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Antipsychotic Induced Hyperprolactinemia and Menstrual Disorders in Women—A Cross-Sectional Study

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Abstract:

Introduction: *Pharmacologic hyperprolactinemia and it's effects on women's menstrual function is a problem of underestimated prevalence. This is due to lack of awareness,lack of externally visible symptoms & patients reluctance to inform doctor.A large group of medications can raise prolactin level especially FGA'S,among SGA'S risperidone,amisulpride and some of antidepressants,like amitriptyline, sertraline, fluoxitineetc Antipsychotic – induced hyperprolactinemiaisthought to account for high rates of menstrual dysfunction.*

Aims: *The aim of this cross-sectional study is to assess antipsychotic induced hyperprolactinemia and the menstrual dysfunction that affects quality of life and therapeutic compliance of women.*

Method:*60 subjects attending outpatient dept. in Govt.Hospital for Mental Carewere recruitedfor this cross-sectional study.The subjects having other risk factors for hyperprolactinemia and menstrual dysfunction were excluded. Factors investigated in this study were age,maritalstatus,diagnosis,duration of illness and medication,type of medication used and h/o menstrual abnormality.*

Results:*Significant elevation of serum prolactin and menstrual dysfunction were observed in this study.Factors that influenced the risk of hyperprolactinemiawere,dose of antipsychotics and type of medication used.FGA's,polypharmacy,among SGA'S risperidone and amisulprideshowed high incidence of hyperprolactinemia when compared with olanzapine. Patients of all agesdemonstrated sensitivity to increased prolactin almost equally.*

Interpretation & conclusion:*Diverse prevalence rates of hyperprolactinemia and menstrual dysfunctions were observed among the patients on different medication in this cross-sectional study.Different studies also supported this finding.Menstruation plays an important role in women,thus understanding, careful assessment, mono-drug therapy especially with prolactin-sparing antipsychotics may improve patients quality of life and therapeutic compliance.*

Keywords: *antipsychotics, hyperprolactinemia,menstrual dysfunction.*

FGA'S-first generation antipsychotics.SGA'S-second generation antipsychotics.PRL-prolactin

I. Introduction

Hyperprolactinemiais an important but neglected adverse effect of antipsychotic medication.It occurs frequently with FGA'S and some SGA'S like risperidone,amisulpride but rarely with other SGA'S.For this reason the terms 'prolactin-sparing'and 'prolactin-raising' are more suitable thanFGA'S and SGA'S when considering the effect of antipsychotics on serum prolactin.During antipsychotic treatment, prolactin level can raise 10- fold or more above pretreatment values. Some symptoms of hyperprolactinemia result from a direct effect of prolactin on target tissuebut others result from hypo-gonadotropic - hypogonadism caused by prolactin, which disrupts the normal functioning of the hypothalamic-pituitary-gonadal axis,there by inhibiting the normal pulsatile secretion of GNRH, this leads to decreased secretion of LH and FSH, this in turndecrease oestrogen and progesterone secretionand leads to menstrual dysfunction, Galactorrheaetc. Another concern is that,

decreased gonadal steroid secretion will lead to premature osteoporosis. Some subjects with hyperprolactinemia have no symptoms.

To understand mechanism of antipsychotic- induced hyperprolactinemia, it is important to know how prolactin secretion regulated and how antipsychotics influence prolactin secretion.PRLsecretion from lactotrophs of the anterior pituitary is controlled by stimulatory as well as inhibitory factors.The important factor that controls PRL secretion is Dopamine,the prolactin inhibitory factor(PIF).Dopamine stimulates D2 receptors located on the surface of the lactotroph pituitary cells and provokes a tonic suppression on prolactin secretion.Whereas,serotonin stimulates prolactinrelease.Inaddition, neuropeptides such as TRH, oxytocin,vasoactiveintestinalpolypeptide and peptidehistidine-methionine,which are under the control of serotonin, promotes PRL secretion.

Antipsychoticsinduceshyperprolactinemia by various mechanisms. FGA'S block non selective dopamine D2 receptors in all regions of the brain,there by removes inhibitory affect on prolactin secretion, a fact that raises plasma prolactin levels.SGA'S are serotonin-dopamine antagonists(SDA'S),while FGA'S are potent D_2 antagonists with low affinity for D1 receptorsand no significant serotonergic effects. Risperidone, although it belongs to SGA'S,shows a high affinity with $5HT_2A$,$5HT_7$,alpha1,H_1,D_2,alpha2&$5HT_2$ D, receptors and does not completely cross the blood-brain barrier,as a result, it binds longer and heavier with D2 receptors in the pituitary rather than the striatum, thereby increasing prolactin levels. Where as olanzapine binds intermediately withD_2receptors and more tightly with $5HT_2$at all doses. So hyperprolactinemia with olanzapine is rare.Amisulpride increases prolactin level even in low doses, because of preferential action on limbic D2/D3 receptors and preferential blockade of presynaptic D2/D3 receptors.

