

# Immunological effects of Flutamide and cyproterone acetate used two Anti-prostate cancer in Rats

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## Summary

This present study was performed to examine the effects of two drugs of anticancer of prostate (flutamide & cyproterone acetate) on some immunological in albino male rats. The animals were divided into two groups, first treatment groups gives orally flutamide at 25 and 15 mg/kg/day and two group gives orally cyproterone acetate at 10 and 5 mg/kg/day, and control divided into two groups, first group gives normal saline and two group gives corn oil and all groups gives orally for 28 days. study immunological parameters including the concentration IgG, IgM, IgA,  $\gamma$ -globulin, IL-4, IL10 and measuring phagocytic activity also measuring total protein. Furthermore, The effects of these drugs have been also tested on some blood components including; WBC, differential WBCs in treatments and control groups (normal saline & corn oil) of rats .

The flutamide (25,15 mg/kg) and cyproterone acetate (10,5 mg/kg) produced significant decreases in total protein except WBC count which show significantly increases, but both drugs above don't effect in, IgA, IgM, IL-10 and phagocytic activity, on the other hand Flu (25 mg/kg) only produced significantly increase in level of IL-4 and significantly decrease in IgG and globulin- $\gamma$  concentration, furthermore, CPA (10 mg/kg) cause only significantly increase in concentration of IgG and neutrophils and significantly decrease in lymphocytes . The results of this study refer that the two drugs show significant change in blood components in treated rats compared with control groups, high dose of Flu showed significant change in immunological parameters.

## Introduction

The prostate cancer has been one of the most common disease for the men in United State of America after pulmonary and colon cancers (Jemal *et al.*, 2006). In Europe, this disease is more prevalence than pulmonary cancer (Boyle and Ferlag, 2005). There are many methods for the therapy of prostate cancer:

1. Androgen deprivation therapy by using hormones, and this method was used for treatment of non-transitional diseases in especially after radical therapy or prostatectomy (Aus *et al.*, 2005).

2. Androgen antagonist therapy, which binding to androgen receptor and therefore , block the androgen (Petrylak , 2002).

3. Testectomy by surgery but the side effects of it was losing of libido (Iversen *et al.*, 2000).

The flutamide and cyproterone acetate drugs represented steroid and steroid antagonists respectively, and both of them acts competitor for androgen receptor, but steroid antagonist also has progesterone activities that minimum the level of testosterone which lead to prevent the erection and other sexual performance (Anderson, 2003). Steroid antagonist dose not decrease testosterone level , therefore, the sexual performance will remain normal (Iversen *et al.*, 2001; Migliari *et al.*, 1999). Using androgen antagonist therapy is increase due to their effects and acceptance from patients compared with surgery in prostate cancer therapy therefore, they

represents an alternative therapy for maintaining of sexual functions in patients (McLeod *et al.*, 2006). The chemotherapy has side effects not only on endocrine and reproductive systems, but also on the immune system (Crisp *et al.*, 1997). Chryssikopoulos *et al.*, (1997) reported that a complex relationship exists between the immune system and the glandular nervous system. The immune cells secrete several hormonal peptides and proteins, such as growth hormone, lactogenic hormone, thyroid stimulating hormone, and adrenal corticotrophin hormone. Some of these hormones are considered as suppressors or stimulators for the immune responses (Gaillard, 1995).

Certain cytokines are produced by immune cells which have the ability to alter certain functions of the glandular nervous system (Rivest and Laflamme, 1995). In recent years, there is an increase in using flutamide by adolescents for treatment of acne and hirsutism treatments (De Amorim *et al.*, 2005). The main aim of the present study is to determine the side effects of the widely used two drugs, flutamide and cyproterone acetate on the immune system of rats by measuring the following:

- 1-Estimation of the concentration of immunoglobulin (IgA, IgG, IgM) and anti-inflammatory cytokines (IL-4, IL-10).
- 2-Estimation of the concentration of total protein and  $\gamma$ -globulin.
- 3-Evaluation of the phagocytic activity.

## **Materials and Methods**

### **1-Laboratory Animals:**

Thirty mature native rats *Rattus rattus* have been brought from the animal house of the University of Kufa. Their blood was tested for bacterial pathogens and their respective specific antibodies, then rats with negative results were kept throughout the experimentation periods at a standard level for ration and housing (Schneider *et al.*, 1990). The average weight of such animals ranged between 300-350 gm and their ages ranged from 4-5 months.

### **2-Preparation of Drug:**

The cyproterone acetate was obtained from a pharmacy and their equipment from a company of Schering AG Germany/Allemagne as tablets in concentration 50 mg/kg, while the equipment of flutamide drug from a company Schering plough Lab.N.N. Belgium as tablets in concentration 250 mg/kg. The tablets were macerated by a blender and dissolved by absolute alcohol, then kept for dryness, after that corn oil was added as well as mixed and the concentration for experiments were done according to the doses for human (Sanchez-Criado *et al.*, 1990).

