Effect of antiandrogen flutamide on liver function and some blood parameter in mature albino male rats

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تأثير مضاد ألأندروجين الفلوتامايد على وظيفة الكبد وبعض معايير الدم في ذكور الجرذان البيض البالغه

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الخلاصة

هدفت هذه الدراسه لمعرفة تاثير مضاد الاندروجين الفلوتامايد على وظيفة الكبد وبعض معايير الدم في ذكور الجرذان البيض البالغه. قسمت الحيوانات الى مجموعتين مجموعة الحقن تحت الجلد (sc) اعطيت الفلوتامابد بالتركيزين ٨ و١٢ ملغم/كغم/يوم (1B, 1A) لمدة ٢١ يوم والسيطرة اعطيت زيت الذرة،ومجموعة التجريع بالفم اعطيت الفلوتامايد ايضا بالتركيزين ٨ و ١٢ ملغم/كغم/يوم (2B, 2A) ولمدة ٢١ يوم والسيطرة اعطيت زيت الذرة. اظهرت النتائج زيادة GOT و GPT في مجموعة الحقن تحت الجلد بالتركيز (1B) وALP في (1A) معنويا($p<o.o5$) مقارنة بمجموعة السيطرة ، وزيادة معنوية($p<o.o5$) في مستوى انزيمي GOTوALP في مجموعة التجريع في 1A و1B ومستوى GPT في 2B فقط مقارنة بالسيطرة،اظهرت نتائج معايير الدم زبادة معنوية ($p<o.o5$) في تركيز الفايبرينوجين والهيموكلوبين والنسبة المئوية لمكداس الدم في مجموعة الحقن تحت الجلد 1B مقارنة بالسيطرة، اما في مجموعة التجريع فقط تركيز الفايبرينوجين 2A و 2B أزداد معنويا في كلا التركيزين ٨ و١٢ ملغم مقارنة بالسيطرة .

Abstract

This stuby was performed to determined the effects of antiandrogen flutamtde on liver function and blood parameter in albino mature male rats.

The animals were divided into two groups, subcuntenous treatment group(sc) gives flutamide at 8(1 A) and 12mg/kg/day(1B) for 21 days, and control gives corn oil, and orally treatment group gives also flutamide 8mg(2A) and 12mg/kg/day(2B) for21days,and control gives corn oil.The results revealed a significant increase ($p<o.o5$)in GOT,GPT in sc group 1B and ALP in 1A compared to control and a significant increase in GOT and ALP in orally group in 2A and 2B ,while, only GPT level increased significantly ($p<o.o5$) in 2B compared to control. The results of blood parameters showed a significant increase ($p<o.o5$) in fibrinogen , Hb and pcv in sc group 1B compared to control, and orally group only fibrinogen level increased significantly in both 1Aand 2B compared with control.

Introduction

Flutamide(2-methyl-N-{4-nitro-3-(trifluoromethyl)phenyl}propanamide),is a nonsteroidal antiandrogen, used in the treatment of prostate cancer, it is occasionally associated with hepatic dysfunction(Goda *et al*,2006) .A group of researcher reported a case of drug induced hepatotoxicity after consecutive treatment with flutamide (Miquel *et al*,2007) .Gomez *et al* (1992) reported a frequency of sever hepatotoxicity of only 0.36%, however,a number reported of haematologic toxicity (Asbell *et al*,1994).

The toxic effect of flutamide range from mild acute reversible hepatitisto fetal fulminant hepatitis (Mcleod ,1997).The incidence of abnormal liver function associated with flutamide range from 4-62% (Denis *et al*,1993;Sogani *et al*,1984),and included elevated aminotransferases, increased serum bilirubin and prolonged prothrombin times (Mcleod,1997). Many studies have shown that administration of antiandrogen following trauma improve cardiovascular and immune function. However, the precise cellular mechanism responsible for salutary effect of the drug remain unknown (Hong Kan *et al* ,2008).It is known that androgens stimulate erythropoisis(Fried and Morley,1985), and decrease in haemoglobin and other red cells series parameters are expected during treatment with antiandrogen .The histological effect of flutamide on hepatic tissues manifested as hydropic degeneration necrosis and marked increase in kupffer cells (Muna *et al* ,2005).

