Pharmacological Profile of Some Cytochrome P 450 Modulators 1. Effect On Some Steroidal Hormones

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ABSTRACT

The present study was carried out to study the effect of ciprofloxacin (CYP-450 inhibitor) and rifampicin (CYP-450 inducer) on some endogenous steroidal hormones (estradiol, progesterone, testosterone and cortisol) and exogenously administered progesterone and testosterone hormones in mature male & female rats. Ninety mature male and female rats were divided into 9 equal groups (each of 5 males and 5 females). The first group was left without treatment and kept as normal control group. The second group was given ciprofloxacin in a dose of 1.8 mg/100 gm. B.wt. i.p daily for 5 days. The third group received rifampicin (2.25 mg/100 gm) i.p for 5 successive days, the 4th group received testosterone 2.5 mg/100 gm) given as a single s.c dose 24 hours before blood sampling and served as testosterone control group, the 5th group received progesterone (1.25 mg/100 gm) as a single s.c injection 24 hours before blood sampling and served as progesterone control group. The 6th and 7th groups received ciprofloxacin plus testosterone and/or progesterone respectively in the same doses given before. Whereas, the 8th and 9th groups were given rifampicin + testosterone and/or progesterone respectively in the same doses. Blood samples were collected after 24 hours of fasting for preparation of serum samples. The results revealed that the administration of the test drugs alone or in combinations with either testosterone or progesterone for 5 successive days afforded a significant decrease in the levels of steroidal hormones under investigation when compared with their respective control groups with few exceptions as follows: A significant increase in serum estradiol level of the 4th and 9th groups of male and female groups. A significant increase in serum progesterone and cortisol levels of the 4th , 7th and 9th groups of male and female rats. From the obtained results we can conclude that care must be taken when using ciprofloxacin and/or rifampicin because of their drug –drug interaction as well as their effect on endogenous steroidal hormones.

INTRODUCTION

Drug metabolism is the main process responsible for biotransformation of different xenobiotics (foreign compounds) in the body to be water soluble and thus more readily excreted in the urine or bile *(1)*.

The biotransformation reactions of xenobiotics are catalysed predominantly by CYP-450 enzymes which are found most predominant in the liver and to a lesser extent in the extrahepatic tissue, like intestine, lungs and other organs *(2)*. Therefore, the CYP-450 enzymes are responsible for the metabolism of numerous xenobiotics, including therapeutic drugs, environmental chemicals, and dietary constituents, as well as endogenous compounds as steroids, vitamin D and bile acid *(3)*. The CYP-450 enzymes may play also an important role in biosynthesis of cholesterol, steroids and thromboxane A_2 *(4)*.

Some drugs may cause induction or inhibition of CYP-450 enzymes which may alter the metabolism of these enzymes substrates either the endogenous compounds or other administered drugs.

The fluoroquinolones are an extremely popular class of antibacterials which have gained widespread use in the treatment of a broad range of bacterial infections, owing to their broad spectrum of activity and the convenience of their i.v. and oral dosage formulations *(5)*. Ciprofloxacin and norfloxacin were found to inhibit CYP3A and CYPIA-mediated biotransformation by a competitive inhibition and that they have the potential to cause drug interactions with agents metabolized by these enzymes *(6)*.

Rifampicin is a semisynthetic derivative of rifamycin B produced by streptomyces mediterranie. The drugs is highly effective in treatment of tuberculosis and leprosy. The antibacterial spectrum of rifampin includes both gram positive and gram-negative organisms *(7)*.

Rifampicin is a well known P-450 enzymes inducer and consequently accelerate the elimination of a large number of compounds such as midazolam, quinidine, cyclosporine A and many steroids *(8)*.

The present study was aimed to investigate the effect of CYP-450 enzymes inducer (Rifampicin) and inhibitor (Ciprofloxacin) on serum level of some endogenous steroidal hormones (Cortisol, estradial, progesterone and testosterone) that are mainly metabolized by CYP-450 enzymes. The present study investigates also their effect on exogenously administered testosterone and progesterone.

MATERIAL AND METHODS

Drugs

I. Ciprofloxacin (Ciprotril)®

Ciprofloxacin (ciprotril)® solution is produced by Vapco Amman, Jordan.

It is available in bottles of 100 ml. each ml. contains 100 mg ciprofloxacin. The human dose was converted to rat dose ***Paget and Barnes (9)*** to be 1.8 mg/100. b.wt.given intraperitoneally.

