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DRUG INDUCED HYPER PROLACTINEMIA: INTERESTING OBSERVATIONS.

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ABSTRACT

Introduction: Drugs are a common cause of hyperprolactinemia. It is essential to differentiate this cause from other pathological causes which avoids unnecessary investigations. Thorough history will help us in finding the responsible drug and holding the same will be rewarding. Here we are reporting such cases of drug induced hyperprolactinemia. **Methods:** It was a cross-sectional observational study. Subjects were recruited from our outpatient department. Hyperprolactinemia was defined as blood prolactin levels >30 ng/mL in females and >24 ng/mL in males, regardless of the presence of symptoms. Serum prolactin was repeated one week after holding the suspected drug(s). Drug induced hyperprolactinemia defined, if holding of responsible drug made normalization of prolactin levels. **Results:** Total of 32 subjects were studied in this study with age of 35.5±10.8years. Predominantly female subjects were present with female to male ratio 5.4. Basal prolactin was 132±68.7ng/mL and after holding the drug prolactin value was 16.9±8.2. Proton pump inhibitors in combination with prokinetics were the leading cause (71.8%) and followed by multiple drug combinations (15.6%), anti-psychiatric drugs (9.3%) and oral contraceptives (3.1%). The mean prolactin in the combination of levosulpride was 176 ng/dl, whereas with domperidone it was 126 ng/dl & with oral contraceptives, respiridone it was 134,151ng/dl respectively. **Conclusion:** Majority cases were clinically symptomatic. Among female subjects commonest presentation was galactorrhea followed by irregular menses and breast heaviness and men presented with erectile dysfunction. Contrary to common belief in our study PPI with prokinetic combination is the most common offending agent than anti-psychotic agents. Levosulpride being the most potent drug in inducing hyper prolactinemia than other agents, though the popular belief was with the Risperidone. As the utility of PPI prokinetic combination is increasing, this might replace anti-psychotic agents as most potent & most common etiology for drug induced hyper prolactinemia.

INTRODUCTION:

Prolactin is a protein produced in the lactotroph cells of the anterior pituitary gland. Secretion is pulsatile and increases with sleep, stress, pregnancy and chest wall stimulation or trauma. Prolactin production can be stimulated by the hypothalamic peptides, thyrotropin-releasing hormone (TRH) and vasoactive intestinal peptide (VIP). Normal fasting values are generally less than 25 ng/mL. Prolactin levels over 250 ng/mL are highly indicative for prolactinomas, while drug-induced hyperprolactinemia doesn't usually exceed 100 ng/mL [1].

Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis. Etiology includes physiological, pathological & pharmacological. Pharmacological agents that inhibit dopamine synthesis or action, such as L-methyldopa, antiemetic or antipsychotics, frequently cause increased serum prolactin. Literature suggests that 'first-generation or typical anti-psychotics have the greatest risk of causing this adverse effect. However, there is also evidence to suggest that 'second-generation anti-psychotics' or atypical, particularly risperidone and paliperidone, also increase prolactin secretion [2].

Hyperprolactinemia has short- and long-term consequences that can seriously affect the quality of life including, menstrual disturbances, galactorrhoea, sexual dysfunction, gynecomastia, infertility, decreased bone mineral density, and possibly breast cancer [3]. Although many of these are linked to elevated prolactin levels, some, such as breast cancer, require further study.

Most clinical guidelines addressing recommended only symptomatic AP-induced HPRL need to be treated [4,5].

Management of drug induced hyper prolactinemia essentially depends on its differentiation from other pathological causes which avoids unnecessary investigations. Thorough history will help us in finding the responsible drug and holding the same will be rewarding. We hereby undertaken this observational study on drug induced hyperprolactinemia, where we have studied common drugs and their potential on this association.

METHODS:

It was a cross-sectional observational study. Subjects were recruited from our outpatient department. Hyperprolactinemia was defined as blood prolactin levels >30 ng/mL in females and >24 ng/mL in males, regardless of the presence of symptoms. Serum prolactin was repeated one week after holding the suspected drug(s). Drug induced hyperprolactinemia defined, if holding of responsible drug made normalization of prolactin levels. Demographics, clinical presentation and offending drug name were entered in pre designed proforma.

RESULTS:

Total of 32 subjects were studied in this study with age of 35.5±10.8years. Predominantly female subjects were present with female to male ratio 5.4. Basal prolactin was 132±68.7ng/mL and after holding the drug prolactin value was 16.9±8.2. Proton pump inhibitors in combination with prokinetics were the leading cause (71.8%) and followed by

multiple drug combinations of oral contraceptive pills with PPI prokinetics and anti-psychiatrics (15.6%), anti-psychiatric drugs (9.3%) and oral contraceptives (3.1%). Highest level of prolactin seen was 317 ng/dl secondary to Pantoprazole and levosulpride combination. The mean prolactin in the combination of levosulpride was 176 ng/dl, whereas with domperidone it was 126 ng/dl & with oral contraceptives, respiridone it was 134,151ng/dl respectively. Overall 86.75% of subjects were having symptomatic presentation. Commonest clinical presentation among the women was galactorrhea (88.9% of female subjects) followed by irregular menstrual cycles (59% of female subjects) and breast heaviness in 29.6%. Among the men erectile dysfunction was common presentation, noted among 80% of them. Asymptomatic presentation was there in 6.25% of subjects. All subjects were improved clinically also after holding the responsible drug.

