

Research Article

The Effect of Flunixin Injection on Reproductive Hormones in Male Mice

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Abstract: Flunixin is an anti inflammatory non steroidal chemical compound which is used as an analgesic and antipyretic drug in veterinary. Considering the frequent use of this drug in recent years this study was conducted to investigate the effects of this drug on pituitary-gonad axis of male mice. Results of this study can be used highly for better use of this drug and saving sexual power of male sex. Five experimental groups with eight male mice in each group were studied as control, Placebo and three treatment groups. Flunixin was injected in 0.5, 1 and 1.5 mg/kg in peritoneum in a twenty-day period. Control group didn't receive any injection and Placebo group received only physiological serum. At the end of twenty days, blood samples were prepared and the amounts of FSH, LH and testosterone hormones were measured. Obtained data were analyzed using SPSS11.5 program. According to results, FSH and LH concentrations were increased significantly ($p < 0.05$) but testosterone was not changed. Results show that flunixin can affect sexual power of male sex by increasing hormones of pituitary-testicle axis.

Keywords: Flunixin, FSH, LH, mice, testosterone

INTRODUCTION

Recent improvements in industry and biotechnology have led to production of goods which improve life style of human but these improvements affect environment via various physical, chemical and biological ways. Considering the sensitivity of reproduction, mentioned factors have caused different injuries on male and female sexual systems such as infertility and low fertility (Butler, 2003), which are various degree of sexual system failures. Infertility has affected 15% of world couples which 40-50% of infertilities are because of male factors (Iammarrone *et al.*, 2003).

Flunixin meglumine is from non steroidal drugs which several health benefits have been ascribed to it (Thomas and Divers, 2008). Non steroidal anti inflammatory drugs act by controlling cyclooxygenase enzyme and after that reduction in production of inflammatory mediators like prostaglandins (Dumont *et al.*, 2000). Flunixin prohibits construction of prostaglandin Precursor and thromboxane from arachidonic acid by controlling cyclooxygenase enzyme and it can show its anti inflammatory effect by prohibiting production of local mediators in response to inflammation (on inflamed tissue). It also enforces its pain killer effect by prohibiting production of compounds which cause sensitivity of pain receivers to mechanical and chemical stimulation. Antipyretic effect of this drug is probably because of its effect on

temperature center of hypothalamus which causes veins to stretch and increases blood stream into skin, then respiration will be increased and body will lose its heat. Prostaglandins affect various actions like blood clotting, onset of labor (Na and Surh, 2003) ovulation, bone metabolism, neural system development, healing, kidney function, renal water regulation, cell division and immune responses (Squires, 2003). Meanwhile, they play an important role in pathophysiology of cancer and inflammation. Considering that there isn't any study on effects of flunixin on male sexual hormones, this study was conducted to investigate the effects of this drug on testosterone, LH and FSH hormones.

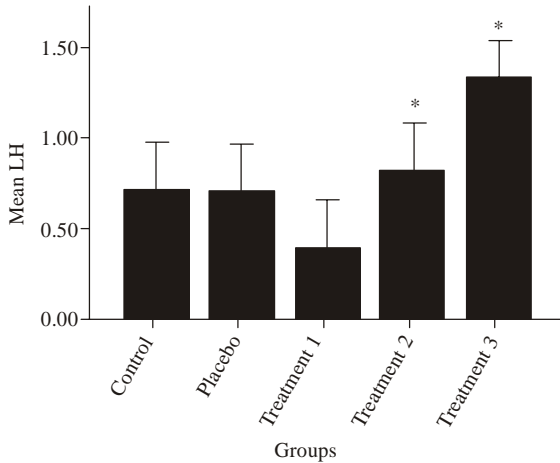
MATERIALS AND METHODS

Forty male mice from Balb/c race were kept in cages for two week to adapt to environment. Samples had free access to food and water and normal light.

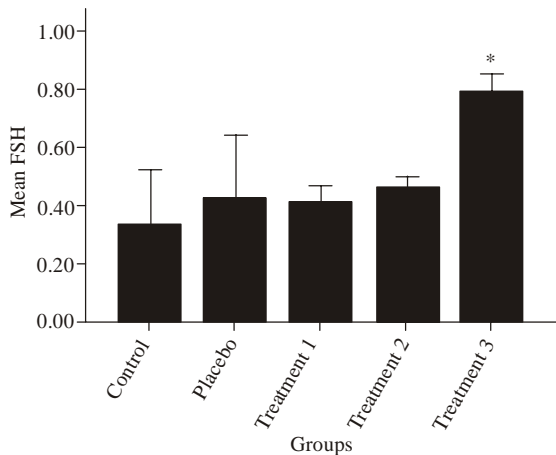
Samples were divided into five groups including control, placebo and three treatment groups. Flunixin was injected in peritoneum in doses 0.5, 1 and 1.5 mg/kg. Injections were done every other day for twenty das. Placebo group received only physiological serum. After injections, blood samples were prepared and were analyzed using Elisa method and gamma counter to measure the amounts of FSH, LH and testosterone hormones.