II. Rifampicin

Rifampicin Rifocin® it was supplied by El-Nasr pharmaceutical Chemicals Co, Cairo, Egypt as amp., each contains 250 mg. It is given i.p in a dose of 2.25 mg/100 gm b.wt. *(10)*.

Testosterone : It was supplied as Cidoteston® ampoule each ampoule contains 250 mg testosterone oenanthate/ml from CID (Chemical Industries Development), Giza, Egypt. It was given S.C in a dose of 2.5 mg/100 gm of rat *(9)*.

Progesterone®. It was supplied as 17-Alfa-hydroxy progesterone 17-Caproate. Each amp. contains 125 mg/ml. It was given S.C in a dose of 1.25 mg/100 gm b.wt. *(9)*. It was supplied by Cid (Chemical Industries Development, Giza, Egypt).

Experimental Design Ninety mature male and female rats were randomly divided into 9 groups (10 rats 5 of each sex) according to the following design:

Group (1): Served as a control group.

Group (2): Received ciprofloxacin (1.8 mg/100 gm. B.wt.) i.p daily for 5 days.

Group (3): Received rifampicin (2.25 mg/100 gm. i.p.) daily for 5 days.

Group (4): Received testosterone (2.5 mg/100 gm) given as single S.C dose 24 hours before blood sampling and served as a testosterone control group.

Group (5): Received progesterone hormone (1.25 mg/100 gm) given as a single S.C injection 24 hours before blood sampling and served as a progesterone control group.

Group (6): Received ciprofloxacin in the same dose given to second group daily for 5 days in addition to testosterone hormone 24 hours before blood sampling.

Group (7): Received ciprofloxacin in the same dose given to 2nd group daily for 5 days in addition to a single S.C injection of progesterone 24 hours before blood sampling.

Group (8): Received rifampicin in the same dose given to 3rd group daily for 5 days in addition to a single S.C injection of testosterone 24 hours before blood sampling.

Group (9): Received rifampicin in the same dose given to 3rd group daily for 5 days as well as a single S.C injection of progesterone 24 hours before blood sampling.

METHODS

Blood sampling and serum preparation

After drugs administration, animals were fasted for 24 hours, after which blood samples were collected, in clean dry test tubes, from the retro-orbital plexus using heparinized microcapillary tubes *(11,12)*. The tubes were allowed to stand for 15 minutes to clot at room temperature, then centrifuged at 3000 r.p.m for 15 minutes using Heraeus sepatech centrifuge (Labofuge 200). The serum was separated and kept at -20 °C until used for assay of hormones.

1) Determination of serum estradiol

Serum 17 β-estradiol level was determined by enzyme immunosorbent assay (Elisa) using Immulite 1000 analyser *(13)* using a diagnostic kit supplied by Simens Medical Solutions Diagnostics (Immulite / Immulite 1000 estradiol) Limited, USA.

2) Determination of progesterone

Serum progesterone level was determined by Enzyme Linked Immunosorbent Assay (Elisa), *(14, 15)*, using a diagnostic kit supplied by Siemens Medical Solution Diagnostics Limited, USA (Immulite / Immulite 1000 progesterone) and the Immulite 1000 analyser .

3) Determination of serum testosterone

Serum testosterone level was determined by Enzyme Linked Immunosorbent Assay (ELISA) *(16)* using a diagnostic kit (Immulite /Immulite 1000 Testosterone) supplied by Siemens Medical Solution Diagnostics Limited, USA and the Immulite 1000

4) Determination of cortisol

It was determined by enzyme linked Immunosorbent Assay (Elisa) *(17)* using a diagnostic kit supplied by Diamed Eurogen cortisol kit, Australia and the Immulite 1000 analyser.

Statistical Analysis

All results are expressed as mean + Standard error of the mean. The results were evaluated for differences from control values using Students "t" test for unpaired data *(18)*. A significant difference was assumed for values of $P<0.05$

RESULTS

1- Effect on serum estradiol

The obtained results revealed that the administration of ciprofloxacin alone in the recommended doses afforded a non-significant change in serum estradiol level of male and female rats respectively. Whereas, rifampicin alone induced a significant decrease in both male and female rats when compared with normal control group. Table (1).

