DOI: https://doi.org/10.54393/fbt.v3i01.36

FUTURISTIC BIOTECHNOLOGY

https://fbtjournal.com/index.php/fbt

Volume 3, Issue 1 (Jan-Jun 2023)

Original Article

Effect of Anti-Hypertensive Drug Atenolol on Liver Function by Evaluating ALT levels

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ARTICLE INFO

Key Words:
ALT level, Hypertension, Atenolol

How to Cite:
Fareed Siddiqui, M., Rasheed, M., Alwazzan, A., & Sarwar, S. (2023). Effect of Anti-Hypertensive Drug Atenolol on Liver Function by Evaluating ALT levels : Drug Atenolol on Liver Function by Evaluating ALT levels. Futuristic Biotechnology, 3(01). https://doi.org/10.54393/fbt.v3i01.36

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Received Date: 10th April, 2023
Acceptance Date: 28th May, 2023
Published Date: 30th June, 2023

ABSTRACT

Hypertension is one of the major causes of cardiovascular and renal pathologies and it is mainly characterized by high blood pressure in blood vessels. Many drugs have been developed to treat hypertension, but these drugs have several side effects. Atenolol belongs to the beta blocker drug class and is used to treat hypertension and cardiovascular diseases. It is an anti-beta-adrenergic agent which inhibits beta receptors in the heart to decrease blood pressure. It has several side effects including hepatic dysfunctions. **Objective:** To analyze the effects of atenolol on hepatic dysfunction by evaluating the ALT level in patients taking either atenolol alone or in combination with other hypertensive drugs. **Methods:** The change in ALT levels were measured upon treatment of atenolol alone or in combination with other anti-hypertensive drugs. Out of selected 80 patients, 43 had been taking atenolol alone, 37 were taking atenolol in combination with other anti-hypertensive drugs and 20 were healthy controls. Micro-laboratory tests were performed for measuring the ALT levels. **Results:** Atenolol did not affect the ALT levels of any group, neither alone nor in combination with other hypertensive drugs. **Conclusions:** Atenolol may cause hepatic dysfunction but according to this study it does not cause change in ALT level of blood and ALT is not elevated in all liver dysfunction as have been reported earlier so it didn't diminish the chance of effect of atenolol on liver functions. Further this study may be employed on larger patient groups for strengthening the outcomes of this study.

INTRODUCTION

Hypertension is a complex chronic disorder which frequently involves cardiovascular and other complications. Hypertension is usually characterized by high blood pressure in the blood vessels i.e., 140/90 mmHg or higher [1, 2], which is diagnosed by using automated blood pressure measurement devices. Major factors play important role in hypertension including genetics and different environmental factors [3, 4]. The central nervous system, microcirculation, endocrine factors and renin-angiotensin-aldosterone system have role in hypertension pathology [5-7]. Different non-pharmacological approaches may reduce the blood pressure. Anti-hypertensive drugs of different classes have been developed which diminish the hypertension. Main classes of anti-hypertensive drugs used to reduce blood pressure includes; ACE inhibitors, alpha blockers, angiotensin receptor blockers, diuretics, beta blockers, renin inhibitors, calcium channel blockers, vasodilators and central alpha agonists [8, 9]. Atenolol belongs to group of beta blockers is a selective β1-receptor antagonist. Its chemical formula is 2-{4-[2-Hydroxy-3-(propan-2-ylamino) propoxy] phenyl} acetamide and firstly it was used as a replacement for propranolol in the treatment of hypertension. It is mainly used to treat cardiovascular diseases. Atenolol reduces the blood pressure at resting and active state by blocking the activity of beta-adrenergic receptor and it also inhibits and reduce the tachycardia and orthostatic tachycardia respectively. It also decreases the