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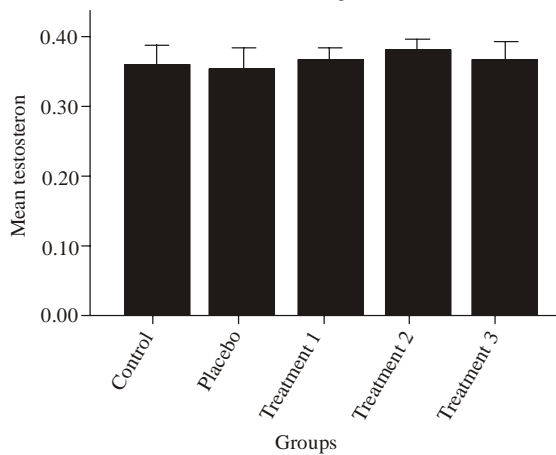
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The mean difference is significant at the 0.05



The mean difference is significant at the 0.05



Error bars: 95% CI

The mean difference is significant at the 0.05

Fig. 1: The concentration of FSH, LH and testosterone hormones in different groups

RESULTS

There was significant difference between FSH amount of third experimental group (1.5 mg/kg) and control group ($p < 0.05$) (Fig. 1).

LH amount of third experimental group (1.5 mg/kg) and first experimental group (0.5 mg/kg) were different from control group significantly ($p < 0.05$) but the other group didn't show any obvious difference.

The study of testosterone hormone showed that there was not any significant difference between testosterone levels of experimental groups and control group.

DISCUSSION

Results of this study showed an increase in FSH hormone by injection of 1.5 mg/kg drug and increase in LH by 0.5 and 1.5 mg/kg doses whereas testosterone was not changed. Mentioned increases are because of flunixin effect on hypothalamus-pituitary-testis axis. This axis is affected by various controlling factors (negative and positive) including nitric oxide (NO) which this active molecule cause increase in gonadotropins and LH secretion, increase in sperm movement and erection enforcement (Sato and Tsukamoto, 2000). Secretion of this neurotransmitter is increased itself by various factors. One of these factors is norepinephrine (NE) which cause, LHRH stimulation and increase in LH secretion via activating nitric oxide (Parvizi and Ellendorff, 1982). Leptin hormone also increases FSH via synthesis of neural nitric oxide. Studies show that low secretion of testosterone let hypothalamus via negative feedback to secrete high amounts of GnRH and then cause increase in LH secretion from testis (Shah *et al.*, 1998). Testosterone reduction has probably also a direct negative feedback on anterior pituitary which increase LH secretion specifically and can increase testosterone secretion by affecting ldydig cells (Willems *et al.*, 1999). Secreted testosterone from testis (in response to LH) has mutual effect on limiting LH secretion from anteriorpituitary. Testosterone does this in two ways:

- The main part of this control is probably due to direct effect of testosterone in reduction of GnRH secretion from hypothalamus. This cause a reduction in LH and FSH from anterior pituitary and LH reduction will reduce testosterone secretion from testis. Low secretion of testosterone leads to high amounts of GnRH from hypothalamus and after that secretion of LH and FSH from anterior pituitary and testosterone from testis will be increased.
- Testosterone can affect anterior pituitary directly and lessen the LH amount but this way is less important than (a) part (9).

When the seminifer tubules are not producing spermatozoid, secretion of FSH from anterior pituitary is being increased considerably but when the rate of spermatogenesis is high, FSH secretion will be reduced.

The reason of this negative effect on anterior pituitary is secretion of inhibin hormone from sertoli cells. This hormone is a kind of glycoprotein like LH and FSH with molecular weight about 10000-30000 Dalton which has direct controlling effect on FSH secretion from anterior pituitary and probably a little controlling effect on GnRH secretion from hypothalamus. Prostaglandins (PGS) interfere in some sexual processes like hypothalamus-pituitary, steroidogenesis of testis, follicle maturity, gamete immigration and implantation.

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