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Comparsion study of the effect of certain antihypertensive drugs on testosterone and estrogen hormones concentrations in white male rats

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ABSTRACT

This study was conducted in the animal house of the department of biology –college of education for women – University of Tikrit to evaluate and compare the effect of certain antihypertensive drugs on testosterone and estrogen hormones in male rats. 50 male rats aged 4-6 months were used, with weights from 250-400 g distributed into five groups, 10 for each group (control, Amlodipine,0.428mg Valsartan 0.68mg, Captopril 0.214mg, and Atenolol 0.42mg) twice daily for 60 days. The samples were analyzed in the COBAS e411 from Roche Hitachi according to the manufacturer, The results of the study showed significant differences ($P \leq 0.01$) decreased the level of testosterone for both amlodipine and atenolol along the duration of the experiment compared with control group, While the results of both valsartan and captopril showed a rise in the level of testosterone, While the level of estrogen increased at significant differences ($P \leq 0.01$) in all treatment of the totals drugs on the period of the experiment compared with the control group. The study suggested that treatment with amlodipine and atenolol may cause abnormalities in the sex hormones of the male reproductive system, which indicate the inhibition of testosterone.

Introduction

Hypertension (HTN) is one of the most common diseases in the world, Where the World Health Organization said on World Health Day 2013 that it is suffering a billion people worldwide from HTN, Causing disease that kills 9 million people a year at the present time [1] World health organizations have been interested in this disease because it is closely linked to cardiovascular disease and kidney damage [2]. Drug Antihypertensive has diversified, where it works in several ways, It removes excess salts and fluids in the body, or slow down the speed of the heartbeat, or working to relax or dilation of blood vessels, drugs that act on the angiotensin converting enzyme (ACE) and drugs that act on calcium channels are considered the most common and widely used. Amlodipine : Calcium Channel Blockers (CCB) Which disrupts the movement of calcium through its channels [3]. Working to reduce the calcium entry from the extracellular fluid into the fluid inside the cell, Where it works on the calcium balance between the inside and outside of the cell [4]. Calcium channel blockers (CCBs) works by relaxing muscles in the walls of arteries, and it is effective in patients with arterial diseases, Heart failure, and exercise on any negative effects of fat on carbohydrates and metabolism [5,6].

Captopril: It lies its importance in the treatment of high blood pressure and reduce Heart failure [7]. Is a competitive inhibitor of angiotensin converting enzyme (ACE) which converts angiotensin I to angiotensin II where the latter works on the narrowing of blood vessels, Which leads to high blood pressure, Therefore captopril works to expand the blood vessels leading to increased blood flow thus lowering blood pressure [8]. It reduces Angiotensin II concentration, which in turn reduces concentration of aldosterone, Decreases fluid retention of sodium and potassium ions and thus lower blood pressure [9]. Captopril can pass through the blood stream to the brain will prevent and inhibits the Renin -Angiotensin System (RAS) it also has anticoagulant effect [10].

Valsartan : Is a selective antagonist of angiotensin II receptors where it works on the dilation of blood vessels Which leads to increased blood flow to the kidneys and increase the production of urine, It is used to treat heart failure and hypertension [11,12].

Atenolol : It is considered a beta channel blocker as it is reduced Cardiac Output Rate by preventing beta receptors β1 in the heart it is similar to catecholamine as it is associated with the receptor β1 of the membranes of nerve clamps and to stop the effect of catecholamine on the heart, and so, reduces heart rate, It is used in the treatment of cardiovascular diseases, including high blood pressure and it helps prevent strokes and kidney problems [13,14]. It also limits the release of renin from the glomerular cells in the kidney by reducing the activity of the sympathetic nervous system [15].

