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RESEARCH ARTICLE

EFFECT OF CIPROFLOXACIN ON CERTAIN BIOCHEMICAL PARAMETERS IN THE BLOOD SERUM OF ALBINO RATS

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A B S T R A C T

Healthy adult male albino rats of wistar stain weighing 180 – 225gms were used. They were fed with a standard balanced diet and clean drinking water. The drug ciprofloxacin hydrochloride T.P was used for the animals. The weighed animals divided into the four groups, of five animals each and received of treatment. After treatment of weighed the rats, serum was separated immediately after the sacrifice by centrifugation and stored until used for hormone assays. Elisa of FSH, LH and Testosterone was estimated. In the present study, there was consistent reduction in serum FSH alone but not serum LH which suggest diminished production of FSH only from pituitary. This may be due to the decreased response of gonad tropes to GnRH stimulation. The lowered testosterone, raised normal LH titres as well as low serum FSH levels in this study suggest that there is poor negative feedback control by the testicular hormones to the hypothalamo - hypophysical regions.

INTRODUCTION

NSAIDs are chemically diverse group of substances that exert several distinct pharmacological properties such as the ability to increase inflammation, ability to relieve moderate pain (analgesic), the ability to decrease elevated body temperature associated with fever (antipyretic) and the ability to decrease blood clotting, by inhibiting platelet aggregation (anticoagulant) (Narma and Mayeux, 1989).

Conventional non-steroidal anti-inflammatory drugs (NSAID) are associated with significant toxicities that can frequently limit their use despite their substantial clinical benefits in the management of rheumatoid arthritis, osteoarthritis, pain, and other musculoskeletal complaints (Goldstein, 2000). Ciprofloxacin is a useful, orally available, non toxic broad spectrum antibiotic (Smyth and Pallet, 1989). It is used to treat bacterial infections. Ciprofloxacin penetrates many hard tissues in the body and kills a wide variety of bacteria. Ciprofloxacin is widely distributed throughout the body through circulation. The volume of distribution of quinolones is high, with concentrations of quinolones in urine, kidney, lung, stool, bile, macrophages and neutrophil higher than serum levels. Studies have not been done in humans (Priyadharshini and Vanithakumari, 2013).

The first 1-cyclopropyl fluoroquinolone ciprofloxacin was synthesized in 1983 (Wentland, 1990) and was found to have a range of potencies depending on the nonpolar aliphatic substitutes at N-1. The antibiotic was remarkable among the quinolones for its high activity. *In vitro* and in mice, it was atleast twice as potent as norfloxacin against the *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Ciprofloxacin is considerably more active than the similar isopropyl quinolones (Wentland, 1990). Results from animal studies have shown that NSAIDs can impair the tooth movement process. Until long-term human data are obtained acetaminophen remains an appropriate alternative to NSAIDs for treating orthodontic associated pain (Walker and Buring, 2001). Isolated cases of eosinophilia, thrombocytosis, monocytosis and leukopenia are known with ciprofloxacin treatment (Ball, 1986). In one case, mild leukopenia resolved after reducing the ciprofloxacin dosage from 1g to 500mg daily (Eron *et al*., 1985).

MATERIALS AND METHODS

Healthy adult male albino rats of Wistar strain weighing 180 - 225 gms were used in the present investigation. They were housed in clean cages in a well ventilated room with 12 ± 1 hour light and 12 ± 1 hour dark schedule. They were fed with a standard balanced diet and clean drinking water was made available *ad libitum*. The drug Ciprofloxacin hydrochloride T.P. manufactured by Okasa Limited, Goa, India was used for the The animals were weighed and divided into the following four groups, of 5 animals each, and received the following regimen of treatment.

Group I: Control: Rats received distilled water and oil orally, respectively.
Group II: Short Duration: Rats received ciprofloxacin hydrochloride for one week

Group III: Short Duration + Withdrawal: Treatment as for group IV plus 14 days of drug withdrawal
Group IV: Long Duration: Rats received ciproflaxacin hydrochloride for four weeks
Group V: Long Duration +Withdrawal: Treatment as for group IV plus 60 days of drug withdrawal.

Group II and Group IV were further subdivided into five sub groups.

1. Low dose ciprofloxacin treated group : The rats received ciprofloxacin (250 mg/60 kg body weight)
2. High dose ciprofloxacin treated group : The rats received ciprofloxacin (400 mg/60 kg body weight)
3. High dose ciprofloxacin + vitamin 'A' treated group: The rats received ciprofloxacin (400 mg / 60 kg body weight) and vitamin 'A' (7.5 mg / 60 kg body weight), respectively.
4. High dose ciprofloxacin + vitamin 'C' treated group: The rats received ciprofloxacin (400 mg/60 kg body weight) and vitamin 'C' (500 mg / 60 kg body weight), respectively.
5. High dose ciprofloxacin + vitamin 'E' treated group: The rats received ciprofloxacin (400 mg/60 kg body weight) and vitamin 'E' (600 mg / 60 kg body weight), respectively.

