

## SPIRONOLACTONE/DIGOXIN INDUCED GYNECOMASTIA (A COMPARATIVE CASE STUDY)

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### ABSTRACT

Gynecomastia is an abnormal proliferation of breast tissue in males. It has a broad range of causes that are classified as either physiological or pathological, although in many cases there is no specific causes can be found. Most of the causes for gynecomastia are due to Drugs (10-25%). This pathological case study is about a 54-years male patient who received digoxin & spironolactone as a treatment of choice in dilated cardiomyopathy. Here we are suspecting gynecomastia due to spironolactone and digoxin as the pathological cause. These two drugs may have adverse drug reaction due to drug-drug interactions, that we are discussing in this case study. Interactions were evaluated by Medscape multi drug interaction checker, as well as Micromedex solutions which suggested that ADR due to Drug interaction is possible.

**KEY WORDS:-** Gynecomastia, Digoxin, Spironolactone, Pathological study.

### INTRODUCTION

Gynecomastia is defined as a benign enlargement of the male mammary glands, resulting in palpable sub alveolar tissue<sup>1</sup>. Gynecomastia results from conditions that cause an imbalance of estrogenic and androgenic effects on the breast, resulting in an increased or unopposed oestrogen action on the breast tissue. Gynecomastia is one of the well-known extra cardiac side-effect of digoxin as well as spironolactone. Hence the chances of gynecomastia could be enhanced if these two drugs are co-administered. Mechanism of gynecomastia due to spironolactone results from an altered oestrogen-androgen balance, in favour of oestrogen, or

from of increased breast sensitivity to a normal circulating oestrogen level. Whereas mechanism of gynecomastia due to digoxin is poorly understood, but there is evidence digoxin may cause gynecomastia because of oestrogenlike steroid moiety of the digoxin molecule<sup>11</sup>. Prolactin has also been reported to decrease androgen receptors and increase oestrogen and progesterone receptors, which can lead to male gynecomastia<sup>10</sup> but it is rare condition.

Approximately 10% - 25% cases of gynecomastia are due to drugs<sup>2</sup>. The overall prevalence of gynecomastia is estimated at 30% to 50%, with three peaks of occurrence during the life span<sup>1, 4</sup>. The neonatal period (60%–90%), puberty (50%–60%), and older adulthood between the ages of 50 and 70 years (60%–70%)<sup>3, 5</sup>. Physiologic gynecomastia related to a relative increase in the ratio of oestrogen to androgen occurs during the neonatal period and puberty, while gynecomastia in older adulthood usually reflects aging-related physiologic changes involving declining androgen levels, accumulation of adipose tissue, and increasing aromatase activity. The most common side effect with spironolactone is that of breast complaints, with a minimum of 10% of men noting breast tenderness at a dose of 50 mg. but gynecomastia due to digoxin is a rare condition. The structural similarity of the digitalis glycosides aglycones to the cyclopentano-perhydrophenanthrene radical of the steroidal hormones. According to Rahman et al, gynecomastia is the adverse drug reaction due to drug interaction between digoxin and furosemide. Gynecomastia is generally corrected on discontinuation of the drug; however, the time required for reversibility can be prolonged, particularly if gynecomastia is at an advanced stage. Here we reporting such an interesting case of gynecomastia suspected to have resulted from the co-administration of both the drugs digoxin & spironolactone.

### Case History

A 54-year-old male patient attended the general medicine outpatient department with complaints of exertional breathlessness, orthopnoea, swelling of the lower limbs and PND. On examination, pulse rate 118b/min, BP 100/70mm.hg, LVS<sub>3</sub> heard, bilateral basal crepitations and pedal pitting oedema present. After an electrocardiogram and echocardiography, he was diagnosed as a case of dilated cardiomyopathy disease. He was advised tablet Clopidogrel 75mg, tablet losartan 25mg, tablet acenocoumaral 3mg, tablet digoxin 0.25mg, tablet Torsemide 10mg, tablet Spironolactone 25mg, tablet Bisoprolol 10mg and advised follow-up for two months. At the one-month follow-up visit, he complained of

painful enlarged breast tissue on both sides of chest. There was no past history of liver failure, thyroid diseases, testicular tumors, etc. On examination, a firm, increased size of nipples were present. Then he was diagnosed as bilateral gynecomastia and advised tablet aceclofenac 100mg and paracetamol 500 mg combination as SOS to reduce the pain. Both digoxin and spironolactone were stopped. Spironolactone was substituted with Eplerenone. There was significant reduction of gynecomastia when the patient was reviewed after 1 month.

