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LIVER ENZYMES ELEVATION IN HYPERTENSIVE PATIENTS TREATED WITH ANGIOTENSIN CONVERTING ENZYME INHIBITOR DRUGS IN A RURAL GENERAL HOSPITAL IN THE KINGDOM OF SAUDI ARABIA

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ABSTRACT

Background: Adverse drug reactions are reported as part of using drugs in treatment of diseases. In a disease which needs lifelong treatment the side effects add more problems. Treatment of hypertensive patients with angiotensin converting enzyme inhibitors (ACE inhibitors) can elevate liver enzymes in some patients. **Objective**: To evaluate the effect of ACE inhibitors on the liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST). **Methodology**: This paper is a part from the study: Evaluation of the Management of Hypertension in a Rural General Hospital in the Kingdom of Saudi Arabia. The study was a prospective cross-sectional hospital-based study. An interview-guided direct questionnaire was used. In the study, the Saudi guideline for management of hypertension was followed to manage 382 hypertensive patients coming to the department of internal medicine in a rural general hospital, the Kingdom of Saudi Arabia, from February 2013 to December 2015. ALT and AST were tested in 197 patients treated with ACE inhibitors. Perindopril, captopril, lisinopril and enalapril were used. **Result:** ACE inhibitors were the most antihypertensive agents used in the treatment. ALT was found increased in 22

patients and AST was increased in other 22 patients. Elevation was more than three upper normal limit in six patients. No patient reported any symptom of hepatotoxicity. In all patients, the elevation of the enzymes did not need stopping ACE inhibitors. **Conclusion:** The study had revealed a mild to moderate elevation in ALT and AST caused by the ACE inhibitors that did not need to stop them.

KEYWORDS: Hypertension. Angiotensin converting enzyme inhibitors. ACE inhibitors. Liver enzymes. ALT. AST.

1. INTRODUCTION

The untoward effect of the drugs, adverse drug reactions (ADRs), are the reason behind admission of 7-8% patients to the hospital, 10% of them in fatal situations. The side effects of the drugs may be systemic or localized and range from mild to fatal reactions. The treatment calculates the risk of adverse drug reactions caused by the dosage used to reach the maximum therapeutic effect.[1]

The metabolic homeostasis of the body is the function of the liver. Beside the detoxification, liver is involved in the processing of the amino acids, carbohydrates, lipids, and vitamins, synthesis of proteins and excretion of the products of detoxification of endogenous waste and xenobiotics in the bile. Thus, liver is vulnerable to adverse drug reactions. This toxic effect adds liver problem to the most common disease such as heart disease and diabetes, which need lifelong treatment.[1]

A secondary liver problem caused by the drugs is hepatotoxicity. Hepatotoxicity occurs by injury of the liver cell with impaired liver function caused by the drug or a noninfectious agent. Liver injury can be indicated by the liver enzymes level (alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase) while total and conjugated bilirubin level indicate the liver function.[1]

FDA Center for Drug Evaluation and Research, the Pharmaceutical Research and Manufacturers of America and the American Association for the Study of Liver Diseases use alanine aminotransferase (ALT) level of more than three times the upper limit of normal and a total bilirubin level of more than twice the upper limit as combined test to define clinically abnormalities.[2]

The level of enzymes is not an indication of serious hepatotoxicity because liver had great capacity to healing form injury even with three- times upper limit elevation in the enzymes. However, fatigue, anorexia, nausea, discomfort in the right upper quadrant and dark urine are signs of serious hepatotoxicity.[3]

Increased liver enzymes in some patients by angiotensin converting enzyme inhibitors (ACE inhibitors) used in the treatment of hypertensive patients, is the subject of many studies. ACE inhibitors can lead to hepatotoxicity.[4]

The uses of ACE inhibitors in all cardiovascular risk management are increasing dramatically.[5] They inhibit the action of angiotensin converting enzyme, which transforms the angiotensin II from angiotensin I and bradykinin, a potent vasodilator, from the kininogen under the name plasma kininase. Their antihypertensive effect comes from their ability to decrease the peripheral vascular resistance with no significant change in the cardiac output and heart rate.[6]

Near to 20% of hypertensive patients, have low renin activity and other 20% have high activity. Patients with high plasma renin activity respond well to drugs, which block the action of renin-angiotensin-aldosterone system.[6]

Renin converts angiotensinogen to angiotensin I, which is changed to angiotensin II by angiotensin-converting enzyme. Angiotensin II is an arterial vasoconstrictor having sodium-retaining activity. In the adrenal gland, angiotensin II is converted to angiotensin III. Angiotensin II and angiotensin III together stimulate the release of aldosterone.[6]

Drugs that impair renin-angiotensin-aldosterone system are three types according to their site of action:

- ACE inhibitors- block the change of angiotensin I to angiotensin II.
- Angiotensin receptor blockers (ARBs) - inhibit the action of angiotensin II at the angiotensin II type 1 (AT_1) receptor.
- Renin antagonist, aliskiren.

Other drugs like potassium sparing diuretics, spironolactone and eplerenone, are aldosterone receptor inhibitors. β-blockers also reduce the renin activity as a part of their antihypertensive effect.[6], [7]

ACE inhibitors side effects include:

- Dry cough- produced by block of kininase is the main reason to discontinue the ACE inhibitors in the 10-20% of the patients.
- Hypotension- at the time of starting treatment.
- Hyperkalemia- decrease in aldosterone causes potassium retention.
- Angioedema.
- Renal impairment.
- Altered taste.
- Hepatotoxicity, usually cholestatic in nature.[4], [5], [6], [7]

The study of the hepatotoxicity of cardiovascular agents by De Marzio et al. (2013) mentions that transient ALT elevations occur at a low rate during therapy with ACE inhibitors. Hepatotoxicity was reported with benazepril, captopril, enalapril, fosinopril and lisinopril but not moexipril, perindopril, quinapril and trandolapril, perhaps because they are infrequently used.

