integrity Research Journals

Journal of Public Health and Diseases
Volume 3(4), pages 82-84, August 2020
Article Number: E57E205E1
ISSN: 2705-2214
https://doi.org/10.31248/JPHD2019.056
https://integrityresjournals.org/journal/JPHD

Case Report

Spironolactone-digoxin synergizes gynecomastia: A case report

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Received 27th January, 2020; Accepted 27th February, 2020

ABSTRACT: Gynecomastia refers to a proliferation of breast tissue in the males that causes imbalances in estrogen and androgen levels, resulting in increased or unopposed estrogen action on breast tissue, where underlying aetiology might be physiological or pathological. Approximately 10 to 25% cases of gynecomastia are in associated with drugs. There are many drugs (Spironolactone, Furosemide, Digoxin etc.) capable to induce gynecomastia on individual basis, but practically it is not seen often. Simultaneously, when two or more similar drugs (capable to induce gynacomastia) are administered concomitantly, it is seen often for its synergistic side effect as a drug induced gynecomastia. In the present case study, a 65 years old male patient who had been taking Digoxin and Spironolactone for Ischemic Heart Disease (IHD) with Left Ventricular Failure (LVEF) in the past one year. On his regular follow up, it has been observed/noticed that the patient has developed a gynecomastia. Hence, it is presumed that the drug induced gynecomastia may be due to synergistic side effect of Spironolactone and Digoxin *per se*.

Keywords: Breast enlargement, drug- induced, male patients.

INTRODUCTION

Gynecomastia is enlargement of breast tissues differentiated from excess adipose tissue in the males due to elevated estrogen action which results in imbalanced estrogen/androgen ratio with proliferation of glandular component with deposition of fat (Fauci et al., 2018). Breast enlargement may originate from the breast, chest wall or even representing a secondary metastasis (Saboori and Behzadnia, 2019). The effects of gynecomastia can be either physiological or pathological conditions which includes drug induced, endocrine disorders (hyperthyroidism, testicular or pituitary tumours) and non-endocrine (cirrhosis, starvation, stress and renal failure) (Fauci et al., 2018; Almah, 2011). Due to overlapping morphological characteristics of malignant and benign male breast masses, any recognizable breast enlargement should be differentiated, interpreted and approached cautiously (Saboori and Behzadnia, 2019). Approximately 10 to 25% gynecomastia cases are associated with drugs such as, potassium sparing diuretic (spironolactone), mineralocorticoid receptor antagonists (eplerenone), antibiotics (metronidazole, isoniazid), tricyclic antidepressants (amitriptyline), cardiac glycosides (digoxin), calcium channel blockers (verapamil, amlodipine, nifedipine), ACE inhibitors (captopril, enalapril), centrally acting agents (methyldopa, clonidine), anti-arrhythmic (amiodarone), anti-androgens (flutamide, nilutamide, bicalutamide), and gonadotropin releasing tropin hormone agonist (Leuprolide) (Almah et al., 2009; Başaran et al., 2009; Kauser et al., 2014; Veeregowda et al., 2018).

CASE REPORT

Past medical and medication history

A 65 years old male patient visited medical OPD with the complaints of breathlessness, swelling of lower limbs,

orthopnoea, PND (paroxysmal nocturnal dyspnoea), pitting pedal oedema. He has a past medical history of ischemic heart disease in the past 2 years and followed improper medication. The patient was admitted to the medical ward. On examination, the following were observed, Pulse: 88 bpm; BP: 130/90 mmhg, CVS: S1 & S2 are heard, S3 gallop heard; RS: B/L NVBS+, crepitus heard, no organomegaly. After assessing the electrocardiogram, the patient was diagnosed with IHD with left ventricular failure. On the day of admission, capsule Ecospirin gold 10 mg (Clopidogrel + Atorvastatin + Aspirin), tablet Nicostar 5 mg (Nicorandil), tablet Aldactone 50 mg (spironolactone), tablet lanoxin 0.25 mg (digoxin), tablet Clopivas 75 mg (clopidogrel) were administered. The therapy was continued for next two days, then capsule Ecospirin gold and tablet Aldactone was discontinued and tablet Lasix was prescribed. On the last day tablet Lasix was discontinued and tablet Imdur 30 mg (isosorbide mononitrate) and tablet Lacilactone 50 mg (Spironolactone + Furosemide) was prescribed. On the day of discharge, his discharge medication includes tablet Imdur 30 mg, tablet Lacilactone 50 mg, tablet Nicostar 5 mg, tablet Lanoxin 0.25 mg, tablet Clopivas 75 mg, tablet pan 40 mg. The patient was advised to continue the medication and follow up.

