Ultrastructural Effects of Tamoxifen on Uterus in Rats

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Tamoxifen is a triphenylethylene derivative commonly used in the treatment of breast cancer The Wistar rats (9 weeks old, 180–200 g body weight) used in these trials were divided into two groups of 20 animals each (control and experimental group). Animals of the experimental group were given drinking water containing 200 µg/kg tamoxifen citrate for a period of 30 day. At the end of exposure, body and uterus weights were measured. There was no statistical difference in the uterus weights between the control and treated groups ($p < 0,05$). Squamous metaplasia, characterized by the presence of stratified squamous epithelium on the lumenal surface of the uterus and the lining of the luminal surface of uterine glands was seen in some animals that had received tamoxifen. Ultrastructural changes were revealed in the form of vacularization of cell cytoplasm and The cytoplasm contained areas of low electron density. Not only was the cytoplasm full with intense crystalized and degeneration in mitochondria.

Key words: Tamoxifen citrate, uterus, electron microscopy, rat

INTRODUCTION

Tamoxifen is the only compound known to prevent breast cancer incidence in healthy women [1]. Tamoxifen is known to have varied biological effects ranging from complete estrogen antagonism to pure estrogen agonism depending upon its concentration, the sex of the animal, and the target organ [2, 3]. In humans and rats, tamoxifen is predominantly antiestrogenic with residual estrogenic activities [2]. Since the 1990s, however, epidemiological evidence has accumulated with regard to causation of uterine endometrial cancers, seen as second primary cancers after the use of Tamoxifen for the treatment of breast cancer [4, 5]. The aim of this study was to evaluate the histopathological effects ultrastructurally on uterus of rat treated with tamoxifen.

MATERIAL AND METHODS

The Wistar rats (9 weeks old, 180–200 g body weight) used in these trials were divided into two groups of 20 animals each (control group and experimental group). Animals of the experimental group were given drinking water containing 200 µg/kg tamoxifen citrate for a period of 30 day. The rats were obtained from the Department of Medical Science Application and Research centre of Dicle University. All the animals were indivially housed in stainless steel cages at room temparature. The animals had free Access to standart laboratory rat pellet and water. The total body and uterus weights of rats were taken. The data were analyzied statistically by using student's t-test. The animals were sacrificed by decapitation under ether anesthesia uterus tissue were then quickly removed. The total body of rats were taken. Sample preparation for light microscopy. After fixation of tissues by formaldehyde 10% solution, they are directly dehydrated in a graded serious of ethanol and embedded in parafine. Thin sections 5–6 micrometre were cut using a microtome and stained with Trichrom-Masson and then examined using a light microscope. The samples were placed in the gluteral aldehide which is prepared with phosphate cushion of % 2, 5 the stabilization cyling was made. After tissue section were passed in the osmium tetroxide solution tissue were taken in to the CY-964 araldit. Thin sections of 70nm thick were stained with lead citrate-uranyl acetate and examined and photographed under Zeiss Electron microscope 9S.

RESULTS

There was no statistical difference in the body weights between the control and treated groups ($p < 0.05$), There was no statistical difference in the uterus weights between the control and treated groups. ($p < 0,05$), (Table 1). Histopathologically, Squamous metaplasia, characterized by the presence of stratified squamous epithelium on the luminal surface of the uterus and the lining of the luminal surface of uterine glands was seen in some animals that had received tamoxifen (Fig. 1) No histological changes were detected in the remaining uterine stromal and myometrial compartments. Cross-section of a control group of normal endometrial epithelial and stromal structure in view of the protection has been observed (Fig. 2). Ultrastructural changes were revealed in the form of vacuolarization of cell cytoplasm and The cytoplasm contained areas of low electron density. Not only was the cytoplasm full with intense crystalized and degeneration in mitochondria (Fig. 3) endometrial epithelial cells to maintain normal view incytoplasm organels any change in structure was observed with nucleus (Fig.

