Impact of Digoxin on Endocrine Glands in Male Rats

Abbas A. Khudhair [1], Kassim F. Abdulkareem[2], Muhsin S.G. Al_Mozie'l [3]

[1]Assitant Lecturer, [2]Assitant Professor, [3]Lecturer, Department of Clinical Laboratory Science, College of Pharmacy, University of Basrah, Iraq

Abstract

This study is performed to provide the pathological changes of thyroid gland, pancreas and adrenal gland that occurred due to exposure to the digoxin drug. The study uses twenty four adult male rat randomly divided into 3 equal groups as follows: G1 control group treated with distilled water, G2 dosed with 0.3mg/kg digoxin and G3 dosed with 0.9mg/kg digoxin given orally by gavage daily for 60 days. All animals were sacrificed at the end of experiment and organs were collected in 10% buffered formalin for histopathological evaluation. Result reveals dilation of thyroid follicles with flattened follicular epithelium which increase with high dose group digoxin in comparison with control. Adrenal gland showed moderate atrophy of cortical layers especially zona reticularis with hyperplasia of medulla cells probably of digoxin like ouabain-producing cells, on the other hands pancreas doesn't reveal remarkable changes except congestion of vessels in high dose group compared to control.

Keywords: *male rats; endocrine glands; pathological study and digoxin*

Introduction

Digoxin is one of the old medicine for heart failure and still the drug of choice in this condition[1,2], several drug have been developed but for treatment of symptoms of disease to complete cure and these drug is too expensive without any benefit that can be added above digoxin to replace it [3]. Digoxin increase force of contraction of myocardial muscle cells that is inotropy which exerted through blockage of Na^+-K^+ ATPase pump[4]. The most problems that accompanied digoxin it is narrow therapeutic window which make it toxicity sever to be occur so any mistake of drug toxicity denote [5,6]. Ouabain is an endogenous substance similar to digoxin that is produced from adrenal medulla cells. Ouabain previously used for treatment of heart failure[7]. Because digoxin is prescribed for all aged group patients so this study is designed to investigate the histopathological changes of digoxin on thyroid gland, pancreas and adrenal gland.

Materials and Methods

Experimental animals

This study administered 24 adult male rat divided randomly into 3 groups as follows; G1 is control group processed with distill water, G2 treated with 0.3mg/kg digoxin and G3 treated with 0.9mg/kg digoxin orally by gavage daily for 60 days. The animals were kept for adaptation for 3 weeks before experiment at the laboratory animal house of College of Pharmacy – University of Basrah. Animals were housed as eight rats in each cage under conditions (Mechanical ventilation, 12\12 hours light on, pellet, tap water and room temperature 24 ± 2°C).

Histopathological study:

After 60 days of digoxin dosing, all rats were sacrificed and organs collected in 10% formalin for histopathological processing [8] and stained with hematoxylin and eosin according to Drury [9], to be assessed by light microscope.

Results

Histopathology of control group

Thyroid gland shows normal thyroid follicles apparently of different sizes with cuboidal compact

epithelium and homogenous pinkish colloid material. Pancreas show normal pancreatic glands and in between shows islets of Langerhans in the vicinity of blood vessels. Adrenal gland shows two layer outer one represent adrenal cortex showing three layers including zona glomerulosa, zona fasciculata and zona reticularis, the other layer resembling adrenal medulla showing medullary cells which appear similar to neuronal bodies. Showed in figure1.

Histopathology of low dose group

Thyroid gland showed dilated thyroid follicles with flattened follicular cells filled with thick colloid material, early stage of hypothyroidism and some areas of the glands appear unchanged. Pancreas appear with un remarkable changes showing exocrine glands and in between islets of Langerhans. Adrenal cortex appear atrophied with blurred layers and hyperplasia of the adrenal medulla which occupies most of adrenal tissue. Showed in figure 2.

Histopathology of high dose group

Thyroid gland with moderate to severe flattening of follicular epithelial cells with engorgement of the follicular lumen by faint colloid material. Pancreatic islets of Langerhans show unremarkable pathological changes compared to control slides and there is only congestion of blood vessels. Adrenal gland shows moderate atrophy of adrenal cortical layers especially the zona reticularis with hyperplasia of adrenal medullary cells which appears hypercellular studied with neuron like cells. Showed in figure 3.