High blood pressure HTN is often associated with sexual impotence, Sexual impotence is high among hypertensive patients receiving antihypertensive drugs [16]. The occurrence and exacerbation of sexual problems through drug treatment and high blood pressure, which may reduce compliance to lower blood pressure [17]. There is evidence that some classes of antihypertensive drugs, Such as diuretics, Beta blockers, especially non-selective, have a greater impact on the sexual function than other categories, Such as calcium antagonists and inhibitors of angiotensin-converting enzyme and other drugs [18]. Therefore, this study was designed and implemented to investigate the effect of certain antihypertensive drugs on the Testosterone and Estrogen hormones in serum and it's reflects on sexuality performance, in white male rats.

Material and Methods

This study was conducted over 60 days from the beginning of October until December in 2016 in the Animal House of department Biology in the College of Education for Women-Tikrit University, Male rats were used where they distributed to 5 groups randomly each group includes 10 rats has been dosage Twice daily, These totals were (Control, Amlodipine,0.428mg, Valsartan 0.68mg, Captopril 0.214mg, and Atenolol 0.42mg). Collection of samples: It was taken about 4 ml of blood by dragging it from the eye every two weeks throughout the trial period, The serum was separated by a centrifuge, and use of the serum for the analysis. Hormones Estrogen and Testosterone concentrations were estimated by screening using a hormone analysis device COBAS e411 technical which was used from[19] from the German company Roche Hitachi according to manufacturer's instructions.

Statistical analysis: All results were expressed in mean ± SD using a system (ANOVA) One-way for contrast analysis, It was used to find the effect and comparison of drugs used on Sex hormones the value P≤ 0.01 was considered statistically significant [20].

Results

Effect of Antihypertensive drugs on Testosterone:

Results of the present study showed a difference in testosterone concentrations Of using drugs compared to the control group Figure (1) shows concentration levels of testosterone in the blood serum, Testosterone concentrations were low for drugs - treated groups, Amlodipine(0.58±0.8) ng/ml Atenolol (1.74±0.2) Captopril (1.09±0.7) Compared with the control group (1.78±0.4) While the drug Valsartan increased significantly(2.01±0.2) ng/ml in the first week. While the second week study results showed a significant decrease in both Amlodipine (0.49±0.2) Atenolol (0.78±0.8) ng/ml in testosterone concentrations compared to the control group (0.90±0.6) while rising in Valsartan (2.62±0.1) ng/ml and Captopril (2.17±0.5) ng/ml. The third week, the results of the study showed a significant decrease in both of Amlodipine (0.28±0.1) ng/ml and Atenolol (0.60±0.7) ng/ml in testosterone concentrations compared to the control group (0.96±0.5)While rising in Valsartan (2.22±0.8) and Captopril (1.09±0.3). Fourth week study results showed a significant decrease in both Amlodipine (0.42±0.4) ng/ml and Atenolol (0.20±0.5) ng/ml in testosterone concentrations compared to the control group (0.83±0.5) ng/ml while rising in Valsartan (2.61±0.7) ng/ml and Captopril (1.36±0.3) ng/ml.

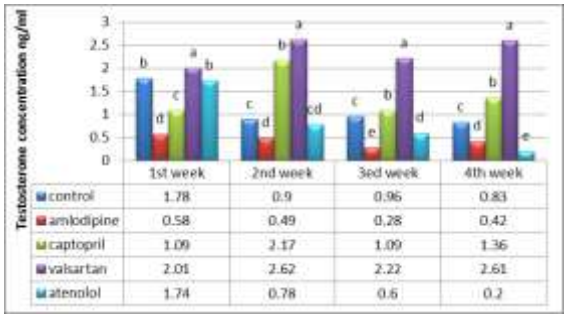

Figure (1) shows the effect of some antihypertensive drugs in serum concentrations of testosterone.