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Table 1

Groups	Body weight (g)	Uterus weight (g)
Control group (n = 10)	200 ± 6.0	2.18 ± 0.01
200 µg/kg tamoxifen citrate n = 10	180 ± 6.0	2.17 ± 0.02

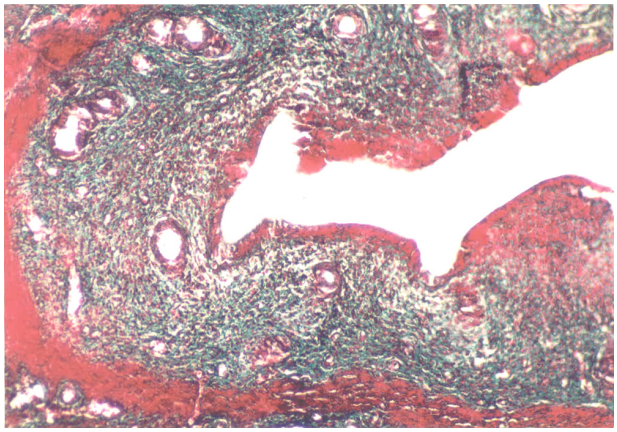

Fig. 1 Squamous metaplasia in epithelium (arrow) epithelium into the lumen in the fall. and any changes in the connective tissue was observed myometrium. (Trichrom-masson X82)

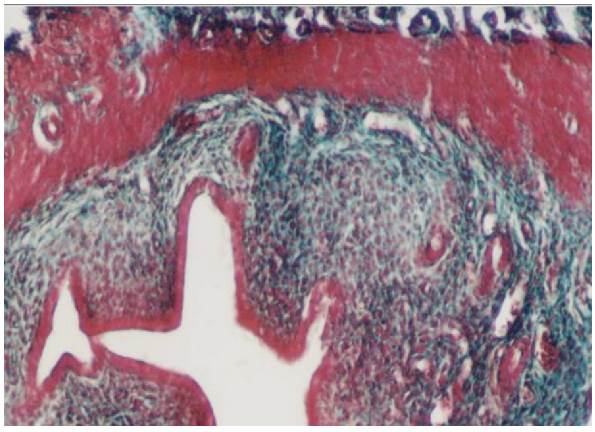

Fig. 2 Connective tissue and muscle layer of the epithelium to a regular outline any changes were seen. (Trichrom-masson X82)

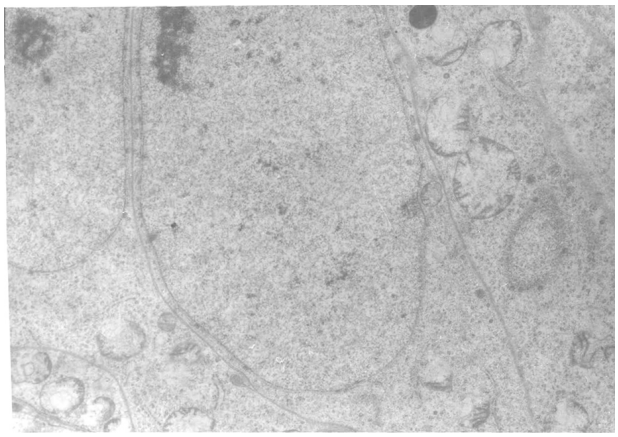

Fig. 3 Vacuolarization in cytoplasm, degeneration in mitochondria and Dilatation and irregularity of the cisternae of granular endoplasmic reticulum, (Uranyl acetate-lead citrate- X8800)

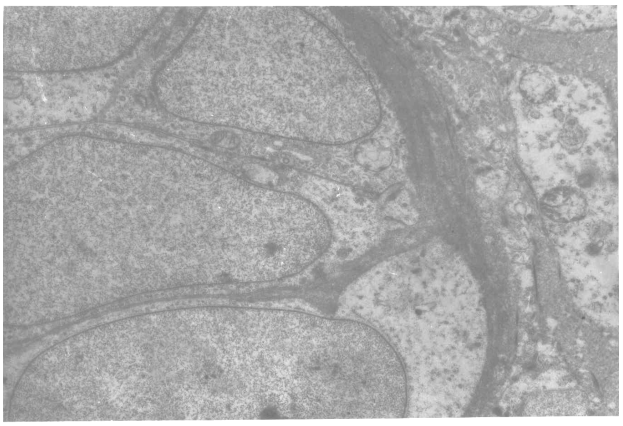

Fig. 4 Normal appearence of endometrium (Uranyl acetate- lead citrate- X8800)

4).

