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The Effect of Candesartan on Renal Function and Renin-Angiotensin-Aldosterone System (RAAS) in Hypertensive Patients

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Abstract

Nearly half of all strokes, heart failure, myocardial infarction, and kidney damage are caused by hypertension, one of the most important drugs used extensively to treat hypertension is candesartan. In the present study, on a sample of patients with hypertension, the impact of candesartan was examined. The impact of the medication was determined on a number of critical hormones, including angiotensin, renin, and aldosterone as well as the concentration of creatinine, uric acid, and blood urea. The one hundred and twenty individuals who participated in the study were divided into three groups. Each group had forty individuals, group one (G1) (negative control) included apparently healthy individuals with normal blood pressure, while group two (G2) included individuals with high blood pressure who were being treated with a drug other than candesartan; this group represents positive control. As for group three (G3), it included individuals with high blood pressure who were being treated with a drug candesartan. The findings demonstrated that patients with hypertension who were treated with candesartan had lower levels of blood urea, uric acid, and creatinine. With regard to the hormones angiotensin, renin and aldosterone, the results indicated that the levels of these hormones in patients taking candesartan were close to normal levels in healthy people.

Introduction

Hypertension is a disease that affects about half of the adult population globally and is defined by blood pressure that is often higher than 130/80 mmHg [1]. Hypertension is the main cause of disability and mortality in the world. Nearly half of all diseases, including renal damage, cognitive impairment, heart failure, and myocardial infarction, are at risk due to hypertension [2]. One of the most important strategies to control hypertension is pharmacological methods [3]. Several

pharmacological treatment options are used. These options include drugs (antihypertensive) such as ACE-inhibitors, diuretics, calcium channel antagonists and angiotensin-II-receptor blockers [4]. Candesartan is a brand-new drug that acts as a blocker of the angiotensin II (Ang II) receptor. After oral administration, the digestive system immediately absorbs it [5]. It works pharmacologically by interacting noncompetitively with type I Angiotensin II receptors, which are highly selective and produce potent, long-lasting effects. It lowers blood pressure by inhibiting the effects of the hormone Angiotensin II in the body [6]. The RAAS is a critical system in maintaining of blood pressure through balancing blood volume and electrolyte levels, it is a complex endocrine system that has the three essential elements of the hormonal system which are renin, angiotensin II, and aldosterone. Through these elements, the RAAS have the capacity to control blood pressure. Nevertheless, when the RAAS is pathologically activated, it produces excessively in vasoconstriction and muscular hypertrophy within the cardiac and vascular systems. The dysregulation and imbalance of the (RAAS) is noticed in many pathologies, such as hypertension and heart failure [7]. Renin is a key hormone in the regulation of blood pressure and several other physiological processes [8]. It is rate-limiting in the generation of Angiotensin II, a hormone that essentially unites renal and cardiovascular function in controlling of blood pressure as well as sodium and volume homeostasis [9]. The stimulation of renin release elevates plasma levels of Angiotensin II, which in turn enhances the secretion of aldosterone from the adrenal glands. The activation of Angiotensin II and aldosterone production promotes sodium reabsorption, which increases the body's sodium content [10]. Aldosterone is one of the most important regulating hormones which functions to organize the coupling of Na+ reabsorption with K+ and transported of Na+ in the distal nephron [11]. The production of aldosterone by the adrenal cortex is regulated by two important factors, the first is angiotensin II (Ang II) and the second is circulating potassium levels. Physiologically, aldosterone plays a major role in the conservation of blood pressure and intravascular volume through sodium retention in the kidney and high levels of aldosterone that lead to heart complications and also causes hypertension [12]. Angiotensin II is considered one of the important mediators in hypertension, which promotes salt retention by the kidney, causes vasoconstriction, increases thirst, and enhances the release of catecholamines from nerves and the adrenal gland [13]. The renin-angiotensin system is blocked by Angiotensin receptor blockers (ARBs) which are considered the first class treatment option for the controlling of patients with hypertension [14]. Angiotensin receptor blockers (ARBs) provide effective inhibition of angiotensin II by interacting selectively at the receptors site, like candesartan which blocks the angiotensin receptor [15]. The pathogenesis of hypertension has been demonstrated to be significantly influenced by inflammatory processes [16]. Candesartan treatment

may reduce a variety of pathological effects and affect some physiological factors, including creatinine, uric acid, and the levels of hormones like aldosterone and Renin [17].