Effect of Antihypertensive drugs on Estrogen

Results of the study showed treatment of all drugs in the experiment high levels of estrogen at significant difference (P≤0.01) according to Figure (2) shows concentration of estrogen in the serum, The results were in a drug Amlodipine (10.92±4.3) pg/ml Atenolol (6.1±1.9) pg/ml Valsartan (7.15±2.1) pg/ml were high in the first week, While there were no significant differences in Captopril (5.4±0.8) compared to control group (5.15 ± 0.6) pg/ml . In the second week, the results showed a significant increase in Amlodipine (12.32±5.8) Atenolol (10.73±2.8) pg/ml Valsartan (12.9±2.9) pg/ml and Captopril (13.09±12.9) pg/ml compared with control group (5.05±0.6). The third week, the results of the study showed a significant increase in both Amlodipine (20.53±6.0) Atenolol (17.08±3.5) Valsartan (13.80±4.9)pg/ml Captopril (15.02±10.1) pg/ml compared with control group (5.10±0.6). Fourth week study results showed significant increase in both Amlodipine (23.51±6.8) pg/ml Atenolol (22.90±6.7) pg/ml Valsartan (18.50±5.6) pg/ml Captopril (18.39±10.0) pg/ml.

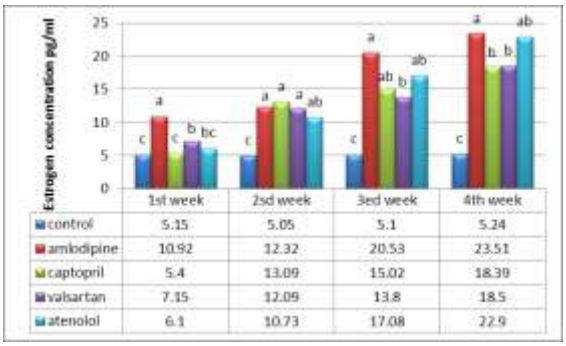

Figure (2) shows the effect of some antihypertensive drugs in concentrations of estrogen level in the serum.

Discussion

The study results showed that the antihypertensive drugs (Calcium channel blockers Amlodipine and beta blockers Atenolol) in addition to (Angiotensin converting enzyme inhibitors Captopril and Anti angiotensin receptor Valsartan) showed differentiated effects on sexual function and testosterone which show the negative impact for Amlodipine and Atenolol on sexual function This is consistent with many studies[18,21,22,23]. Also it showed similar results conducted on animals low levels of testosterone on 30 males on amlodipine with a doses of 5,10 mg for 50 days [24]. The same result was conducted on human 28 males for 30 days where testosterone is low [25]. The proposed mechanisms that may cause sexual dysfunction for Atenolol drugs it is the inhibition of the sympathetic nervous system which participates in the ejaculation process and regulate the secretion of the LH hormone and stimulate the release of testosterone [26]. As for the amlodipine drugs the low level of testosterone it may be due to the impact of the management Calcium channel blockers(CCBs) this causes significant oxidative stress in the male reproductive medium during the Catalase reduction period, Glutathione enzymes in the activities of the testes leading to the production of free radicals, Which cause damage in lydge cells and a sharp drop in testosterone in the blood [27]. It is also believed that the internal and external flow of calcium it must be tightly regulated by the presence of calcium in the cells and transported across the cell membrane via calcium channel blockers CCBs which can significantly effect on sperm and Steroidogenesis [28].

As for Valsartan the results showed a rise in testosterone where it came matching with the study conducted by the [29] on women where he explained the improvement of sexual function and sexual desire unlike atenolol which reduced the level of libido. In addition to the study conducted on men, Where testosterone level increased and improved sexual activity, Where the patients who received treatment valsartan has seen an increase in sexual contact rate to 21%, The reason may be due to the antagonists of angiotensin II receptors are working to relax the smooth muscles smooth and an erection[18,30,31]. It can also be a riser interaction of some angiotensin-2 metabolite with the Central Dopaminergic System where animal data have proved that a major role on sexual behavior [32,33].

