OPIS PRZYPADKU / CASE REPORT
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Omeprazole-induced gynecomastia – a case report and literature review

Ginekomastia po omeprazolu – opis przypadku i przegląd piśmiennictwa

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Streszczenie

Wstęp. Ginekomastia to powiększenie jednego lub obu gruczołów sutkowych (piersi) u mężczyzn. Choć występowanie tej dolegliwości jest dość powszechne, temat ten jest często pomijany, gdyż może być źródłem wstydu i poczucia wykluczenia dla mężczyzn. Zaburzenia hormonalne jest najczęstszą przyczyną ginekomastii, zwłaszcza w okresie dojrzewania, ale także u dorosłych i osób starszych i może być wywołane zmianami hormonalnymi związanymi z wiekiem, rzadziej zmianami nowotworowymi, a czasami może mieć charakter idiopatyczny. Ginekomastia jest również (często lekceważonym) działaniem niepożądanym niektórych leków. Zaliczają się do nich inhibitory pompy protonowej (PPI), często przepisywane w leczeniu zgagi, refluksu żołądkowego i wrzodów żołądka. **Materiał i metody**. Przedstawiamy przypadek 48-letniego pacjenta, u którego wystąpiła ginekomastia w trakcie leczenia omeprazolem. **Wyniki**. Zaobserwowano zmniejszenie piersi po tygodniu od odstawienia omeprazolu. **Wnioski**. Opisany przypadek potwierdza ryzyko wystąpienia działania niepożądanego w postaci ginekomastii u mężczyzn zażywających leki z grupy inhibitorów pompy protonowej. *(Farm Współ 2021; 14: 149-154) doi: 10.53139/FW.20211419*

Słowa kluczowe: Ginekomastia, powiększenie piersi, działania niepożądane leku, inhibitory pompy protonowej, omeprazol, esomeprazol

Summary

Background. Gynecomastia is an enlargement of one or both of the mammary glands (breasts) in men. Although the prevalence of this ailment is quite common, this topic is often disregarded, as it may be a source of shame and a feeling of exclusion for men. Hormonal disturbance is the most common cause of gynecomastia, especially during puberty, but also in adults and older people and can be induced by age-related hormonal changes, rarely by neoplastic changes, but sometimes its nature may be idiopathic. Gynecomastia is also (sometimes neglected) an adverse effect of some drugs. Some of them are proton pump inhibitors (PPIs), widely used to relieve symptoms of acid reflux, or gastroesophageal reflux disease. **Material and methods**. We describe a case report of a 48-year-old patient who experienced an adverse reaction of gynecomastia due to the therapy with omeprazole. **Results**. Breast size reduction was observed one week after omeprazole withdrawal. **Conclusions**. Described case confirm the risk of adverse reaction of gynecomastia in men taking drugs from the proton pump inhibitor group. *(Farm Współ 2021; 14: 149-154) doi: 10.53139/FW.20211419*

Keywords: Gynecomastia, breast enlargement, adverse drug reactions, proton pump inhibitors, omeprazole, esomeprazole

Introduction

Gynecomastia, also described as the enlargement of the mammary glands in men, is derived from the Greek terms gynec (female) and mastos (breast). It is a clinical condition characterized by ductal epithelial hyperplasia and an increase in stromal and periductal connective tissue, extending concentrically from the nipple (e.g., bilateral or rarely unilateral) of one or both breasts. It is also defined as a palpable, subareolar breast tissue with a diameter of 2 cm or greater. In general, gyne-

comastia is asymptomatic, frequently benign and may resolve spontaneously- sometimes, it is even not noted by patients. However, it is a troublesome condition for many men, causing psychosocial discomfort, lowered self-esteem, and many concerns about health that should be treated for preventive, aesthetic, and therapeutic reasons. Gynecomastia usually results from hormonal changes- increased action of exogenous or endogenous estradiol and absolutely or relatively reduced effects of androgens [1-3].It is known that many drugs may induce gynecomastia through various mechanisms. Up to 25% of cases of gynecomastia is induced by drugs. These are i.a. antipsychotics, corticosteroids, antiretrovirals, statins and proton pump inhibitors (PPIs)- one of the most commonly prescribed drug class worldwide with esomeprazole at the forefront [3-4]. This review presents a case report of a patient who developed breast enlargement during the therapy with omeprazole.