### **3- Immunization protocol:**

The rats were divided into three groups, 10 replicates for each. The first treated group was divided into two subgroups, the first and second were orally received flutamide at concentrations 15 and 25 mg/kg/day respectively for 28 days, while the second treated group were orally received cyproterone acetate at concentrations 5 and 10 mg/kg/day for first and second subgroups consecutively and also for 28 days. The last group (control) was divided also into two

subgroup, the first and second were orally normal saline (negative control) and corn oil(positive control) respectively for 28 day.

#### **4- Blood samples:**

The blood samples were collected directly from the treated and controlled rats by heart puncture, seven days after the last immunization. The small amount of these samples were kept in sterile tubes containing anticoagulant (heparin)AFM-Dispo and placed in refrigerator at 4 °C in order to measure the phagocytic activity. The remainder of these samples were kept in sterile centrifuge tubes (without anticoagulant) to separate the sera, and then measuring the concentration of the total protein,  $\gamma$ -globulin, immunoglobulins (IgA, IgG, IgM) and anti-inflammatory cytokines (IL-4, IL-10).

#### **5-Immunological Assay:**

##### 5-1 Determination of serum protein :

The concentration of total protein (g/l) was estimated according to manual procedure of linear chemical procedure (company of Almacen Joaquim . Costa, Motagat, Barcelone, Spain), while the concentration of  $\gamma$ -globulin was evaluated according to Bishop *et al.*, (1985).

##### 5-2 Single Radial Immunodiffusion Assay:

This test was used to determine the concentration of IgM, IgG and IgA according to Mancini *et al.*, (1965).

##### 5-3 Determination of IL-4 and IL-10:

The concentration of IL-4 and IL-10 were determined by ELISA according to kit procedure (Company of Endogen, Canada).

##### 5-4 Phagocytic activity test:

The means of phagocytosis by phagocytes for *Candida albicans* were measured according to Metcalf *et al.*, (1986) with certain modifications. The test was done by mixed fresh blood of immunized and controlled rats, with suitable amount of *C. albicans* isolate, then incubated at 37 °C, after that prepare the slide, stain and examine under oil immersion microscope. The percentage of phagocytic activity were calculated according to the following equation:

$$= \frac{\text{number of phagocytes for } C. albicans}{\text{Total number}} \times 100$$

#### **6- Biometry:**

The results for experiments were analyzed using statistical (programme spss version 17, and the mean, standard error as well as significant differences were done by using one-way anova (Joda, 2008).

## Results

There were a decreased in mean of concentration of total protein in treated groups in comparison with control groups , and there is a significant differences at ( $P<0.05$ ) compared with control groups , also the means of concentration of  $\gamma$ -globulin in animals primed by drugs were lower then that in control groups, but the concentration in rats immunized by cyproterone acetate 10 mg/kg were higher in comparison with other treated groups and there is a signhificant differences between animals primed with flutamide 25 mg/kg and control groups.Meantime, there were no significant differences at ( $P<0.05$ )in percentage of phagocytic activity between treated and controlled groups (Table 1).

Table (1) : the concentration of total protein (gm/dl) and  $\gamma$ -globulin (gm/dl) as well as the percentages of phagocytic activity in rats primed orally by flutamide and cyproterone acetate drugs.

parameter Nature of treatment	Total protein gm/kg Mean $\pm$ S.E.	$\gamma$ -globulin gm/kg Mean $\pm$ S.E.	Percentage of phagocytic activity %Mean $\pm$ S.E.	probability
Negative control (normal saline )	7.25 $\pm$ 0.56	3.73 $\pm$ 0.29	38.39 $\pm$ 1.16	–
Positive control (corn oil)	6.55 $\pm$ 0.38	3.43 $\pm$ 0.56	40.03 $\pm$ 2.81	–
Flutamide 25mg/kg	*5.43 $\pm$ 0.24 **	*2.09 $\pm$ 0.05 **	42.23 $\pm$ 3.76	0.05
Flutamide 15mg/kg	*5.66 $\pm$ 0.47 **	2.75 $\pm$ 0.22	35.58 $\pm$ 2.38	0.05
Cyproterone acetate 10mg/kg	*5.79 $\pm$ 0.32 **	3.06 $\pm$ 0.37	37.87 $\pm$ 2.9	0.05
Cyproterone acetate 5 mg/kg	*5.99 $\pm$ 0.04 **	2.86 $\pm$ 0.32	42 $\pm$ 5.33	0.05

\*: significant difference in comparison with negative control.

\*\* : significant difference in comparison with positive control.

