetics with a half-life of 52 h.

As endoxifen is a relatively new drug, the safety of endoxifen at higher doses is not established yet [8]. The clinical data on overdosage of endoxifen and its management are still lacking. Here, we present the first-of-its-kind case report of a 37-year-old female who ingested seven tablets (56 mg) of endoxifen with the intent to commit suicide.

CASE HISTORY

A 37-year-old MBA graduate female, working in an audit firm, married for 8 years with no children, presented to our psychiatry clinic with a sad mood, decreased interest in daily activities, inability to perform household and professional work properly, unrefreshing sleep, irritability, thoughts of running away from home, and staying alone for previous 2 years which gradually worsened over last 6 months.

She was diagnosed with major depressive disorder and prescribed tablet escitalopram 10 mg/day, which led to an improvement in irritability and thoughts of running away. However, inattention, sadness, and sleep disturbances did not show any improvement. Her husband also reported that she had symptoms of mood swings with anger outbursts without provocation, wherein she threw household items or beat family members. Episodes of binge eating were also reported, wherein she binged on chips, cakes, and chocolates and then felt guilty about overeating.

Tablet divalproex sodium extended-release 250 mg/day was added. This resulted in considerable improvement in sadness, impulsivity, and sleep disturbances. However, she started gaining weight, which she attributed to the medication and eventually discontinued all her medicines.

After 2 months of stopping medicines, she returned with symptoms of sadness, irritability, and inability to experience pleasure. She was prescribed vortioxetine 10 mg and endoxifen 8 mg/day, but she did not take any medications. She had thoughts of self-harm and committing suicide, for which she consumed seven tablets of endoxifen 8 mg (total of 56 mg). Her husband noticed this and rushed her to the emergency department, where she was admitted and kept under observation for 24 h. On arrival at the emergency department, her pulse was 90 beats/min, blood pressure 124/84 mm of Hg, respiratory rate 16/min, and oxygen saturation of 98%. She did not have any symptoms of

Access this article online	
Received - 29 January 2025 Initial Review - 01 March 2025 Accepted - 23 March 2025	Quick Response code
DOI: 10.32677/ijcr.v11i4.5018	

Correspondence to: Dr. Sagar Karia, OPD 21, Department of Psychiatry, 2nd Floor, New OPD Building, LTMMC and GH, Sion, Mumbai - 400022, Maharashtra, India. E-mail: kariabhai117@gmail.com

overdose except mild nausea. All her blood parameters and electrocardiogram (ECG) findings were normal. ECG was rechecked after 24 h, and there was still no evidence of QTc prolongation, thromboembolism, or any other abnormality. Her ophthalmic examination also did not reveal any abnormality. After 24 h of observation, she was discharged from the hospital. No other specific medicines or stomach wash were necessitated. Her husband was advised to supervise her medications, keep all the medications in lock and key facility, and keep all sharp objects away from her. She was referred to a counselor too.

At discharge, she was prescribed a fixed-dose combination containing dextromethorphan plus bupropion (D + B) once daily and lamotrigine 50 mg at night. The dose of D + B was increased to twice daily after 15 days. She was not prescribed endoxifen after the overdose incidence. She came for a follow-up after 4 months of incidence of overdosage of endoxifen, and she was doing well.

DISCUSSION

Endoxifen has shown a good tolerability profile in clinical trials and also in post-marketing real-world studies [4,5,9]. The commonly reported adverse events include headache, gastritis, insomnia, etc., which are mild in nature. Anecdotal case reports have shown endoxifen to be safe in special populations such as patients with renal and hepatic impairment and elderly patients [10,11]. Chakladar (2022) and Thanvi also showed the long-term safety of endoxifen in clinical practice [12]. Overall, the tolerability profile of endoxifen is good. However, we have not been able to find any case report or information on the overdosage of endoxifen in the public domain.

Information related to the overdosage of any drug is important as it helps to understand the possible outcomes and potential clinical management options. Not much data related to the safety of high doses of endoxifen is available. As endoxifen is an active metabolite of tamoxifen, we tried to look for acute toxic effects of tamoxifen, such as changes in ECG, eye toxicity, and routine laboratory parameters such as liver and renal function tests [13].

