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CLINICO-BIOCHEMICAL STUDY OF SAFETY AND TOLERABILITY OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) IN A TERTIARY MEDICAL COLLEGE IN WEST BENGAL

Biochemistry

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ABSTRACT

INTRODUCTION: Selective serotonin reuptake inhibitors (SSRIs) are a class of drugs that selectively increase the levels of serotonin in the synaptic cleft by blocking its uptake by serotoninergic neurons. They are now extensively used to treat various psychiatric disorders like depression, panic disorders, obsessive compulsive disorders and are now being evaluated in the treatment of a number of other psychiatric disorders like bulimia nervosa and social phobia. In this scenario we try to elucidate the serum electrolyte level, serum serotonin level, renal function test and platelet count to check out the changes as in different papers demonstrated that there are variations in different parameters of renal function occurred with chronic administration of SSRI.

Objectives: To evaluate serum electrolyte level, serum serotonin level, renal function tests and platelet count of patients with major depressive disorder on chronic SSRI therapy and screen for any adverse drug reactions (if any)

Materials and Methods: A cross-sectional observational study conducted in the Department of Psychiatry, Department of Biochemistry and Department of Pharmacology of Medical College and Hospital, Kolkata . The study protocol was approved by the Institutional Ethics Committee. Written consent was obtained from the subjects included in the study.

Results and Discussion: After evaluating the biochemical parameters, it was observed that long term (more than 6 months) SSRI therapy can cause decline Platelet count (29.76%) and Serum Sodium Levels i.e. Hyponatremia (29.76%); whereas the serum serotonin levels (17.86%) were found to be elevated. Further, a negative correlation of -0.605 was observed between the serum sodium levels (in subjects with hyponatremia) and the duration for which the subjects were taking SSRI whereas a positive correlation of +0.407 was observed between the serum serotonin levels (in subjects with above normal serum serotonin levels) and the duration for which the subjects were taking SSRI.

A number of adverse drug effects were reported. 28 subjects (33.33%) reported at least any one of the following symptoms like Headache, Sedation, Dizziness, Anxiety, Agitation. 12 subjects (14.28%) reported having recurring suicidal thoughts. 21 subjects (25.00%) reported GIT Problems like nausea/ vomiting/ constipation/ dyspepsia. 13 subjects (15.48%) reported reduction in sleep time while 20 subjects (23.81%) reported reduction in appetite. Sexual Problems like decreased libido, ejaculation difficulty or impotence was reported by 19 subjects (22.62%). 25 subjects (29.76%) reported that they had gained weight after the therapy. Discontinuation Symptoms were reported by 59 subjects (70.24%).

Conclusion: The hemogram of patients on SSRI therapy should be monitored from time to time and their biochemical parameters should be evaluated to prevent any untoward adverse effects in the subjects. The patients on SSRI therapy should be closely monitored for adverse effects like sexual problems, GIT problems, CNS manifestations, suicidal thoughts, discontinuation symptoms among others.

KEYWORDS

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are a class of drugs that selectively increase the levels of serotonin in the synaptic cleft by blocking its uptake by serotoninergic neurons [1]. They are now extensively used to treat various psychiatric disorders like depression, panic disorders, obsessive compulsive disorders and are now being evaluated in the treatment of a number of other psychiatric disorders like bulimia nervosa and social phobia [1].

Depression is a common form of mood disorder. In the most recent surveys, major depressive disorder (MDD) has the highest lifetime prevalence (almost 17%) of any psychiatric disorder [2]. The prevalence of depression in India as observed in previous studies varies from 1.8% (severe) to 39.6% (mild to moderately severe), depending on study methods [3-8].

The primary indication of antidepressant agents is the treatment of MDD [2]. The use of specific pharmacotherapy along with psychotherapy approximately doubles the chance that a depressed patient will recover in 1 month [2].

Numerous classes of antidepressants are available, many with different mechanism of action, represents indirect evidence for heterogeneity of putative biochemical lesions [2]. Currently, SSRIs are frequently prescribed agents. There are six available SSRIs most common antidepressants in clinical use, they are - Fluoxetine, sertraline, citalopram, paroxetine, fluvoxamine and escitalopram [9].

SSRIs are often recommended as first-line antidepressants because of their relatively benign safety profile higher toxic dose & few mild side effects. However, adverse effects are increasingly being reported nowadays.

