Levosulpiride and Esomeprazole Induced Hyperprolactinemia
Case Report of Drug Induced Hyperprolactinemia

H Rajgadhi*, H Makwana, S Malhotra***, P Patel******

*2nd Year Resident, Department Of Pharmacology, Associate Professor, **Department Of Emergency Medicine, V.S. General Hospital, ***Professor And Head, Department Of Pharmacology, ****Dean, NHL Medical College, NHL Municipal Medical College Ahmedabad-380006

Abstracts: Hyperprolactinemia is a condition of raised serum prolactin levels which can be drug induced also manifesting as galactorrhea, menstrual problems and infertility in women. Levosulpiride is used in the treatment of psychoses, anxiety disorders and now a days also used in treatment of GERD. The action of Levosulpiride is attributed to 5-HT4 receptors agonism in the enteric system. This is the case report of 22-year-old lady who presented with galactorrhea due to intake of two drugs Levosulpiride and Esomeprazole prescribed for the treatment of Gastroesophageal Reflux Disease.[H Rajgadhi NJIRM 2017; 8(3):158-160]

Key Words: Galactorrhea, Hyperprolactinemia, Levosulpiride(LEVO), Esomeprazole(OMZ)

Author for correspondence: Supriya D Malhotra, 2, Amrut bagh colony ,Nr J K Shah classes Opposite Sardar Patel stadium . Navrangpura, Ahmedabad 380014 E- Mail: supriyadmalhotra@gmail.com M:9727760262

Introduction: Drug induced hyperprolactinemia is a condition of elevated serum prolactin levels, manifesting as galactorrhoea and menstrual irregularities in women. Levosulpiride [LEVO]is a Dopamine D2 receptor antagonist. It is an antipsychotic and prokinetic agent.[1]Esomeprazole [OMZ] is a proton Pump inhibitor employed in the treatment of GERD. They covalently bind to and inactivate the H+/K+ adenosine triphosphatase (ATPase) enzyme located on the apical membrane of the gastric parietal cell, thereby blocking the final common pathway for gastric acid secretion. [2]

As with other typical antipsychotics LEVO can also block dopaminergic receptors which are inhibitory for prolactin release. This can result in hyperprolactinemia and the case mentioned below supports it[3]

OMZ a proton pump inhibitor used in the case below also was co prescribed to the patient. OMZ itself can lead to raised serum prolactin level. Here we report a case of hyperprolactinemia which occurred due to oral tablet of LEVO and OMZ taken for the treatment of Gastroesophageal reflux. Our case report is unique because the patient was receiving both these drugs concurrently which lead to hyperprolactinemia in this case.

Case report: A 22-year-old healthy well- nourished female working as practicing physiotherapist had come to outpatient department (OPD) of Obstetrics and Gynecology department with chief complain of bilateral breast heaviness and galactorrhea. While taking history in detail it was found that since last ten days, she was taking Tablet Levosulpiride 75 mg once a day orally and Tablet Esomeprazole 20 mg once a day orally for Gastroesophageal reflux disease prescribed by private practitioner. She was married before one and half years with healthy sexual life. She was not on any contraceptive pills. There was no significant medical or surgical history. Her menstrual cycle was regular. Her LMP was 1 week before the onset of symptoms.

On general examination, nothing was significant. While examining breast, inspection was normal, oozing of milk was present from bilateral breasts, without any palpable mass.

Laboratory test in form of S. Prolactin, S. TSH, LFT and RFT were ordered. Her Prolactin level was 40 ng/ ml (normal being 2.7-22.4ng/ml), which was significantly high compared to normal. Other investigations were normal. Her USG breast was normal. Tablet Levosulpiride and Tablet Omeprazole were discontinued. She recovered within 1 week without any medical treatment. After one week, her S. Prolactin levels returned to 17.5 ng/ ml (normal). This case was reported to the nearest Pharmacovigilance center, PVPI ID :2016-03862.

Discussion: Hyperprolactinemia is a common drug induced biochemical abnormality. Its prevalence is often under estimated. Most of the drugs lead to increase prolactin plasma concentration by removing inhibitory pathways for prolactin. The classical dopaminergic blockers used for the treatment of psychosis are well known to cause this adverse effect but reports have now been published regarding association of other dopaminergic blockers(prokinetics)used for GIT indications also causing hyperprolactinemia.

LEVO is the levo-enantiomer of sulpride. LEVO is known to cause side effects but rise in prolactin secretion has been seen only in few reports.[4]

In our case the patient was also receiving OMZ a PPI for GERD, PPIs themselves cause hyperprolactinemia, this mechanism is unrelated to dopaminergic receptor blocking. The likely mechanism for Esomeprazole induced galactorrhea is not clear. Although few small studies done so far have reported that Esomeprazole does not apparently interact with the CYP3A4 system. OMZ has an inhibitory effect on CYP3A4 which may retard the metabolism of estrogen increasing the serum estrogen levels. Estrogen has also known to stimulate prolactin gene transcription. Estrogen may also inhibit the dopamine synthesis in the tuberoinfundibular pathway and remove the inhibitory influence of dopamine on prolactin. This mechanism was also postulated in the case by P rietoet al. Detailed pharmacokinetic trials are needed to confirm this postulation. The Netherlands pharmacovigilance center Lab and the WHO database have monitored a few case reports of esomeprazole induced gynecomastia in their data base, which further support the postulated mechanism of esomeprazole induced hyperprolactinemia stated above.[5]

Although PPIs are generally well tolerated and they are most commonly prescribed for acid peptic diseasesand this adverse effect of rise in serum prolactin should always be watched out for.

Hyperproteinemia induced by drugs doesn't required further therapy. Withdrawal of the offending drug alone is sufficient to bring down the raised serum prolactin levels to base line. Similar thing was observed in our case where the prolactin levels returned to normal. Drug induced hyperprolactinemia is reversible and prolactin levels returns to normal as in our case in 7 days.

The increase in prolactin that occurs through the use of conventional antipsychotics develops within a few hours of starting treatment and remains elevated throughout the period of use. Once treatment stops, prolactin levels return to normal within 2-3 weeks. It has been suggested that with chronic treatment, a partial tolerance may occur although patients treated for long periods of time still have higher prolactin levels compared to untreated healthy controls.[6]

LEVO did not improve the esophageal motor abnormality, but was effective for esophageal symptoms, which might be the result of the antidopaminergic effect on the central nervous system. Hyperprolactinemia developed in all patients, but it was normalized within a week, and symptoms for hyperprolactinemia were seen in only a few cases.[7]

It's important to keep a watch on prolactin levels during treatment with LEVO. For patients who present asa confirmed case of hyperprolactinemia it is important to exclude other causes of prolactin elevation such as tumors in the hypothalamic-pituitary area, pregnancy, hypothyroidism, chronic renal insufficiency. Management options include reducing the dose of the antipsychotic agent, switching to an atypical antipsychotic which do not influence prolactin levels, introducing a dopamine receptor agonist if it is due to antipsychotic treatment. In our case such was not the scenario since the patient had been prescribed LEVO for GERD. Hence prescribers need to be vigilant and informed about this adverse effect and may choose other treatment options, not related to dopaminergic blockade.

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