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Case Series

Escitalopram-Induced Hyponatremia and Neurological Adverse Effects: A Case Series

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Abstract

Escitalopram is a Selective Serotonin Receptor Inhibitor (SSRI) prescribed for the management of anxiety, major depressive disorders, agitation, and dementia. Hyponatremia is a familiar side effect of SSRIs; however, there are only a few pieces of literature that give evidence of escitalopram-induced hyponatremia and hyponatremic encephalopathy. SSRIs are also known to cause rare neurological side effects, such as extrapyramidal symptoms like tremulousness, Parkinsonism, which often go unlisted. SSRIs also shows an example of drug-induced psychiatric disorders such as visual hallucinations.

Keywords: Selective Serotonin Receptor Inhibitors, hyponatremia, hyponatremic encephalopathy, Parkinsonism, Escitalopram

INTRODUCTION

Escitalopram belongs to the class of medicines called Selective Serotonin Reuptake Inhibitors (SSRIs). It enhances the serotonergic activity by binding to the primary target i.e., the 5HT binding site also called orthosteric site on the serotonin transporter (SERT), responsible for serotonin reuptake. Thus, it binds to the same receptors where the endogenous serotonin binds and hence inhibits its reuptake into the presynaptic vesicles.[1,2]

There are large numbers of Adverse Drug Reactions (ADRs) associated with SSRIs, hyponatremia being the most common, with an account of 3 times more risk compared to other antidepressants.[3,4] Syndrome of inappropriate antidiuretic hormone secretion (SIADH) could cause hyponatremia. SIADH is characterized by

sodium level <135 mmol/L, urine osmolarity >200 mmol/kg and urine sodium level >20 mmol/L [3,4]. SSRIs act by working on norepinephrine (NE). NE binds to alpha 1 adrenergic receptor releasing Antidiuretic Hormone (ADH). NE is degraded followed by signal termination. SSRIs inhibit NE reuptake, increasing ADH release[5]. ADH, or Vasopressin, regulates the amount of water in the body, which leads to the decreased excretion of water followed by retention, which in turn dilutes sodium, causing hyponatremia. This can result in a transcellular shift from Extracellular fluid **(**ECF) to brain cells causing cerebral edema and symptoms (confusion, fatigue, anorexia, nausea, vomiting)[6].

SSRIs are also known to cause extrapyramidal symptoms (EPS) amongst which Escitalopram induced EPS accounts for 12%. Escitalopram alters dopamine receptors in the basal ganglia causing motor disturbances .[7] Visual hallucinations are probably developed due to the imbalance between serotonin and acetylcholine systems[14]. The hallucinations likely result from the medication's impact on serotonin neurotransmission, causing temporary disruptions in sensory processing and perception[20-21].

The tremor is likely related to the medication's impact on neurotransmitter systems, specifically serotonin modulation. Approximately 1-10% of patients may experience tremor as a side effect, with most cases being mild and self-limiting[22].

CASE STUDY

CASE 1 – Escitalopram induced Hyponatremia

74 year old male presented to Physical medicine and rehabilitation (PMR) Outpatient department (OPD) with complaints of (%) difficulty in balancing and walking and then was admitted for neurorehabilitation on 20th October, 2023.The patient is a known case of (k/c/o) Parkinsonism, Hepatocellular carcinoma (HCC), Type 2 Diabetes Mellitus (T2DM), Systemic Hypertension (S.HTN), Coronary Artery Disease(CAD) Surgical procedure (S/P) Percutaneous Transluminal Coronary Angioplasty (PTCA), and recurrent Urinary tract infection (UTI). The patient was on the following medication Tab. Levodopa and Carbidopa 125 mg 1 ½ tablets 5 times daily, Tab. Nexito (Escitalopram) 5 mg BD (1-0-1), Tab Levetiracetam 500 mg OD (0-0-1), Tab. Teneligliptin +Metformin 20 mg +500 mg OD (1-0-0), Tab. Perindopril arginine + Indapamide 4mg OD (0-1-0), Tab. Trimetazidine 35 mg BD (1-0-1), Tab.Nitrofurantoin 100mg BD (1-0-1). The patient was advised Tab. Nexito (Escitalopram) 5 mg BD (1-0-1) from the neurology department. He developed hyponatremia on 21st October, 2023 with sodium level 130 mmol/L. The patient's bystander complained that the patient showed disoriented behavior when sodium level dropped below 138 mmol/L. Consequently, a neurology and general medicine consultation was sought which suggested that hyponatremia is attributed to Parkinsonism and the drugs, following which the escitalopram dose was reduced (0-0-1) OD. Hyponatremia resolved (Na-138) on treating with Tab. Tolvaptan 15 mg OD and intravenous fluid (IVF) normal saline (NS) on 23rd October 2023.

CASE 2- Escitalopram induced Hyponatremia

A 50-year-old female patient was admitted in general medicine department with hyponatremia on 18th November 2023. He is a k/c/o Depression and HTN. She was on Escitalopram 5mg OD since 2023. The sodium levels were 96 mmol/L, following which Escitalopram was withdrawn on 18th November 2023.