In the Saudi hypertension management guideline, the treatment of hypertension starts with restricting the diet if the hypertension is not in severe levels, increasing the exercise, decreasing salt, alcohol, smoking and observing the patient over months. The first line drugs are ACE inhibitors or ARBs, calcium channel blockers (CCB) or thiazide diuretics (THZ-D). The choice of any of these classes depends on the patient's age, presence of target organ damage, tolerability, other diseases, potential interactions with other drugs, implications for adherence and cost.[9]

In general, the drug of choice in the young, less than 55 years, white patients is ACE inhibitor or ARB and in the old, more than 55 and black patients is CCB or THZ-D. When considering adding a second drug, it is recommended to consider ACE-I or ARB plus CCB or ACE inhibitors or ARB + low-dose THZ-D.[9]

2. MATERIALS AND METHODS

This paper is a part from the study: Evaluation of the Management of Hypertension in a Rural General Hospital in the Kingdom of Saudi Arabia. The study was a prospective cross-sectional hospital-based study. An interview-guided direct questionnaire was used. It included 382 hypertensive patients followed in the internal medicine clinic in Adam general hospital, Kingdom of Saudi Arabia, form February 2013 to December 2015. In the study, 197

patients (101 males and 96 females) were treated with ACE inhibitors. Their age ranges from 28-100 years old.

2.1 LIVER ENZYMES BLOOD INVESTIGATIONS

Patients' blood level of ALT and AST was done by The COBAS c311 analyzer from ROCHE HITACHI Company.

2.2 STATISTICAL ANALYSIS

The data analysis included 197 patients who completed the questionnaire and followed to at least one-year. The data was collected and was analyzed by using Statistical Package for Social Science (SPSS) ver. 21.

3. RESULTS AND DISCUSSION

The study included 382 hypertensive patients. The most antihypertensive drugs used were ACE inhibitors, 197 (65.6%) of the patients. CCB in 96 (32%), β blockers in 80 (26.7%), diuretics in 79 (26.3%), ARBs in 32 (10.7%) and α agonist in 3 (1%).

Table-1: Antihypertensive drugs used in the study.

Medications (Antihypertensive)	Yes	No	Percent
ACE INHIBITORS(n=300)	197	103	65.7%
CCB (n=300)	96	204	32%
β BLOCKERS (n=300)	80	220	26.7%
DIURETICS (n=300)	79	221	26.3%
ARBS (n=300)	32	268	10.7%
ALPHA AGONIST(n=300)	3	297	1%

The use of ACE inhibitors was adherent to the Saudi hypertension management guideline. Study of Hypertension control in a community health center at Riyadh, Saudi Arabia (2001) found ACE inhibitors were the most antihypertensive drugs used by the patients in the health center.[10]

Captopril was used in 69 patients, lisinopril in 64, perindopril in 42 and enalapril in 22 patients. Their doses and frequency are shown in table -2.

Table -2: The types of ACE inhibitors, their doses and frequency.

ACE INIBITORS	Dose (mg)	Frequency (Hours)	Number of patients
LISINOPRIL (n=65)	5	12	1
		24	2
	10	12	27
		24	34
CAPTOPRIL (n=69)	12.5	8	1
		12	9
	25	8	10
		12	33
		24	13
	50	12	3
ENALAPRIL (n=22)	10	12	13
		24	7
	20	12	2
PERINDOPRIL(n=42)	2.5	24	2
	5	12	9
		24	30
	7.5	12	1

3.1. BLOOD INVESTIGATIONS

ALT was increased in 22 patients, AST was increased in 22 patients while in 12 patients both were increased.

Table-3: Numbers and percentages of normal and increased AST and ALT.

	Normal	Percentage	Increased	Percentage
ALT(n=197)	175	88.82	22	11.18
AST(n=197)	175	88.82	22	11.18

The mean level of the enzyme in patients was 52.49 U /L for ALT and 61.65 U/ L for AST. The increase in ALT was in 22 patients (11.18%) and in AST in 22 patients (11.18%) who were using ACE inhibitors. In 6 patients more than three upper normal limit (123 for ALT and 120 for AST). One patient with increased ALT used perindopril, 2 patients with increased AST used perindopril, 2 patients with increased AST used lisinopril and one patient with increased AST used captopril.

The increase in the enzymes was mild to moderate. The elevation in the liver enzymes is supported by the study of the hepatotoxicity of cardiovascular agents by De Marzio DH et al (2013), which mentions that transient ALT elevations occur at a low rate during therapy with ACE inhibitors.

4. CONCLUSION

The ACE inhibitors were the mostly used drugs in the treatment of hypertension in the hospital. The use of ACE inhibitors lead to moderate increase in the liver enzymes in some patients, ALT was increased in 22 patients (11.18%) and AST was increased in 22 patients (11.18%) who were using ACE inhibitors. The patients with elevation in the liver enzyme did not have any symptom of hepatotoxicity.

The use of ACE inhibitors needs more caution in patients. Liver enzymes test and bilirubin should be done routinely for patients treated with ACE inhibitors. The patients need more time spent for them to be educated about their disease and the importance of adherence to the treatment to achieve control of their blood pressure to avoid the complications.

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