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Research Article

Drug-Hormone Interference Affects Pituitary-Thyroid-Adrenal Axis in Urinary Tract Infection

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ABSTRACT

Nitrofurantoin has been used commonly as an antimicrobial treatment for urinary tract infections. Although the combination of lung and liver cytotoxicity is very rare, it may occur up on treatment with nitrofurantoin. Nitrofurantoin-associated pulmonary interactions are common among females. The anticholinergic and antimuscarinic effects of Flavoxate hydrochloride enhance the selective relaxant activity of strong smooth muscle on the urinary tract to relief pain and vesicourethral spasms. It used for urinary frequency and incontinence associated with the urinary tract inflammations. Although various studies indicated the presence of burden effects of Nitrofurantoin and Flavoxate, there is a lack of literature studied the impact of those drugs on pituitary-thyroid-adrenal axis in urinary tract infections. Blood samples were withdrawn *via* venipuncture from male and female patients at the end of the treatment period and healthy controls to measure serum Follicle-stimulating hormone (FSH), Estradiol (E2), Luteinizing hormone (LH), Prolactin, Progesterone, Dehydroepiandrosterone (DHEAS), Testosterone, Thyroid-stimulating hormone (TSH), Triiodothyronine (T3), Thyroxine (T4), Fasting Insulin, and Cortisol. The circulating hormonal levels were measured quantitatively using Enzyme-link immunosorbent assay (ELISA). Hormonal profiling showed that there were remarkable signatures could be of great interest to underline some recommendations and guidelines optimizing the drug dosage to avoid burdens associated with those drugs as well as maintain the physiological and psychological performances of both sexes.

Keywords: Nitrofurantoin, Flavoxate, pituitary-thyroid-adrenal axis, urinary tract infection.

INTRODUCTION

Nitrofurantoin, a furan analogue, has been used widely as an antimicrobial treatment for urinary tract infections (UTI). But, its burden effect on hepatic injury induction was first observed in 1961[1]. Its spectrum includes *Escherichia coli*, *Citrobacter*, *Streptococci B*, enterococci, *Staphylococcus aureus*, *S. epidermidis*, *Klebsiella pneumonia*, and *Enterobacter* species[2]. Since then a wide spectrum of interactions with nitrofurantoin has been seen, ranging from lung disease and acute hepatitis to chronic hepatitis, leading to cirrhosis or even death[3]. In addition, it is one of the causes of autoimmune liver disease[4]. Thus, nitrofurantoin is well known as a cause of burden drug interactions.

Although the combination of lung and liver cytotoxicity is very rare, it may occur up on treatment with nitrofurantoin[5-9]. Nitrofurantoin-associated pulmonary interactions are common among females, because they are more susceptible to UTI recurrence[10,11].

Nitrofurantoin inhibits some bacterial enzymes participating in carbohydrate metabolism through Krebs cycle[2] and interfering with cell wall synthesis[12]. The functional site of nitrogroup on the drug's furan ring has to be activated by microbial nitroreductases[13].

It has been found that antacid may increase the nitrofurantoin ionization, decreasing its absorption. Moreover, nitrofurantoin is a strong inhibitor of primary adenine diphosphate-induced platelet conglomerate. It changes the levels of some laboratory parameters include elevation of urine creatinine, as well as serum urea, glucose, alkaline phosphatase, and bilirubin elevated[2].

The anticholinergic and antimuscarinic effects of flavoxate hydrochloride, a flavone derivative, enhance the selective relaxant activity of strong smooth muscle on the urinary tract to relief of pain and vesicourethral spasms resulting from surgery. It used for urinary frequency and incontinence associated with the urinary tract inflammations[14].

Flavoxate hydrochloride, a tertiary-amine antimuscarinic, is used for its antispasmodic characteristics in the symptomatic therapy of numerous urological disorders. This occurs by increasing the capacity of urinary bladder, owing to its effect on the detrusor muscle[15]. Although the common risk of suffering from angle closure glaucoma after treatment with anticholinergics[16], there is no previous case study of flavoxate-induced glaucoma except which reported by Mohammed et al. [17]

Recently, the influence of some digestive, colon, and anti-gout drugs on the pituitary-thyroid-adrenal axis was investigated previously[18,19]. They reported significant changes in serum FSH, E2, LH, Prolactin, Progesterone, DHEAS, Testosterone, TSH, T3, T4, Fasting Insulin, and Cortisol up on treatment with Spasmo Canulase, Librax[18], and Allopurinol[19]. Accordingly, authors recommended

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drug dose optimizations depending on the drug effect on each human hormone and new medical guidelines to avoid negative side effects that could harm patients.

