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Case Report

Levosulpiride Induced Galactorrhea: A Case Report

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ABSTRACT

Drug induced galactorrhea is a condition of increased prolactin level in the serum resulting in irregular menstrual cycle and galactorrhea in women. Levosulpiride is a novel drug with antipsychotic, anti-depressant, anti-emetic and anti-dyspeptic actions. Galactorrhea is the secretion of milky discharge from breast in men or women who are not breastfeeding for one year. It may result from excessive secretion of prolactin or increased sensitivity of breast tissue to prolactin. A rare case on levosulpiride induced elevated serum prolactin level presenting as a distressing adverse effect of galactorrhea in a female patient was reported. It's important to keep a watch on prolactin levels during treatment with levosulpiride. For patients who present as a confirmed case of hyperprolactinemia, it is important to exclude other causes of prolactin elevation. Reporting the case would be a learning point for the fellow pharmacists and health care professionals in optimizing the therapy and requirement of strict monitoring of prescription that would minimize the medication errors.

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INTRODUCTION

Levosulpiride is the levorotatory enantiomer of sulpiride, a substituted benzamide. It is gastro protective agent which is used for different dyspeptic symptoms underlying with varied etiologies. Apart, it is meant to use in other conditions including depression, psychosis, somatoform disorders, premature ejaculation and burning mouth syndrome. It is a novel drug with antipsychotic, antidepressant, antiemetic and anti-dyspeptic actions. The main action of levosulpiride is D₂ dopaminergic receptor blockade; those located on the presynaptic membrane of the dopaminergic pathways in the central nervous system and gastrointestinal tract. The antagonistic action on central D₂ receptors leading to the therapeutic action as well as due to its inhibiting nature towards prolactin resulting adverse effect i.e. hyperprolactinemia¹.

Galactorrhea is the secretion of milky discharge from breast in men or women who are not breastfeeding for one year. It may result from excessive secretion of prolactin or increased sensitivity of breast tissue to prolactin. Most of the times it is caused by elevation of prolactin and is often associated with menstrual abnormalities. Prolactin is a peptide hormone released from anterior pituitary which in turn is regulated predominantly by inhibitory effect of dopamine and to a

small extent by the stimulatory effect of thyrotropin-releasing hormone, oxytocin, vasopressin, vasoactive intestinal peptide and angiotensin-II². Any condition that produces imbalance in these substances can lead to elevation of prolactin and cause galactorrhea and menstrual abnormalities³. Varied conditions like stimulation of breast, chest wall diseases, drugs or pathological conditions like pituitary tumors can cause galactorrhea as a symptom. Drugs like antipsychotics, antidepressants, estrogen-containing drugs, prokinetics, antihypertensives, opioids that act by blocking D₂ receptors or decrease synthesis of dopamine can reduce the hypothalamic inhibitory tone on pituitary and thereby can increase in prolactin secretion which may cause galactorrhea⁴.

Usually the prolactin elevation due to drugs is <100ng/ml except for few antipsychotics which can increase up to 250 ng/ml^{4,5}. According to Petit *et al.* the rates of hyperprolactinemia according to therapeutic drug classes were 31% associated with neuroleptics, 28% with neuroleptic-like drugs, 26% with antidepressants, 5% with H₂-receptor antagonists, and 10% with other drugs⁵. Recent increased use of D₂ blockers for the treatment of gastro esophageal reflux disease (GERD) seems to have increased the prevalence of hyperprolactinemia and galactorrhea due

to D₂ blockers as we have observed in our clinical practice⁶. Presenting the case with the concern of the patient.

Objective:

To report a case of levosulpiride Induced Galactorrhea.

CASE REPORT:

A non-pregnant female patient of age 38 years contacted a secondary care hospital with chief complaint of galactorrhea. All her vital signs were normal and her past medical history was summarized in the Table 1.