The injection of each of testosterone and /or progesterone elicited a significant increase and decrease in serum estradiol level of male rats when compared with normal control group. Meanwhile, the combinations of testosterone and /or progesterone with ciprofloxacin and /or rifampicin afforded a marked decrease in serum estradiol level of male and female rats compared with their respective controls except groups injected with combinations of rifampicin with progesterone which showed a significant increase in serum estradiol level in both male and female rats.

The injection of each of testosterone and /or progesterone into female rats afforded a significant decrease ($P< 0.05$) in serum estradiol level when compared with normal control group. The same table and figure revealed that the combinations of testosterone and /or progesterone with each of ciprofloxacin and rifampicin elicited a significant decrease ($P<0.05$) when compared with their respective controls.

Table 1. Effect of ciprofloxacin 1.8 mg/100 gm b.wt., rifampicin 2.25 mg/100gm b. wt., testosterone 2.5 mg/100gm b.wt., progesterone 1.25 mg/100gm b.wt. and their combinations on serum estradiol of rats. (Mean ± S.E.) (n = 5)

Group	Treatment	Estradiol pg/ ml	
		Male	Female
I	Normal Control	44.46 ± 0.376^{B}	79.96 ± 1.296^{A}
II	Ciprofloxacin treated	52.18 ± 5.17^{AB}	78.38 ± 0.751^{A}
III	Rifampicin treated	39.60 ± 0.678^{C}	68.56 ± 0.924^{B}
IV	Testosterone treated	53.4 ± 0.60^{A}	62.00 ± 0.547^{C}
V	Progesterone treated	38.80 ± 0.735^{C}	65.00 ± 0.447^{C}
VI	Ciprofloxacin + Testosterone	31.38 ± 0.393^{D}	44.92 ± 2.17^{D}
VII	Ciprofloxacin + progesterone	26.30 ± 0.344^{E}	46.78 ± 1.02^{D}
VIII	Rifampicin + testosterone	18.00 ± 0.207^{F}	49.12 ± 1.08^{D}
IX	Rifampicin + progesterone	46.36 ± 0.306^{B}	72.02 ± 0.335^{B}

Means within the same column bearing different superscripts are significant at $P \leq 0.05$.

2- Effect on serum progesterone

Table 2, illustrates the effect of test drugs and hormones on serum progesterone level of male and female rats. The serum progesterone level was significantly and non-significantly decreased in groups given ciprofloxacin and rifampicin respectively in both male and female rats. In addition to a significant decrease in its level in male rats treated with progesterone alone. The combination of testosterone with either ciprofloxacin or rifampicin elicited a significant decrease in serum progesterone of male and female rats. Whereas, a significant increase was recorded in male rats given combinations of progesterone with either ciprofloxacin or rifampicin compared with their respective controls. In female rats, the same previous picture observed in male rats was reported.

Whereas, a significant increase ($P< 0.05$) was observed in male rats injected with testosterone compared with normal control group.

Table 2. Effect of ciprofloxacin 1.8 mg/100 gm b.wt., rifampicin 2.25 mg/100gm b. wt., testosterone 2.5 mg/100gm b.wt., progesterone 1.25 mg/100gm b.wt. and their combinations on serum-progesterone of rats. (Mean ± S.E.) (n = 5)

Group	Treatment	Serum Progesterone ng/ ml	
		Male	Female
I	Normal Control	1.64 ± 0.075^{D}	3.94 ± 0.136^{D}
II	Ciprofloxacin treated	1.142 ± 0.032^{E}	3.446 ± 0.212^{D}
III	Rifampicin treated	1.04 ± 0.1327^{E}	1.864 ± 0.092^{E}
IV	Testosterone treated	258.0 ± 9.338^{A}	1289.8 ± 96.14^{A}
V	Progesterone treated	1.06 ± 0.169^{E}	4.04 ± 0.364^{D}
VI	Ciprofloxacin + Testosterone	1.92 ± 0.0374^{D}	1.47 ± 0.03^{F}
VII	Ciprofloxacin + progesterone	5.04 ± 0.156^{B}	6.7 ± 0.114^{C}
VIII	Rifampicin + testosterone	2.28 ± 0.281^{D}	1.88 ± 0.086^{F}
IX	Rifampicin + progesterone	5.98 ± 0.456^{B}	7.42 ± 0.146^{B}

Means within the same column bearing different superscripts are significant at $P \leq 0.05$.