Follow up

After 1 year 2 months of follow up (16th September 2019), patient complained of painful chest swelling, fever, breathlessness, pitting pedal edema. On examination of electrocardiogram (ECG) and colour doppler, the findings include severe LV dysfunction with LVEF, grade 2 mitral regurgitation, LA/LV dilated, global hypokinesia of LV with akinesia of inferior wall and distal region apex thinner out. By physical examination, increased size of breast was found and diagnosed as drug induced bilateral gynecomastia (Figure 1). There was no history of liver failure, thyroid diseases, and testicular tumours. As the patient was taking the medications for past 1 year 2 months, he developed chest swelling due to interaction between Lacilactone and Lanoxin. Tablet Lacilactone (Spironolactone + Furosemide) was stopped and substituted by tablet Lasix (Furosemide *per se*) 20 mg and tablet Lanoxin (Digoxin) 0.25 mg was continued. In the next follow up (October, 2019), it was noticed that there was a reduction in the size of the breasts and advised the patient to continue the therapy.

DISCUSSION

Gynecomastia is a clinical condition consisting of a benign proliferation of male's breast glandular tissue which is more than 2 cm in diameter. Its representative symptom is pain and swelling of the breast (Kauser et al., 2014).

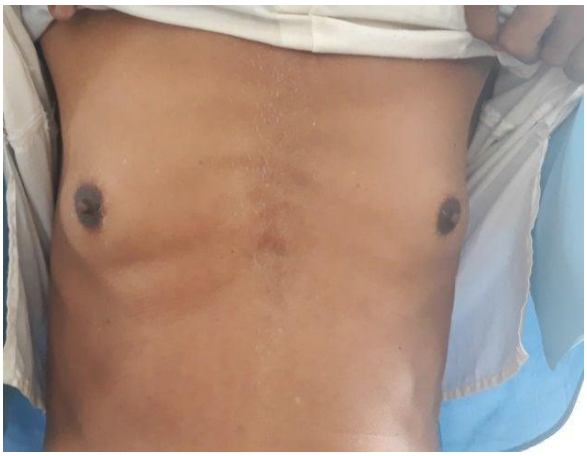

Figure 1. Bilateral Breast enlargement (Gynecomastia).

Digoxin is a cardiac glycoside, has positive inotropic effect by inhibiting Na+ K+ ATPase enzyme on myocardial cells (Almah et al., 2011). It phyto-estrogen binds with the estrogen receptors and interrupts the A/E ratio (Biggar, 2012). The adverse effects of digoxin are both cardiac and extra cardiac (Almah et al., 2011). Spironolactone alters the estrogen-androgen balance which leads to estrogen sensitivity and increased metabolic clearance of testosterone. Gynecomastia is one of the well-known extra cardiac side effects of digoxin as well as spironolactone. Hence the chances of gynecomastia are enhanced when both drugs are co-administered and also depend upon the dose and duration of the treatment.