CASE 3- Escitalopram induced Hyponatremic Encephalopathy

58 year old female presented to the general medicine department on 25th July 2022 with c/o reduced sleep, restlessness, confused speech, decreased orientation for 2 days. The patient is a k/c/o psychiatric illness, T2DM, Hypothyroidism, S.HTN. She was on the following medications Tab. Escitalopram 20 mg OD, Tab.Teneligliptin 20mg OD (1-0-0), Inj. H.Mixtard 20-0-15 units ,Tab.Thyroxine sodium 100 mcg OD1-0-0, Tab.Spironolactone 25 mg BD (1-0-1). She was on Tab. Escitalopram 20 mg OD since 1½ years. On admission her sodium levels were deranged 126 mmol/L (26th July 2022), 131 mmol/L (28th July 2022),127 mmol/L (9 th August 2022),127 mmol/L (10 th August 2022). Psychiatry consultation was sought which resulted in withholding Escitalopram on 12th August 2022. Her sodium levels recovered (Na^+- 135 mmol/l) on treatment with Tab. Tolvaptan 15 mg OD and i.v. fluids.

CASE 4-Escitalopram induced Parkinsonism

79 year old male came for review in general medicine OPD with c/o bilateral mature cataract on 13th November 2023. He is a k/c/o depression, T2DM, HTN, CAD. He was on the following medications Tab. Escitalopram 10 mg HS, Tab.Teneligliptin 20 mg OD (1-0-0), Inj. Human Mixtard HS (0-0-10) units, Tab. Metoprolol XR 50 mg, Tab. Cilnidipine 10 mg BD (1-0-1), Tab. Aspirin 75 mg OD (0-1-0). He has been taking Tab. Escitalopram 10 mg HS, since 2017 from another local hospital. On General Examination the patient had left hemiplegia, generalized rigidity. Tab. Escitalopram was withdrawn on 13th November 2023, as on examination the symptoms of Parkinsonism were seen. He was prescribed Tab. Trihexyphenidyl Hydrochloride 2 mg OD (1-0-0) and symptoms improved on next visit.

CASE 5- Escitalopram induced Tremulousness

75 year old female presented to the Department of Psychiatry with complaints of tremulousness, paresthesia in both legs and sleep issues on 21st June 2024. The patient is k/c/o DM, HTN, DLP, she had a history of multiple surgeries on the tongue. She was on treatment with Tab. Escitalopram 5 mg HS (0-0-1) and Tab. Pregabalin 75 mg HS (0-0-1) from the psychiatry department since 14th November 2023. She experienced tremulousness. She was asked to withdraw Tab. Escitalopram 5 mg on 21st June 2024 after which her condition improved.

CASE 6- Escitalopram induced Visual Hallucinations

17 year old female presented to the Department of Psychiatry with complaints of visual hallucinations and difficulty sleeping on 14th November 2023. She is a k/c/o anxiety disorder and was on treatment with Tab. Escitalopram 10 mg HS (0-0-1) and Tab. Clonazepam 0.25 mg HS (0-0-1) from the psychiatry department on 20th October 2023. She was asked to stop Tab. Escitalopram on 14th November 2023. She was started on treatment with Tab. Vortioxetine 5 mg HS (0-0-1) and Tab. Aripiprazole 2 mg (1-0-0). At present, she is fine.

Table 1: Causality Assessment of the ADRs

Patient No.	Adverse Drug Reaction	Causality Assessment				
		WHO - UMC Scale	Rawlin and Thompsons Classification	Hartwig's Severity assessment Scale	Schumock and Thornton Scale	Naranjo's Scale
1.	Escitalopram induced hyponatremia	Probable	Type B	Moderate Level-4A	Probably preventable	Probable
2.	Escitalopram induced hyponatremia	Probable	Type B	Severe Level-5	Probably preventable	Probable
3.	Escitalopram induced hyponatremic encephalopathy	Probable	Type B	Moderate Level 4b	Probably preventable	Probable
4.	Escitalopram induced Parkinsonism	Probable	Type C	Moderate Level 3	Probably preventable	Probable
5.	Escitalopram induced tremulousness	Probable	Type A	Moderate Level 3	Probably Preventable	Probable
6.	Escitalopram induced visual disturbances	Probable	Type B	Moderate Level 3	Probably preventable	Probable

Table 2: Type and Severity of ADR with Preventability and Outcome

Case no.	Causality assessment	Type of ADR	Severity	Preventability	Outcome
1.	Probable	Bizarre	ModerateLevel-4A	Probably preventable	Recovered
2.	Probable	Bizarre	Severe Level-5	Probably preventable	Recovered
3.	Probable	Chronic	Moderate Level 4b	Probably preventable	Recovered
4.	Probable	Bizarre	Moderate Level 3	Probably preventable	Recovered
5	Probable	Augmented	Mild Level 3	Probably preventable	Recovered
6	Probable	Bizarre	Moderate Level 3	Probably preventable	Recovered

DISCUSSIONS

Escitalopram is an SSRI approved by FDA in 2002 for the treatment of major depressive disorder [4,19].It is an active S-enantiomer of citalopram that causes increased ADH secretion leading to SIADH.[19] This case series underlines 6 case reports focusing on the different adverse effects of Escitalopram.

