Escitalopram Induced Serotonin Syndrome: A Case Report

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ABSTRACT

Escitalopram is a selective serotonin reuptake inhibitor (SSRI) and S-enantiomer of racemic escitalopram, enhances serotonergic activity in the central nervous system (CNS). It is indicated for the Major depressive disorder and Generalized Anxiety Disorder. It is having SEROTONIN SYNDROME as a major side effect. Other uses are OCD, panic disorder, premenstrual dysphoric disorder, social phobia, depression due to severe trauma and mix anxiety and depressive disorder. A 13 year old female child had complain of headache and the hiccups for that she went to hospital from their she was prescribed with the Tab. CLONAZEPAM (2.5 mg, ½ Tab, hs) and Tab. ESCITALOPRAM (5 mg, ½ Tab, hs) for 4 days and followed by 1 Tab. hs. Patient had completed duration of half tablet of ESCITALOPRAM and took full tablet and after 1-2 hour she developed up rolling of eye balls and involuntary movements of both upper and lower limb. Afterwards she was admitted in ICU. Better vigilance is necessary for implementation of safe and effective treatment for each individual patient. In-order to prevent serious adverse drug reactions of this drug, close monitoring during treatment course, creating awareness, recognition of the problem and careful management of all patients who receive this medication are essential.

Key words: Selective Serotonin Reuptake Inhibitor, Suspected ADR, Escitalopram, Serotonin syndrome.

INTRODUCTION

SSRIs are mainly given for the treatment of Depression. In depression there is a depletion of serotonin level thus the SSRI is given which can affect the level of serotonin or it increase the level of serotonin. Excessive serotonin in at synapse site can aggravate or increase the chance of serotonin syndrome.

Escitalopram is a selective serotonin reuptake inhibitor and an antidepressant. It is mainly used for the Major depressive disorder and Generalized Anxiety Disorder as per the FDA use. Other Non FDA use is also found such as OCD, panic disorder, premenstrual dysphoric disorder, social phobia, depression due to severe trauma and mix anxiety and depressive disorder.[1-5] In patient with mild to moderate impairment of renal dose adjustment is not necessary where as in severe renal impaired condition it should be used with caution. In hepatic impaired patient dose should be 10 mg/day orally and in geriatric patient same dose should be given. Patient can take it without regard of meals. Escitalopram is contraindicated as it increases risk of serotonin syndrome with concomitant use with an MAOI, including linezolid or IV methylene blue, or use of escitalopram within 14 days of discontinuing an MAOI used to treat psychiatric disorders, or use of an MAOi used to treat psychiatric disorders within 14 days of discontinuing escitalopram, cannot be used concomitantly with pimozide and also its use is limited in patient who are having hypersensitivity to citalopram, escitalopram, or any other component of the product.[1]

It is also having black box warning that is Antidepressants increased the risk of suicidal thinking and behaviour in children, adolescents and young adults with Major Depressive Disorder (MDD) and other psychiatric disorders in short-term studies. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults beyond age 24 and there was a reduction in risk with

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antidepressants compared with placebo in adults aged 65 or older. This risk must be balanced with the clinical need. Monitor patients closely for clinical worsening, suicidality, or unusual changes in behaviour. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Not approved for use in paediatric patients less than 12 years of age.[1]

Points which are to be monitores after administration of Escitalopram are as follow:[1]

Sodium levels: Baseline screening and after 3 to 4 weeks in high-risk patients (older than 65 years, previous history of antidepressant-induced hyponatremia, low body weight, concomitant use of thiazides or other hyponatremia-inducing agents); monitor levels regularly in the elderly.

Bipolar disorder: Prior to initiating therapy in patients with depressive symptoms.

Bone mineral density: Consider in patients on long-term therapy, especially in those at-risk (e.g., elderly, women, fracture history, history of falls, low vitamin D, hypogonadism, hyperparathyroidism, thyroid dysfunction, systemic inflammatory disorders, corticosteroid use, physical inactivity, alcohol use and smoking).

Discontinuation symptoms: Particularly with abrupt treatment cessation.

ECG: Consider in high-risk patients.

Serotonin syndrome: Especially if coadministered with other serotonergic drugs Sexual dysfunction.

Weight and growth: In paediatric patients.

Weight gain: Metabolic profile may be advisable to detect early weight gain at 3, 6 and 12 months, then yearly, in all patients (not just in patients who are obese or overweight) and if receiving combination therapy, especially with atypical antipsychotics.

Worsening of depression, suicidality, or unusual changes in behaviour; especially during first few months of therapy or with dose adjustments; at least weekly face-to-face contact with patients or their family members or caregivers during the initial 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks and then as clinically indicated beyond 12 weeks. More frequent monitoring may be required in more severely depressed or suicidal patients.

