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EFFECTS OF ALDACTONE ,A POTASSIUM SPARING DIURETIC, ON KIDNEY AND LIVER FUNCTION IN RAT

Mahammed A. Dabbi* and Ahmed O. Hussain
Department of Biotechnology, College of Biotechnology, Al-Qasim Green University, Iraq
*Corresponding Author E-mail:Maldabbi99@gmail.com

ABSTRACT

Forty albino male rats were Albino rats, ages were less than twenty weeks and average weight 190±10gm were divided randomly into four equal groups and treated for 90 days as following :First group (C) was given normal saline only as a control group. Second group (T1) was given aldactone (8.8 mg/day). Third group (T2) was given aldactone (17.6 mg/day).And fourth group was given aldactone (35.2 mg/day). In the end of the experiment all animals were sacrificed and blood samples were collected directly from the heart and serum samples were isolated to measure sodium, potassium concentration and to estimate renal function. The results of study regarded the potassium concentration were revealed a significant difference ($p \leq 0.05$) represented by increase in potassium concentration in T1group compared with C group. Also, there was a significant difference represented by increase in potassium concentration in T2group compared with C group.T3 show significant increase in potassium concentration compared with C group. The results of sodium were revealed no significant difference in sodium concentration in T1group compared with C group. Also, there was a significant difference represented by decrease in sodium concentration in T2 and T3 group compared with C group. The result of renal function test revealed there were no significant difference in the concentration of urea between T1group and C group. Also, there was a significant difference ($p \leq 0.05$) represented by increase in urea concentration in T2group compared with C group. And there was a significant difference represented by increase in T3 group compared with C groups. The concentration of creatinine increased with consumption of aldactone but with no significant difference. The results of liver function test revealed there was significant difference ($p \leq 0.05$) represented by increase in GOT concentration in T1group compared with C group. Also there were significant difference between T1group C group. And there was a significant difference represented by increase in T3 group compared with C groups. The concentration of GPT there were no significant difference between T1group and T2 group. Also, there was significant difference in T2 group compared with C group. And significant difference ($p \leq 0.05$) represented by increase in GPT concentration in T3group compared with other groups.

***Keywords*:** Aldactone, potassium concentration, sodium, urea, GPT, GOT and creatinine concentration.

Introduction

Aldactone (spironolactone) is a potassium sparing diuretic that removes excess fluid from the body in congestive heart failure, cirrhosis of the liver, and kidney disease. It also can be used in combination with other drugs to treat diuretic-induced low potassium (hypokalemia) and high blood pressure (Davies and Wilson, 2015). Aldactone (spironolactone) is a specific pharmacologic antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule (Gudmundsson *et al.,* 2014). Spironolactone is rapidly and extensively metabolized in the liver upon oral administration and has a very short terminal half-life of 1.4 hours. The major metabolites of spironolactone have much longer elimination half-lives than spironolactone of 13.8 hours, 15.0 hours, and 16.5 hours, respectively, and are responsible for the therapeutic effects of the medication (Jewell *et al.*, 2016). Spironolactone is a nonselective aldosterone receptor antagonist (ARA) and a potassium-sparing diuretic. Primary aldosteronism can result in hypertension, but any increase in aldosterone levels can result in increased blood pressure. Therefore, medications that block the aldosterone receptor would be useful in the management of resistant hypertension or in cases where aldosterone escape occurs in patients receiving an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) (Marrs, 2014). The main ARA mechanism of action useful in the treatment of hypertension is the competitive blockade of the mineralocorticoid receptor in the distal convoluted tubule in the kidney, preventing the upregulation of the epithelial sodium channel and sodium-potassium-adenosine triphosphatase. The result is increased diuresis and circulating potassium with an overall decrease in volume. Other potential ARA mechanisms in the management of resistant hypertension include reductions in sympathetic tone and changes/reductions in vascular tone and stiffness (Belden *et al.,* 2017). Spironolactone has been considered as an antagonist at the aldosterone receptors of the epithelial cells of the kidney and was clinically used in the treatment of hyperaldosteronism and occasionally as a potassium-sparing diuretic. Spironolactone may also be useful in the treatment of other conditions such as: portal hypertension, cirrhosis, and left ventricular hypertrophy(Morimoto and Ichihara, 2020). Spironolactone is a synthetic steroid that competes for the cytoplasmic aldosterone receptor. It increases the