In the present case patient's age was excluded as the physiological cause of gynecomastia. Liver dysfunction test was done and it can be ruled out as there were no abnormalities. Patients past medication history was reviewed and identified as there is a suspected drug interaction between tablet Lanoxin (Digoxin) and tablet Lacilactone (Spironolactone + Furosemide) which was advised for ischemic heart failure with left ventricular failure. Interaction between these drugs, spironolactone will increase the digoxin levels by p- glycoprotein efflux transporter (Kauser et al., 2014; Biggar, 2012). As a result, half-life of digoxin increases which leads to more estrogen levels as it alters the A/E ratio. The treatment for the drug induced gynecomastia is to withdraw the causative drugs but in this case tablet Lanoxin (Digoxin) 0.25 mg need to be continued because of his IHD with LVEF and tablet Lacilactone (Spironolactone + Furosemide) was discontinued and substituted by tablet Lasix (Furosemide *per se*) 20 mg. Furosemide is a loop diuretic which has lower affinity than spironolactone to cause gynecomastia (Almah et al., 2011; Innocenti et al., 2019).

After a few days, reduction in the swelling of the breast was noticed and advised the patient to continue the therapy. Patient was counselled about the adverse drug

interaction and informed medication adherence. The patient was also advised not to discontinued the drugs without consulting the physician and OTC medications should be avoided (Kauser et al., 2014).

Conclusion

Spironolactone and digoxin induced gynecomastia is common adverse drug interaction but early identification save the patients from life threatening conditions such as breast cancer because it is benign premalignant condition (Kauser et al., 2014). Co-administration of many medications may lead to gynecomastia. It is very essential to have a precise clinical examination, use of relevant para-clinics such as ultrasonography, CT scan and MRI may involve some informative data for early detection and cost effective treatment of the breast tumours (Saboori and Behzadnia, 2019). Hence physicians/medical practitioners should be cautious while prescribing the drugs as a polypharmacy and patients should be thoroughly monitored for drug interactions and its possible adverse drug events.

CONFLICT OF INTEREST

Authors do not have any conflict of interest.

ACKNOWLEDGEMENT

We thank the following doctor of pharmacy, Kohima, Purnagopinath and Vijakumari for their contribution in collection of primary date and working on literature review. We are thankful to physicians, Dr. Bentoor and Dr. L S. Patil for giving their expertise suggestions. We extend our thanks to principal and management of BLDE Association for providing the necessary facilities for making this article successfully.

REFERENCES

Almah, U., Haseeen, M. A., & Rahman, S. Z. (2009). Gynecomastia: An ADR due to drug interaction. Indian Journal of Pharmacology, 41(6), 286-287.

Başaran, Y., Ünal, H. U., Taşlipinar, A., Bolu, S. E. (2009). Digoxin induced gynecomastia: Case report. *Turkiye Klinikleri Journal of Endocrinology*, 3(4), 104-106.

Biggar, R. J. (2012). Molecular pathways: Digoxin use and estrogen-sensitive cancers—risks and possible therapeutic implications. *Clinical Cancer Research*, 18(8), 2133-2137.

Fauci, A. S., Kasper, D., Hauser, S. L., Harrison T. R. (2018). *Harrison's principles of internal medicine*, 20th edition Part 12; Pp. 2779-2781.

Innocenti, A., Ghezzi, S., & Innocenti, M. (2019). Correction of tuberous nipple areolar complex deformity in gynecomastia: The deformity that can get forgotten. *Annals of Plastic Surgery*, 83(3), 367.

Kauser M. M., KasiJagadeesh, M., Kumaraswamy, R. C., Manoj Kumar, M., & Jagadeesh, K. V. (2014). Spironolactone/digoxin induced gynecomastia: A comparative case study. *World Journal of Pharmaceutical Research*, 3(6), 1014-1018.

Saboori, F., & Behzadnia, M. J. (2019). Gynecomastia, as an extremely rare presentation of chest wall lymphoma, a case report and review the articles. *Acta Medica Iranica*, 57(4), 276-279.

Veeregowda, S. H., Krishnamurthy, J. J., Krishnaswamy, B., & Narayana, S. (2018). Spironolactone-induced unilateral gynecomastia. *International Journal of Applied and Basic Medical Research*, 8(1), 45-47.