## DISCUSSION

Gynecomastia is a common clinical condition consisting of a benign proliferation of male breast glandular tissue<sup>6</sup>. Its representative symptom is pain and swelling of the breast. Gynecomastia itself is not a disease but rather, a symptom of an underlying imbalance in hormonal physiology specifically, an increase in oestrogen action relative to androgen action at the breast tissue level<sup>[1,7]</sup>. A 51-year old man developed gynecomastia during treatment with digoxin for mitral-valvulopathy complicated by arrhythmia with atrial fibrillation<sup>11</sup>. Gynecomastia seen with starvation and malnutrition is probably due to reduced gonadotropin and testosterone levels relative to oestrogen and may worsen with refeeding, owing to a rise in estradiol production that outpaces the increases in gonadotropin and testosterone. Rarely, digoxin has been shown to cause Gynecomastia is mentioned in many textbooks as a side effect, thought to be due to the oestrogen-like steroid moiety of the digoxin molecule<sup>11</sup>. To know the causes of this, patient past medication history was analysed and identified as it was drug induced gynecomastia suspected by resulting between interaction of digoxin and spironolactone. According to Medscape reference, spironolactone will increase the level of digoxin by p-glycoprotein efflux transporter. So increase the half-life of digoxin & subsequent toxicity occur. Rose, et al, reported that 6 of 16 patients treated with spironolactone developed gynecomastia<sup>8</sup>. According to their report, blood testosterone levels were lower and estradiol were levels higher in the gynecomastia group than they were in the control group, indicating the disturbance in hormone balance with oestrogen predominating. Moscovitz et al conducted on the endometrial histomorphometry of oophorectomized mice study says that digoxin have a potency of causing gynecomastia<sup>[11]</sup>. Combination of cardiac glycosides (digoxin) and diuretics (furosemide) have the adverse effect of gynecomastia due to drug interaction<sup>12</sup>. The treatment for drug-induced gynecomastia is withdrawal of the causative drug, leading to the disappearance of the symptom. But in this patient, it is necessary to continue spironolactone because of his known case of dilated cardiomyopathy.

After few days there is a chance of reducing his breast size and if it is more we will go for discontinuation of drug and replacing it by another other aldosterone antagonist like eplerenone. It is having five hundreds-fold lower affinity for androgen and progesterin receptors than spironolactone<sup>13</sup>. So severe cases of gynecomastia, spironolactone is substituted by eplerenone. To reduce pain he was advised tablet Aceclofenac 100mg plus Paracetamol 500mg combination as a SOS. Patient was counselled well regarding adverse drug reaction and informed medication adherence, without consulting physician should not withdraw drug and should not have any OTC drug.

## CONCLUSION

Spironolactone & digoxin induced gynecomastia is a common adverse drug reaction. But identifying earlier is helpful to patient to save him from life threatening conditions like breast cancer because it is a benign premalignant condition. By co-administration of these two drugs in dilated cardiomyopathy reduces the mortality rate in the diseased population. Drugs like Clomiphene (anti oestrogen), Tamoxifen (oestrogen antagonist) and other, less frequently used drugs include danazol (synthetic derivative of testosterone), are used to treat the gynecomastia. Our study suggests that there may be an interaction between any two of the drugs that leads to adverse drug reaction. So medical professionals should be careful while giving poly pharmacy in the given prescription. Patient counselling is necessary to improve medication adherence. As spironolactone has shown to provide definite survival benefit in congestive cardiac failure, it is prudent to substitute it with Eplerenone.

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