Effect of Captopril on some Liver Function Tests in Hypertensive Patients

Mohammed Nathem Mohammed Ali * Wahda Basheer Al-Youzbaki **

Abstract

Background: Liver damage caused by drugs ingestion has become an important public health problem, contributing to more than 50% of acute liver failure cases.

Objective: To evaluate the effect of captopril monotherapy on some liver function tests in hypertensive patients, in relation to the age of patients, dose and duration of captopril use and to compare with the control.

Subject & Methods: This is a case control study conducted in the Consultation Clinic for Internal Medicine in Bin-Siena Teaching Hospital in Mosul city for the period 15th of October 2010 to the 15th of April 2011. A total number of 90 patients (50 males and 40 females) with mild to moderate primary hypertension , non diabetic , neither having liver diseases nor other chronic illnesses, were taken and divided into two groups: First group included 45 patients using captopril (captopril group) for more than three months , with age ranged from 37 to 61 years (48.89 ± 7.35 years). The second group included 45 newly diagnosed untreated hypertensive patients (control group), matched with the first group by age, sex, and BM. The serum obtained from the blood samples from all participants in this study was used to measure some liver function tests by using the available commercial kits. The blood pressure (BP) was measured by sphygmomanometer in the sitting state, and BMI obtained by dividing weight in (kg) by square of height in (meter).

Results: There is a significant reduction of systolic and diastolic blood pressure in captopril group in comparison with the control group. There was a significant higher level of serum alkaline phosphatase activity (ALP) in the captopril group as compared with the control group and non significant differences for the other liver function tests. There were no significant differences in the liver function tests in relation to the age of captopril using patients. No significant effect of the dose of captopril and the duration of captopril therapy on the liver function tests except that serum ALP was significantly increased with increasing of the dose of captopril.

Conclusion: The use of captopril therapy causes a smooth BP reduction effect with no effects on liver function tests except that captopril therapy causes a significant higher level of serum ALP when compared with control group and the increase in the dose of captopril causes increase in the serum ALP level . The duration of use of captopril and the age of the patients have no significant effect on the liver function tests.

Key words: Captopril, bilirubin, liver enzymes

Introduction

Liver damage caused by drug ingestion has become an important public health problem, contributing to more than 50% of acute liver failure cases [1].

Although drugs are usually metabolized without injury to the liver, many fatal and near-fatal drug reactions occur each year but the overall mortality rate for drug induced liver injury is about 5% [2].

On the other hand, many drugs are capable of causing some degree of liver injury and most drug induced liver injuries resolve once the offending agent is withdrawn , but morbidity may be severe and prolonged as recovery ensure [3].

Reviews of litterateurs identify and suggest that hepatotoxicity is well established; however, it is rare adverse effect of captopril. Schattner *et al*, [4] reported 12 cases of cholestatic jaundice due to captopril which is resolved quickly when the treatment was stopped. Myhr[5], demonstrated that rare cases of cholestatic jaundice and of hepatocellular injury have been reported in patient receiving captopril, most of hepatotoxicity is mild and transient which can be resolved after discontinuation of the therapy. Yeung *et al*, [6] in a report concerning hepatotoxicity of ACEI show that at least 32 cases of captopril therapy induced liver injury have been reported since 1982. The majority of cases had cholestatic liver injury.

The aim of this study is to investigate the effects of captopril on some of liver function tests (total serum bilirubin, ALP, ALT, AST, serum protein and serum albumin) in relation to the age of patients, dose and duration of captopril use and to compare with the control.

Subjects and Methods

This study was conducted in the Consultatory Clinic for Internal Medicine in Bin-Siena Teaching Hospital in Mosul city.

A total number of 90 patients (40 males and 50 females) with mild to moderate primary hypertension, non diabetic, neither having renal diseases nor other chronic illnesses, were taken and divided into two groups:

First group included 45 patients using captopril (captopril group) for more than three months, with age ranged from 37 to 61 years (48.89 ± 7.35 years).

The second group included 45 newly diagnosed untreated hypertensive patients (control group), with age ranged from 36-58 years (44.5 ± 8.60 years) and matched with the first group by age , sex , and BMI (weight in (kg) over height in (square meter)) .

Five ml of venous blood were withdrawn, using a disposable syringe from the captopril group and control group.

The blood was allowed to clot in a plain tube at room temperature and then the serum was separated by centrifugation at 3000 rpm for 10 minutes and then kept frozen at –20°C to be analyzed thereafter. The serum obtained from the blood samples from all participants in this study was used to measure:

1. Serum bilirubin concentration was measured colorimetrically using kit supplied by Bio Labo, France.
2. Serum alkaline phosphatases activity (ALP) was estimated using kit supplied by BioMerieux, France.
3. Serum ALT and AST activities were determined using kit supplied by Biomerieux Company (France).
4. Total serum protein (TSP) was measured calorimetrically using kit supplied by Bio Labo, France.
5. Serum albumin concentration was measured using kit supplied by BioMerieux, France.