Case report

A 48-year-old patient reported to the family doctor complaining of enlargement, pain and tenderness of both breasts. For ten years, the patient has been suffering from type 2 diabetes, which is effectively and safely treated with metformin at a dose of 1000 mg/day. In addition, for many years, the patient has been following a diet and has performed regular physical exercise to achieve proper glycemic and weight control. For three months, due to post-traumatic pain, the patient has been taking orally different NSAIDs (alternatively ibuprofen, ketoprofen, meloxicam). After a week of treatment with NSAIDs, the patient developed gastrointestinal disorders (abdominal pain, indigestion, heartburn), which resulted in the addition of omeprazole 20 mg/day into the patient's treatment regimen. The patient noticed breast enlargement after about two months of using a PPI. Palpation revealed a palpable, tender, elastic and displaceable tissue fragment. An ultrasound of both nipples (to exclude neoplasm of the mammary gland and differentiate between gynecomastia and lipomastia) and testicles revealed no changes. An interview with the patient and test results indicated a temporary gynecomastia due to omeprazole intake. One week after withdrawal of the PPI, a decrease in the size of both breasts was observed.

Discussion

Gynecomastia, defined as the proliferation of breast glands in males, is caused by non-cancerous growth of glandular tissue, sometimes with adipose tissue growth (but it should be differentiated from pseudo gynecomastia in obese males), with or without tenderness on touch (mastalgia). It is a common complaint that entails psychosocial discomfort and health concerns, and it may be the symptom of a clinically relevant disease [1-3].The prevalence of breast development in men is common, and it may affect people of all ages. In the adult population of healthy men, the incidence of gynecomastia is estimated at an average of 30 to 55%. Gynecomastia is classified into four categories: physiological, pathological, drug-induced, and idiopathic. Physiological gynecomastia occurs in up to 25% of them; for another 25%, there is no identified cause of gynecomastia. Sometimes breast enlargement may be iatrogenic or related to an underlying condition. Physiologically gynecomastia occurs more frequently during three phases of life:

I. in newborns (30–90%)- partly caused by high levels of estradiol and progesterone produced by the mother during pregnancy but also due to the increased conversion of steroid hormone precursors to sex steroids and a neonatal surge of gonadotropins. The greatest intensity of changes is observed between the 10th and 12th day of life. It may last for several weeks after birth; sometimes it may be accompanied with lactation and resolves spontaneously;
II. in juveniles, during puberty (50–60%)- in this case, gynecomastia may occur physiologically (it can be asymmetrical and unilateral); the greatest number of cases occurs at the age of 13-14, and almost 90% of them resolves within three years of onset. According to some studies, boys with gynecomastia (in comparison with boys without this ailment) have a decreased androgen to estrogen ratio and increased aromatase activity in the skin fibroblasts. Thus, either decreased production of androgens or increased aromatization of circulating androgens (leading to the increase of the estrogen to androgen ratio) might stand for the development of the pubertal gynecomastia.
III. in older people (70%)- the main causes of gynecomastia in men in this group (aged 50-69 years) are systemic disease, medication and andropause-related hypogonadism. Many cases of asymptomatic gynecomastia in older people may result from increased aromatase activity, which is a consequence of (associated with aging) the increase in total body fat and

SHBG (sex hormone binding globulin- a protein that binds androgens), a decrease in serum testosterone concentrations and relatively elevated LH (luteinizing hormone) concentrations. [1-3].

Different mechanisms appear to be involved in the development of gynecomastia:

- increased estrogen biosynthesis (physiologically during puberty, in tumours of the testes, in adrenal hyperplasia)
- decreased androgen biosynthesis (in hypogonadism or in older men)
- increased hepatic production of sex steroid binding protein (SHBG; e.g. in hyperthyroidism), which has a greater affinity for testosterone than for estradiol
- slow metabolism of estrogens and androgens (e.g. in cirrhosis of the liver or chronic renal failure)

Table I. Drugs and substances related to gynecomastia [1,3-4,5,7-9]
Tabela I. Leki i substancje wywołujące ginekomastię [1,3-4,5,7-9]