Case Report -1 depicts Escitalopram induced hyponatremia which accounts for approximately 2.96 % of all cases reported to the Uppsala Monitoring Centre (UMC) under the World Health Organization (WHO) initiative for worldwide drug monitoring[13]. This case of Escitalopram induced hyponatremia (WHO UMC ID: IN-IPC-300815228) was reported by our AMC. The causality was determined as probable using the WHO-UMC causality assessment scale, and the type of ADR was determined to be type B (Bizarre ADR) using the Rawlins-Thompson classification. The severity was assessed by Modified Hartwig's scale and was found to be level 4A, and the outcome of the reaction was determined by WHO criteria as "recovered." The ADR was found to have been probably preventable according to the Schumock and Thornton Scale.

Case Report -2 depicts Escitalopram induced hyponatremia which accounts for approximately 2.96 % of all cases reported to the UMC under the WHO initiative for worldwide drug monitoring [13]. This case of Escitalopram induced hyponatremia (WHO –UMC ID: IN- IPC -300844356), was reported by our AMC. The causality was determined as probable using the WHO-UMC causality assessment scale, and the type of ADR was determined to be type B (Bizarre ADR) using the Rawlins-Thompson classification. The severity was assessed by Modified Hartwig's scale and was found to be level 5, and the outcome of the reaction was determined by WHO criteria as "recovered." The ADR was found to have been probably preventable according to the Schumock and Thornton Scale.

Case Report -3 depicts Escitalopram induced hyponatremic encephalopathy which accounts for approximately 0.004 % of all cases reported to the (UMC) under the (WHO) initiative for worldwide drug monitoring [13]. This case of Escitalopram induced hyponatremic encephalopathy (WHO –UMC ID: IN- IPC -300662147), was reported by our AMC. The causality was determined as probable using the WHO-UMC causality assessment scale, and the type of ADR was determined to be type B (Bizarre ADR) using the Rawlins-Thompson classification. The severity was assessed by Modified Hartwig's scale and was found to be level 4B, and the outcome of the reaction was determined by WHO criteria as "recovered." The ADR was found to have been preventable according to the Schumock and Thornton Scale.

Case Report -4 depicts Escitalopram induced Parkinsonism which accounts for approximately 0.24% of all cases reported to the UMC under the WHO initiative for worldwide drug monitoring.[13] This case of Escitalopram induced Parkinsonism (WHO –UMC ID: IN- IPC -300841398), was reported by our AMC. The causality was determined as probable using the WHO-UMC causality assessment scale, and the type of ADR was determined to be type C (Chronic ADR) using the Rawlins-Thompson classification. The severity was assessed by Modified Hartwig's scale and was found to be level 3, and the outcome of the reaction was determined by WHO criteria as "recovered." The ADR was found to have been probably preventable according to the Schumock and Thornton Scale.

Case number 5, depicts tremulousness which accounts for 3.80% of all cases reported to the UMC under the WHO initiative for worldwide drug monitoring [13]. The WHO-UMC ID of this report submitted by our AMC was IN-IPC 300997398. The causality was determined to be probable using the WHO-UMC causality assessment scale, the type of ADR was found to be Type A (Augmented ADR) using the Rawlins-Thompson classification, the seriousness was determined using WHO criteria as "prolonged/initial hospitalization," the severity defined by Modified Hartwig's scale was at level 3. The reaction's outcome was determined by the WHO criteria as "recovered.". The reaction was observed to be probably preventable according to Schumock and Thornton Scale. Case number 6, is an example of visual hallucinations which accounts for 0.35% of all cases reported to the UMC under the WHO initiative for worldwide drug monitoring [13]. The WHO-UMC ID of this report submitted by our AMC was IN-IPC 300918004. The causality was determined to be probable using the WHO-UMC causality assessment scale, the type of ADR was found to be Type B (Bizarre ADR) using the Rawlins-Thompson classification, the seriousness was determined using WHO criteria as "other medically important," the severity defined by Modified Hartwig's scale was at level 3. The reaction's outcome was determined by the WHO criteria as "recovered.". The reaction was observed to be probably preventable according to Schumock and Thornton Scale.

CONCLUSION

Although SSRIs are beneficial, the adverse reactions are more prevalent than those listed in the literature documents. Health professionals should focus on collecting previous patient history regarding exposure to drugs

and proper medication adherence. They should also focus on the management of these ADRs with proper documentation.

CONFLICT OF INTEREST

Conflict of interest declared none.

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