Materials and Methods

The current study included the participation of one hundred and twenty individuals, and the number was divided into three groups, each group consisted of 40 individuals. Each of these groups was subjected to three different tests that included physiological tests, which consisted of kidney function tests (creatinine - blood urea - uric acid), and hormonal tests including (angiotensin, renin, and aldosterone). Blood samples were collected from patients and healthy people through venous blood draw, and then the blood was placed in two types of tubes for each person who participated in this study. The first type of tube had an anticoagulant, and the other contained a gel to separate the serum. Then we transferred tubes on a daily basis and directly to the laboratory to conduct the study. The following are the totals adopted by the current study:

Group 1: This group (negative control) included apparently healthy individuals who do not have hypertension.

Group 2: This group included individuals with hypertension who were being treated with a drug other than candesartan, this group represent positive control.

Group 3: This group included individuals with hypertension who were treated with candesartan.

Results and Discussion

Table (1) showed that there was a significant ($P < 0.05$) increase in the level of uric acid in the G2 group (8.26±1.29 mg/dl) compared with the G1(5.19±1.05 mg/dl) and G3(5.23±6.34 mg/dl) groups. At the same time, the results did not record a significant ($P < 0.05$) difference between the G1 and G3 groups. While the results of blood urea levels were recorded a significant ($P < 0.05$) difference in the level of blood urea nitrogen between the three groups, and between the statistical analysis there was a significant ($P < 0.05$) increase in the level of blood urea nitrogen in group G2 (45.45±13.1mg/dl) compared with positive group G1(30.17±6.18 mg/dl) and G3 (36.07±9.91mg/dl). Besides, the results recorded a significant increase in blood urea in group G3 compared with G1. Finally, the results of creatinine levels were recorded a significant ($P < 0.05$) increase in Creatinine levels in the group G2 (1.08±0.47 mg/dl) compared to the G1(0.83±0.13 mg/dl) and G3(0.90±0.22 mg/dl) groups. At the same time, the results did not record a significant difference between the first and third groups.

Table 1: Comparison between studied groups in uric acid, blood urea and serum creatinine concentration

Groups	Uric acid concentration (mg/dl)	Blood urea concentration (mg/dl)	Serum Creatinine concentration (mg/dl)
G1	5.19±1.05B	30.17±6.18C	0.83±0.13B
G2	8.26±1.29A	45.45±13.1A	1.08±0.47A
G3	5.23±6.34B	36.07±9.91B	0.90±0.22B
P value	0	0	0.001
LSD	1.67	4.50	0.140

Table (2) shows the significant differences between the study groups and the hormones angiotensin, aldosterone, and renin. The study showed that the levels of Angiotensin in the three groups differed significantly. According to the statistical analysis, Group G2 (37.73±8.33) had a significantly ($p < 0.05$) higher level of Angiotensin than Groups G1 (15.22±4.9) and G3 (18.29±3.56), and Group G3 had a significantly higher level of Angio than Group G1. Moreover, the results revealed that the aldosterone levels in the three groups differed significantly. According to the statistical analysis, group G2 (42.68±6.76) aldosterone level increased significantly ($p < 0.05$), when compared to groups G1 (17.8±3.59) and G3(14.82±5.99), and group G1. Aldosterone level increased significantly when compared to group G3. Regarding the renin hormone the results recorded a significant ($p < 0.05$) increase in renin levels in group G2 (32.36±6.74) compared with the G1 (10.56±1.48) and G3 (10.95±2.17) groups, and at the same time. The results did not record a significant difference between the G1 and G3 groups.