Overdosage of endoxifen for 56 mg produced only mild nausea in our patient. We did not observe any significant clinical adverse event or any change in laboratory parameters, ECG, or eye examination. Goetz *et al*. have previously reported that endoxifen at a dose of 160 mg/day leads to a serum concentration of 55 mmoL/L and still does not produce any eye toxicity [7]. One patient was reported to have developed thromboembolism at 60 mg [7]. However, no change was observed in any of these parameters and the patient was discharged without any consequences. This experience further strengthens the good safety profile of endoxifen.

CONCLUSION

Endoxifen at a dose as high as 56 mg only causes mild nausea. This case adds to our knowledge about the safety of endoxifen in case of overdosage and also the potential management of such patients.

REFERENCES

1. Ali SM, Ahmad A, Shahabuddin S, Ahmad MU, Sheikh S, Ahmad I. Endoxifen is a new potent inhibitor of PKC: A potential therapeutic agent for bipolar disorder. Bioorg Med Chem Lett 2010;20:2665-7.
2. Saxena A, Scaini G, Bavaresco DV, Leite C, Valvassori SS, Carvalho AF, *et al*. Role of protein kinase C in bipolar disorder: A review of the current literature. Mol Neuropsychiatry 2017;3:108-24.
3. List of New Drugs Approved in the Year 2019 Till Date. Available from: https://cdsco.gov.in/opencms/resources/uploadcdscoweb/2018/uploadapprovalnewdrugs/newdrugaapproaldec [Last accessed on 2024 Dec 27].
4. Ahmad A, Sheikh S, Shah T, Reddy MS, Prasad B, Verma KK, *et al.* Endoxifen, a new treatment option for mania: A double-blind, active-controlled trial demonstrates the antimanic efficacy of endoxifen. Clin Transl Sci 2016;9:252-9.
5. Ahmad A, Sheikh S, Khan MA, Chaturvedi A, Patel P, Patel R, *et al.* Endoxifen: A new, protein kinase C inhibitor to treat acute and mixed mania associated with bipolar I disorder. Bipolar Disorder 2021;23:595-603.
6. Jayaraman S, Reid JM, Hawse JR, Goetz MP. Endoxifen, an estrogen receptor targeted therapy: From bench to bedside. Endocrinology 2021;162:bqab191.
7. Goetz MP, Suman VJ, Reid JM, Northfelt DW, Mahr MA, Ralya AT, *et al*. First-in-human phase I study of the tamoxifen metabolite z-endoxifen in women with endocrine-refractory metastatic breast cancer. J Clin Oncol 2017;35:3391-400.
8. Zonalta. Endoxifen 8 mg Tablets. Prescribing Information. Available from: https://zonalta.in/wp-content/uploads/2021/03/10-4731-0-6004212-zonalta-pil-1 [Last accessed on 2024 Dec 27].
9. Patel P, Jain AB, Dave N. Real-world evidence for endoxifen in the treatment of patients with bipolar I disorder: A 12-week open-label study. Eur J Pharm Med Res 2024;11:355-61.
10. Gautam N, Abhilasha P. Endoxifen in bipolar disorder with hyperammonemia and renal impairment: A case report. Cureus 2025;17:e76839.
11. Biswal J, Srivastava H. A new dawn for geriatric bipolar disorder: Promising impact of endoxifen - a case report. Indian J Clin Psychiatry 2024;4:57-61.
12. Thanvi V. Real-world long-term experience on endoxifen in bipolar disorder with psychotic symptoms. Case Rep Psychiatry 2022;2022:3684181.
13. Tamoxifen Citrate. Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda-docs/label/2002/17970s37s44s49lbl [Last accessed on 2025 Feb 27].

Funding: Nil; Conflicts of interest: Nil.

How to cite this article: Dave N, Karia S. Successful treatment of endoxifen overdose: A case report. Indian J Case Reports. 2025; 11(4):167-168.