3- Effect on serum testosterone

The serum testosterone level of male and female rats given ciprofloxacin, rifampicin, and their combination with testosterone and progesterone was significantly decreased when compared with their respective control rats. Whereas, groups given either testosterone or progesterone each alone afforded a significant elevation in serum testosterone level of male and female rats compared with normal control group Table (3)

Table 3. Effect of ciprofloxacin 1.8 mg/100 gm b.wt., rifampicin 2.25 mg/100gm b. wt., testosterone 2.5 mg/100gm b.wt., progesterone 1.25 mg/100gm b.wt. and their combinations on serum testosterone of rats.(Mean ± S.E.) (n = 5)

Group	Treatment	Serum Testosterone ng/ ml	
		Male	Female
I	Normal Control	60.2 ± 1.77^{D}	15.82 ± 0.213^{G}
II	Ciprofloxacin treated	47.6 ± 2.99^{E}	9.08 ± 0.124^{H}
III	Rifampicin treated	49.14 ± 2.93^{E}	18.22 ± 0.037^{F}
IV	Testosterone treated	558.0 ± 6.63^{A}	124.8 ± 2.245^{A}
V	Progesterone treated	71.8 ± 1.28^{C}	101.2 ± 1.157^{B}
VI	Ciprofloxacin + Testosterone	267.6 ± 9.59^{B}	52.14 ± 0.765^{F}
VII	Ciprofloxacin + progesterone	27.04 ± 0.16^{F}	59.38 ± 0.514^{E}
VIII	Rifampicin + testosterone	247.00 ± 4.35^{B}	88.60 ± 0.60^{C}
IX	Rifampicin + progesterone	45.4 ± 0.40^{E}	81.72 ± 0.185^{D}

Means within the same column bearing different superscripts are significant at $P \leq 0.05$.

4- Effect on serum cortisol

It was apparent from Table and Fig. 4 that the administration of ciprofloxacin, testosterone and progesterone alone elicited non-significant changes in serum cortisol level of male rats compared with normal control group whereas, group given rifampicin showed a significant decrease ($P< 0.05$).

Whereas, in female rats, ciprofloxacin elicited a significant increase in serum cortisol level, while a significant decrease was noticed in female rats given rifampicin, testosterone and progesterone each alone when compared with normal control group. The combination of testosterone with either ciprofloxacin or rifampicin afforded a significant decrease in serum cortisol level of both male and female rats compared with their respective controls. On the other hand the combinations of progesterone with either ciprofloxacin or rifampicin induced a significant increase in serum cortisol level of both male and female rats.

Table 4. Effect of ciprofloxacin 1.8 mg/100 gm b.wt., rifampicin 2.25 mg/100gm b. wt., testosterone 2.5 mg/100gm b.wt., progesterone 1.25 mg/100gm b.wt. and their combinations on serum cortisol of rats. (Mean ± S.E.) (n = 5)

Group	Treatment	Serum Cortisol µg/ ml	
		Male	Female
I	Normal Control	29.28 ± 0.332^{B}	29.20 ± 0.860^{B}
II	Ciprofloxacin treated	28.26 ± 0.354^{B}	30.50 ± 0.184^{B}
III	Rifampicin treated	24.96 ± 0.452^{C}	8.864 ± 0.045^{H}
IV	Testosterone treated	28.60 ± 0.40^{B}	26.40 ± 0.509^{C}
V	Progesterone treated	28.20 ± 0.583^{B}	8.96 ± 0.074^{G}
VI	Ciprofloxacin + Testosterone	11.48 ± 0.354^{E}	7.14 ± 0.067^{H}
VII	Ciprofloxacin + progesterone	37.26 ± 0.04^{A}	10.22 ± 0.132^{F}
VIII	Rifampicin + testosterone	24.1 ± 0.332^{C}	12.2 ± 0.328^{E}
IX	Rifampicin + progesterone	36.90 ± 0.473^{A}	20.24 ± 0.371^{D}

Means within the same column bearing different superscripts are significant at $P \leq 0.05$.

DISCUSSION

Cytochrome P-450 (CYP-450) enzymes are a group of hemoproteins embedded primarily in the lipid bilayer of the endoplasmic reticulum of hepatocytes *(19)*. They catalyze the oxidative, peroxidative and reductive metabolism of a wide variety of endogenous and exogenous compounds *(20)*. The induction or inhibition of CYP-450 expression is probably the most common cause of documented drug interactions *(21)*.