Table 2: Comparison between studied groups in angiotensin, aldosterone and renin levels.

Groups	Angiotensin (mg/dl)	Aldosterone (mg/dl)	Renin (mg/dl)
G1	15.22±4.94C	17.8±3.59B	10.56±1.48B

G2	37.73±8.33A	42.68±6.76A	32.36±6.74A
G3	18.29±3.56B	14.82±5.99C	10.95±2.17B
P value	0	0	0
LSD	2.64	2.48	1.85

Different letters between any two means denote to the significant difference at $p<0.05$.

Angiotensin II needs a protein (referred to as a receptor) to attach to in order for blood vessels to constrict in a way that raises blood pressure. When angiotensin levels rise, various changes take place in the body, including fluid retention. The receptor proteins are blocked by angiotensin receptor blockers like candesartan, preventing angiotensin from binding and constricting blood vessels. Therefore, the blood vessels can unwind and continue to be open. The blood will then flow naturally and without exerting too much power [18]. Diuretics can lower blood pressure by encouraging the excretion of sodium in the urine. Hence, RAAS can be activated by raising circulating angiotensin levels. On the other hand, angiotensin receptor blockers are believed to exert their therapeutic effects by inhibiting the activity of metastatic RAAS. This kind of thinking has become somewhat acceptable, although it may not always be the best. Indeed, when the activity of the RAAS is increased by a diuretic, the effectiveness of the ARB may be slightly reduced [19]. Regarding hormone aldosterone, many antihypertensive drugs, especially those belonging to the class of ABRs, were found to be inhibited by their action on the RAAS because some of the drugs, such as Olmesartan, according to its mechanism of action, have a side effect represented by raising the level of aldosterone, and on the contrary, the drug Candesartan inhibits the level of aldosterone [20]. Candesartan may attenuate sympathetic tone by inhibiting presynaptic AT1 receptors. This assumption is based on the observation that in isolated perfused mesenteric vasculature of spontaneously hypertensive rats (SHR), candesartan cilexetil inhibited the release of norepinephrine induced by electrical stimulation of periarterial adrenergic nerves. Candesartan cilexetil markedly reduced plasma aldosterone levels elevated by intravenous infusion of angiotensin II [21]. Candesartan cilexetil inhibits the angiotensin type-1 (AT1) receptor, blocking the actions of angiotensin II. Angiotensin II, the primary vasoactive hormone of the renin-angiotensin-aldosterone system, has several physiological effects, such as vasoconstriction, stimulation of aldosterone

secretion, and sodium reabsorption in the kidneys [22]. As for the resonance hormone, the renin-angiotensin-aldosterone system is impacted by renin inhibitors or direct renin inhibitors. Direct inhibition of the proteolytic enzyme renin, which is secreted by the kidney, is proved by how renin inhibitors operate. They stop renin from converting angiotensin to angiotensin I, which then turns into angiotensin II. The blood arteries stay dilated and the blood flow is maintained without angiotensin II resulting in a drop in blood pressure [23]. Some antihypertensives, including angiotensin receptor blockers like candesartan, cause what might be referred to as "functional" side effects associated with RAS inhibition, particularly hyperkalemia which is caused by inhibition of aldosterone secretion and a severe and reversible decrease in glomerular filtration rate (GFR), usually between 10% and 20% depending on the baseline glomerular filtration rate [24]. This drop in glomerular filtration rate is brought about by the ability of ACE inhibitors and angiotensin receptor blockers to lower systemic blood pressure and widen the vasculature emerging from the renal arterioles, hence lowering intraglomerular pressure [25].

Conclusion

Candesartan is a kind of medication which is used to treat hypertension that is part of the Angiotensin Blocked Receptors (ABRs) family. The kidneys are safe when using this medication. Because of its beneficial influence on the RAAS system, it efficiently lowers blood pressure. It also lowers the renal filtration rate and inhibits the action of the angiotensin hormone, which is significant in high blood pressure. Consequently, using this medication as a successful treatment is advised for those who experience elevated blood pressure.

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