Short duration treatment rats received ciprofloxacin orally for seven consecutive days and long duration treatment rats received the same dosage of ciprofloxacin orally for 4 weeks. And further the drug was withdrawn for the next 14 days and 60 days, respectively, Experiment. The drug was dissolved in distilled water and was administered orally.

CHEMICALS AND REAGENTS

All chemicals and reagents used for the experiments were of analytical grade and were obtained from BDH (British Drug House, England and India), E. Merck (Germany and India), Sigma chemical company (USA), Loba chemie (Indo austranol Co, India) Qualigens fine chemicals division (Mumbai).

EXPERIMENTAL PROCEDURE

The animals were weighed before and after treatment. Twenty four hours after the last treatment schedule the animals were sacrificed by decapitation method. Serum was separated immediately after the sacrifice by centrifugation of blood at 3000 x g for 30 minutes and stored at –20^{o}C until used for hormone assays.

BIOCHEMICAL ANALYSIS

ELISA of Follicle Stimulating Hormone (FSH) assay was estimated by the method of Abranham, 1981 and Uotila *et al.*, 1991. ELISA of Luteinising Hormone (LH) assay was estimated by the method of Shome and Parlow, 1974 and Uotila *et al.*, 1991. The serum of testosterone was assayed by ELISA methods Bricaire *et al.*, (1991) and Tietz, 1995.

RESULTS

EFFECT ON SERUM FSH (TABLE 1)

There was a lowering (20%) of FSH levels when ciprofloxacin was administrated at high dose for 7days. Vitamin A and E supplementation to these drug treated rats could partially restore their serum FSH levels. Vitamin C supplementation was ineffective in preventing the decrease in FSH levels caused by the drug. Withdrawal of drug treatment for 15 days was effective in restoring completely the FSH levels to normalcy. Long duration treatment as in short duration group, the FSH levels were lowered only slightly (12%) in high dose ciprofloxacin treated groups. Similarly, vitamin A and E supplementation to the above drug treated rats and drug withdrawal could bring about an increase in hormone levels back to normal.

EFFECT ON SERUM LH (TABLE 1)

Serum LH concentration increased by 22% with ciprofloxacin treatment at high dose. However, vitamin A, C, E s upplementations individually to these drug treated animals, lowered the hormone level significantly by nearly 20%, bringing the hormone levels to near controls. Withdrawal of the drug in this high dose group lowered the LH levels to control values. Long duration treatment as the drug, ciprofloxacin did not bring about any significant change in the LH levels at both low and high doses used and this effect was

Table1 Effect of Ciprofloxacin with and without vitamins supplementation on serum FSH, LH and Testosterone titres of rats

GROUPS	TREATMENTS	FSH (ng / ml serum)	LH (ng/ml serum)	TESTOSTERONE (ng / ml serum)
I	***Control***	$0.145^{d} \pm 0.002$	$0.102^{de} \pm 0.001$	$3.185^{a} \pm 0.004$
II	***Short duration*** Low dose	$0.136^{f} \pm 0.001$	$0.097^{f} \pm 0.002$	$0.980^{i} \pm 0.001$
	High dose	$0.118^{j} \pm 0.003$	$0.125^{a} \pm 0.003$	$0.748^{l} \pm 0.001$
	High dose + vitamin 'A'	$0.124^{i} \pm 0.007$	$0.082^{h} \pm 0.002$	$1.648^{b} \pm 0.001$
	High dose + vitamin 'C'	$0.111^{k} \pm 0.001$	$0.081^{h} \pm 0.001$	$1.342^{d} \pm 0.003$
	High dose + vitamin 'E'	$0.126^{hi} \pm 0.003$	$0.090^{g} \pm 0.003$	$1.514^{c} \pm 0.002$
III	**Withdrawal**	$0.148^{c} \pm 0.005$	$0.100^{e} \pm 0.005$	$1.104^{h} \pm 0.003$
IV	**Long duration** Low dose	$0.138^{ef} \pm 0.005$	$0.096^{f} \pm 0.004$	$0.813^{k} \pm 0.005$
	High dose	$0.127^{h} \pm 0.003$	$0.103^{d} \pm 0.005$	$0.548^{m} \pm 0.002$
	High dose + vitamin 'A'	$0.160^{b} \pm 0.002$	$0.117^{b} \pm 0.004$	$1.221^{e} \pm 0.003$
	High dose + vitamin 'C'	$0.131^{g} \pm 0.002$	$0.106^{c} \pm 0.002$	$1.120^{g} \pm 0.001$
	High dose + vitamin 'E'	$0.140^{e} \pm 0.002$	$0.096^{f} \pm 0.002$	$1.214^{f} \pm 0.002$
V	**Withdrawal**	$0.171^{a} \pm 0.006$	$0.089^{g} \pm 0.002$	$0.818^{j} \pm 0.002$