Hyponatraemia is known to be a relatively frequent form of electrolyte disturbance amongst psychiatric patients [10-12] undergoing SSRI therapy. Hyponatraemia can cause significant morbidity, such as lethargy, headache, confusion, convulsions, coma, and can occasionally cause death [13, 14]. The clinical symptoms of hyponatraemia are, however, variable and depend mainly on its severity and abruptness of onset. Hyponatremia is defined as the serum sodium less than 135 mmol/L.

Serotonin syndrome is typically caused by the use of two or more serotonergic medications or drugs [10]. This may include selective serotonin reuptake inhibitor (SSRI) among others. Symptoms include high body temperature, agitation, increased reflexes, tremor, sweating, dilated pupils, and diarrhea. Body temperature can increase to greater than 41.1 °C (106.0 °F). Complications may include seizures and extensive muscle breakdown [15]

Major depressive disorder (MDD) is prevalent among patients with chronic kidney disease (CKD) and is associated with morbidity and mortality. The efficacy and adverse events of selective serotonin reuptake inhibitors in these patients are unknown [16].

Now in recent years one important parameter coming into the picture is platelet because blood Serotonin is normally stored in platelet. More over Platelet shares a common mechanism of release and uptake of

serotonin as also observed in nerve endings. So it's worthwhile to take platelet count in to our account to determine whether there is any significant contribution of platelet in the study [17].

OBJECTIVES:
To evaluate serum electrolyte level, serum serotonin level, renal function tests and platelet count of patients with major depressive disorder on chronic SSRI therapy and screen for any adverse drug reactions (if any)

MATERIALS AND METHODS
TYPE OF STUDY AND STUDY DESIGN:
The proposed study was a prospective, prescription event monitoring (PEM) study, therefore was a non-interventional, observational cohort form of study by nature. The patients were investigated for clinical signs & symptoms of ADRs due to SSRIs.

ETHICAL CONSIDERATION:
Prior permission for the study was taken from the due authorities, namely the Principal, the Medical Superintendent and Vice Principal and the *Institutional Ethics Committee*. Ethical clearance certificate was dated 30/04/2019.Ref no :MC/KOL/IEC/NON-SPON/360/04-2019.ICMR Ref id: 2019-09661.

The present piece of work had a clinical component and a biochemical component. The clinical part was a non-interventional, observational cohort form of study whereby the nature, magnitude and extent of SSRI - induced adverse reactions was investigated by regular monitoring and by using pre-designed questionnaire and through structured interview of 84 patients of major depressive disorder in psychiatry OPD who were on SSRI treatment. The biochemical part was an assessment of relevant biochemical parameters like serum electrolytes (Na+/K+), serum serotonin levels and renal function test (urea). Attempts were made to understand the correlation between the clinical findings and biochemical studies. Appropriate statistical methods were followed for investigational analysis.

STUDY POPULATION:
A. Clinical Part - Patients attending the psychiatry out-patient department receiving either of the four SSRIs- fluoxetine, paroxetine, escitalopram, sertraline for an optimum duration of 6 months or more

B. Biochemical Part - Biochemical parameters of patients reporting adverse effects following SSRI therapy.

SAMPLE SIZE:
Leveraging upon the previous studies from published literature [17], Prevalence of anxiety (as side effects) = 48% [17] and considering attrition rate = 10%, Sample Size = 84.

DURATION OF STUDY: 2 months, From 16/05/19 to 10/07/19

INCLUSION & EXCLUSION CRITERIA FOR CLINICAL PART:

INCLUSION CRITERIA:
Patients >18 years of age who have consumed the SSRI drugs for 6 months or more

EXCLUSION CRITERIA:
Patients < 18years of age who have major systemic alignment according to physician's discretion and also who are unable to understand the procedure and hence refuse to provide informed consent.

LABORATORY INVESTIGATIONS:
Blood collected from clinical population for

1. Electrolytes (Na^+/K^+): Estimation done by ISE Roche Electrolyte Analyser
2. Serotonin Level estimation: By ELISA method.
3. Renal function test (urea): Done by Berthelot method in Auto Analyser
4. Platelet count: By Haematology Cell Counter

STATISTICAL ANALYSIS:
The study specific data was collected in a case record form (CRF). The data from the CRF was transcribed onto an excel database and analysed using *SPSS* statistical software.

