Ranitidine-induced galactorrhea: Exploring the intricacies

Sir,

In reference to the case report titled "Ranitidine-induced galactorrhea in a postmenopausal female" by Agrawal *et al.*,[1] we would like to supplement it by exploring the intricacies involved with the development of the condition.

As compared to cimetidine, ranitidine is generally associated with lesser adverse drug reactions related to the central nervous system (CNS) since it is less lipophilic and significantly less concentrated in the cerebrospinal fluid. While a study concluded that ranitidine does not cross the blood-brain barrier (BBB) from the fact that the serum prolactin (PRL) was not raised by a significant amount,[2] inferences regarding its action on the central dopaminergic system have been made in one other study.[3]

It has been hypothesized that H_2 receptors play role in reducing the prolactin levels by increasing dopamine release which, in turn, acts on the D_2 receptors present on the lactotrophs, thus reducing the secretion of prolactin.[3] *In vitro* experiments have demonstrated that ranitidine acts neither as a dopamine receptor antagonist nor as a dopamine agonist at the level of the pituitary, thus does not alter the secretion of PRL by any action on the pituitary.[4] Further studies to understand its action on the higher CNS centers are needed.

Histamine has got both inhibiting (minor) and stimulating (major) effect on the secretion of PRL. One of the hypotheses for this is its stimulatory action through H_1 receptors and indirect inhibitory actions through GABA-ergic interneurons and GABA receptors on the lactotrophs.[3] H_2 receptor antagonists like ranitidine remove the inhibitory effect of GABA on the lactotrophs, thus causing increased PRL secretion.

A positive relationship between PRL levels and postmenopausal breast cancer risk is a known fact, making chronic use of H_2 blockers a potential risk factor for breast carcinoma. A study exploring the same concluded that although the usage of H_2 blockers is not generally associated with an increased risk of breast carcinoma, the current use of ranitidine increases the risk of hormone-receptor-positive invasive ductal carcinoma.[5] Although ranitidine raises the PRL levels only modestly as compared to cimetidine, it is still possible for it to cause increased breast cancer risk through this pathway.

Since ranitidine is hypothesized to act on the central dopaminergic pathways, potential drug-drug interactions (pDDIs) with various dopaminergic agonists and antagonists used for the management of conditions such as Parkinson's disease and schizophrenia need to be looked out for. Chronic treatment with ranitidine has been shown to reduce levodopa-induced dyskinesia (LID).[6] A study has shown ranitidine to be effective in reducing the negative symptoms of schizophrenia.[7] Ranitidine blocks the inhibitory signals normally transmitted via the H_2 receptors and thus alleviates the negative symptoms of schizophrenia.[7]

Cimetidine, known to cause galactorrhea, inhibits the metabolism of estradiol by acting as an inhibitor of CYP450 enzymes, resulting in increased estrogen levels.[8] This is associated secondarily with a rise in serum prolactin.[9] Ranitidine, on the other hand, has a much weaker enzyme inhibitory effect which, even if demonstrable, is proven to be statistically non-significant.[10] Hence, the rise of prolactin levels associated with ranitidine cannot be explained by enzyme induction.

Considering that the patient needs to continue taking medication for the acid peptic disorder, switching to another drug in the same class of H_2 receptor antagonist or prescribing a proton-pump inhibitor (PPI) which is not associated with hyperprolactinemia is the most preferred way to solve the problem of galactorrhea. For example, esomeprazole has been shown to be associated with galactorrhea[11] and hence, would not be a preferred alternative. Thus, consideration must also be given to the potential adverse effects of alternative medications.

The number of reported cases of galactorrhea available at VigiAccess and associated with cimetidine (110) is higher than that with ranitidine (88) as reported till date[12] probably because the latter came into the market several years after the introduction of cimetidine in 1983. Although it overtook cimetidine in the United States by 1987, the popularity decreased after the introduction of the PPIs in the late 1980s and 1990s.[13]

In light of the case report and the recent findings of ranitidine having multiple potential therapeutic uses, it is worth deciphering the complex pathways associated with its action, especially considering that it is a common medication prescribed in routine clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Agrawal P, Pursnani N, Parihar A, Singh B. Ranitidine-induced galactorrhea in a postmenopausal female. J Family Med Prim Care 2019;8:3057-8.
2. Singh OJ, Singh TI, Valte V, Babycha L. Comparison of serum prolactin level between I.V. ranitidine and I.V cimetidine administration in albino rabbits and possible role of histamine 1 and 2 receptors in prolactin secretion. Ind Med Gaz 2013;2013:14-7.
3. Singh OJ, Singh TI, Valte V. Cimetidine-induced hyperprolactinemia. J Med Soc 2013;27:165-8.
4. Yeo T, Delitala G, Besser GM, Edwards CRW. The effects of ranitidine on pituitary hormone secretion *in vitro*. Br J Clin Pharmac 1980;10:171-3.
5. Mathes RW, Malone KE, Daling JR, Porter PL, Li CI. Relationship between histamine 2-receptor antagonist medications and risk of invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2008;17:67-72.
6. Cui G, Yang X, Wang X, Zhang Z, Yue X, Shi H, *et al*. Ranitidine reduced levodopa-induced dyskinesia in a rat model of Parkinson's disease. Neuropsychiatr Dis Treat 2014;10:39-46.
7. Mehta VS, Ram D. Role of ranitidine in negative symptoms of schizophrenia--An open label study. Asian J Psychiatr 2014;12:150-4.
8. Galbraith RA, Michnovicz JJ. The effects of cimetidine on the oxidative metabolism of estradiol. N Engl J Med 1989;321:269-74.
9. Gudelsky GA, Nansel DD, Porter JC. Role of estrogen in the dopaminergic control of prolactin secretion. Endocrinology 1981;108:440-4.
10. Smith SR, Kendall MJ. Ranitidine versus cimetidine. A comparison of their potential to cause clinically important drug interactions. Clin Pharmacokinet 1988;15:44-56.
11. Pipaliya N, Solanke D, Rathi C, Patel R, Ingle M, Sawant P. Esomeprazole induced galactorrhea: A novel side effect. Clin J Gastroenterol 2016;9:13-6.
12. Uppsala Monitoring Centre. VigiAccess™. Available from: http://www.vigiaccess.org/[Last accessed on 2019 Nov 20].
13. Berndt E, Bui L, Reiley D, Urban G. Information, marketing, and pricing in the U.S. antiulcer drug market. Am Econ Rev 1995;85:100-5.

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