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Animals

This study was performed at 2007. Included 30 albino male rats (*Rattus rattus*) aged(3-4) monthes .These animals were placed individually in wire mess cages housed in college of Science, Babylon University .The animals were maintanid on 12-hour light and 12- hour dark, food and water were supplied *ad libitum.*

Antiandrogen

Flutamide(tablet 250mg) were obtained from medochemic limited –MLT Ciprus . Flutamide dissolved in 10ml of pure corn oil,and each 1ml contain 25 mg of flutamide (Sanchez-Craido *et al*,1999).

Treatment

The animals were divided as following:

1- sc group (group 1)

Then group 1 divided into : group 1A treated with 8mg/kg/day for 21 days.
group1B treated with 12mg/kg/day for 21 days.

2- Oral group(group 2)

Then group 2 divided into : group 2A treated with 8mg/kg/day for 21 days.
Group 2B treated with 12mg/kg/day for 21 days.

3- Control group mainted on corn oil.

Liver enzymes and blood parameters

The animals were sacrificed and trunk blood collected, serum separated for subsequent analysis of blood element levels.The studied parameter include (Liver enzymes glutamic oxaloacetate transaminase(GOT),glutamic pyruvic transaminase (GPT),measured according to Ritman and Frankel (1957), and alkaline phosphatase (ALP) measured according to previously validated methodologies King and Kind (1954). Haematological parameter included fibrinogen levels according toGrannis(1970), haemoglobin levels(Hb) and packed cell volume (pcv %) according to previously method Ahmad and Salih(1994).

Statistical Analysis

All data analysed by one-way analysis of variance (ANOVA) followed by a least significant difference(LSD).

Results

Results indicat that treatment with flutamide caused a significant effects in male rats.

Liver enzymes levels

The result showed a significant increase ($p<0.05$) in GOT and GPT levels in sc group 1A and 1B compared to control, and significant increased ($p<0.05$)in ALP in 1A sc group compared to control (table 1).Group 2(orally) reaveled significant increase($p<0.01$)in GOT in both 2A *and 2B, and ($p<0.05$) in GPT level in 2B compared to control, but ALP level increased significantlly($p<0.05$) in both 2A and 2B group compared to controlgroup (table 2).

When compared between sc and orally group 1Aand 2Agroup ,results showed a significant increased($p<0.05$) in GPT and ALP levels in sc group compared to orally group(fig 1),but 2A group and 2B only GPT levels increased significantally ($p<o.o5$) in sc group compared to orally group (fig. 2).

Table 1:Effect of antiandrogen flutamide in liver enzymes levels in male rats treated subcuntenously for 21 days . n=5

Liver Enzyme / treatment	GOT U/L	GPT U/L	ALP U/L
group 1A	15.41 ± 2.36a	20.28 ± 1.12 a	71.28 ± 5.73 a
group 1B	18.24 ± 3.48 a	30.63 ± 1.37 b	57.83 ± 4.81 b
control	10.81 ± 2.47 b	13.62 ± 1.05 c	53.00 ± 4.93 b
Significant level	<0.05	<0.01	<0.05

The values is $\bar{X} \pm SE$

Table 2:Effect of antiandrogen flutamide in liver enzymes levels in male rats treated orally for 21 days . n=5

Liver Enzyme / treatment	GOT U/L	GPT U/L	ALP U/L
group 2A	12.8 ± 0.63^a	15.00 ± 2.33^a	63.4 ± 4.87^a
group 2 B	18.6 ± 1.72b	25.6 ± 4.53b	65.2 ± 5.47^a
control	7.33 ± 0.14c	14.3 ± 1.12^a	48.00 ± 3.25b
Significant level	<0.01	<0.05	<0.05