Each value in the mean ±SE; Means followed by a common letter are not significantly different at the 5% Level of DMRT.

similated by drug withdrawal also. Supplementation with vitamin A only caused an elevation in the LH levels by 14%, while the other two vitamins had no significant effect on the hormone levels.

EFFECT ON SERUM TESTOSTERONE LEVELS (TABLE 1)

Ciprofloxacin treatment at both short and long duration caused a marked decrease in testosterone titres in a dose dependent manner. Withdrawal of the drug could not restore the hormone level to normal values at both durations of the drug treatment. Supplementations of vitamins A, C and E to the high dose drug treated groups, in both the duration of treatments, could not prevent the drug induced further decrease in the testosterone levels.

DISCUSSION

EFFECT ON SERUM FSH AND LH

Abuse of various compounds invariably leads to a state of dependency. Prescription as well as over the counter drugs are often abused. The long term effects of substance abuse are contingent on the compounds that are used. They may result in organ damage, medical complications, vascular injury and refractory state with chronic headache disorder. Significant toxicities occur with NSAIDs usage that limits their use despite their substantial clinical benefits in the management of many diseases (Goldstein, 2000).

Ciprofloxacin is a first oral antimicrobial drug with broad spectrum of activity that can be used to treat serious infection. This drug toxicity has been recorded in the kidney, liver, joints, eyes, central nervous systems, mutagenecity and in pregnancy (Lutz and Eigenbordt, 1990). Study in animals has largely been conducted on short and long term effects of ciprofloxacin. In the present study, the data on serum gonadotropins especially serum FSH, along with serum testosterone suggest an inhibitory influence of ciprofloxacin upon hypothalamo-hyphophysal-testicular axis. It is well-known that hypothalamic factor, gonadotropin releasing hormone (GnRH) is secreted in a pulsatile fashion to stimulate parallel pulsatile release of LH and FSH (Belchetz *et al*., 1978; Conn *et al*., 1987; Haisenleder *et al*., 1990). GnRH elevates subunit messenger RNA (mRNA) levels, α and β subunit translation, glycosylation and release of gonadotropins from the anterior pituitary (Starzee *et al*., 1986; Gharib *et al*., 1990). GnRH binds to specific receptors on the surface of the gonadotrope cells of the anterior pituitary gland and stimulates the secretion of FSH and LH (Papavasiliou *et al.*, 1986).

In the present study, there was consistent reduction in serum FSH alone but not serum LH which suggest diminished production of FSH only from the pituitary. This may be due to the decreased response of gonadptropes to GnRH stimulation. The gonadotropins are controlled by a classical negative feedback effect of testosterone and estradiol through effects at the level of hypothalamus (Sherins and Loriause, 1973; Plant *et al*., 1978). Negative feedback at the level of pituitary would reduce the sensitivity of the pituitary to stimulation by GnRH, whereas feedback at the hypothalamus would suppress the secretion of GnRH which inturn would reduce the frequency of LH pulse (Tilbrook *et al*., 1991). Although receptors for testosterone and estradiol are localised in the hypothalamus and pituitary (Thieulant and Pelletier, 1979), the principal site of negative feedback of the testicular steroids is the hypothalamus and that feedback effects directly at the level of anterior pituitary is minimal (Tilbrook *et al*., 1991).

In the adult rat testis, the ability of Leydig cells to respond to sustained gonadotropic stimulation with increased androgen production is limited by the development of a refractory state associated with loss of LH receptors and steroidogenic enzymes (Aquilano *et al*., 1985). In the present study, serum level of LH was high in short duration of ciprofloxacin treatment. Leydig cells might have been less stimulated to produce testosterone. Similarly, the FSH levels were also low and these data suggest an alteration in the normal hypothalamo-hypophyseal-testicular axis. Gonadotropin induced steroidogenic lesion in adult rat testis include late steroidogenic lesion at the site of conversion of progesterone to androgen, leading to a decrease *in vitro* of testosterone response to human Chorionic Gonadotropin (hCG) (Cigorraga *et al*., 1978). Nozu *et al*. (1981) suggest an early lesion before pregnenolene formation, leading to a decrease in pregnenolone and testosterone's response to hCG. The early lesion appears to be caused by an hCG – regulated mitochondrial protein probably located at the inner mitochondrial membrane, where it could influence the electron transport among one or more components of the side-chain cleavage enzyme.