The previous observations promoted us to investigate, as the first time, the drug-hormone interference of the Nitrofurantoin and Flavoxate hydrochloride, as therapeutic drugs for urinary tract infections, on the pituitary-thyroid-adrenal axis as follow; a) Sex hormonal profile includes Follicle-stimulating hormone (FSH), Estradiol (E2), Luteinizing hormone (LH), Prolactin, Progesterone, Dehydroepiandrosterone (DHEAS), and Testosterone, b) Thyroid hormonal profile includes Thyroid-stimulating hormone (TSH), Triiodothyronine (T3), and Thyroxine (T4), c) Fasting Insulin and Cortisol.

MATERIALS AND METHODS

Subjects

The current study has been conducted on 100 adult individuals with ages ranging from 20 to 60 years. Volunteers have been divided into two groups; 50 patients group suffered from urinary tract disease and 50 healthy controls. Age and weight were noticed and determined during the duration of the study. Patients and controls had the same average of age and weight. The protocol and informed consent were approved by the Ethics Committee of National Research Centre. Patients received 50 to 100 mg of Nitrofurantoin and 100 to 200 mg of Flavoxate hydrochloride therapies orally 3 to 4 times daily for a week were enrolled in the prospective study.

To exclude other drug interactions with Nitrofurantoin and Flavoxate, over-the-counter medicines, vitamins, and herbal products, and any medicine other than those two drugs were avoided during the period of therapy.

Enzyme-linked assay for hormonal profiling

Blood samples were drawn *via* venipuncture from male and female patients at the end of the treatment period and healthy controls to measure serum Follicle-stimulating hormone (FSH - mIU/ml), Estradiol (E2 - pg/ml), Luteinizing hormone (LH - mIU/ml), Prolactin (ng/ml), Progesterone (ng/ml), Dehydroepiandrosterone (DHEAS - µg/dl), Testosterone (ng/dl), Thyroid-stimulating hormone (TSH - µIU/ml), Triiodothyronine (T3 - ng/ml), Thyroxine (T4 - ng/ml), Fasting Insulin (mIU/ml), and Cortisol (mg/dl).. Blood samples were collected from patients, and then all circulating hormonal levels were investigated quantitatively using Enzyme-link immunosorbent assay (ELISA) kits purchased from (DRG International, Inc., USA, Diagnostic Systems Laboratories. Inc., and Adaltis Italia SPA Company, Italy).

Statistical Analysis

Data were statistically analyzed using statistical computer program: SPSS (Statistical Package for the Social Science; SPSS Inc., version 17.0, USA). Data were described in terms of mean and standard errors when appropriate. Comparison of variables between the study groups was performed using analysis of variance (ANOVA) test. A probability value (P-value) less than 0.05 has been considered statistically significant.

RESULTS

Follow up data obtained from all patients treated with Nitrofurantoin and Flavoxate hydrochloride drugs and healthy individuals were performed. Figures (1-5) illustrates the hormonal levels of the pituitary-thyroid-adrenal axis obtained from the adult patients received Nitrofurantoin and Flavoxate hydrochloride drugs.

