

## Rabeprazole and Domperidone Induced Hyperprolactinemia in a Patient with Type 2 Diabetes Mellitus, Hypothyroidism and Peptic Ulcer Disease: A Case Report

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### Abstract

Drugs are a common cause of hyperprolactinemia. They are common in patients taking antipsychotics, antiemetics, opioids, antidepressants, prokinetics and proton pump inhibitors (PPI). Rabeprazole is a relatively newer PPI and domperidone is a well-known prokinetic and antiemetic drug. There are few reports of hyperprolactinemia & galactorrhea with fixed drug combination (FDC) of rabeprazole (20 mg) and domperidone (30 mg). Here, we report a case of 39-year-old diabetic and hypothyroid female patient who was on the above FDC for peptic ulcer disease on and off for the last four years and developed hyperprolactinemia. She showed neither clinical signs of galactorrhea nor amenorrhea. On routine blood investigations, she had increased prolactin level. Radiological evaluation of brain was normal. The drug was stopped and repeat prolactin was normal within one week of withholding. A diagnosis of rabeprazole and domperidone induced hyperprolactinemia was reached based on clinical, laboratory judgement and causality assessment.

**Keywords:** adverse drug reaction, domperidone, hyperprolactinemia, hypothyroidism, rabeprazole, diabetes mellitus

## Introduction

Prolactin is a polypeptide hormone secreted by the lactotroph cells of the anterior pituitary gland involved in milk induction and lactation. Physiologic control of prolactin secretion is exerted by the inhibiting action of dopamine<sup>1</sup>. Hyperprolactinemia is defined as an increase in concentration of prolactin levels from 15 to 25 ng/mL in women and 15 to 20 ng/mL in men<sup>2</sup>. Prevalence of drug-induced hyperprolactinemia ranges from 15 to 45%<sup>3,4</sup>. Frequent clinical presentations of hyperprolactinemia are menstrual irregularities, galactorrhea and sexual dysfunctions or they can be asymptomatic as well<sup>5,6</sup>. Proton pump inhibitors (PPI) in combination with prokinetics were the leading cause (71.8%) followed by antipsychotic drugs (9.3%) and oral contraceptives (3.1%) in females of reproductive age group<sup>7</sup>. Recent increased in use of combination of prokinetics and PPI for gastroesophageal reflux disorder has contributed to increase in prevalence of elevated prolactin levels<sup>5</sup>. Though levosulpiride and domperidone are commonly implicated drugs, PPI also have been linked to the development of hyperprolactinemia with or without associated sexual disorders<sup>8</sup>. Comorbid conditions like hypothyroidism increases the risk of hyperprolactinemia in women due to the increase in prolactin response to thyroid release hormone (TRH) caused by estrogen<sup>9</sup>. There are very few reports of PPI induced galactorrhea and hyperprolactinemia. This case report highlights hyperprolactinemia occurring due to rabeprazole and domperidone in a patient of hypothyroidism emphasizing the importance of pharmacovigilance towards this commonly consumed drug combination for dyspepsia.

## Case Presentation

A 39-year-old female patient who is a known case of hypothyroidism and type 2 diabetes mellitus (T2DM) for seven years.

She consulted endocrinologist for follow-up and on routine evaluation. It was found that her serum prolactin (PRL) levels were elevated (143.67 ng/mL). On detailed history, she was non-pregnant and non-lactating, no symptoms of galactorrhea, amenorrhea or other manifestation of hyperprolactinemia. On further history, she complains of burning sensation in epigastrium and frequent episodes of vomiting for which she was on & off, combination of rabeprazole 20 mg and domperidone 30 mg for four years. Her gastric emptying scintillagrapy showed delayed gastric emptying (around 63%). She underwent CT brain which was normal without signs of micro or macroadenoma in pituitary. Laboratory findings are summarized in Table 1. Her concomitant therapy included tablet glimepiride with metformin (2 mg + 500 mg) twice daily for T2DM and tablet thyroxine 75 ug once daily for eight years. The endocrinologist attributed cause of hyperprolactinemia to be drug induced secondary to rabeprazole and domperidone and advised her to stop these medications. She repeated her serum PRL levels after seven days and measured 12.29 ng/mL without any medical intervention. The causality assessment was done using WHO-scale. The causal analysis showed a probable association of the ADR with both rabeprazole-domperidone

## Discussion

This case report discusses a 39-year-old female who developed asymptomatic hyperprolactinemia due to the combination of rabeprazole with domperidone for peptic ulcer disease. The endocrinologist advised to stop the medication and the levels of serum prolactin resumed to normal without any medical intervention.

In this case report patient had hypothyroidism and diabetes. These conditions can be risk factor for hyperprolactinemia. A study by

Adele et al. showed an increased prevalence of hyperprolactinemia in patients of hypothyroidism which may be due to stimulant effect of thyrotropin releasing hormone on prolactin<sup>9</sup>, while Rasheed et al. observed an elevated prolactin levels in type 2 diabetes mellitus patients on treatment with sulfonylureas<sup>10</sup>. Even though PRL is elevated there were no clinical symptoms of hyperprolactinemia in this patient. This is referred to as “macroprolactinemia” where large amount of circulating PRL without clinical symptoms<sup>11</sup>.

Mechanism of rabeprazole or other PPI induced hyperprolactinemia is unclear. Ashfaq et al. observed affinity between dopamine D2 receptor and PPI through molecular docking techniques which may be involved in drug induced hyperprolactinemia<sup>12</sup>. Ortiz-Guerrero et al. highlighted that about 15% of single dose of PPI reaches the central nervous system as they traverse through blood-brain-barrier and its responsible for neurological adverse effects<sup>13</sup>. Not many reports of rabeprazole with domperidone resulting in hyperprolactinemia and galactorrhea are reported. Ashfaq et al. commented that omeprazole was the common PPI producing hyperprolactinemia as there were only four reports of rabeprazole<sup>7</sup>. Findings of Patrascu et al. in two cases of galactorrhea in patients who were on rabeprazole and domperidone supports our observation of elevated PRL with this FDC<sup>14</sup>.

Rabeprazole was introduced to Indian market in the year 2001 and its FDC with domperidone was approved in year 2004. This combination is approved for treatment of gastroesophageal reflux disorder if not responding to rabeprazole monotherapy<sup>15</sup>. Hyperprolactinemia or galactorrhea due to rabeprazole is unlisted ADR and not included in the package insert/labelling instructions of

Food & Drug Administration (FDA)<sup>16</sup>.

## Conclusion

This report highlights the need of appropriate advice and frequent monitoring in patients who were on long term PPI either prescribed or self-medicated. Even though the exact mechanism of hyperprolactinemia by PPI is unclear but not uncommon. However, in patients who are on long term FDC of PPI and prokinetic along with other endocrine disorders such as hypothyroidism and diabetes require periodic assessment of serum prolactin level to avoid clinically symptomatic cases of galactorrhea, amenorrhea and infertility. Also, there are very few studies or case reports establishing the long-term effect of rabeprazole on endocrine system and serum prolactin level.

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## Conflict of Interest

None declared.

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**Table 1. Relevant blood parameters of the case**

<b>Blood Parameter</b>	<b>Measured value</b>	<b>Biological Reference Range</b>	<b>Unit</b>
Fasting blood sugar	151	70-100	mg/dL
Post prandial blood sugar	268	< 140	mg/dL
Glycated hemoglobin	7.5	< 5.7	%
Total T3	1.6	0.9 – 2.8	ng/dL
Total T4	3.8	5 – 12	ug/dL
Thyroid stimulating hormone	2.4	0.4 – 4	mIU/L