secretion of water and sodium, while decreasing the excretion of potassium, by competing for the aldosterone sensitive Na^+/K^+ channel in the distal tubule of the nephron (Agarwal and Mirshahi, 2014). Increased levels of the mineralocorticoid, aldosterone, are present in primary and secondary hyperaldosteronism. Edematous states in which secondary aldosteronism is usually involved include congestive heart failure, hepatic cirrhosis, and the nephrotic syndrome. By competing with aldosterone for receptor sites, Aldactone provides effective therapy for the edema and ascites in those conditions (Nappi and Sieg, 2016). Spironolactone is highly protein bound (>90%) and is primarily excreted through the urine and to a small degree in bile. Consumption with food increases the oral bioavailability of spironolactone and possibly decreases its first-pass metabolism (Mackenzie *et al.,* 2017). Spironolactone not only inhibits production of several cytokines involved in the pathology of many disease, it can also be considered for prolong periods as an economically attractive alternative to modern anti-inflammatory agents (Durante *et al.,* 2016). Spironolactone acts as androgen receptor antagonist but is also able to directly block the synthesis of both adrenal and gonadal steroids (Simitsidellis *et al.,* 2018).

Materials and Methods

Experimental design

Forty albino male rats were Albino rats ,ages were less than twenty weeks and average weight 190±10gm were divided randomly into four equal groups and treated for 90 days as following :First group (C) was given normal saline only as a control group. Second group (T1) was given aldactone (8.8mg/day). Third group (T2) was given aldactone (17.6mg/day).And fourth group was given aldactone (35.2 mg/day).In the end of the experiment all animals were sacrificed and blood samples were collected directly from the heart and serum samples were isolated to measure sodium, potassium concentration and to estimate renal function by using ELISA technique.

Atomic Absorption Spectrophotometer 2380 (AAS) for Determination of potassium, sodium, urea and creatinine concentration

Spectrophotometer was achieved according to the method described by the manufacturing company (Perkin Elmer, Germany)

Results and Discussion

Evaluation serum potassium and sodium Concentration

Table (1) show there was significant difference ($p\leq 0.05$) represented by increase in potassium concentration in T1group (4.56 ± 0.09) which given aldactone (8.8 mg/kg/B.W). Compared with C group (3.77 ± 0.11) which given normal saline only. And there was a significant difference represented by increase in T3 group (5.04 ± 0.40) given aldactone (35.2mg/kg/B.W) compared with other groups . While there were no significant difference between T1group (4.56 ± 0.09) and T2 group (4.76 ± 0.05).

The concentration of sodium reduced with consumption of aldactone. Table (1) show there was significant difference ($p\leq 0.05$) represented by decrease in sodium concentration in T2group (129.49±4.01) compared with T1group (144.04±8.95). And in T3 group (124.65±0.97) compared with T1 group (144.04±8.95) and C group (145.40±5.14). While there were no significant difference between T1 group (144.04±8.95) and C group (145.40±5.14).

Table 1 : Effect of aldactone on serum potassium and sodium levels

Groups / Parameters	C group	T1 group	T2 group	T3 group
Potassium (mmol\L)	3.77± 0.11	4.56 ± 0.09	4.76 ± 0.05	5.04 ± 0.40
Sodium (mmol\L)	145.4±0.4	144.04±8.95	129.4 ± 4.1	124.6 ± 0.97

Effect of spironolactone on renal function tests:

Table (2) show there was significant difference ($p\leq 0.05$) represented by increase in urea concentration in T2group (28.73±3.68) compared with C group (19.15±3.07). And there was a significant difference represented by increase in T3 group (30.86±2.46) compared with other groups. While there were no significant difference between T1 group (23.40± 0.61) and C group (19.15±3.07).