Mechanism	Drug/substance
Increase in serum estrogen	Aromatisable androgens, hCG, human GH
Estrogenic effect	Estrogens (e.g. in creams)
	Cardiac glycosides (digoxin)
	Herbal products
Decrease in serum testosterone or dihydrotestosterone	Imidazoles (ketoconazole, metronidazole)
	Chemotherapeutics (methotrexate, Vinca alkaloids)
	Finasteride/Dutasteride
	Diuretic (Spironolactone)
Androgen receptor antagonism	Antiandrogens (bicalutamide, flutamide, cyproterone acetate)
	H2 antagonists (cimetidine, ranitidine)
	Diuretic (spironolactone)
Testosterone synthesis and androgen action disorders	Imidazoles (ketoconazole)
	Diuretic (spironolactone)
	Antibiotic (metronidazole)
Displacement of the estrogens from complexes with SHBG	Diuretic (spironolactone)
	Imidazoles (ketoconazole)
Increase in serum prolactin	Antipsychotic agents
Enhanced aromatization	Androgens (exogenous)
	Anabolic steroids (metandienone)
	Androgen precursors (i.e. androstenedione and DHEA)
Uncertain mechanisms	Human GH
	Cardiac and antihypertensive medications: – Calcium antagonists (amlodipine, diltiazem, felodipine, nifedipine, verapamil) – ACE inhibitors (captopril, enalapril, lisinopril), – amiodarone, methyldopa, reserpine, nitrates
	Central nervous system agents – amphetamines, diazepam, haloperidol, methyldopa, phenytoin, reserpine, tricyclic antidepressants)
	Drugs for infectious diseases – antiretroviral therapy for HIV/AIDS (e.g. efavirenz), isoniazid, ethionamide, griseofulvin, minocycline
	Drugs of Abuse: – amphetamines, heroin, methadone
	Others: – theophylline, omeprazole, auranofin, diethylpropion, domperidone, penicillamine, sulindac, heparin, methotrexate

- locally increased aromatase (an enzyme that converts testosterone into estradiol), e.g. in obesity or due to alcohol abuse
- excessive sensitivity of the mammary gland to estrogens
- congenital defect of the androgen receptor or its blockage with exogenous factors, e.g. by anti-androgenic drugs (spironolactone, ketoconazole, enalapril, verapamil, ranitidine, omeprazole) [1,3-7].

Breast tissue contains many estrogen and androgen receptors- the former are known to stimulate proliferation of the milk ducts and promote stromal vascularization and connective tissue hypertrophy, while the latter inhibits this process. The mammary gland in men, although undeveloped, are still receptive to hormonal stimulation and able to grow. The imbalance in these sex hormones- an excess of estrogens, deficiency of androgens, or an increased ratio of free estrogen : free androgen, and the effects elicited by these hormones on intracellular receptors located in breast tissue- is primarily responsible for the development of gynecomastia [4,8]. After pubertal gynecomastia, drugs and substances are the most common causes of gynecomastia. Drug-induced breast enlargement stands for up to 25% of all gynecomastia cases. A vital piece of information is that older patients may take various medications associated with gynecomastia- even 80% of cases of gynecomastia may be at least partially due to medications. Drugs recognized to be linked to the development of this ailment are, among others, exogenous hormones, cardiovascular agents, antipsychotics, antibiotics, antiretrovirals, and gastrointestinal agents [4, 7]. Drugs that are implicated in gynecomastia and supposed mechanisms through which these substances may lead to the development of this ailment are listed in Table I.

In a study by Batteux et al., an association between gynecomastia and drug exposure was analyzed. They examined 255,345 reports of gynecomastia from the French national pharmacovigilance database (FPVD) from the period between 2008 and 2015. Nearly 70% of patients were over 50 years old (mean age of men with gynecomastia was 58.1 ± 19 years). The association between gynecomastia and drug exposure was quantified through the reporting odds ratio (ROR). 221 different drugs were considered potential causatives in gynecomastia cases, of which 54 active compounds occurred to show statistically significant ROR. There were 327 relevant cases of gynecomastia, which accounted for 0.31% of all adverse reactions reported over this period; thus, the overall percentage is low. In 59% of these cases, a single drug was considered to responsible for gynecomastia. The drug classes most frequently associated with the occurrence of breast enlargement were antiretrovirals (23.5%), diuretics (15.5%), proton pump inhibitors (11.9%), HMG-CoA reductase inhibitors (9.1%), neuroleptics and related drugs (6.5%), calcium channel blockers (6.3%), and 5-alpha reductase inhibitors (4%). A molecule with the highest ROR was spironolactone (34.67), and its effect appeared to be dose-dependent. Proton pump inhibitors, which accounted for 11.9% of drug-induced gynecomastia reports, is a class of drugs frequently reported in the literature considering this issue [4].