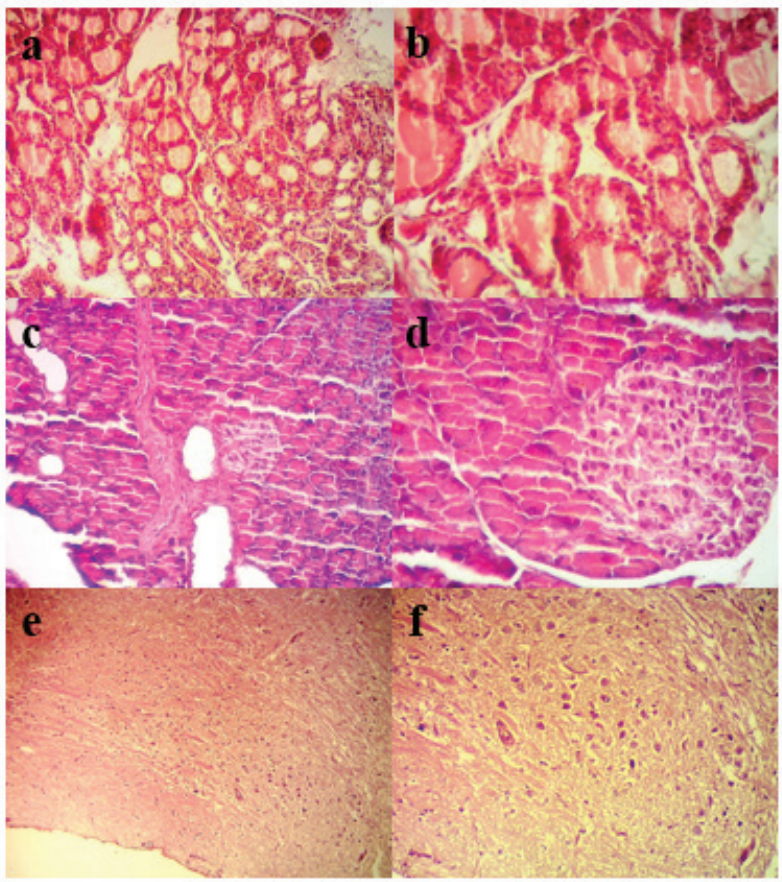

Figure 1: Control group, show normal architecture of thyroid follicles (a 200X &b 400X), pancreas show exocrine gland & islets of langerhance (c 200X &d 400X) and adrenal gland show cortex layers with medulla (e 200X &f 400X).