Captopril showed high levels of testosterone it came in line with the study conducted on mice, Where increasing testosterone levels significantly [34]. While previous studies have shown that levels of testosterone and LH or FSH are not affected by captopril [35]. Subsequent studies indicated the captopril works to improve sexual function perhaps because of its expanded effect for blood vessels [36]. Recent studies have not shown its effect on the quality of semen and therefore the occurrence of infertility in males, While it may affect the rate of sperm fusion in the egg through preventing the activity of angiotensin-converting enzyme ACE which launches through Capacitation and Acrosome reaction [37]. While previous studies have shown different results Testosterone levels in rats are low [38]. Results of the study showed treatment with all antihypertensive drugs an increase in the proportion of estrogen levels this was in line with the study conducted on men, this was in line with the study conducted on men for both drugs Captopril and Amlodipine who are suffering from gynecomastia due to increased levels of Estradiol E2 and increased conversion of testosterone to estradiol [39]. One of the previous studies have also indicated link to amlodipine the occurrence of the case of gynecomastia in men by increasing the amount of estradiol [40]. Other results were also shown on mice the role of captopril in the inhibition of the production of angiotensin II and restore metabolic processes in bone and structural mineralization in estrogen-deficient in mice [41]. One previous study indicated the effect of atenolol on the rise of estrogen (estradiol) slightly, but there was no significant effect of captopril on sex hormones [34]. High estrogen works to lower blood pressure through the mechanism in which this hormone works, It regulates the action of the renin angiotensin system RAS in the kidneys this in turn affects the expansion of blood vessels, thus lowering blood pressure [42]. In conclusion, the results of the present study indicate differences between (Amlodipine and atenolol) and (valsartan and captopril) in their effect on levels of testosterone although similar impact on the levels of estrogen, where both valsartan and captopril showed a rise in testosterone which may provide an advantage in terms of sexual activity, Therefore, this study was performed to monitor and compare the impact of both amlodipine, atenolol,, valsartan and captopril on testosterone and estrogen hormones in male rats.

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دراسة مقارنة تأثير بعض الادوية الخافضة لضغط الدم في تراكيز هرموني التستوستيرون والاستروجين في ذكور الجرذان البيضاء

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الملخص

أجريت هذه الدراسة في البيت الحيوانية في قسم علوم الحياة – كليه التربية للبنات – جامعه تكريت . لتقييم ومقارنه تأثير بعض الأدوية الخافضة للضغط علي هرموني التستوستيرون والاستروجين في ذكور الجرذان. أستخدم 50 من ذكور الفئران تراوحت أعمارهم 4–6 أشهر وأوزانهم 250–400 غم وزعت في خمس مجموعات، بواقع 10 حيوانات في كل مجموعه (السيطرة، والمجاميع التي تم إعطائها عقارات علاج ارتفاع ضغط الدم Amlodipine,0.428mg، Valsartan 0.68mg، captopril 0.214 mg، و Atenolol 0.42mg) مرتين يوميا لمده 60 يوما. تم تحليل العينات في جهاز cobas e411 من شركة روش هيتاشي وفقا للمصنع، وأظهرت نتائج الدراسة اختلافات معنوية عالية ($P\leq0.01$) انخفض مستوي التستوستيرون لكل من املوديبين واتينولول علي طول مده التجربة مقارنه مع مجموعه السيطرة، في حين ان نتائج كل من فالسارتان وكابتوبريل أظهرت ارتفاعا في مستوي هرمون تستوستيرون، في حين وأزداد تركيز الاستروجين معنويا ($P\leq0.01$) في جميع مجاميع الحيوانات التي تم إعطائها العقارات التي شملتها الدراسة مقارنه مع مجموعه السيطرة. واقترحت الدراسة ان العلاج مع املوديبين و اتينولول قد يسبب اضطرابات في تراكيز الهرمونات الجنسية في الجهاز التناسلي للذكور، بسبب قيامها خفض هرمون التستوستيرون.