Proton pump inhibitors (PPIs) are a group of drugs widely used to treat and prevent upper gastrointestinal complaints such as heartburn, gastroesophageal reflux disease (GERD) and gastric or duodenal ulcers, constituting one of the most frequently prescribed drugs all over the world [10]. These drugs are also administered to prevent ulceration of the upper gastrointestinal tract with long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) and in combination therapy aimed at eliminating H-pylori strains from the body [11]. All currently approved PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) are benzimidazole derivatives, i.e. heterocyclic organic molecules with a pyridine and benzimidazole moiety linked by a methylsulfinyl group [12]. Esomeprazole, the S-isomer of omeprazole, is currently the most widely prescribed drug from this group [10] . The mechanism of their action relies on blocking gastric acid secretion by inactivating hydrogen-potassium adenosine triphosphatase enzymes (by binding to sulfhydryl groups of cysteines) found on gastric parietal cells. This inhibition is irreversible, and thus, to resume acid secretion, new H+,K+-ATPase needs to be expressed. These drugs are considered relatively safe- they may cause few adverse effects, but they are usually available over-the-counter in many countries. The adverse reactions (ADRs) induced by PPIs (especially during long-term use) include mild gastrointestinal disorders, deficient absorption of micronutrients, increased susceptibility to bacterial infections, hypergastrinaemia, dementia, pneumonia, bone fractures, kidney diseases, gastric cancer and reactions affecting the CNS, such as migraine,

insomnia, vertigo, states of confusion, depression. Apart from that, this group of drugs has also been linked to various pleiotropic effects, which may result from interactions of PPIs with other relevant biological mechanisms that are not directly associated with gastric acid secretion suppression. An understudied adverse reaction of some PPIs is the aforementioned gynecomastia. The amount of information about the pathological causes of this symptom is still inadequate, and the mechanisms of gynecomastia development in patients taking PPIs are not fully explained [13-15]. A proton pump inhibitor- omeprazole- contributes to an increase in the estrogen:androgen ratio by inhibiting estradiol metabolism, which leads to an increase in serum estradiol, inducing gynecomastia. High concentrations of this PPI has been found to inhibit cytochrome P450 (CYP)3A4, a liver enzyme responsible for the catalysis of estradiol oxidation in its catabolic pathway. Hence, the estradiol level increases [14,16]. CYP2C19 plays a major role during omeprazole metabolism. There are more than 15 variant alleles for this cytochrome resulting in reduced or absent CYP2C19 enzyme activity (CYP2C19 intermediate and poor metabolizers), and thus, higher plasma concentrations of omeprazole. In this situation, patients treated with higher doses of this PPI for long periods are at greater risk of developing gynecomastia [13,17]. According to few case reports, it takes approximately three months from the initiation of PPI use to the onset of gynecomastia. It can be concluded that patients taking higher doses of omeprazole for long periods are more prone to breast enlargement [14]. Carvajal et al. identified 24 cases of PPI-related gynecomastia from the database of the Spanish Pharmacovigilance System, collected from the period between 1982 to 2006. The mean age of patients reporting this adverse effect was 65.5 years (range 26–90 years) and the time to onset for the reaction ranged from 8 days to 4.8 years. A temporal relationship between gynecomastia and PPI treatment was observed in all cases. In most of them (11 of 15 patients), PPI withdrawal led to improvement or resolution of gynecomastia, and the median recovery period was 76 days (range 18–303 days). In 5 of 6 patients who did not withdraw the medication, the condition continued. There were also ten patients for whom no other drugs or conditions (known to be related to gynecomastia) were reported. Although no clear characteristics could be identified in patients who developed gynecomastia, this survey supports an association between the use of PPIs and the development of this adverse effect [13]. A retrospective cohort study by He et al. aimed to assess the risk of breast enlargement secondary to PPI use confirmed that people using drugs from this group are at higher risk of developing gynecomastia. They found 389 cases of gynecomastia diagnosed among 220,791 new PPI users. The researchers compared the outcome from this group to a comparator group that took amoxicillin- a medication not known to be associated with gynecomastia. There were 996 gynecomastia cases among 837,740 new amoxicillin users. Thus, in this survey, PPI users were 30% more likely to develop gynecomastia than amoxicillin users (the crude HR for PPI use compared to amoxicillin use was 1.70) [14]. Considering a possible endocrine disruptions in men treated with PPIs, it was suspected that therapy with omeprazole might affect semen quality. However, a survey by Banihani compiling the results of various studies on this subject concludes that omeprazole at a daily dose of 30 mg for four weeks and 40-60 mg for one week does not affect/preserves the basal levels of the pituitary-gonadal hormones (testosterone, luteinizing hormone, follicle-stimulating hormone and prolactin) in healthy male subjects [18]. The percentage and absolute risk of drug-induced gynecomastia might be low, with a relatively small number of drugs related, and it is generally considered a symptom of low health and life-related harm. This may stand for the explanation for underreporting of pharmacovigilance reports. [14]. Considering the problem of overprescribing and overuse of PPIs through recent years, clinicians should not disregard gynecomastia [19-20].