Table 1: Scheduling of consultant visits

No. of visits	Complaints	Consultant Physician	Investigations	Diagnosis	Medications
1	Neurologist	LBA since 4 years, Increased pain since 15 days, radiating to lower limb, burning sensation in abdomen	MRI-LUMBO-SACRAL SPINE: -Protruded L3-L4 Disc causing compression on thecal sac and neural foramina, indenting on transverse and exiting nerve roots - Degenerated L4- L5 Disc	Lumbar PIVD	1) Diclofenac sodium 100mg OD (sos) 2) Tolperisone 450mg OD 3) Pregabalin 75mg+ Nortriptyline 10mg OD 4) Pantaprazole 40mg OD
2	Neurologist	With increased LBA, paresthesia of left lower limb especially in night, Head ache since 2 days, Vomiting 1 episode the day before the visit.	No investigations advised.	Lumbar PIVD	1) Diclofenac gel 2) Diclofenac sodium 100mg OD(sos) 3) Tab gabapentin 100mg morning 300mg evening 4) Pantaprazole 40mg+ levosulpirid 75mg OD 5) Lumbar support belt
3	Gynaecologist	Galactorrhea	Serum prolactin : 40 ng/ml	Hyperprolactinemia	Referred to endocrinologist
4	Endocrinologist	Galactorrhea	No investigation	Drug Induced Hyperprolactinemia	Cabergolin 0.25 mg 2 times a week.

Since local and central causes of hyperprolactinemia were ruled out a diagnosis of levosulpiride-induced galactorrhea was arrived based on the existing data. Causality assessment was carried out using the Naranjo's causality assessment scale which showed highly probable causal association.

DISCUSSION

Serum prolactin levels ranged from 40ng/ml to 261.81 ng/ml for drug-associated galactorrhea and 140 ng /ml to 3241 ng/ml for prolactinoma. There was a considerable overlap between the serum prolactin levels of drug-induced galactorrhea and that of prolactinoma. A study by Fujino *et al.*⁷ on the effect of intravenous domperidone on healthy volunteers had shown serum prolactin rise above 160 ng/ml in 15 minutes in some cases. Even low-dose amisulpiride can elevate serum prolactin levels to 110.7 ± 49.3 ng/ml in females. So, drug intake can commonly lead to increase in serum prolactin more than 100 ng/ml and often more than 200ng/ml⁸. Few case reports have also reported that levosulpiride and domperidone-induced galactorrhea can be associated with serum prolactin of more than 100 ng/ml and sometimes up to 271ng/ml. Hence, history of drug intake should always be elicited in all patients with galactorrhea or hyperprolactinemia before considering further evaluation^{9,10}. This would avoid the unnecessary costly investigations. However, a serum prolactin of >300 ng/ml is unlikely to be associated with prokinetic use and can be considered for further evaluation of hyperprolactinemia.

Stopping the implicated drug for 72 hours or more and repeating serum prolactin level helps to confirm the drug-induced galactorrhea. However, it should be kept in mind

that serum prolactin may not normalize by 72 hours in few patients and may take a week or more to do so. But all patients with drug-induced galactorrhea had at least 50% fall in serum prolactin by 72 hours of stopping the implicated drug and the same can be used as a criterion to define drug-induced hyperprolactinemia. These patients can be followed up till 2 weeks after stopping the drug for further normalization of serum prolactin.

Apart from being an anti-psychotic and prokinetic agent, levosulpiride also shows its efficacy in treating chemotherapy induced nausea and vomiting¹. The role of 5-HT₄ receptor stimulation has also been postulated as a prokinetic agent. It is known to cause movement disorders, dopaminergic inhibitions in the nigrostriatal pathways resulting in parkinson's characters acute dystonia, rabbit syndrome, akathisia. Levosulpiride can block the dopaminergic receptors which are normally inhibitory in nature with respect to prolactin release thus leading to increased prolactin secretion resulting in hyperprolactinemia. Hyperprolactinemia is a side effect occurring with all antidopaminergic prokinetics however in this case it is not recommended to indicate levosulpiride for one episode of vomiting for duration of 30 days which has led to the development of galactorrhea.

Intervention

Levosulpiride is not recommended in this case for one episode of non chemotherapy induced vomiting and it has been given for a period of 30 days which is not advisable.

CONCLUSION

Finally, Pharmacist and health care professionals should consider checking the history of antipsychotic drugs (even though the indication may differ) in patients presenting with galactorrhea. It's important to keep a watch on prolactin levels during treatment with levosulpiride. For patients who present as a confirmed case of hyperprolactinemia, it is important to exclude other causes of prolactin elevation such as tumors in the hypothalamic-pituitary area, pregnancy, hypothyroidism and chronic renal insufficiency. Prokinetic use was the most common cause of galactorrhea in our study and treated with D₂ agonists. Hence, there is a need to ensure measures to reduce the non-specific use of prokinetics and increase awareness regarding the occurrence of galactorrhea with prokinetics use, to reduce unnecessary investigations and treatment. Galactorrhea is an adverse drug reaction not commonly encountered. Hence, physicians should be aware of such uncommon side effects of common drugs to avert unnecessary worry and intervention.

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CONFLICTS OF INTEREST: Nil.

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