Standard statistical methods were used to determine the mean and standard deviation (SD).

Unpaired student t-test was used to compare the results for measured biochemical parameters between hormonal contraceptive users and non-users. ANOVA Test (Analysis of Variance) was used to identify the variation in the different variables in relation to the duration of hormonal contraceptive user groups. P-value of < 0.05 was considered to be statistically significant.

The approval of the study protocol by an ethic committee has been obtained from the local health committee of Ministry of Health and College of Medicine - University of Mosul – Iraq.

Results

A total number of 90 hypertensive patients (men 60) and (women75) were included in this study, 45 of them were using one antihypertensive therapy (captopril) and the remaining 45 were newly diagnosed untreated hypertensive patients were taken as a control group, Tables 1 demonstrates that captopril caused a significant decrease in SBP and DBP in comparison to the control group

Table 1: Comparison between mean of SBP and DBP of captopril group and control group

Parameters	Mean ± SD		P-Value
	Captopril group (n= 45)	Control group (n= 45)	
SBP (mmHg)	161.33 ± 5.78	142.11 ± 9.44	0.000
DBP (mmHg)	87.93 ± 9.84	82.01 ± 4.19	0.001

Table 2 shows a significant higher value of serum ALP in the captopril group as compared with the control group and non significant differences for the other liver function tests.

Table 2: Comparison of liver function tests between captopril group and control group.

Parameters	Mean ± SD		P-value
	Captopril group (n=45)	Control group (n=45)	
S. Bilirubine (µmol/L)	7.98 ± 3.44	8.59 ± 3.77	(NS)
S.ALP (U/L)	61.04 ± 16.96	83.22 ± 24.94	0.002
S.ALT (U/L)	9.32 ± 4.78	9.77 ± 4.48	(NS)
S.AST (U/L)	13.62 ± 5.91	13.86 ± 6.24	(NS)
T.S. Protein (gm/L)	68.44 ± 6.91	66.86 ± 7.13	(NS)
S. Albumin (gm/L)	36.82 ± 4.02	36.66 ± 5.26	(NS)

Table 3 demonstrates that there were no significant differences in mean of liver function tests in relation to the age of captopril using patients.

Table 3: Distribution of liver function tests according to age of the patients in captopril group.

Age (year) / Parameters	Mean ± SD			p-value
	30-39 (n=4)	40-49 (n=14)	≥ 50 (n=27)	
S. Bilirubine (µmol/L)	7.12 ± 3.18	10.33 ± 4.24	7.90 ± 3.25	(NS)
S. ALP (U/L)	74.50 ± 15.92	69.57 ±12.80	91.59 ± 15.66	(NS)
S. ALT (U/L)	10.05 ± 5.10	8.10 ± 4.16	8.72 ± 4.56	(NS)
S. AST (U/L)	13.75 ± 5.27	13.64 ± 6.43	12.33 ± 5.61	(NS)
T.S. Protein (gm/L)	66.75 ± 10.50	68.64 ± 5.42	64.92 ± 6.21	(NS)
S. Albumin (gm/L)	37.75 ± 6.84	37.85 ± 4.40	35.88 ± 5.50	(NS)

Table (4) shows no significant differences in the mean serum of liver function tests except that mean serum ALP was significantly increased with increasing of the dose of captopril.

Table 4: Distribution of captopril dose on liver function tests in captopril group.

Dose / Parameters	Mean ± SD			p-value
	25-50 mg/day (n=15)	75-100 mg/day (n=21)	150 mg/day (n=14)	
S. Bilirubine (µmol/L)	9.25 ± 3.11	8.86 ± 2.32	307 ± 29.65	(NS)
S.ALP (U/L)	64.44 ± 14.25	83.32 ± 23.53	5.20 ± 0.73	0.013
S.ALT (U/L)	9.25 ± 3.64	10.50 ± 4.02	86 ± 16.92	(NS)
S.AST (U/L)	12.90 ± 4.64	6.22 ± 1.85	91.79 ± 16.8	(NS)
T.S. Protein (gm/L)	66.97 ± 7.28	66.28 ± 6.70	140.61 ±2.91	(NS)
S. Albumin (gm/L)	36.39 ± 5.09	38.14 ± 6.38	4.79 ± 0.32	(NS)

Table 5 shows that there was no significant effect of duration of captopril therapy on liver function tests in captopril group.

Table 5: Distribution of liver function tests according to duration of therapy in captopril group.