The animals treated with flutamide revealed decreased at significant ( $P<0.05$ ) in concentration of IgG (mg/dl) in comparison with control groups, while rats treated with cyproterone acetate 10 mg/kg showed increases at significant ( $P<0.05$ ) compared with untreated groups. The concentration of IgM (mg/dl) showed no significant differences at ( $P<0.05$ ) between treated and control groups, but their was decreased in concentration of this antibody in animals primed with cyproterone acetate drug, furthermore, there were no significant differences at ( $P<0.05$ ) in concentration of IgA (mg/dl) between immunized and control groups as illustrated in table (2).

Table (2): The concentration of immunoglobulins IgM, IgG and IgA in rats primed orally by flutamide and cyproterone acetate.

parameter Nature of treatment	Concentration of IgM mg/dl Mean±S.E.	Concentration of IgG mg/dl Mean±S.E.	Concentration of IgA mg/dl Mean±S.E.	probability
Negative control (normal saline)	94.63±8.99	1714.26±175.38	238±58.99	—
Positive control (corn oil)	93.03±9.44	1810.86±144.64	265.03±27.70	—
Flutamide 25mg/kg	107.3±16.71	*810.40±42.20 **	223.53±75.53	0.05
Flutamide 15mg/kg	100.4±17.22	*1021.10±248.31 **	234.43±25.84	0.05
Cyproterone acetate 10mg/kg	73.9±12.19	*2432.20±95.80 **	184.33±106.08	0.05
Cyproterone acetate 5 mg/kg	82.73±19.55	1726±285.07	263.13±67.71	0.05

\*: significant difference in comparison with negative control.

\*\* : significant difference in comparison with positive control.

Table (3) illustrated increases in concentration of IL-4 pg/ml in treated group by flutamide 25 mg/kg in comparison with control groups, as well as there were no significant differences at ( $P<0.05$ ), but there were no significant differences at ( $P<0.05$ ) between other treated groups and untreated groups. Meantime, the means of IL-10 pg/ml revealed no significant differences between primed and control groups.

Table (3) : The concentration of IL-4 and IL-10 pg/ml in rats immunized orally by flutamide and cyproterone acetate drugs.

parameter Nature of treatment	Concentration of IL-4 pg/ml Mean±S.E.	Concentration of IL-10 pg/ml Mean±S.E.	Probability
Negative control (normal saline )	49.31±1.28	27.79±8.15	–
Positive control (corn oil)	49.64±1.82	24.47±13.99	–
Flutamide 25mg/kg	*73.76±7.24 **	20.49±3.04	0.05
Flutamide 15mg/kg	50.8±5.11	23.81±6.33	0.05
Cyproterone acetate 10mg/kg	60.79±6.24	22.28±8.44	0.05
Cyproterone acetate 5 mg/kg	61.27±3.6	27.78±4.78	0.05

\*: significant difference in comparison with negative control.

\*\* : significant difference in comparison with positive control.

## Discussion

The means of concentration of total protein show a decreases in treatments compared with control groups at the same time the concentration of  $\gamma$ - globulin is lower in treatments compared with control groups (table 1). Duques de Amorim *et al.*, (2005) found that the total protein and  $\gamma$ -globulin was natural in patients used flutamide for treatment of acne, also the decreases in level albumin , which is the major protein in serum probably related with lower concentration of total protein. The decrease in means of  $\gamma$ -globulin may be associated with level of IgG, which represents the major component of  $\gamma$ -globulin .However, the concentrations of cyproterone acetate 2 and 5 mg/kg don't inhibited the synthesis of globulin- $\alpha$ 2 (Roy, 1976). There is no significant differences at ( $P<0.05$ ) in phagocytic activity between treatments and control groups. Srinivasan *et al.*, (1997) reported that the flutamide alone was unstimulated for polymorphonuclear cells, but in low concentration increases release the myeloperoxidase, in addition, high concentration of this drug inhibits the activation of phagocytes in presence of phorbol myristate (PMA), also both drugs donot effect on expression Fc $\gamma$ R on surfaces of phagocytes (Gomez *et al.*, 2000), and

this receptor mediated the phagocytosis by opsonization of molecules as well as stimulate this cells to degrade engulfed particles (Abbas *et al.*, 2003).