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activity of plasma renin, concentration of aldosterone in plasma, urinary excretion of kenin and prostaglandin E [10]. The anti-hypertensive drugs used to control blood pressure may have efficacy but also have several serious side effects. As atenolol have found to cause constipation, confusion, indigestion, dry mouth, depression, dysfunction of cardiovascular, central nervous system, and gastrointestinal system, and insulin level disturbance. One of the major side effects of atenolol is hepatic dysfunction as it causes damage to the liver cells and leads to liver function impairment by causing various symptoms [11]. Liver function tests (LFTs) are used in clinical biochemistry laboratories to indicate the liver dysfunctions. As in this study it is performed to analyze the effect of atenolol on hepatic dysfunction [12]. Abnormal LFTs have been found in patients with high blood pressure [13]. Alanine aminotransferase (ALT) a relatively sensitive indicator of hepatic damage from different diseases can be used a biomarker. However, the elevated value of ALT alone cannot be absolutely associated with liver disease. As the elevated level of this enzymes may occur due to muscle damage [14]. However, ALT level is frequently used for detection of liver inflammation due to any injury or damage its normal range for male lies within <45U/L and for females <34 U/L [15].

So, this study was based on finding the effect of atenolol on hepatic functions by measuring the ALT level in hypertension patients after they are treated with atenolol alone or in combination with other anti-hypertensive drugs.

METHODS

In this study, effect of atenolol on hepatic dysfunction was evaluated in hypertensive patients. Hepatic dysfunction in these patients was assessed by measuring ALT levels. 80 hypertensive patients were divided into two main groups. One group was treated with atenolol alone and second group was treated with atenolol in combination with other anti-hypertensive drugs. While 20 cases with normal blood pressure were taken as control. Patients were selected from Punjab Institute of Cardiology, Lahore for the evaluation of hypertension status. Those with hypertension taking atenolol alone or in combination were selected and their ALT levels were measured. All the positive hypertensive patients were included and those on treatment with multi-drug therapy or with concomitant disorder were excluded in this study. While those with normal blood pressure were taken as control for comparison. After collection of blood from the all the persons, blood was centrifuged at 3000rpm for 5 min to separate the serum. Then the ALT level indirectly was measured by measuring the timely change in absorbance of sample due to the conversion of NADH to NAD^+ that was measured by using a photometer 5010plus at 340/410nm rate technique. As the ALT enzyme catalyzes the reaction of conversion of 2-oxoglutarate into L-glutamate and pyruvate. This pyruvate is then quantitatively measured by LDH-NADH reaction. The decrease in absorbance due to oxidation of NADH to NAD is monitored at 340nm. Addition of pyridoxal-5-phosphate (P-5-P), recommended by IFCC, stabilizes the activity of transaminases and avoids falsely low values in sample containing insufficient endogenous P-5-P, from patients with hypertension.

RESULTS

The effect of atenolol on hepatic dysfunction was studied by measurement of ALT level in hypertensive patients. Figure 1 indicates the non-significant change in ALT level in patients treated with atenolol alone (mean value = 40.4) as compared to patients treated with atenolol in combination with other anti-hypertensive drugs (mean value = 36.3), or to the control group (mean value = 36.8).

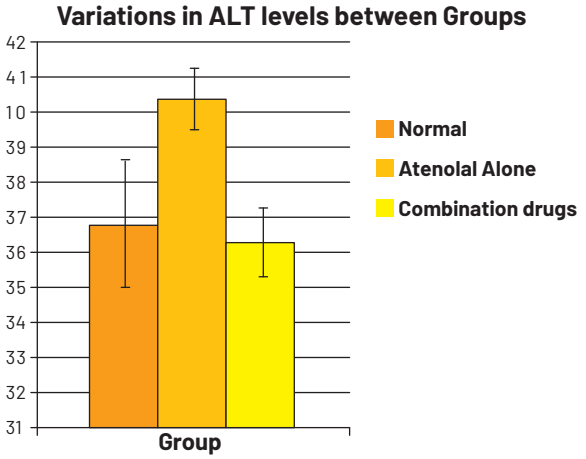

Figure 1: Graphical representation of non-significant disturbance in ALT level of patients divided in three groups.

Table 1 shows that in the control group of 20 people of random age and gender having blood pressure within normal range have ALT levels in normal range for male lies within <45U/L and for females <34 U/L.