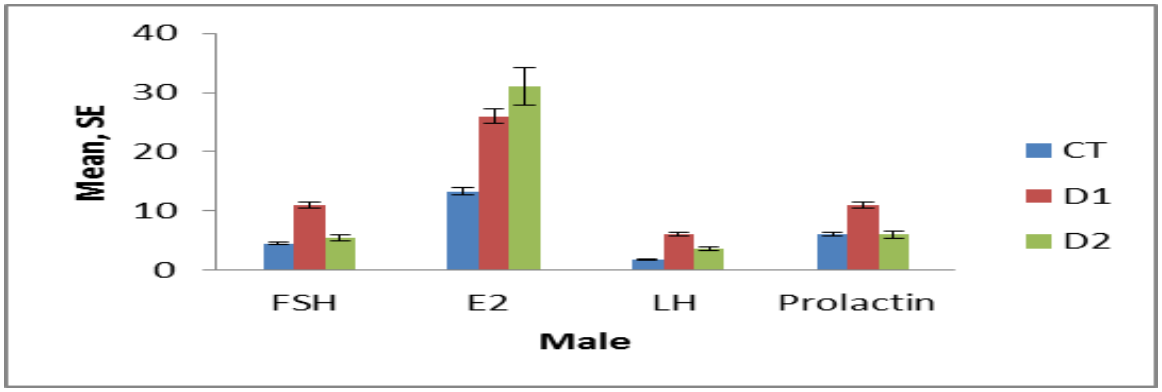
Intriguingly, male and female patients received Flavoxate hydrochloride and Nitrofurantoin drugs have high significant increase ($P<0.01$) of serum Estradiol (E2), while males only have high significant increase ($P<0.01$) of Luteinizing hormone (LH) compared to healthy controls. In addition, male and female patients received Flavoxate hydrochloride drug has significant increases ($P<0.01$) of serum Follicle-stimulating hormone (FSH) and Prolactin compared to healthy controls. On the other hand, female patients received Nitrofurantoin drugs have significant increases ($P<0.01$) of serum Prolactin levels compared to controls as illustrated in (Figure 1).

Figure (2) shows high significant increases ($P<0.01$) of Progesterone concentrations in male and female patients received Nitrofurantoin drug compared to controls. In addition, there were significant elevations ($P<0.01$) of Testosterone levels in female patients received Flavoxate and Nitrofurantoin drugs compared to healthy controls. On the contrary, there were significant decreases ($P<0.01$) of Testosterone levels in male patients received Flavoxate and Nitrofurantoin drugs compared to healthy controls.

Figure (3) shows that there were high significant increases ($P<0.01$) of serum Thyroid-stimulating hormone (TSH) and Thyroxine (T_4) when comparing male and female patients received Flavoxate and Nitrofurantoin drugs with healthy controls. Although the significant increases ($P<0.01$) of serum Triiodothyronine (T_3) levels in male patients received Flavoxate and Nitrofurantoin drugs, there were high significant increases ($P<0.01$) of serum T_3 levels in female patients received just Nitrofurantoin drug with healthy controls.

Intriguingly, patients received Flavoxate hydrochloride drug have high significant decreases ($P<0.01$) of serum Dehydroepiandrosterone (DHEAS) levels compared to healthy controls. On the contrary, patients received Nitrofurantoin drug have high significant increases ($P<0.01$) of serum DHEAS concentrations compared to healthy controls as illustrated in (Figure 4).

Figure (5) shows that male and female patients received Flavoxate hydrochloride drug have high significant increases ($P<0.01$) of serum Fasting Insulin, while male and female patients received Nitrofurantoin drug have significant decreases ($P<0.05$) of serum Fasting Insulin compared to healthy individuals. In addition, male and female patients received Flavoxate hydrochloride and Nitrofurantoin drugs have significant decreases ($P<0.01$) of serum Cortisol concentrations at morning compared to controls. On the other hand, male and female patients received Nitrofurantoin drug have significant increases ($P<0.01$) of serum Cortisol levels at night compared to control group. While, female patients received Flavoxate



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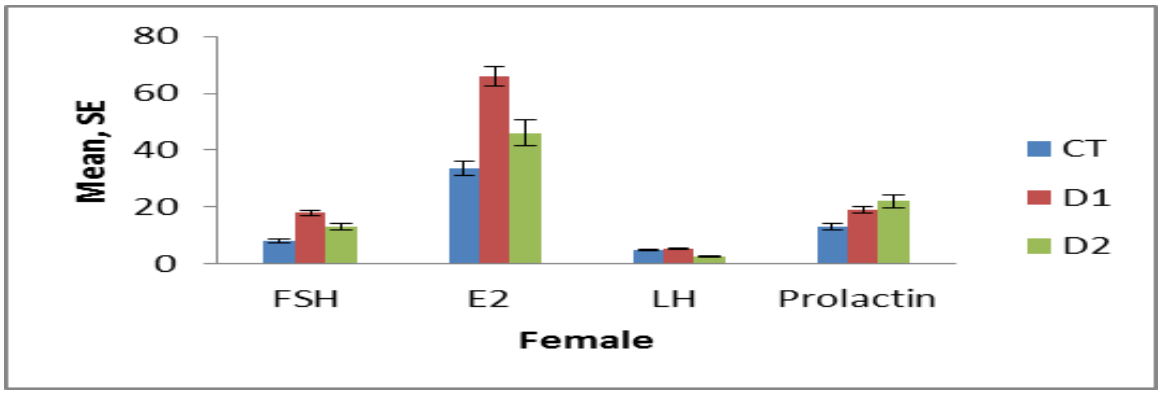