Thus it is ideal to use prolactin-sparing antipsychotics to prevent hyperprolactinemia induced menstrual dysfunctions and other short term and long term affects and to improve drug compliance.

Aims of the study:

1. To study the serum prolactin level in patients on antipsychotic treatment.
2. To assess the risk of menstrual dysfunction .
3. To correlate with other studies.

II. Material and methods

It is a cross – sectional study conducted in outpatient dept. in Govt. Hospital for mental Care, Andhra medical college,Visakhapatnamover a period of one month from April 1st to May1st, 2015.

1.Selection of subjects:60 subjects attending outpatient dept. on antipsychotics were recruited for this study.

2.Inclusive criteria:

A) Women of 18 to 45 years age group .
B) Subjectson antipsychotics for at least 6 months duration.
C) Patients who have given informed consent.

3.Exclusive criteria:

A)Subjects having other risk factors for hyperprolactinemia and menstrual dysfunction were excluded.

After taking informed consent, data was collected.The data collected includes age,maritalstatus,diagnosis,duration of illness and medication,type of medication and menstrual history.Forestimation of serum prolactin,5ml of venous blood sample was collected and sent for analysis.

III. Results & discussion

Results: Results were tabulated in tables. 1 to 4.

Table 1. Association between prolactin level and social and clinical variables.

Variables	No.of patients (60) (n) (%)	Serum prolactin level(ng/ml) Normal(20). (n)(%).	Elevated(40) (n). (%)
1)Age			
18 to 25y	14 23.3%	5 35.7%.	9 64.3%
25 to 45 y	46 76.7%	15 32.6%	31 67.4%
2)Marital status			
Married	33 55%	11 33.3%	22 66.7%
Single	27 45%	9 33.3%	18 66.7%
3)Diagnosis			
Schizophrenia	36 60%	13 36.1%	23 63.9%
Affective disorder	24 40%	7 29.2%	17 70.8%
4)Duration of medication			
6 months to 12 months	24 40%	8 33.3%	16 66.7%
12months to24months	11 18.3%	3 27.3%.	8 88.9%
>12 months	25 41.7%	9 36%.	16 64%
5)Type of medication			
FGA'S	9 15%	1 11.1%	8 88.9%
SGA'S	39 65%	18 46.2%.	21 53.8%
Polypharmacy	12 20%	1. 8.3%	11 91.7%
6)Menstrual dysfunction			
Normal	27 45%	20 74.1%	7 25.9%
Oligomenorrhea	19 31.7%	0 0.0%	19 100%
Amenorrhea	14 23.3%	0 0.0%	14 100%
7) Total no.of cases studied	60	20 33.3%	40 66.7%

Table 2.Associationbetween SGA'S and hyperprolactinemia.

SGA'S	(n). (%) (39)	Serum prolactin level (ng/ml) Normal. (n) (%)	Elevated. (n) (%)
Risperidone	3179.5%	10 32.3%	21 67.7%
Olanzapine	7 17.9%	7 100%	0 0.0%
Amisulpride	1. 2.6%	0 0.0%	1 100%

Table 3.Among 40 hyperprolactinemia cases—type of menstrual dysfunction .

Menstrual dysfunction	Hyperprolactinemia (n) (%)
Normal menstruation	7 17.5%
Oligomenorrhea	19 47.5%
Amenorrhea	14 35%

Table 4. Association between serum prolactin values and type of menstrualdysfunction.

Menstrual dysfunction	(n) (%)	Values of serum prolactin in ng/ml 7to25ng/ml (n). (%).	30to60ng/ml. (n). (%).	60to150ng/ml. (n). (%).	>150ng/ml. (n). (%).
Normal	27 45%	20 74.1%	7 25.9%	0 0.0%.	0 0.0%
Oligomenorrhea	19 31.7%	O O.O%	O O.O%.	19 100%	O O.O%
Amenorrhea	14 23.3%	O O.O%	O O.O%.	5 35.7%.	9 64.3%

Discussion

Elevated prolactin levels were found in subjects on FGA'S,polypharmacy,where as among SGA'S subjects on risperidone&amisulpride were found to be associated with hyperprolactinemia compared to olanzapine, this observation is in agreement with other studies.[1 to13] subjects of all age groups demonstrated sensitivity to increased prolactin.