The concentration of creatinine increased with consumption of aldactone but with no significant difference ($p\geq 0.05$). Table (2) show there was no significant difference in creatinine concentration when comparison between groups occurs.

Table 2 : Effect of aldactone on serum urea and creatinine:

Groups / Parameters	C group	T1 group	T2 group	T3 group
Urea mg\dl	19.15±3.07	23.40± 0.61	28.73±3.68	30.86±2.46
Creatinine mg\dl	0.740±0.03	0.785±0.02	0.790±0.01	0.795±0.02

Effect of aldactone on levels of GOT and GPT

Table (3) show there was significant difference ($p\leq 0.05$) represented by increase in GOT concentration in T1group (205.57±7.28) compared with C group (184.31±18.16). And there was a significant difference represented by increase in T3 group (427.46±7.16) compared with other groups. While there were no significant difference between T1group (205.57±7.28) and T2 group (212.68±20.13).

The concentration of GPT increased with conception of aldactone. Table (3) show there was significant difference ($p\leq 0.05$) represented by increase in GPT concentration in T3group (192.07±1.58) compared with other groups. And in T2 group (61.35±6.96) compared with T3 group (192.07±1.58) and C group (46.60±3.27).While there were no significant difference between T1group (53.66±6.16) and T2 group (61.35±6.96).

Table 3 : Effect of aldactone on GOT and GPT:

Groups / Parameters	C group	T1 group	T2 group	T3 group
GOT	184.31±18.16	205.57±7.28	212.68±20.13	427.46±7.16
GPT	46.60±3.27	53.66±6.16	61.35±6.96	192.07±1.58

Result of this study showed the use of spironolactone lead to significant increase in the mean serum level of potassium. This result was similar to a finding by (Pitt *et al.,* 2015; Dyckner *et al.,* 2016; Han *et al.,* 2017), who stated that serious hyperkalemia can be resulted from spironolactone due to physiological regression of renal function, higher dose of spironolactone and impaired renal function.

Potassium and sodium play a key role in the function of the myocardium; therefore, their concentration gradients are strictly maintained. Any imbalance of this concentration gradient affects the ability of the heart to maintain a normal rhythm. The concentration gradient is maintained by the sodium potassium ATPase pumps located on the cellular membrane that actively pump sodium outside and potassium inside the cell (Parham *et al.,* 2016). Serum sodium exhibits significant reduction in the spironolactone treated groups this result was consistent with results that obtained by (Yuwen *et al.,* 2016; Smith, 2016). Spironolactone is a potassium-sparing diuretic (water pill). It prevents your body from absorbing too much salt and keeps your potassium levels from getting too low. This medicine is also used to treat or prevent hypokalemia (low potassium levels in the blood) (Schaefer, 2015). Spironolactone blocks aldosterone receptors, and cyclosporine causes hyperkalemia by enhancing chloride reabsorption(Yasky *et al.,*2015).Renal function tests showed significant increase in urea concentration with nonsignificant increase in serum creatinine, this result was similar to that obtained by (Svensson and Custafsson, 2013), who assured that spironolactone can cause significant increase in serum creatinine levels and the chance for raised level of serum creatinine will increase with elderly patients due to increasing risk of renal impairment with advanced age and higher dose of spironolactone. The results show that the administered of spironolactone have improved the concentrations of liver enzymes (GOT and GPT). These results was agreement with result of (Luo *et al.,* 2015) who found that the AST and ALT concentration was significantly increased with aldactone consumption. The rises in the serum ALT activity with enlargements in the hepatic ALT activity are believed to the damage to, and leakage from, hepatocyte cell membranes, causing in a release of the enzymes from a cytosol to the blood (Akpek *et al.,* 2015).

Conclusions

From this study, it was found that, There was elevation of serum potassium level with significant reduction in sodium levels and Serum creatinine level was not significantly increased with consumption of spironolactone, with significant increase in urea levels.

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