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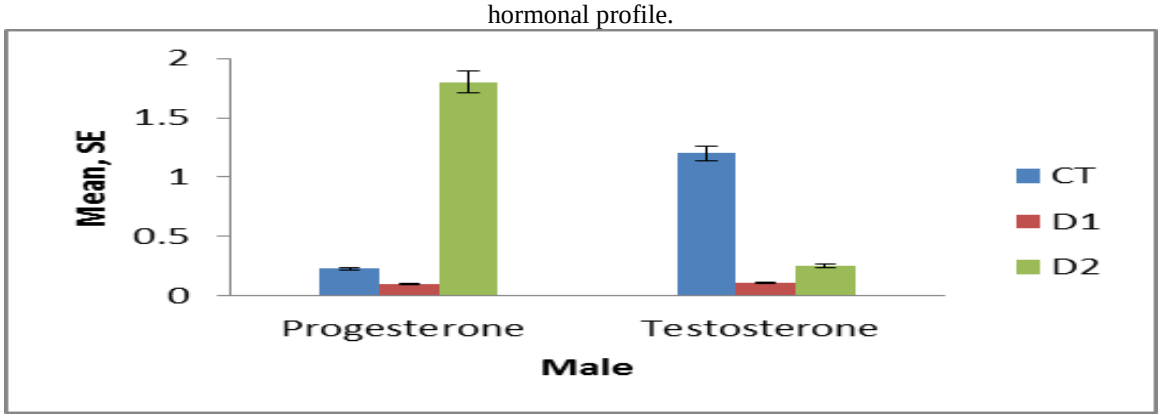
Figure 1: The impact of Flavoxate (D1) and Nitrofurantoin (D2) on male (a) and female (b) FSH, E2, LH, prolactin hormonal profile.



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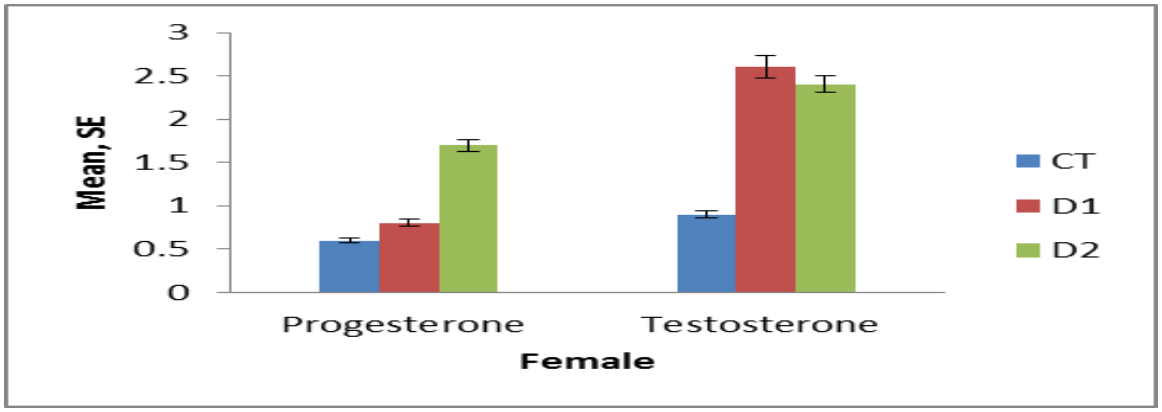

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Figure 2: The impact of Flavoxate (D1) and Nitrofurantoin (D2) on male (a) and female (b) progesterone and testosterone human hormonal profile.