Conclusion

Although gynecomastia is considered benign and does not pose a great threat to the health and life of patients, it is often a source of many complaints, such as discomfort from local pain and tenderness but also aesthetic concerns, social anxiety that may result in self-identity disorders, depression, and even suicide. Therefore, during the diagnosis of gynecomastia, it is vital to precisely determine the patient's medical history, with particular insight into the medications used, alcohol consumption, the presence of chronic diseases (liver, kidneys), hyperthyroidism, decreased libido, erectile dysfunction, and the presence of gynecomastia in the family. It is also important to assess the dynamics of gynecomastia development. In each case of sudden onset and rapidly progressing gyneco-

mastia, the neoplastic process of the gonads, adrenal glands, pituitary and nipple should be excluded first. Although breast cancer is rare in men, the appearance of gynecomastia is a concern for patients and therefore they often consult the physician.

Conflict of interest
None

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References

1. Nuttall FQ, Warrier RS, Gannon MC. Gynecomastia and drugs: a critical evaluation of the literature. Eur J Clin Pharmacol. 2015;71(5):569-78.
2. Soliman AT, De Sanctis V, Yassin M. Management of Adolescent Gynecomastia: An Update. Acta Biomed. 2017;88(2):204-13.
3. Sansone A, Romanelli F, Sansone M, et al. Gynecomastia and hormones. Endocrine. 2017;55(1):37-44.
4. Batteux B, Llopis B, Muller C, et al. The drugs that mostly frequently induce gynecomastia: A national case - noncase study. Therapie. 2020;75(3):225-38.
5. Korzeniowska K, Kowal J, Szałek E. Ginekomastia. Gynecomastia. Farm. Współcz. 2011(4):4,171-4.
6. Constanzo PR, Pacenza NA, Aszpis SM, et al. Clinical and Etiological Aspects of Gynecomastia in Adult Males: A Multicenter Study. Biomed Res Int. 2018,8364824
7. Swerdloff RS, Ng CM. Gynecomastia: Etiology, Diagnosis, and Treatment. [Updated 2019 Jul 7]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-.]
8. Bowman JD, Kim H, Bustamante JJ. Drug-induced gynecomastia. Pharmacotherapy 2012;32:1123-40.
9. Cuhaci N, Polat SB, Evranos B et al. Gynecomastia: Clinical evaluation and management. Indian J Endocrinol Metab. 2014;18(2):150-8.
10. Pipaliya N, Solanke D, Rathi C, et al. Esomeprazole induced galactorrhea: a novel side effect. Clin J Gastroenterol 2016;9:13–6.
11. Ali Khan M, Howden CW. The Role of Proton Pump Inhibitors in the Management of Upper Gastrointestinal Disorders. Gastroenterol Hepatol (N Y). 2018;14(3):169-75.
12. Strand DS, Kim D, Peura DA. 25 Years of Proton Pump Inhibitors: A Comprehensive Review. Gut Liver. 2017;11(1):27-37.
13. Carvajal A, Macias D, Gutiérrez A, et al. Gynaecomastia Associated with Proton Pump Inhibitors. Drug-Safety 2007;30,527–531
14. He B, Carleton B, Etminan M. Risk of Gynecomastia with Users of Proton Pump Inhibitors. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 2019. 39. 10.1002/phar.2245
15. Tanus-Santos JE, Pinheiro LC. Proton pump inhibitors: New mechanisms of action. Basic Clin Pharmacol Toxicol. 2019;125(2):87-8.
16. Eckman, A., & Dobs, A. (2008). Drug-induced gynecomastia. Expert Opinion on Drug Safety 2008;7(6):691–702.
17. Royal Dutch Pharmacists Association (KNMP). Dutch Pharmacogenetics Working Group (DPWG). Pharmacogenetic Guidelines [Internet]. Netherlands. CYP2C19: omeprazole [Cited 2020]. Available from: https://www.g-standaard.nl/risicoanalyse/B0001841.PDF
18. Banihani SA. Omeprazole and Semen Quality. Basic Clin Pharmacol Toxicol. 2016;118(3):181-3.
19. Hálfdánarson ÓÖ, Pottegård A, Björnsson ES, et al. Proton-pump inhibitors among adults: a nationwide drug-utilization study. Therap Adv Gastroenterol. 2018;11:1756284818777943.
20. Abrahami D, McDonald EG, Schnitzer M, et al. Trends in prescribing patterns of proton pump inhibitors surrounding new guidelines. Annals of Epidemiology 2021;55:24-6.