DISCUSSION

Tamoxifen is known to have varied biological effects ranging from complete estrogen antagonism to pure estrogen agonism depending upon its concentration, the sex of the animal, and the target organ [2, 3]. Tamoxifen administration in postmenopausal women has been associated with decreased serum levels of FSH and LH, likely due to an estrogenic e.ect on the hypothalamus [6, 7]. In addition, tamoxifen therapy has been associated with increased incidences of endometrial cancer, likely due toits estrogenic e.ects [8, 9] Tamoxifen at 200 µg/kg per day had uterotrophic activity in the epithelial and glandular compartments, causing hypertrophy/hyperplasia of the epithelial and glandular cells, but overall there was a reduction in uterine weight, presumably due to antiestrogenic activity in the remaining stromal and myometrial compartments. These compartmentalized uterotrophic and antiestrogenic effects of tamoxifen have been previously described in the rat after 28 days of oral administration at 1 and 10 mg/kg per day [10]. Tamoxifen had uterotrophic activity in the epithelial compartment, causing marked Squamous metaplasia of the luminal and glandular epithel cells. Inhibition in the case of tamoxifen (200 µg/kg for 28 days) appeared mitochondria with degenerating cristae. Affect the use of the cellular structure of Tamoxifen in endometrium to occur a number of changes were seen.

REFERENCES

1) Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 90: 1371–1388, 1998.
2) Furr BJA, Jordan VC (1984) The pharmacology and clinical uses of tamoxifen. Pharmacol Ther, 25: 127–205.
3) MacNab MW, Tallarida RJ, Joseph R (1984) An evaluation of tamoxifen as a partial agonist by classical receptor theory-an explanation of the dual action of tamoxifen. Eur J Pharmacol 103: 321–326.
4) I. Cohen, M.M. Altaras, S. Lew, R. Tepper, Y. Beyth and G. Ben-Baruch, Case report. Ovarian endometrioid carcinoma and endometriosis developing in a postmenopausal breast cancer patient during tamoxifen therapy: a case report and review of the literature. *Gynecol. Oncol.* 55 (1994), pp.443–447.
5) M.A. Killackey, T.B. Hakes and V.K. Pierce, Endometrial adenocarcinoma in breast cancer patients receiving antiestrogens. *Cancer Treat. Rep.* 69 (1985), pp.237–238.
6) Buckley MMT, Goa KL (1989) Tamoxifen, a reappraisal of its pharmacodynamic and pharmacokinetic properties, and therapeutic use. Drugs 37: 451.
7) Jaiyesimi IA, Buzdar AU, Decker DA, Hortobagyi GN (1995) Use of tamoxifen for breast cancer: twenty-eight years later. J Clin Oncol 13(2): 513.
8) Fornander T, Rutqvist LE, Cedermark B, Glas U, Mattsson A, Silfversward C, Skoog L, Somell A, Theve T, Wilking N, Askergren J, Hjalmar ML (1989) Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. Lancet 1(8630): 117.
9) Goel V (1998) Tamoxifen and breast cancer prevention: what should you tell your patients? Can Med Assoc J 158(12): 1615.
10) Nephew KP, Osborne E, Lubet RA, Grubbs CJ, Khan SA (2000) Effects of oral administration of tamoxifen, toremifene, dehydroepiandrosterone, and vorozole on uterine histomorphology in the rat. Proc Soc Exp Biol Med, 223: 288–294.