ADR of Escitalopram is as follow:[1]

System	ADR
	Common
Dermatologic	Diaphoresis (3% to 8%)
Gastrointestinal	Abdominal pain (2%), Constipation (3% to 6%), Diarrhea (6% to 14%), Indigestion (2% to 6%), Nausea (15% to 18%), Vomiting (up to 3%), Xerostomia (4% to 9%)
Neurologic	Dizziness (4% to 7%), Headache (24%), Insomnia (7% to 14%), Somnolence (4% to 13%)
Reproductive	Disorder of ejaculation (9% to 14%), Erectile dysfunction (3%), Orgasm incapacity (females, 2% to 6%), Reduced libido (3% to 7%)
Other	Fatigue (5% to 8%), Withdrawal symptom (56%)
	Serious
Hematologic	Hemorrhage, Abnormal
Psychiatric	Depression, worsening, Suicidal thoughts, Suicide
Other	Serotonin syndrome

The Serotonergic System

Serotonin (5-hydroxytryptamine; 5-HT) is a monoamine neurotransmitter synthesized from the amino acid tryptophan. Small amounts of serotonin are found in the central nervous system; most is located in the platelets and the gastrointestinal tract. Serotonin is stored in vesicles in presynaptic neurons. After release from the vesicles, the transmitter binds to and activates serotonin receptors on postsynaptic membranes. Seven classes of serotonin receptors (and many subtypes) exist and the activation of these receptors by serotonin, the subsequent modulation of cellular processes and the functions of serotonin are numerous, complex and not completely understood.[2,3] In the central nervous system, serotonin helps regulate functions such as appetite, memory, mood and sexual activity; peripherally it helps regulate clotting, peristalsis and vascular tone.

Serotonin is a compound present in blood platelets and serum, which constricts the blood vessels and acts as a neurotransmitter. Serotonin plays the significant role in body as 80-90 % serotonin is produced in GI tract. But serotonin which is utilised in brain is supposed to be produced within it. It affects mood and social behaviour, appetite and digestion, sleep, memory and sexual desire and function. Serotonin Syndrome is a drug induced syndrome characterised by a cluster of dose related adverse effects that are due to increased serotonin concentrations in the central nervous system. It

mainly occur when the combination of the two or more serotonergic drug has been given. We can say the most culprit drug is MAOI.[1] It is a potentially life-threatening syndrome that is precipitated by the use of serotonergic drugs and overactivation of both the peripheral and central postsynaptic 5HT-1A and most notably, 5HT-2A receptors. This syndrome consists of a combination of mental status changes, neuromuscular hyperactivity and autonomic hyperactivity.[4]

Drug which are responsible for the causing Drug induced Serotonin Syndrome are as follow:[4,5]

- SSRIs
- SNRIs
- Bupropion
- Tricyclic Antidepressants
- MAOIs
- Anti-Migraine Medications
- Pain Medications
- Lithium
- Illicit Drugs
- Herbal Supplements
- OTC Medications
- Anti-Nausea Medications
- Linezolid
- Ritonavir

Management of Serotonin Syndrome

Management of Serotonin Syndrome is done according to its stages. Cyproheptadine, chlorpromazine and olanzapine, all of which are capable of blocking 5-HT2A receptors, have exhibited excellent efficacy in the setting of serotonin syndrome.[6] Serotonin Syndrome is also having different severity stages and all stages are having different treatment. Which are as following:

Management[7]		
Stages	**Symptoms**	**Treatment**
Mild	Mild hypertension, tachycardia, mydriasis, diaphoresis, shivering, tremor, myoclonus, hyperreflexia	Discontinue the offending agent/agents Support via stabilizing vital signs, cooling measures Mild agitation, fever, hypertension and tachycardia: benzodiazepines (diazepam) Observe for at least 6 h
Moderate	Above plus temperature of at least 408°C, hyperactive bowel sounds, ocular clonus, agitation, hypervigilance, pressured speech	All of the above Severe agitation and hyperthermia: 5HT-antagonist (cyproheptadine) Admission to hospital for cardiac monitoring and observation
Severe	Above plus temperature greater than 41.18°C, dramatic swings in pulse rate and blood pressure, delirium, muscle rigidity.	All of the above Severe hypertension/ tachycardia: esmolol or nitroprusside, Sedation and paralysis with a nondepolarizing agent and intubation/ventilation Admission to the intensive care unit.

Case

A 13 year old female child came to Hospital with complain of up rolling of eye balls and involuntary movement of both upper and lower limb.

Before 1 month patient was having complain of hiccups and headache. For that they went tertiary care hospital for diagnosis where she was prescribed with Tab. CLONAZEPAM (2.5 mg, ½ Tab, hs) and Tab. ESCITALOPRAM (5 mg, ½ Tab, hs) for 4 days and followed by 1 Tab. hs. Patient had completed duration of half tablet of ESCITALOPRAM and took full tablet and after 1-2 h she developed up rolling of eye balls and involuntary movements of both upper and lower limb. Afterwards she was admitted in ICU.