RESULT
Table 1 Biochemical parameters in different age groups

Parameters	18-35age group	36-55 age group	more than 55 age group	Total
Hyponatremia				
Male	0(0.00%)	6(60.00%)	4(40.00%)	10
Female	7(46.67%)	6(40.00%)	2(13.33%)	15
High serotonin				
Male	0(0.00%)	5(83.33%)	1(16.66%)	6
Female	6(66.67%)	1(11.11%)	2(22.22%)	9
High Serum Urea				
Male	5(14.70%)	11(32.35%)	18(52.94%)	34
Female	12(31.57%)	20(52.63%)	6(15.78%)	38
Low platelet Count				
Male	3(16.67%)	9(50.00%)	6(33.33%)	18
Female	1(14.28%)	5(71.42%)	1(14.28%)	7

The serum sodium level was found to be low (hyponatremia) in 25 subjects, 10 males and 15 females (considering the normal serum sodium level to be 135-145 mEq/L [the reference range value was provided by the laboratory]).Out of the 10 males 6 were from the age group 36-55 years and 4 from the age group greater than 55 years. Further, all of them were prescribed escitalopram. Similarly, out of the 15 females, 7 were from the Age group 18-35 years, 6 from the age group 36-55 years and 2 from the age group greater than 55 years. Further, 12 of them were prescribed escitalopram and 3 of them were taking sertraline.

The serum serotonin level was found to be high in 15 subjects, 6 males and 9 females (considering the normal serum serotonin level to be 70-270 ng/mL [the reference range value was provided by the laboratory]). Out of the 6 males, 5 were from the age group 36-55 years and 1 from the age group greater than 55 years. Further, all of them were prescribed escitalopram.

Out of the 9 females, 6 were from the Age group 18-35 years, 1 from the age group 36-55 years and 2 from the age group greater than 55 years. Further, 6 of them were prescribed escitalopram and 3 of them were taking sertraline.

The serum urea levels were found to be high in 72 subjects, 34 males and 38 females (considering the normal serum urea level to be 5-20 mg/dl). Out of the 34 males 5 were from the age group 18-35 years, 18 from the age group 36-55 years and 11 from the age group greater than 55 years. Further, 27 of them were prescribed escitalopram, 4 of them were taking fluoxetine and 3 of them were taking sertraline. Out of the 38 females, 12 were from the Age group 18-35 years, 20 from the age group 36-55 years and 6 from the age group greater than 55 years. Further, 25 of them were prescribed escitalopram, 11 of them were taking sertraline and 2 of them were taking fluoxetine.

The platelet count was found to be low in 25 subjects, 18 males and 7 females (considering the normal platelet count to be 150-450 thousand/mm^3 [the reference range value was provided by the laboratory]). Out of the 18 males, 3 were from the Age group 18-35 years, 9 from the age group 36-55 years and 6 from the age group greater than 55 years. Further, 14 of them were prescribed escitalopram, 3 of them were taking fluoxetine and 1 of them was taking sertraline. Similarly, out of the 7 females, 1 was from the Age group 18-35 years, 5 from the age group 36-55 years and 1 from the age group greater than 55 years. Further, 5 of them were prescribed escitalopram and 2 of them were taking sertraline.

All the patients who met the inclusion criteria were analysed. This included all 84 patients randomized into four treatment arms. During the study period, a total of 78 subjects were suspected of having at least one adverse drug reaction (ADR). On causality assessment, 9 of these 78 cases were considered to have insufficient evidence about causality (WHO-UMC causality status "unlikely" [24]) and they were excluded from further analysis. From the remaining 69 subjects, 198 ADRs were tabulated. Thus 82.14% of study subjects reported ADRs with at least "possible" causality.

Causality assessment revealed that 146 ADRs (73.74%) belonged to "probable" category, whereas 52 (26.26%) were of "possible" type according to the WHO-UMC Scale. No case was labelled "certain" as rechallenge was not attempted by the psychiatrist, once a drug was

withdrawn. Overall, out of the 198 ADRs from 69 subjects - 6 subjects (8.70%) in the fluoxetine arm, 0 subjects (0.00%) in the paroxetine arm, 55 subjects (79.71%) in the escitalopram arm and 8 subjects (11.59%) in the sertraline arm reported at least one event.