Table 1: Evaluation of ALT in control population

Sr. No.	Gender	Age	ALT
1	Male	35	23
2	Male	45	33
3	Male	37	41
4	Male	48	46
5	Male	51	49
6	Male	36	25
7	Male	42	45
8	Male	41	41
9	Male	55	50
10	Male	34	25
11	Female	35	29

DOI: https://doi.org/10.54393/fbt.v3i01.36

12	Female	44	33
13	Female	45	39
14	Female	46	41
15	Female	44	35
16	Female	55	42
17	Female	35	25
18	Female	33	26
19	Female	57	42
20	Female	42	46

Table 2 indicates that the patients takings atenolol alone with random age and gender have non-significant variation in ALT levels.

Table 2: Evaluation of ALT level in hypertensive patients taking atenolol alone

Sr. No.	Gender	Age	Duration of Administration	Dose (mg)	ALT
1	Female	34	2 years 2 months	100	27
2	Female	35	1 week	50	55
3	Female	38	8 years	50	26
4	Female	38	1 years	50	19
5	Male	39	4 months	100	49
6	Female	42	1 year 1 month	50	46
7	Female	43	7 months	50	30
8	Female	43	7 years	100	37
9	Female	45	1 week	100	30
10	Male	45	9 months	100	23
11	Female	45	4 months	100	33
12	Male	47	6 months	25	50
13	Male	47	1 year	100	35
14	Female	47	1 year 3 months	100	45
15	Female	48	2 years 10 months	100	208
16	Female	48	1 year 1 month	50	30
17	Male	48	7 months	25	25
18	Male	50	1 year 3 months	100	27
19	Male	50	1 year 1 month	50	42
20	Female	50	3 years	100	44
21	Female	50	1 year 2 months	50	43
22	Female	50	6 months	100	41
23	Female	50	5 months	50	38
24	Female	51	7 months	20	39
25	Female	52	9 months	100	35
26	Female	54	1 year 3 months	50	37
27	Male	56	2 years	50	41
28	Male	60	1 month	20	30
29	Male	60	1 month	25	45
30	Female	60	6 years 1 months	50	64
31	Female	60	10 months	100	39
32	Female	60	2 years 2 months	100	22
33	Female	60	1 year 9 months	50	29
34	Female	60	5 months	100	33
35	Female	60	7 years	50	32
36	Male	61	7 years	100	36
37	Female	62	4 months	100	30
38	Male	65	2 years 7 months	50	57
39	Female	67	6 months	50	31
40	Male	70	1 year	50	38
41	Female	70	5 months	100	28
42	Female	70	1 year 2 months	50	38
43	Male	77	2 weeks	100	34

Table 3 shows that the patients treated with atenolol in combination with other antihypertensive drugs with random age and gender have non-significant disturbance in ALT level.

Table: 3 Evaluation of ALT level in hypertensive patients taking atenolol in combination

Sr. No.	Gender	Age	Duration of Administration	Dose (mg)	ALT
1	Male	33	1 year	100	42
2	Female	35	8 years 2 months	100	32
3	Male	40	3years 3 months	100	54
4	Female	40	8 months	50	40
5	Male	41	1 year 3 months	100	35
6	Male	43	1 month	50	48
7	Male	44	5 years 4 months	50	45
8	Female	45	9 months	100	50
9	Male	45	5 months	50	45
10	Male	48	1 week	100	40
11	Female	48	4 years 5 months	50	25
12	Female	50	1 week	100	33
13	Male	50	6 years	100	33
14	Male	50	1 week	100	21
15	Female	50	1 year	50	53
16	Female	50	1 week	50	33
17	Female	54	3 years 3 months	100	58
18	Male	54	2 months	50	46
19	Female	55	9 years	50	44
20	Male	55	4 years 3 months	100	45
21	Male	56	1 year 1 month	100	24
22	Male	57	4 years 3 months	100	30
23	Male	58	1 year 5 months	50	26
24	Male	58	10 years	50	37

When the results were further subjected to statistical analysis by applying standard deviation and standard error, non-significant value of 0.604 was obtained (Table 4).