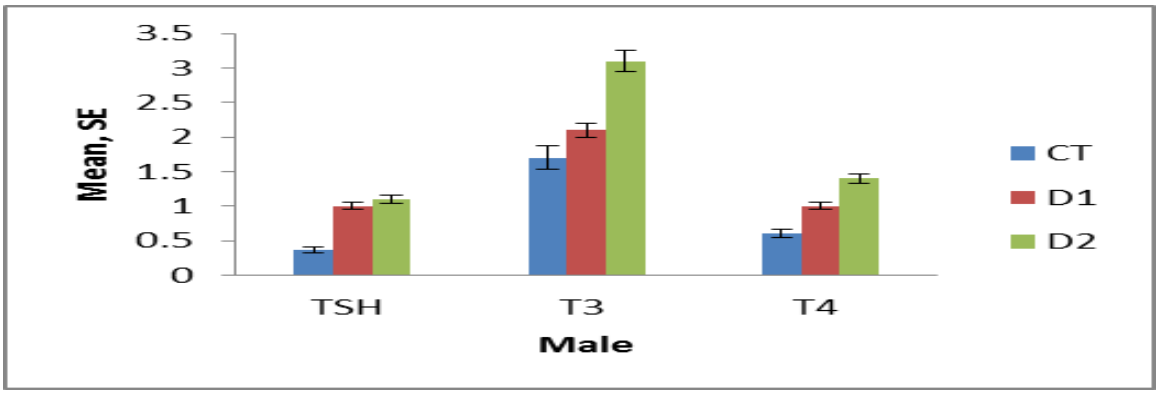
hydrochloride drug have significant decreases (P<0.01) of serum Cortisol levels at night compared to control group.

DISCUSSION

Intriguingly, patients treated with Flavoxate hydrochloride and Nitrofurantoin drugs have revealed significant elevations in thyroid hormones (T_3, T_4, and TSH) compared to healthy controls which may lead to severe dysfunction in thyroid system and imbalance in the functional homeostasis of the body accompanied with burden side effects. These observations are in agreement with some previous studies indicated that Spasmo Canulase and Librax drugs induce thyroid[18], thyroid-stimulating hormones[20], and thyrotropin-releasing hormone receptor[21], therefore it seems to go in parallel with the significant elevations of the thyroid hormones among patients treated with Flavoxate hydrochloride and Nitrofurantoin drugs.

In the present study, patients treated with Flavoxate hydrochloride and Nitrofurantoin drugs have remarked changes in serum sex hormones (FSH, E2, LH, Prolactin, Progesterone, DHEAS, and Testosterone) compared to controls. The current output have been supported by Eskander et al[18] and Kamat et al[22] reported that Spasmo Canulase and Librax activate luteinizing hormone-releasing hormone (LHRH) *via* releasing of reactive oxygen species from neurons.

Generally, nitrofurantoin is a comparatively safe therapy[23-25], however adverse interactions observed, mainly related to long-term usage, have included gastrointestinal disturbances, skin eruptions, hematologic disorders, neurological defects, hepatotoxicity,



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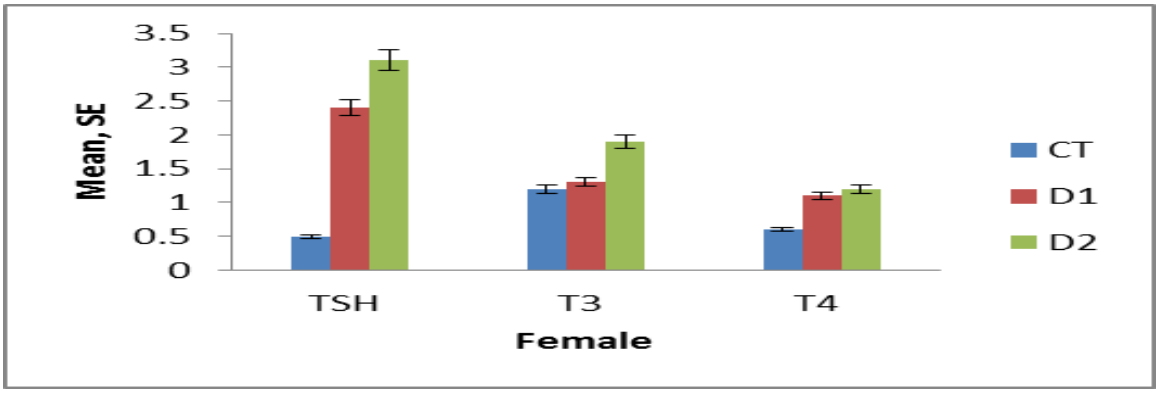

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Figure 3: The impact of Flavoxate (D1) and Nitrofurantoin (D2) on male (a) and female (b) human thyroid hormonal profile.