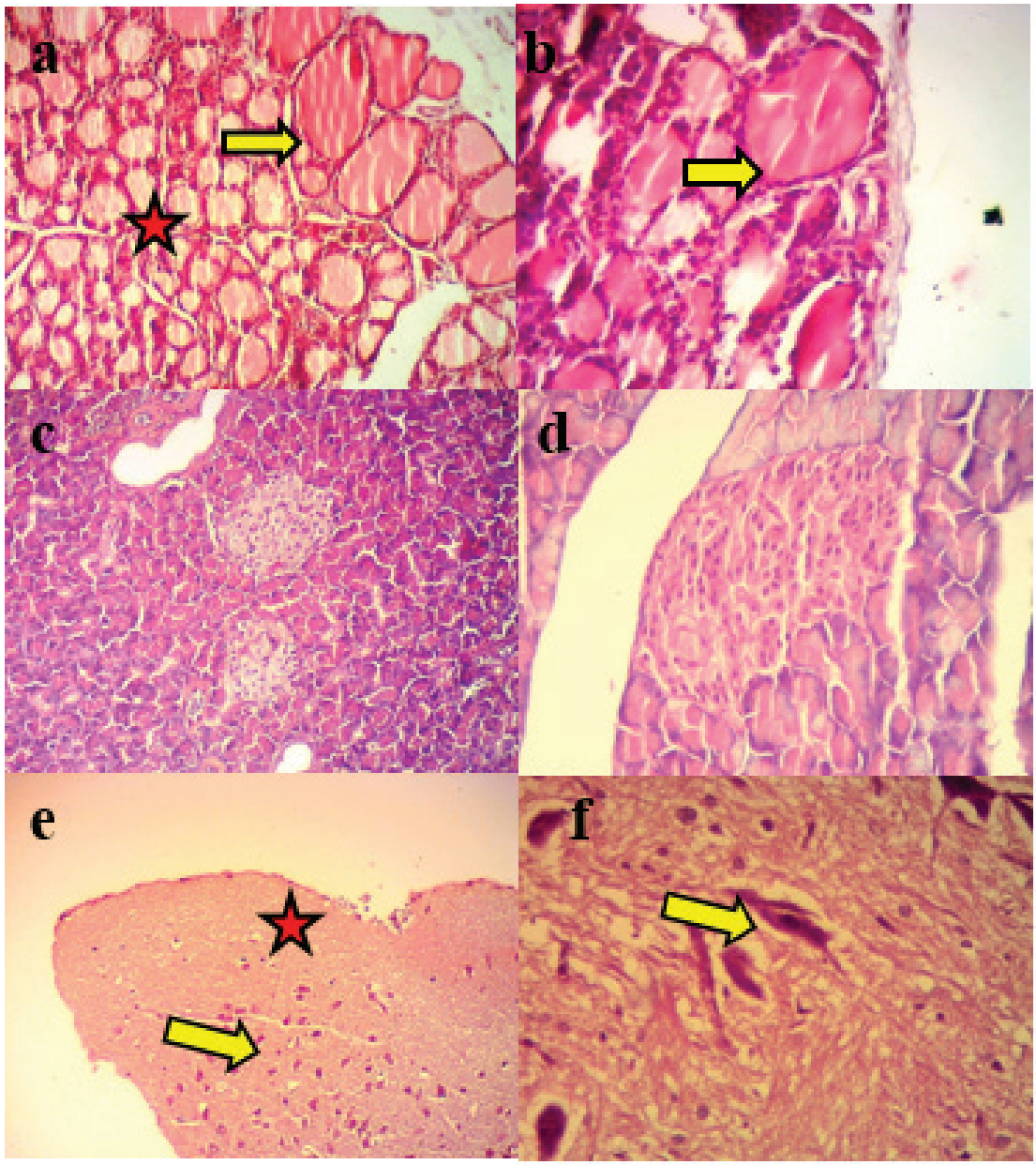

Figure 2: Low digoxin group, show dilation of thyroid follicles (yellow arrow) and some area without changes (red star) (a 200X &b 400X), pancreas don't show any changes in exocrine gland & islets of langerhance (c 200X &d 400X) and adrenal gland show atrophy of cortex layers (red star) with hyperplasia of medullary cells (yellow arrow) (e 200X &f 400X).