This inhibitory substance that competitively modulates the activity of cholesterol side-chain cleavage enzyme appears to contribute to the early steroidogenic lesion and appears to serve as endogenous modulator of the steriod hormone biosynthesis (Dufau *et al*., 1984; Aquilano *et al*., 1985 and Tsai – Moris, 1987). This lesion was found to be preceeded by a cAMP mediated activation of aromatase enzyme activity, increased estrogen production and binding to estrogen receptor in the nucleus (Nozu *et al*., 1981).

It is well known that both testosterone and estradiol exert a potent reversible inhibitory effect upon LH and FSH synthesis and secretion (Schally, 1978). When serum testosterone level is low, serum gonadotropins may be expected to be high by a negative feedback control. The gonadotropin secretion is not only controlled by testicular hormones but also by the hypothalamic factors (Khar *et al*., 1978). Under androgenisation, the diminished feedback inhibition on gonadotropins results in high LH and FSH concentrations (Cosentino *et al*.,1990).

In the present study, the lowered testosterone levels may be due to the reduced Leydig cell number as observed histologically probably caused by direct action of the drug on the testis. Such a decrease in Leydig cell number has been observed by Vijaya (1996) after the administration of Caffeine as well as Acetaminophen. Selvaraj (2002) has reported inhibitory effect of NSAID – Diclofenac sodium to reduce serum gonadotropin levels as well as testosterone level.

The lowered testosterone, raised normal LH titres as well as

low serum FSH levels in this study suggest that there is poor negative feedback control by the testicular hormones to the hypothalamo – hypophysical regions. Rather the drug effect appears to be directly on testicular axis. Administration of supplements, the antioxidant vitamins A and E were partially effective in restoring the gonadotropins levels suggesting a severe impairment of hypothalamo – hyphophyseal axis and a need for higher doses or longer duration of antioxidant supplementations.

EFFECT ON SERUM TESTOSTERONE

Cholesterol is an obligate precursor for Leydig cell steroidognesis (Anderson and Dietschy, 1978; Hou *et al*., 1990). Several studies have shown that rat Leydig cell preferentially utilizes cholesterol derived from plasma lipoproteins for steroidogenesis (Freeman and Ascoli, 1982; Schreiber *et al*., 1982). High density lipoprotein (HDL) cholesterol has been suggested to be a major source of substrate for testosterone biosynthesis in rodents rather than endogenously synthesised cholesterol (Anderson and Dietsuhy, 1978). Thus, any alteration in the availability of cholesterol for steroid hormone synthesis or change in the ability of Leydig cells to utilise cholesterol consequently would have a profound effect on testosterone production and secretion

Besides LH, FSH also influences testosterone production by increasing the number of LH receptors on Leydig cells and the steroidogenic response of Leydig cells to LH (Nazian and Mahesh, 1981; Dalterio *et al*., 1986). Any change in serum FSH is likely to alter LH binding on Leydig cells. In the present study, a decrease in serum FSH level observed may likely to lower steroidogenesis by limiting the number of LH receptors and Leydig cells responsiveness to LH. Therefore, the decline in serum FSH may also be another reason for the observed reduction in serum testosterone level.

Superoxide dismutase, one of the lipidperoxidation enzyme, has been shown to act as an alternate regulatory switch in testicular steroidogenesis (Kumar *et al*., 1990). The cytochrome P_{450} enzymes of the steroidogenic pathway are known to produce free radicals. These free radicals are produced as a result of electron leakage due to the interaction of steroid products or other pseudosubstrates with the enzymes. The inability of the pseudosubstrate to be oxygenated promotes the release of reactive oxygen species (Peltola *et al*., 1996). In the present study also, the testicular superoxide dismutase activity was considerably lowered and lipid peroxidation increased after ciprofloxacin treatment suggesting the inhibition of testicular steroidogenesis due to free radical formation and oxidative stress as suggested by Kumar *et al*. (1990).

The antioxidant vitamins like vitamin E, C and A, though were capable of lowering the lipid peroxidation to a limited extent could not, however, completely restore the superoxide dismutase activity as well as testosterone levels. This data suggests the adverse effect of the drug to be permanent. Ineffectiveness of the drug withdrawal in restoring the above parameters to normalcy corroborates the above suggestion. Like the present data, a decrease in serum FSH, Testosterone and unalteraed LH levels has been reported by Badri Shriman Narayanan (1995) after methotrexate treatment. Lindane administration has been shown to alter testicular steroidogenesis via superoxide dismutase antioxidants system like the present observation (Sujatha *et al*., 2001).

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