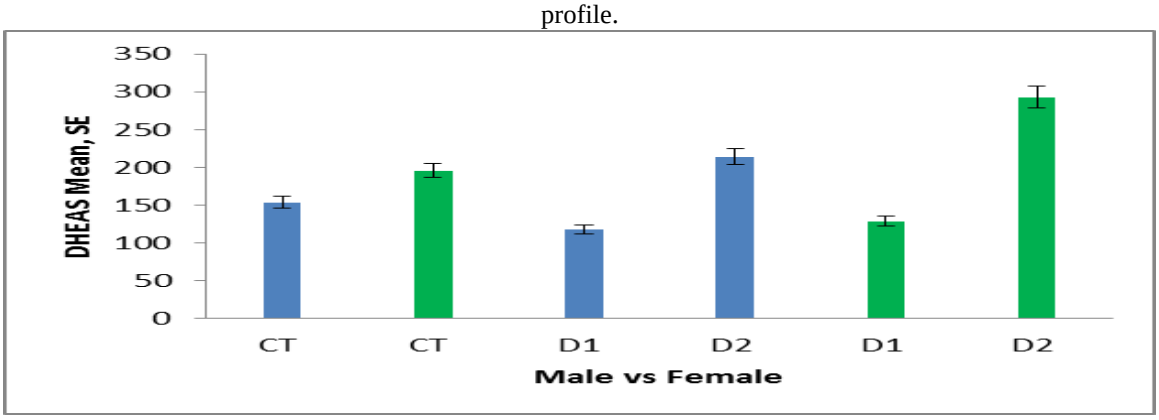


Figure 4: The impact of Flavoxate (D1) and Nitrofurantoin (D2) on male versus female DHEAS levels.

pulmonary complications, and miscellaneous abnormalities.

Many adverse reactions are shown, ranging from gastrointestinal disturbances (anorexia, nausea, and vomiting), skin eruption (macular or urticarial lesions), and hemolytic anemia in patients have low amounts of enzyme glucose-6-phosphate dehydrogenase (G6PD)[3], to peripheral neuropathy and reversible hepatotoxicity[26]. However, drug-induced pulmonary reactions are common in many patients characterized by the sudden onset of fever, cough, and dyspnea. Primary care systems should underline the guidelines of pulmonary toxicity, which is may be reversible in early stages[27].

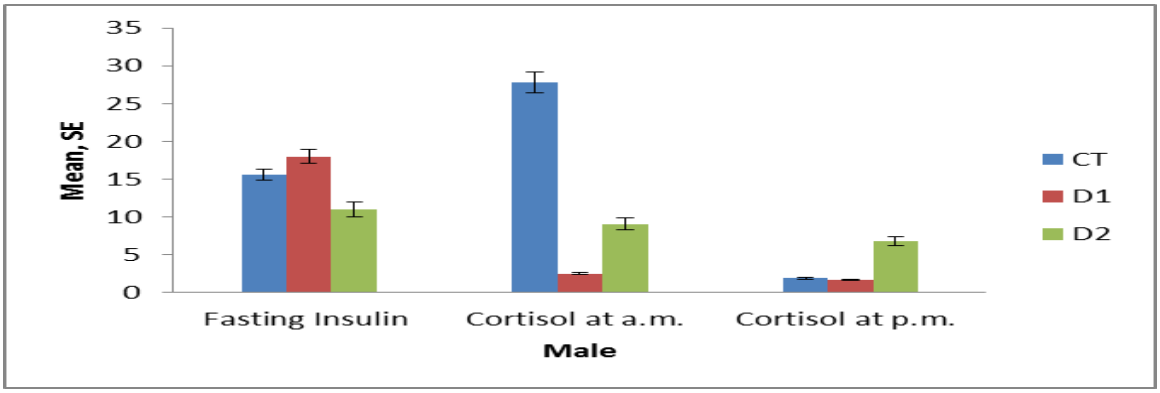
However some medical literature defines nitrofurantoin as a relatively safe antibiotic during pregnancy, new concerns about congenital and cardiovascular malformations[28,29]. However, numerous studies have reported that nitrofurantoin is not associated with increased teratogenic risks[30-35]. This observation has been supported by Goldberg *et al.*[36] who treat a large cohort of pregnant women suffered from UTI with nitrofurantoin and failed to detect teratogenic risks, because it does not penetrate the placenta[37], therefore, the fetus will be safe except in the advanced stages[38].