Fludroquinolones are an extremely popular class of antibacterials which have gained widespread use in the treatment of a broad range of bacterial infections, owing to their broad spectrum of activity and the convenience of their i.v and oral dosage formulations *(6)*. Ciprofloxacin and norfloxacin were found to inhibit CYP 3A and CYPIA- mediated biotransformation by a competitive inhibition and that they have the potential to cause drug interactions with agents metabolized by these enzymes *(6)*.

Rifampicin is a well known P-450 enzymes inducer and consequently accelerate the elimination of a large number of compounds such as midazolam, Quinidine, Cyclosporine A and many steroids *(8)*.

In the present study, administration of ciprofloxacin non-significantly increased serum estradiol level in male rats, while it did not alter serum estradiol level in the female rats *(22, 23)*. The administration of cimetidine (CYP -450 inhibitor) in male rats and human resulted in an increase in the serum estradiol level. This increase is related to the inhibition of estradiol hydroxylation mediated by CYP-450. Moreover, serum estradiol level in female rats

and in premenopausal women were not altered by cemitidine. The lack of effect of cimetidine on serum estradiol in female rats could be explained by the fact that the hydroxylation of estradiol is mainly catalysed by CYP 2 C11, which is male specific CYP-450 and specifically inhibited by cimetidine ***(24-26).*** Similar response was obtained on using combinations of ciprofloxacin with either testosterone or progesterone.

Our results showed also that the administration of rifampicin for 5 consequtive days to both male & female rats afforded a significant decrease in serum estradiol concentrations. *(27)* . It has been reported that17-alpha-ethynylestradiol is extensively sulfated but the sulfate is thought to primarily a storage form this estrogen-2-hydroxylation is clearly the major oxidative reaction, and the 2-hydroxy derivative is further transformed by methylation and glucuronidation prior to urinary and fecal excretion. Alteration in the rate of 2-hydroxylation can have major effects on the pharmacokinetics and effectiveness of 17-alpha-ethynylestradiol as a contraceptive. The major human catalyst of the 2-hydroxylation reaction is liver microsomal cytochrome P-450 111 A4. less amounts of this enzyme are found in other tissues such as the intestine and may contribute to the overall clearance of the orally administered contraceptive. In individuals with very low amounts of this enzyme other forms of cytochrome P-450 may make some contribution. Levels of cytochrome P-450 111A4 vary widely among individuals and can explain the variation in the rates of 17-alpha ethynyl-estradiol 2-hydroxylation. The known inducibility of the enzyme by rifampicin explains its effect in enhancing 17-alpha-ethynyl estradiol clearance and reducing the effectiveness of the drugs.

Treatment of patients with rifampicin 600 mg for 6-10 day, caused a 4 fold increase in the rate of hydroxylation of estradiol and ethinyl estradiol at positions C-2, C-4 of ring A and C-6/ C-7 of ring B *(28)*. The acceleration of estrogen hydroxylation by rifampicin paralleled by an increase in microsomal cytochrome P-450 and also by microsomal reduction of rifampicin– Quinone, a reactive metabolite of rifampicin. The increased aromatic hydroxylation of estradiol and ethinyl-estradiol leads to enhancement of their irreversible binding to microsomal protein. These data provides an explanation for the diminished efficacy of estrogens in contraceptive formulations given to patients under treatment with rifampicin.

On a similar basis the antituberculous drug rifampicin causes an inducing effect on liver enzymes and that is the reason why rifampicin treatment resulted in undesired pregnancy and bleeding disorders during contraception by combination of ethinyl-estradiol and levonogesterol or desogesterol tablets ***(29)***. The significant decrease of estradiol obtained in this study in response to treatment with the combination of rifampicin with progesterone could be also interpreted as previously mentioned with rifampicin.

Concerning the effects of various treatments on serum testosterone level, our results revealed that ciprofloxacin and rifampicin each alone afforded a significant decrease in serum testosterone level of male and female rats. Additionally, the combinations of ciprofloxacin, rifampicin with either testosterone and/or progesterone afforded a significant decrease in the hormone level of both male and female rats compared with their respective controls.

The decreased testosterone level obtained in this study in response to treatment of male & female rats with combinations of ciprofloxacin and /or rifampicin with either testosterone or progesterone could be possibly attributed to decreased L.H hormone level observed in this study. Although both antipyrine and rifampicin (an enzyme inducing drugs) increased antipyrine clearance by about 60%. They produced contrary effects on testosterone, antipyrine lowered total morning plasma testosterone and plasma testosterone AUC following Tu, while rifampicin led to an increase of about 20% and 78% respectively ***(30)***.