The suspected ADR profiles are listed in Table2

General Adverse Events	Fluoxetine (n=6)	Escitalopram (n=63)	Sertraline (n=15)
Headache/Sedation/Dizziness/Anxiety/Agitation	3 (50.00%)	20 (31.75%)	5 (33.33%)
Suicidal thoughts	2 (33.33%)	8 (12.70%)	2 (13.33%)
GIT Problems like nausea /vomiting/ constipation/ dyspepsia	1 (16.67%)	20 (31.75%)	0 (0.00%)
Sleep Pattern (reduced sleep time)	0 (0.00%)	7 (11.11%)	6 (40.00%)
Appetite(reduced)	1 (16.67%)	17 (26.98%)	2 (13.33%)
Sexual Problems like decreased libido/ejaculation difficulty/impotence	1 (16.67%)	14 (22.22%)	4 (26.67%)
Weight Gain	3 (50.00%)	18 (28.57%)	4 (26.67%)
Dermatological manifestations	0 (0.00%)	1 (1.59%)	0 (0.00%)
Discontinuation Symptoms	2 (33.33%)	44 (69.84%)	13 (86.67%)

ANALYTICAL STATISTICS -

The study specific data was collected in a case record form (CRF). The data from the CRF was transcribed onto an excel database and analyzed using SPSS statistical software.

Two important conclusions were drawn –

1. A negative correlation of -0.605 was observed between the serum sodium levels (in subjects with hyponatremia) and the duration for which the subjects were taking SSRI.

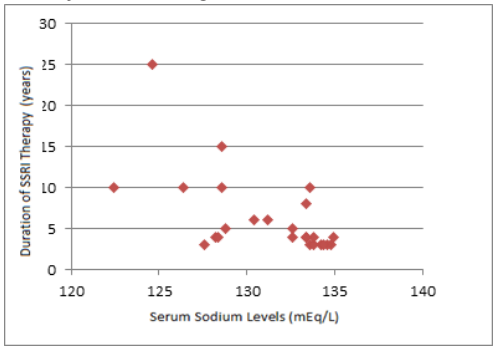

Figure1: Scatter diagram showing negative correlation between the serum sodium levels (in subjects with hyponatremia) and the duration for which the subjects were taking SSRI

2. A positive correlation of +0.407343 was observed between the serum serotonin levels (in subjects with above normal serum serotonin levels) and the duration for which the subjects were taking SSRI.

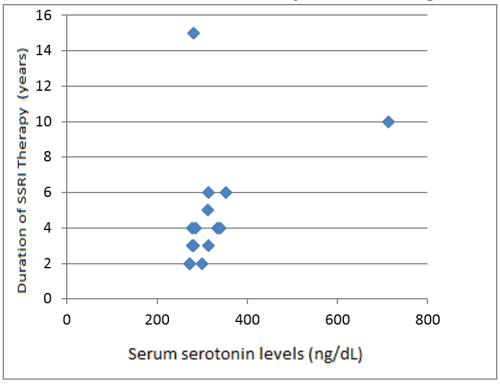

Figure2: Scatter diagram showing positive correlation between the serum serotonin levels (in subjects with above normal serum serotonin levels) and the duration for which the subjects were taking SSRI

DISCUSSION

It was observed in our study that long term SSRI therapy can cause Hypernatremia [a negative correlation of -0.6052 was observed between the serum sodium levels (in subjects with hyponatremia) and the duration for which the subjects were taking SSRI]. We can opine that it is not only that SSRI causes Hyponatremia but also it is duration dependent so long term therapy with SSRI should be avoided as far as possible unless proven risk benefit ratio is there. This is supported by Susan Jacob , Sarah A Spinler in their study Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults, PMID: **16896026** DOI: 10.1345/aph.1G293

Another important fact is coming out of our study which states that long term SSRI therapy can also cause elevated serum serotonin levels [a positive correlation of +0.4073was observed between the serum serotonin levels (in subjects with above normal serum serotonin levels) and the duration for which the subjects were taking SSRI]. Now this is a major concern as many groups of drugs can elevate serotonin level and if given along with SSRI for a long duration can precipitate one dreaded clinical c by Jacqueline Volpi-Abadie, MD,[*] Adam M. Kaye, PharmD, FASCP, FCPhA,[†] and Alan David Kaye, MD, PhD[‡] in their study on serotonin syndrome published in The OSCHNER journal in 2013, PMCID: PMC3865832, PMID: 24358002

Our third major finding is the platelet count found to be low in 25 subjects (29.76%). This can explain the bleeding manifestations reported by few subjects. Reported cases of abnormal bleeding were associated with fluoxetine treatment, accompanied by a decrease in ADP, epinephrine, ristocetin, AA, collagen, and epinephrine induced platelet aggregation, respectively, which were reversible after discontinuation of the drug (positive dechallenge) found in the study of Citalopram-induced bleeding due to severe thrombocytopenia by Frank Andersohn , Christine Konzenondition known as Serotonin Syndrome;Frank Andersohn , Christine Konzenondition, Elisabeth Bronder, Andreas Klimpel, Edeltraut Garbe PMID: **1956777** DOI: 10.1176/appi.psy.50.3.297