The drug-drug interactions after treatment of UTI patients and the adverse effects were counted and these interactions were measured using WHO Causality Categories[39] and the Naranjo ADR Probability Scale[40]. Usage of those two techniques showed a 'probable' link between these burden effects and flavoxate hydrochloride treatment.

Currently, the anticholinergic therapies are the most effective drugs to combat overactive bladder symptoms. Moreover, this therapeutic group can improve frequency and incontinence by interfering with receptors localized on the detrusor muscle cells. Blurred vision, dry mouth, and constipation are common side effects of the anticholinergic therapies. In addition, they induce pupillary dilatation and narrowing the angle of the anterior chamber causing angle closure glaucoma, thereby interfering with the aqueous circulation and movement of the iris diaphragm, led to what so called "papillary block glaucoma" in some rare cases[16]. Sung *et al.*[41] published a case like that; 80 year old woman had acute angle closure glaucoma after treatment with oxybutynin, a flavoxate-like agent.

Flavoxate hydrochloride has been commonly used therapeutically for the overactive bladder. The exact mechanism of action for urge incontinence is obscure but its anticholinergic features should play an important role[15]. Several studies[42-44] have found no significant changes when comparing between flavoxate hydrochloride and placebo in case of urge incontinence, therefore, it is difficult to recommend its usage as a first line treatment, because there is a lack of adequate data to support its usage in this condition[45].

Eventually, blurred vision, as a burden effect of anticholinergics, is due to relaxation of the ciliary muscle as well as temporary impairment of visual accommodation associated with elevated intraocular pressure[46], therefore when diagnosis is uncertain, ophthalmology should be intervene.



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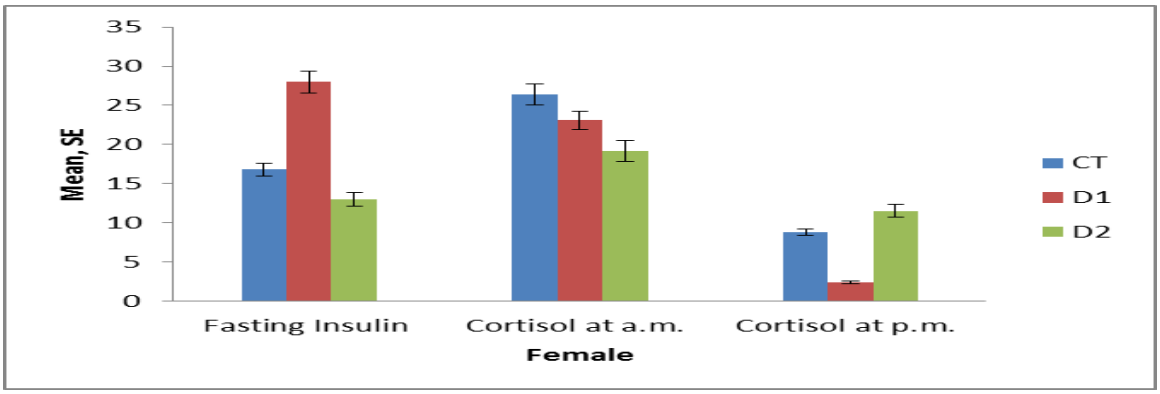

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Figure 5: The impact of Flavoxate (D1) and Nitrofurantoin (D2) on male (a) and female (b) fasting insulin and day/night cortisol levels.

These hormonal signatures could be of great interest; its alteration may lead to malfunction in the physiological performance of both sexes associated with bad psychological effects, thus dosage optimization depending on drug-hormone interference effect is an important key element that must be taken into consideration in the treatment of urinary tract diseases using Flavoxate hydrochloride and Nitrofurantoin.

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