The values is $\bar{X} \pm SE$

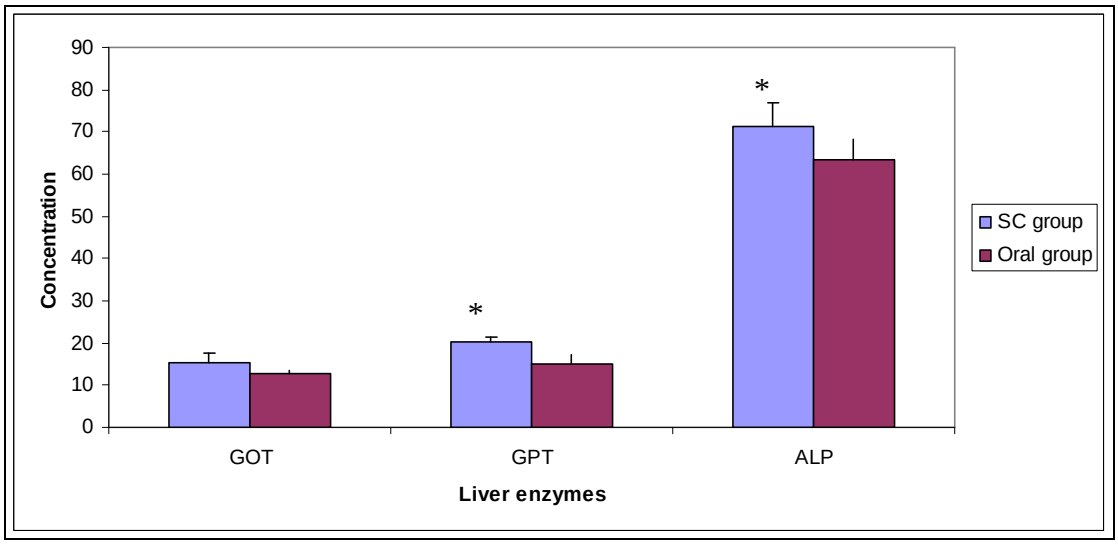

Fig 1:Compare between sc group and oral group in male rats that treated with flutamide 1A and 2A(8mg/kg/day) for 21 days.

* P<0.05

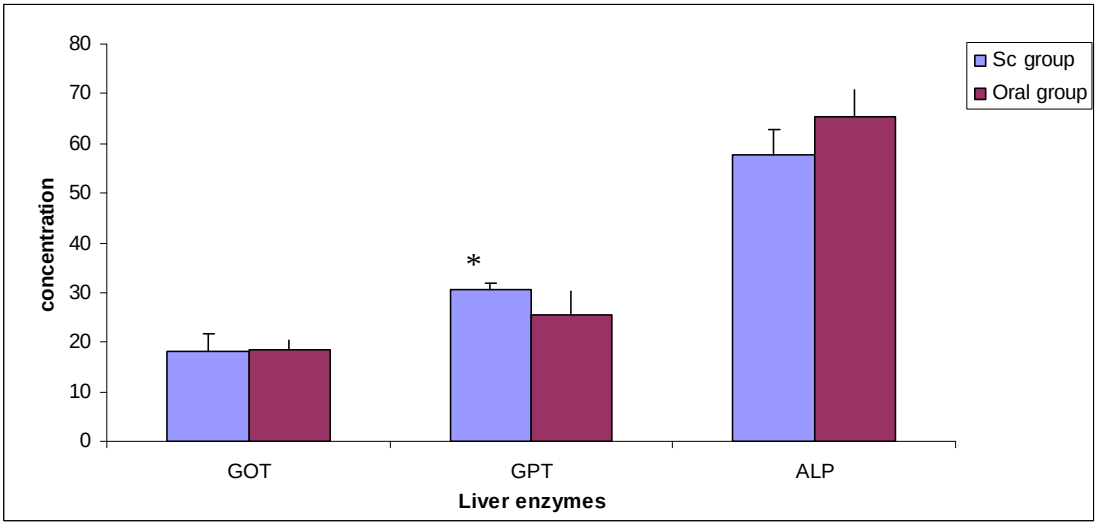

Fig 2:Compare between sc group and oral group in male rats that treated with flutamide 1B and 2B(12mg/kg/day) for 21 days.