Sexual Problems like decreased libido, ejaculation difficulty, and impotence was reported by 19 subjects (22.62%). Hence SSRIs should be used with caution in the reproductive age group. Sexual dysfunctions such as low libido, anorgasmia, genital anesthesia, and erectile dysfunction are very common in patients taking selective serotonin reuptake inhibitors (SSRIs). It has been assumed that these side effects always resolve after discontinuing treatment as documented by a study on Persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors Antonei B Csoka, Audrey Bahrick, Olli-Pekka Mehtonen PMID: 18173768 DOI: 10.1111/j.1743-6109.2007.00630.x

12 subjects (14.28%) reported having recurring suicidal thoughts. In depth interviews should be arranged to address this issue.

21 subjects (25.00%) reported GIT Problems like nausea, vomiting, constipation, dyspepsia. 28 subjects (33.33%) reported Headache, Sedation, Dizziness, Anxiety, Agitation. 25 subjects (29.76%) reported that they had gained weight after the therapy. Hence alternative medications should be used in obese subjects. 13 subjects (15.48%) reported reduction in sleep time while 20 subjects (23.81%) reported reduction in appetite. These results are again posted to enlighten the importance of alternative therapy.

Discontinuation Symptoms were reported by 59 subjects (70.24%). This is also a major concern and needs to be explored in further study and more follow up is needed. Hence, SSRIs should not be abruptly stopped in patients who have been on medication for a period of 6 months or more.

Last but not the least we should also focus on the fact that is it is the female pre ponderous seen in lower age groups while males are more affected in higher age group as compared to female. Now the causality may be checked in further studies.

CONCLUSION(s)

The hemogram of patients on SSRI therapy should be monitored from time to time and their biochemical parameters should be evaluated to prevent any untoward adverse effects in the subjects. The patients on SSRI therapy should be closely monitored for adverse effects like sexual problems, GIT problems, CNS manifestations, suicidal

thoughts, and discontinuation symptoms among others. All such ADRs should be reported to update the data base and benefit the community at large by keeping it informed of the possible ADRs SSRIs can cause.

Patient Hospital ID -

Questionnaire For Assessment Of ADR Potential Of SSRIs			
Number	**Questions**	**Yes**	**No/NA**
1.	Do you know why you are taking this medication?		
2.	Does your mouth turn dry or do you sweat profusely ?		
3.	Do you suffer from headache/ sedation/ dizziness/ tremor/ anxiety/ agitation?		
4.	Is there any unusual sensory perception like tingling/ pricking/ chilling/burning/numb sensation on the skin?		
5.	Have you ever experienced blurring of vision?		
6.	Do you find life unsatisfactory/too demanding/boring?		
7.	Do you suffer from any gastrointestinal problems like nausea/ diarrhea/constipation/dyspepsia?		
8.	Do you suffer from muscle pain/tenderness?		
9.	Has there been any abnormal bleeding episodes like epistaxis/ hemoptysis/hematuria/melena?		
10.	Have you experienced any difficulty in movement and locomotion?		
11.	Is you sleep pattern normal/regular ?		
12.	Is your appetite normal/regular ?		
13.	Do you suffer from any sexual problems like decreased libido/ ejaculation difficulty/impotence ?		
14.	Do you have any urinary problems?		
15.	Has there been any dermatological manifestations		
16.	Do you have persistent cough/shortness of breath/wheezing?		
17.	Have you suddenly, inappropriately and undesirably lost /gained weight?		
18.	Do you have chest pain/swollen ankles/altered blood pressure/altered heart rate?		
19.	If your menstrual cycle normal/regular?		
20.	Has there been any discontinuation syndrome?		

N.B. - ALL THE ADVERSE EFFECTS APPEARING EXCLUSIVELY AFTER SSRI THERAPY SHOULD BE REPORTE

Signature Of Principal Investigator:	Signature Of Co Investigator:
Date - ...../...../.....	Date - ...../...../.....

LIMITATION(s)

Though this work has been done meticulously but follow up should be done for a long period which may help other researchers to bring about the side effects which may not show in short term. More samples can be introduced to make the study more fruitful which may be lacking in our form of study. Last but not the least this study may become the helping hand to the researchers who are looking for alternatives to SSRI from the dreaded side effects associated with this as anti-depressant mono therapy point of view.

Conflict of Interest: No Such

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