Consequently she has given some symptomatic treatment which is listed below in table:

Treatment given here in present Hospital is as follow:

Days	Ward	Treatment Given
Day 1	NEURO TO ICU	Inj. 0.9% DNS (Dextrose Normal Saline) (65 ml/h) Inj. PANTOP (Pantoprazole) (40 cc) (OD), Inj. EMSET (Ondansetron) (1 cc) (OD), Inj. MIDAZ (Midazolam) (2 cc upto 5 cc)
Day 2 to Day 4	ICU	Previous medications were stopped. Tab. RISDON MT (Resperidone) (0.5 mg)(1/2 hs f/b 1 h) Tab. CLONAM (Clonazepam) (0.25 mg) (1/2-0-1 (h)) Tab. PANTOP (Pantoprazole) (40 mg) (1-0-0) Tab. EMSET (Ondansetron) (8 mg) (1 tab sos) Tab. MVBC (Multivitamin/B-Complex) (0-1-0) Tab. CIPLACTIN (Cyproheptadine) (4 mg stat then 2 mg q4h) From day 3

Day 5 to Day 9	ICU	Tab. CLONAM (Clonazepam) (0.25 mg) (1/2-0-1 (h)) Tab. CIPLACTIN (Cyproheptadine) (4 mg stat then 2 mg q4h) Other medications were stopped. Tab. NAXDON (Neproxen) (From Day 7) (250 mg) (1 tab sos) Tab. LEVIPIL (Levitarcetam) (250 mg) (1-0-1) (From Day 8)
Day 10 to Day 14	ICU TO PSYCHIATRY	Previous medication were continued. Tab. OLENAZ (Olanzepine) (2.5 mg)(1/2-0-1/2) Tab. LOPEZ MD (Lorazepam) (1 mg) (1/2-1/2-1) Inj. Haloperidol + Inj. Promethazine (1/4 amp) (IM Stat) (On Day 11 and Day 12)

On day 14 she was discharged as her condition was recovered completely. Discharged medication were rational which is described in following Table:

Drug (Brand Name)	Generic Name	Dose	Freq.	Indication
Tab. Olapad	Olanzepine	2.5 mg	1/2-0-1/2	For Serotonin Syndrome
Tab. Lopez-MD	Lorazepam	1 mg	1/2-1/2-1(Hs)	To calm patient

Causality Assessment

Causality and severity assessment has done with the help of five different scales and results are following:

Scale's Name	Result
WHO	Probable
NARANJO'S ALGORITHM	Probable
SHUMOCK AND THRONTON	Preventable
KARCH AND LASAGNA	Probable
HARTWIGS AND SIEGEL	Moderate (Level 4(b))

CONCLUSION

Better vigilance is necessary for implementation of safe and effective treatment for each individual patient. In-order to prevent serious adverse drug reactions of this drug, close monitoring during treatment course, creating awareness, recognition of the problem and careful management of all patients who receive this medication are essential. And for some signs of serotonin syndrome should be counselled to patients care giver or parents.[8]

Strength of the study: The present study reviews the prescribing pattern for Escitalopram Induced Serotonin Syndrome. The study can be utilized by the researchers in direct to carry out the same at larger sample size.

Controversies: No controversies were raised while collecting and reporting the ADR to the AMC.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

5-HT Antagonist: 5-hydroxytryptamine antagonist; **ADR:** Adverse Drug Reactions; **AMC:** Adverse Drug Reaction Monitoring Centre; **FDA:** Food and Drug Administration; **hs:** Hora Somni(at bedtime); **ICU:** Intensive Care Unit; **IM:** Intramuscular; **Inj.:** Injection; **MAOI:** Monoamine Oxidase inhibitors; **MDD:** Major Depressive Disorder; **mg:** Milligram, **MVBC:** Multi Vitamins + B-Complex; **OCD:** Obsessive Compulsive Disorder; **OTC Medication:** Over The Counter Medications; **SNRIs:** Serotonin and norepinephrine reuptake inhibitors; **SSRIs:** Selective serotonin reuptake inhibitors; **stat:** Statum (immediately); **Tab.:** Tablets.

SUMMARY

Drug induced ADRs are a preventable event that at some extent if it does not meet serious criteria.If medications are given under observations of the healthcare professional and patient, there will be fewer chances for such type of incidences. Clinical Pharmacists possess valuable role in this, as they are aware about all possible and probable ADRs in patients. With their background in assessing and resolving Drug induced ADRs, they are in a distinctive position of being appropriate initiators of a management of ADRs.

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