In this study, among all the variables, the type of medication and dosage of medication are the factors significantly associated with hyperprolactinemia. Elevated prolactin level with FGA'S is 88.9% and polypharmacy 91.7%, in case of SGA'S it is 53.8%.Which indicates hyperprolactinemiaismore with FGA'S andpolypharmacy and with some of SGA'S,which is in agreement with other studies.[1to10]

Among SGA'S,hyperprolactinemia is found more with risperidone at 67.7% of cases compared to olanzapine ,which did not show any hyperprolactinemia even with dose of 20mg/d which was the highest dose in this study group.This observation is in agreement with study by Kapur et al (1998)[10],a dose of olanzapine above 30mg/d inducedhyperprolactinemia, equivalent to Risperidone induced hyperprolactinemia.

In this study hyperprolactinemiais observed in 40(66.7%) subjects. Among hyperprolactinemiasubjects,the menstrual dysfunctions observed were oligomenorrhea in 47.5%(n=19), amenorrhea in 35%(n=14) and normal mentrual cycles in 17.5%(n=7) of subjects receiving antipsychotics.This indicates that menstrual dysfunction is associated with hyperprolactinemia it is in agreement with other studies.[1to9]

It is observed that subjects on olanzapine showed no increase in prolactin level, this observation is in agreement with the study by Kim KS et al where Switch over from risperidone to olanzapine showed normalisation of elevated prolactin and reversal of its adverse effects[5] and their study suggested that switching to olanzapine is a safe and effective alternative to improve compliance.

Subjects on low doserisperidone and low dose FGA'S showed normal prolactin level and normal menstrual function, this indicates that hyperprolactinemia is dose dependent.This observation is in agreement with other studies.[4,6,9.]

Among 60 subjects studied,27 had normal menstrual cycles(45%) ,19 cases had oligomenorrhea (32.7%), remaining 14 cases had amenorrhea(23.3%).

On analysing our results, it is found that most of the subjects with amenorrhea(64.3%) had prolactin levels of more than 150 ng/ml and few subjects with a amenorrhea (35.7%) had prolactin level of 100 ng to 150 ng/d.Whereas all subjects with oligomenorrhea (100%) had prolactin levels ranging between 60ng to150ng/ml.Thosesubjects with prolactin level upto 60ng/ml had normal menstrual cycles.However these results can not be generalised due to small sample size. In our study higher prolactin levels(>150ng/ml) are found in subjects who are on FGA'S,risperidone,amisulpride and polypharmacy with dosage towards higher side.As incidence of hyperprolactinemia is dose dependent,it is better to switch to lowest effective dose,mono pharmacy or to prolactin sparing antipsychotics.

Conclusion

In this cross—sectional study, different prevelance rates of hyperprolactinemia and menstrual dysfunction were observed.Hyperprolactinemia has short and long term consequences that can seriously affect quality of life because of menstrual disturbances, Galactorrhea,sexualdysfunction,gynaecomastia, infertility,decreased bone mineral density etc. In subjects who have biochemically conformed hyperprolactinemia, it is important to exclude other causes of prolactin elevation,in particular tumours of hypothamic-pituitary area. If a subject has been suffering from amenorrhea for 1 year or more, investigations should include bone mineral density measurement.These symptoms are little researched.Various studies suggested that they are common but underestimated their prevelance.

Both doctors and patients should be aware of hyperprolactinemiaassociated effects. To prevent hyperprolactinemia and it's adverse effects, various studies advised tailoring medication to each individual

patient is essential. In addition, the incidence of hyperprolactinemia can be minimised by using the lowest effective dose of the antipsychotics as elevation of prolactin is dose dependent.

Changing to prolactin- sparing antipsychotics or to mono pharmacy also decrease incidence of hyperprolactinemia. Alternatively, a dopamine agonist may be added,although this may compromise antipsychotic efficacy. Additional research needed to clarify the appropriate level of monitoring , the long term effects mainly premature decrease in bone density and optional management of antipsychotic induced hyperprolactinemia.

Limitations

- Small sample size.
- Only a few SGA'S and FGA'S were studied as they are the most commonly used in agovt.set up.
- Further study is needed to assess the long term effects of hyperprolactinemia.

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