Table 4: Significance of measured ALT values

Values	N	Mean ± SD	Standard. Error	Significance
ALT	.00	36.80 ± 8.85	1.97963	0.604
	1.00	40.49 ± 27.84	4.24582	
	2.00	36.32 ± 10.08	1.65720	
	Total	38.21 ± 19.62	1.96172	

DISCUSSION

Hypertension is a heterogeneous disease mainly characterize by high blood pressure in blood vessels (140/90 mmHg or higher). According to a report of world health organization, it is a one of the major causes of premature death across the world. Some common factors responsible for hypertension includes; old age, genetic

DOI: https://doi.org/10.54393/fbt.v3i01.36

predisposition, obesity, non-active lifestyle, intake of high salt containing diet and high alcohol consumption [16]. Different drugs to control blood pressure have been developed which targets different homeostatic systems of the body that regulates the blood pressure in blood vessels. These anti-hypertensive drugs include beta blockers class [17]. Atenolol (2-{4-[2-Hydroxy-3-(propan-2-ylamino) propoxy] phenyl} acetamide) belongs to this beta blocker class and it is a beta-adrenergic agent that slow the heart rate and decrease the elevated blood pressure by inhibiting the beta receptor on heart [11]. While treating the hypertension or cardiovascular diseases with atenolol, it has showed several side effects including hepatic dysfunction [18]. Atenolol has been reported to cause liver cells damage and it can be assayed by LFTs. Liver function tests (LFTs) attribute to clinical assays used in clinical biochemistry to tell us about the condition of patient's liver [12]. Alanine aminotransferase (ALT) is a biomarker used in LFTs and its elevated level in serum indicated the inflammatory or damaged liver. However, the condition of liver dysfunction can be inferred from elevated ALT level but this increase in ALT level can also due to some other inflammatory diseases such as muscle damage [14]. But ALT level along AST level measurement is most commonly used test in clinical laboratories owing to its easy, economic method and relative higher sensitivity among other biomarkers [15]. In this study, the side effect of atenolol on hepatic dysfunction is studied in hypertensive patients when they are treated with atenolol. As, in literature many studies have reported the hepatic dysfunction due to atenolol administrations as in one study a complicated case of liver cirrhosis is reported after 3-year administration of atenolol [19]. The main focus of this study is to analyze the effect of atenolol on liver dysfunction by measuring ALT level. For that total 80 patients either treated with atenolol alone or with atenolol in combination with other hypertensive drugs was selected from Punjab Institute of Cardiology, Lahore, while 20 persons with random age and gender with blood pressure within normal range were taken as control. After sampling and blood collection, the serum was separated and ALT level was measured by performing clinical assay. The non-significant results were obtained as there was no variation in level of ALT in patients either treated with atenolol alone (mean value = 40.6) or treated with atenolol in combination with other anti-hypertensive drugs (mean value = 36.3) as compare to the control (mean value = 36.8). However, the effect of atenolol on hepatic dysfunction has been found in previous studies as one of these studies has reported that out of 76,408 people having side effects due to atenolol, 0.15% have abnormal liver function tests. While in sixty the hepatic dysfunction rate increases while using atenolol. Also, this effect of atenolol has found to be relatively more prevalent in females as in females the chance of hepatic dysfunction increases while using atenolol [ ]. Another study reported the effect of atenolol on dysfunction of liver as after atenolol administration liver dysfunction was reported in two hypertensive patients while the diseased state of liver was reverse after withdrawal of drug [20]. However according to this study, ALT level does not get effected by atenolol significantly but this study can't rule out the effect of atenolol on hepatic dysfunction as ALT levels alone didn't give the absolute result of hepatic conditions in all cases [21].

CONCLUSIONS

This study has shown that atenolol causes non-significant changes in ALT levels but as it has already been reported in hepatic dysfunction so may be some other biomarker can be used to evaluate the effect of atenolol on hepatic dysfunction. Further this study can be performed on larger patient groups with more cases for validating the outcomes of this study.

Authors Contribution

Conceptualization: MFS
Methodology: SS, MR
Formal analysis: AA, MFS
Writing-review and editing: SS, MFS, MR

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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