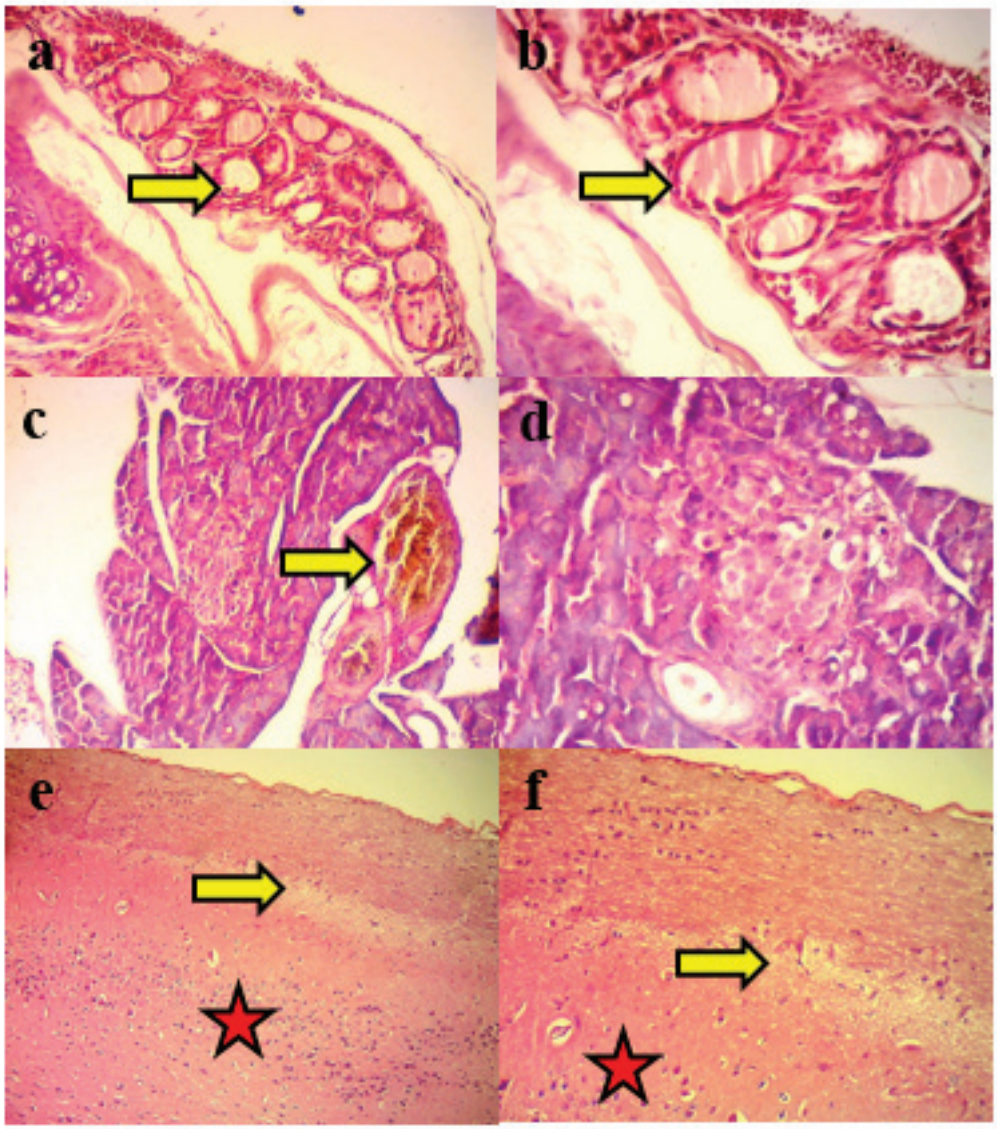

Figure 3: High digoxin group, show moderate to sever flattening of thyroid follicle epithelium filled with colloid (yellow arrow) (a 200X &b 400X), pancreas show unremarkable changes except congestion of blood vessels (yellow arrow) (c 200X &d 400X) and adrenal gland show atrophy of cortex layers especially zona reticularis (yellow arrow) with medullary cells hyperplasia (red star) (e 200X & f 400X).

Discussion

The present study is designed to provide a data base about histopathological changes caused by digoxin drug on thyroid, pancreas and adrenal glands in rats. The control group showed normal architecture of these gland as shown in figure-1. It has been noted that increase dose of digoxin cause more changes in these gland compared to lower dose group, thyroid gland presented as enlarged follicles associated with flattened epithelium which may be related to effect of digoxin on thyroid gland to suppress thyroxin hormone release because of it is anticipated action on myocardium. Digoxin provide positive inotropic effect on the heart, which leads to increase stroke volume, vascular perfusion and improve blood pressure. This might cause a negative feedback on the function of thyroid gland which shows features of hypo functioning thyroid follicles. The present study doesn't reveal significant changes in pancreatic tissue except in high dose digoxin pancreas which revealed congested blood vessels, as shown in figure-3.

Ouabain is an endogenous digoxin-like substance that is produced by adrenal medulla cells and it has a similar mechanism of action to digoxin [7,10]. During heart failure, because digoxin blocks the action of adrenaline effect on the heart, this probably may lead to atrophy of adrenalin producing cells in adrenal medulla which is accompanied by hyperplasia of ouabain synthetic cells. This finding is evident by the histological appearance of hyperplasia of ouabain-producing medullary cells of adrenal gland after digoxin administration which becomes more prominent with increased dosage of digoxin. This result is in line with Takahashi [10], who reported that a monoclonal ouabain antibody was highly distributed in adrenal medulla. Medullary hyperplasia is associated with atrophy of cortical layers of adrenal gland as shown in figures-2 and 3.

Upon reviewing literature regarding the histopathological changes of cardiac glycoside (digoxin), the authors didn't come across any research studying these changes. This research may be the first of it is kind in this field.

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: Self-funding

References

1. Goodman and Gilman The Pharmacological Basis of Therapeutics, 3rd ed. New York, The MacMillan Co., (1970). 653, 665-667.
2. Konstantinou, DM.; Karvounis, H., and Giannakoulas, G. Digoxin in Heart Failure with a Reduced Ejection Fraction: A Risk Factor or a Risk Marker?. Cardiology, (2016). 134: 311–319.
3. Pincus, M. Management of digoxin toxicity. Australian prescriber, (2016). 39:: 18–20.
4. Bagrov, AY., and Fedorova, OV. Cardenolide and bufadienolide ligands of the sodium pump. How they work together in NaCl sensitive hypertension. Front. Biosci., (2005). 10: Pp: 2250-2256.
5. Alves, AJ.; Alves, AQ.; Delima, JG.; Goes, AJS.; Da Silva, ACR.; Da Silva, FF., and Alves, CJ. Pharmacokinetics of a single dose of digoxin in healthy volunteers using the linux operating system. Inter. J. of Bio., Pharmacy and Allied Sciences, (2014). 3(12):Pp: 2932-2943.
6. Roberts, DM.; Gallapatthy, G.; Dunuwille, A., and Chan BS. Pharmacological treatment of cardiac glycoside poisoning. British J. of Clin. Pharm., (2015). 81(3):Pp: 488–495.
7. Valente, R.C. Capella, L.S. et al. Mechanisms of Ouabain Toxicity. The Journal of the Federation of American Societies for Experimental Biology. 2003; 17(12): 1700 – 1702.
8. Bancroft, JD.; Stevens, A., and Turner, DR. Theory and practice of histological techniques (3ed.).Churchill Livingstone, (1990). Pp:21-26.
9. Drury, RA. Carlton's Histological Technique.4th ed. Oxford University Press., Toronto., (1967). Pp:140.
10. Takahashi, H. Ihara, N. Terano, Y. Yamada, H. Nishimura, M. et al. Ouabain-like immunoreactive substances exist in the hypothalamus and the adrenal medulla in rats. Pathophysio1, (1994). :25-28.