Table (2) show a significant increase and decrease in levels of IgG in rats primed by cyproterone acetate and flutamide respectively, while there is no significant difference in levels of IgM and IgA. The low concentration of IgG in animals primed by flutamide may be due to the increase production of IL-4, which inhibits the synthesis of IgG<sub>2</sub> and IgG<sub>3</sub> (Abbas *et al.*, 2003), furthermore, the high level of IgG related with increases activity of gamma glutamyl transferences (GGT) which elevated the amount of intracellular glutathione that lead to stimulate T-cells and leukocytes, meantime, the amount of this enzyme increased by using cyproterone acetate (Gonzalez-Quintela *et al.*, 2003). The intraperitoneal inject of rats by flutamide at 5 and 20 mg/kg for 15 days wasn't effect on level of IgM (Ladics *et al.*, 1998). Q'conner *et al.*, (2002) illustrated that the exposure of rats for flutamide 5, 20, 50 mg/kg was not effect on primary immune response . There is a significant increases in level of IgM in rats primed by cyproterone acetate at 25 mg/kg , and this is may be due to uses high doses of drugs (Ali *et al.*, 2008). Giltay *et al.*, (2000) found that decreases in level of IgA by using CPA drug at 100 mg/kg for three months in patients with sexopathy and interpretation for this case was increased the water in the body as well as plasma which lead to decrease in level of IgA, while Sande and Comp (1983) reported that increases in concentration of IgA in prostate tissue of patients with prostate cancer used CPA, because the immunoglobulin IgA was higher in mucosal tissues than peripheral blood. Table (3) showed increases in level of IL-4 in rats primed by flutamide 25 mg/kg compared with control groups while there is no significant difference in level of IL-10 between immunized and control groups. The increases in level of IL-4 may be related to elevate concentration of IL-2 which stimulate other T-cells to produce cytokines such as IFN-  $\gamma$  and IL-4 (Abbas *et al.*, 2003), also mice primed by flutamide at 25 mg/kg increases production of IL-2, and the later stimulate increases level of IL-4 (Messingham *et al.*, 2001; Wichmann *et al.*, 1997). Vo *et al.*, (2009) showed that rats immunize by flutamide at 10 and 50 mg/kg increased the expression of IL-4 receptor, while the levels of IL-10 was not effected in mice prime by flutamide at 25 mg/kg (Sønder *et al.*, 2006); Hildebrand *et al.*, 2006), furthermore the decreases level of IL-10 in mice showed suppression the immune response for intestinal antigen, due to binding of IL-10 to their receptors on T-cells surfaces suppress the gene transcription of IL-2 which inhibits the proliferation of T-cells (Delves and Roitt, 1998). Testosterone was revealed anti-inflammatory effect by stimulate production of IL-10 as well as inhibited production of TNF- $\alpha$  (D'Agostino *et al.*, 1999), therefore, the antagonist for androgen may be suppress the level of IL-10. The significant of this paper lies in the investigation of the humoral and cellular immune response to two anti-prostate cancer in rats that mimics their actions in human.

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## التأثير المناعي للفلوتاميد وخلات السايبروتيرون المضادين لسرطان الموثة (البروستات) في الجرذان

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### الخلاصة

صممت الدراسة الحالية لبحث فعالية عقارين مضادين لسرطان الموثة (الفلوتاميد FLU وخلات السايبروتيرون CPA) على بعض المعايير المناعية في ذكور الجرذان البيض. قسمت الحيوانات الى مجموعتين المجموعة الاولى جرعت بالفلوتاميد بالتركيزين 25 و15 ملغم/كغم/يوم والمجموعة الثانية جرعت بخلات السايبروتيرون بالتركيزين 10 و5 ملغم/كغم/يوم، اما السيطرة قسمت ايضا الى مجموعتين الاولى جرعت بالمحلول الفسلجي الملحي والثانية بزيت الذرة وكل المجاميع جرعت لمدة 28 يوم. حيث درست المعايير المناعية المتمثلة بتركيز الكلوبولينات المناعية IgG, IgA, IgM وكاما كلوبولين والسايبتوكائينات IL-4, IL-10 والعد التفرقي لخلايا الدم البيض والفعالية البلعمية في دم الجرذان السليمة والمجرعة بتركيز العقارين وكذلك المجرعة بزيت الذرة. لقد تبين أن عقار الفلوتاميد بتركيزي (15, 25 ملغم/كغم/يوم) وعقار خلطات السايبروتيرون بتركيزي (5, 10 ملغم/كغم/يوم) أظهرتا انخفاضاً معنوياً في البروتينات الكلية بينما أظهرتا ارتفاعاً معنوياً في عدد خلايا الدم البيض الكلي، أما عند حقن الحيوانات FLU (15, 25 ملغم/كغم) لم يؤثر معنوياً على IL-10, IgA, IgM. كما ان FLU (25 ملغم/كغم) فقط أدى الى ارتفاع معنوي في IL-4 وانخفاض معنوي في IgG وكاما كلوبولين وكذلك فقط CPA (10 ملغم/كغم) أظهر ارتفاع معنوي في IgG والخلايا متعددة الانوية وانخفاض معنوي في الخلايا اللمفاوية. يستنتج من خلال نتائج الدراسة ان عقاري FLU و CPA لهما تأثيرات سلبية على المناعة في الحيوانات المجرعة مقارنة بحيوانات السيطرة، بينما التركيز العالي من FLU له تأثيرات مناعية أكثر.