DISCUSSION:

Hyperprolactinemia is defined as a serum prolactin level above the normal range (25 ng/mL in premenopausal women and 15 ng/mL in men and postmenopausal women) [6].

The investigation of hyperprolactinemia in people using antipsychotic medications is complicated because of the well-known association between medications and hyperprolactinemia. In patients taking medications known to cause hyperprolactinemia, it is critical to establish that the medication is the cause and that the cause is not a structural lesion in the hypothalamic/pituitary area. Hyperprolactinemia induced by medication should return to normal after the withdrawal of the offending drug. If the prolactin is elevated above 150 ng/mL or does not return to normal after the withdrawal of the offending drug, at which point the likelihood of a prolactinoma would be increased significantly.

A number of drugs, including Metoclopramide, Domperidone, H2 receptor blockers Phenothiazines, Butyrophenones, Tricyclic anti-depressants, MAO inhibitors, anti hypertensives (Verapamil, Methyldopa, Reserpine) and Estrogens cause hyperprolactinemia and can be associated with prolactin levels above 100 ng/mL[7].

In patients treated with antipsychotics, hyperprolactinemia is the consequence of dopamine D2 receptors blockade in the pituitary gland, which is positioned outside of the blood-brain barrier [8]. The ability to cross the blood-brain barrier is variable for antipsychotics [9]. Prolactin levels in patients treated with antipsychotic medication appeared to depend on patients' gender, on the type of antipsychotic medication according to potency of inducing hyperprolactinemia, and on the duration of the psychosis. Female gender, antipsychotic medication according to the potency of inducing hyperprolactinemia, and the duration of psychosis over 10 years appear to influence prolactin serum levels. Studies by Wieck and Haddad estimated that 60% of women and 40% of men treated with anti-psychotics develop a prolactin level above the normal range, possibly 10-fold increases from baseline [10].

Anti-depressive drugs exert their effect on prolactin release through serotonin pathway, the hyperprolactinaemia secondary to this class of drugs are generally mild and causes asymptomatic [11].

Levosulpride, Metoclopramide and Domperidone are common agents with hyperprolactinemic effect. They act via dopamine antagonistic mechanism. However, metoclopramide has an additional inhibitory effect on serotonin receptors of the chemoreceptor trigger zone of the central nervous system. Therefore, metoclopramide is considered to be one of the potent stimuli for prolactin release and the levels can be high as 15-fold in patients on chronic metoclopramide therapy [12].Unlike metoclopramide, domperidone do not readily cross the blood–brain barrier (BBB). Therefore, it was claimed to have lesser effect on prolactin levels in comparison with metoclopramide [13].

Levosulpiride is a potent inhibitor of D2 receptors in the anterior pituitary, action is similar to Metaclopramide. (Through the blockade of enteric (neuronal and muscular) inhibitory D2 receptors, and the ability to interact with Type 4 serotonergic (5-HT4) receptors)[14]. Because of the trend of increasing levosulpride usage as prokinetic agent, more and more patients develop hyperprolactinemia as an unavoidable side effect. The magnitude of hyperprolactinemia is greater as compared to older antidopaminergic prokinetic agents [15]. our observation supports this finding.

Verapamil but no other calcium channel blockers cause moderate hyper prolactinemia [16]. Methyldopa inhibits the enzyme, aromatic-L-amino acid decarboxylase, which converts L- dopa to dopamine, Thereby chronic methyldopa therapy is associated with a three to fourfold rise in the basal prolactin levels. Another less commonly used centrally acting antihypertensive, reserpine also produce moderate hyper prolactinemia.

There is scarcity of data on drug induced hyperprolactinemia from India, to our best knowledge this is the first study which looked at comparison of different medications and their potency on causing hyperprolactinemia. At present we have guidelines recommended only for symptomatic AP-induced HPRL, we hope in future our study helps in recommendation of guidelines for other medications related HPRL.

CONCLUSION

Drug-induced hyperprolactinaemia is a common in clinical practice. In this study, majority were clinically symptomatic. Among female subjects commonest presentation was galactorrhea followed by irregular menses and breast heaviness and men presented with erectile dysfunction. Contrary to common belief in our study PPI with prokinetic combination is the most common offending agent than anti-psychotic agents. Among PPI PR, Levosulpride being the most potent drug in inducing hyper prolactinemia than other agents, though the popular belief was with the Risperidone. As the utility of PPI prokinetic combination is increasing, this might replace anti-psychotic agents as most potent & most common etiology for drug induced hyper prolactinemia. We need larger and well controlled studies to confirm these findings. All were improved clinically after holding the responsible drug(s). So obtaining drug history meticulously is paramount and avoids unnecessary other investigations for hyperprolactinemia.

Limitations of the study was sample size is small and selection bias can't be ruled out as we have evaluated only those psychiatric patients attending to our centre.

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