* P<0.05

Blood Parameters

The results revealed a significant increased(p<0.05) in fibrinogen concenteration ,Hb and PCV% in sc group 1B compared to control(table 3), and in orally group a significant increase (p<o.o5) is seen in fibrinogen level in both 2A and 2B compared to control, but Hb and PCV% did not effect significant (p>o.o5) compared to control (table 4).

Table3:Effect of antiandrogen flutamide in some blood parameter levels in male rats treated subcuntenously for 21 days .
n=5

Blood parameter / treatment	Hb gm/dl	PCV %	Fib. mg/dl
group 1A	14.06 ± 1.08 [a]	43.33 ± 2.16[a]	250.56 ± 6.26[a]
group 1B	12.55 ± 2.34b	38.66 ± 2.76b	377.73 ± 8.94b
control	15.16 ± 1.93[a]	46.36 ± 3.15[a]	233.067 ± 4.39[a]
Significant level	<0.05	<0.05	<0.05

The values is $\bar{X}$ ± SE

Table 4:Effect of antiandrogen flutamide in some blood parameter levels in male rats treated orally for 21 days . n=5

Blood parameter / treatment	Hb gm/dl	PCV %	Fib. mg/dl
group 2 A	14.33 ± 1.63	44.16 ± 3.45	233.87 ± 8.65[a]
group 2 B	13.64 ± 2.54	42.76 ± 3.14	284.15 ± 9.52[a]
control	14.73 ± 2.14	45.21 ± 2.89	176.38 ± 6.34b
Significant level	N.S	N.S	<0.05

The values is $\bar{X}$ ± SE

Discussion

Many experience with arepresentative chorot of male rats indicated considerable potential for adverse side effects related to flutamide therapy(Rosenthal *et. al*.,1996).

On the basis of prevous reports in the literature ,special attention was paid to indexes of haematological and hepatologic function. The result of present study showed a significant increasein($p<0.05$) in serum level of GOT,GPT and ALP in sc group of 1A and 2A ,this result may be related to the toxicities noted espically the hepatotoxicity ,are more likely to flutamide *for several reasons: the mechanism of flutamide associated hepatotoxicity is not established and may be idiosyncratic in nature(Prattichizo,1994;Moller *et al* ,1990) investigation of a rat hepatocyte system ,however; have suggesting that inhibition of mitochondrial respiration and/or an immune response directed against proteins modified by flutamide metabolites may be involved(Asbell *et al*,1994) .

The increased of liver enzymes in recent study agreement with many studies that found increased in serum levels of liver enzymes(Manna *et al*,2005) and increased risk

of sever hepatotoxicity(Miquel *et al*,2007) ,the reason for this results may be due to testosterone receptors that found in almost every cell population (Remmers *et. al*.,1997) immune competent cells,myocytes and hepatocyte(Knoferl *et. al.*,2002),because flutamide blocks the intercellular testosterone receptor,it is possible that testosterone receptor blocked decreases cytokine release,which would be associated with better organ function (Toth *et.al*.,2004) ,and indicate that flutamide adiminstration subcutaneously decreased levels of cytokine/chemokinase
levels(Hongken *et.al*.,2008),the mechanism responsible for salutary effects of flutamide to decrease hepatocytokine remains unclear(Shimizu *et.al*.,2007) .The reason for significant defrances between sc and oral group in levels of liver enzymes (fig.1,2)may be due the rapid absorption of flutamide and metabolized in the liver to OH-flutamide and flutamide-1 by cyp /A2 and carboxyl esterase after adminstration,and this is less toxicity (Goda *et.al.*,2006) .The significant effects in Hb,pcv and fibrinogen levels in this study agreement with our studies (Meriggiola *et.al*.,1998;Asbell *et.al*.,1994) that found slightly decreased in Hb and pcv at week 16 of cyproteron acetate and this may be related to the dose of antiandrogen. Or this decrease may be due to direct inhibition of androgenic action(Diamanti-Kandarakis *et.al.*,1998).

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