Concerning the effects of various treatments on serum progesterone level in both male and female rats, our results revealed a significant

increase in response to treatment with testosterone alone and combinations of ciprofloxacin and /or rifampicin with progesterone when compared with their respective control. Whereas, a significant decrease was recorded in rats treated with progesterone in both male and female rats and in female rats treated with rifampicin alone and combination of ciprofloxacin with testosterone when compared with their respective control groups.

Two mechanisms of action has been for accidental pregnancies occurring in oral contraceptive (OC) users who are currently taking certain antibiotics and antifungal agents suggesting some form of drug interaction *(31)*. First, drugs such as rifampin and griseofulvin induce liver enzymes that break down the estrogen and progestin contained in oral contraceptives reducing plasma hormone level. Second, changes in the intestinal bacterial flora induced by penicillin and tetracycline may reduce the gut's absorption of hormones also compromising efficacy. Cimetidine (a P-450 inhibitor) and phenytoin (a P-450 inducer) significantly reduced serum progesterone levels *(32)*.

Cimetidine was reported to inhibit progesterone metabolism mediated by CYP 2C11 in male rats *(33)*. The inhibition of progesterone metabolism may lead to an initial elevation in its serum level to that needed to produce feedback inhibition and consequent decrease in serum progesterone level. Moreover, the progesterone treatment in male rats produced the same decrease in serum progesterone as did cimetidine in male rats.

Our results revealed that treatment of male rats with progesterone elicited a significant decrease in serum progesterone level. Whereas, female rats treated with progesterone showed non-significant change in serum progesterone level. The effect of progesterone treatment on serum progesterone level in male rats may be attributed to the negative feedback inhibition produced by an initial increase in progesterone level. As progesterone directly inhibits the secretion of L.H from the pituitary gland through progesterone receptors present in gonadotrophs *(34,35)*. Moreover, progesterone down regulates gonadotrophin releasing hormone GnRH receptors with subsequent limitation of its action to stimulate L.H secretion and release *(36, 37)*. This inhibition of L.H secretion, in turn may cause a decrease in progesterone secretion.

On the other hand the lack of such effect of progesterone treatment on progesterone level in female rats could be related the gender difference in progesterone metabolism. Progesterone is known to be mainly metabolized by the male –specific P-450 isoform, CYP 2C11 and CYP 3A2 in male rat liver microsomes into 16 α-oxidized metabolites. Whereas, they are mainly metabolized in the female into the 5 α-reduced metabolites by female predominant 5 α reductase *(38,39)*. The major 5 α reduced metabolites of progesterone were found to stimulate the 5 α-reductase activity producing themselves *(40)*. In other words the main progesterone metabolites in female induce progesterone metabolism in female rats. Taking together from the previous findings, it could be concluded that in female rats, progesterone treatment exerts an autoinduction, so the progesterone level doesn't reach the level required for feedback inhibition to occur. The increased progesterone level obtained in this study in response to treatment with rifampicin alone or its combination with progesterone coincides with the study which showed that phenytoin which is a P-450 inducer induced a significant elevation in serum progesterone in both male and female rats *(32)*.

Regarding the effect of test drugs, hormones and their combinations on serum cortisol level, our results revealed that ciprofloxacin afforded a non-significant change in both male and female rats. It has been observed previously that administration of ciprofloxacin in a dose of 500 mg orally every 12 hours for 4 days to eight healthy subjects afforded no significant differences in the concentration time curve of cortisol when compared with base line values *(41)*. Whereas, the administration of the P-450 inducer rifampicin to both male and female rats elicited a significant decrease in serum cortisol level compared with control group. Rifampicin

increase the catabolism of cortisol following hepatic microsomal enzyme induction by rifampicin *(42)*.

Phenytoin (a potent CYP-450 inducer) elicited a significant decrease in serum cortisol level of both male and female rats *(32)*. These results are in harmony with other studies, which reported that phenytoin caused a decrease in serum cortisol level of both male and female healthy volunteers, epileptic patients and rodent model *(43,44)*. The phenytoin effect on cortisol level can be explained by more than one mechanism represented as follows: phenytoin may increase corticosteroid-binding globulin levels to which cortisol binds with consequent increase in the binding of cortisol and so decrease free active hormone level *(45)*. In addition phenytoin may inhibit pituitary – adrenal secretion in mice and rats *(46)*, which may be referred to its inhibitory effect on steroidogenesis catalysed by cytochrome P-450 mono-oxygenase systems in rats *(47)*. Moreover, phenytoin was reported to accelerate cortisol metabolism, presumably in liver, since it is the chief organ responsible for the cortisol metabolism *(44)*.

The significant increase in serum cortisol level in both male and female rats in response to treatment of rats with the combinations of ciprofloxacin and /or rifampicin with progesterone might be possibly attributed to a competitive antagosis between progesterone and ciprofloxacin and /or rifampicin on the corticosteroid binding globulin resulting in decreased cortisol binding and hence increasing its free level in the blood on one hand, and on the second hand as sequence to increased glucose level induced by rifampicin leading to increased production rate of cortisol. As it is well known that cortisol is a stressor hormone that increased in cases of stress since hyperglycemia is a stress factor.

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الملخص العربى

الصورة الفارماكولوجية لبعض محورات أنزيم السيتوكروم ب ٤٥٠
١- التأثير على بعض الهرمونات الاستيرودية

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تم القيام بهذه الدراسة من أجل دراسة تأثير السيبروفلوكساسين (المثبط لأنزيم السيتوكروم ب ٤٥٠) والريفامبيسين (الذى يزيد انتاج هذا الأنزيم) على بعض الهرمونات الاستيرودية داخل جسم ذكور واناث الفئران البالغة (الاستراديول ، البروجستيرون ، التستوستيرون والكورتيزول).

ولإجراء هذه الدراسة تم استخدام عدد ٩٠ فأر أبيض بالغ تم تقسيمها عشوائيا إلى تسع مجموعات متساوية كل مجموعة عشرة فئران (٥ ذكور و ٥ إناث) . المجموعة الأولى تركت بدون علاج كمجموعة ضابطة ، أما المجموعة الثانية فقد تم حقنها داخل الغشاء البريتونى بجرعة قدرها ١,٨ مجم/١٠٠ جم من وزن الفئران يوميا لمدة خمسة أيام ، المجموعة الثالثة تم حقنها بنفس الطريقة ونفس المدة بعقار الريفامبسين بجرعة قدرها ٢,٢٥ مجم/ ١٠٠ جم من وزن الفئران . المجموعة الرابعة تم حقنها تحت الجلد بجرعة واحدة من هرمون التستوستيرون قدرها ٢,٥ مجم/١٠٠ جرام قبل ذبح الحيوانات بـ ٢٤ ساعة. المجموعة الخامسة تم حقنها تحت الجلد بجرعة واحدة من هرمون البروجستيرون قدرها ١,٢٥ مجم/١٠٠ جرام قبل الذبح بـ ٢٤ ساعة. المجموعة السادسة تم حقنها السبروفلوكاسين مع التستوستيرون بنفس الجرعات السابق ذكرها ونفس الكيفية . أما المجموعة السابعة فتم حقنها بنفس المدة بخليط من عقار السيبروفلوكساسين مع هرمون البروجستيرون . أما المجموعة الثامنة والتاسعة فتم حقنها بخليط من عقار الريفامبسين مع كل من التستوستيرون والبروجستيرون على التوالى. تم ذبح الفئران بعد تصويمها لمدة ٢٤ ساعة وأخذ عينات من الدم لتجميع المصل.

ولقد أظهرت النتائج أن إعطاء العقاقير محل الدراسة كل على حدة أو خليط منها مع التستوستيرون أو البروجستيرون لمدة ٥ أيام متتالية قد أحدث نقصا معنوياً فى مستوى جميع الهرمونات الاستيرودية محل الدراسة وذلك عند مقارنتها بمجموعات الضوابط . فيما عدا بعد الاستثناءات مثل : زيادة معنوية فى مستوى الاستراديول للمجموعة الثانية والتاسعة للذكور والإناث. وكذا زيادة معنوية فى مستوى هرمون البروجستيرون والكورتيزول فى المجموعة السابعة والتاسعة من الذكور والإناث.

ومن هذه النتائج فإننا ننصح بإتخاذ الحذر عند استخدام هذه المستحضرات فى الذكور والإناث وذلك نظراً لتداخلاتها مع الهرمونات الاستيرودية داخل الجسم.