Duration(years) / Parameters	Mean ± SD			p-value
	1 (n=9)	1-3 (n=30)	> 3 (n=6)	
S. Bilirubine (µmol/L)	8.91 ± 4.10	8.38 ± 3.47	9.15 ± 3.54	(NS)
S.ALP (U/L)	81.79 ± 4.04	87.63 ± 4.11	81.71± 8.47	(NS)
S.ALT (U/L)	7.17 ± 1.46	8.13 ± 1.57	6.00 ± 1.3	(NS)
S.AST (U/L)	10.44 ± 4.95	13.83 ± 6.76	13.16 ± 3.48	(NS)
S. Protein (gm/L)	66.33 ± 8.90	67.50 ± 6.68	64.50 ± 7.17	(NS)
S. Bilirubine (µmol/L)	35.33 ± 5.56	37.36 ± 4.96	35.16 ± 6.55	(NS)

Discussion:

The antihypertensive drugs used in this study were captopril (25 and 50 tablets) which is the prototype of angiotensin converting enzyme inhibitors (ACEIs), and is the most commonly used antihypertensive drugs in our society in Mosul and Iraq, because of the efficacy, availability and cheap price.

This study found that the use of captopril in hypertensive patients has resulted in a significant reduction of mean SBP and DBP, these results were in agreement with the results of other studies [7,8,9,10], who reported that captopril significantly decreased BP by blockade of the RAAS by its selective lowering of angiotensin II and may be, through dilating the efferent glomerular arterioles, restore the ability of the kidney to excrete salt and water as well as control glomerular hyper filtration.

The present study found that there is a significant elevation in the serum ALP activity in patients using captopril group than that of the control group. Rahmat *et al.* [11] found that the elevation of serum ALP activity in patients using captopril is mild to moderate and transient and resolved completely after stopping treatment even if the elevation is significant. While Jabar[12], found that captopril therapy caused non significant elevation of ALP activity.

On the other hand this study found a non significant slight elevation of the mean of serum ALT and AST activities of captopril using patients group in comparison with control group.

These results are in agreement with that of Rahmat *et al*, [11] and Myhr, [5] who both reported that most hepatic toxicity caused by captopril is mild and transient and the elevation in the serum ALT and AST activities is mild and resolved after discontinuation of the therapy. This mild cellular damage may be attributed to the accumulation of toxic metabolite of the drug within the hepatocytes causing direct injury or indirect injury by immune mediated cellular damage [13].

However, the effect of captopril on liver cells could be idiosyncratic reaction [11] and the majority of idiosyncratic reaction causes various degrees of necrosis and apoptosis [14] .

This study revealed a non significant slight elevation of the mean of TSB in patients using captopril group than that of the control group, and TSB is still within normal range.

These results together with that of elevation in serum ALP activity suggested that captopril may have mild to moderate cholestatic effect on the liver. These results were in agreement with that of Rahmat *et al*.,[11]

who found that most hepatic toxicity is mild and transient and the elevation of serum bilirubin is also mild and the hepatic injury created by captopril is categorized as mixed hepatocellular cholestatic in nature[15], which could be idiosyncratic reaction [11].

This study demonstrated a non significant slight reduction in the means of serum total protein and serum albumin in patients using captopril group than that of the control group.

These results may be expected because serum albumin and subsequently total serum protein level tend to decrease significantly at an advanced stage of liver diseases, as they are tests of synthetic function of liver[16]. Since the cases in the present study do not reach that advanced stage of liver damage so, the reduction in the mean of total serum protein and serum albumin are not significant.

This study revealed a non significant effect of the age of patients on any parameters of liver function in patients using captopril group. The 2005 American Gastroenterology Association Future Trends Committee[17] report regarding the effects of aging on future trends in gastroenterology states that there is no effect of age on conventional liver function tests, including serum ALT.

While Dong *et al.*, [18] found that ALT which is a marker of liver injury levels decrease with age in both men and women independent of metabolic syndrome components, adiposity signaling biomarkers, and other commonly used liver function tests and suggested that further studies are needed to understand the mechanisms responsible for a decline in ALT with age, and to establish the optimal cut-point of normal ALT in the elderly.

This study showed no significant differences in the mean serum of liver function tests except that mean serum ALP was significantly increased with increasing of the dose of captopril, which could demonstrate that liver injury by captopril could be dose dependant. Review of literature did not show any evidence about the distribution of hepatic parameters at different dosage of captopril.

The present study found a non significant effect for the duration of therapy on any parameters of liver function in patients using captopril group than that of the control group, this indicate that the effect of captopril on the liver may be initiated at any time after starting therapy.

These results are in agreement with those found other investigators such as Crantock *et al,* [15] who demonstrated that the period for development of abnormalities lies between 1 week and 20 months of treatment. While Rahmat *et al,*[11] reported that the duration of onset of symptoms of hepatic injury due to captopril is between 21 to 300 days. Yeung *et al,*[6] reported that the duration of use of captopril before detection of hepatotoxicity ranged from 5 days to 3 years.

Conclusion:

The use of captopril therapy causes a smooth BP reduction effect with no effects on liver function tests except that captopril therapy causes a significant higher level of serum ALP when compared with control group and the increase in the dose of captopril causes increase in the serum ALP level.

The duration of use of captopril and the age of the patients have no significant effect on the liver function tests.

References

1-Bonacini M, Miyashita L, (2002). Drug Induced Hepatotoxicity: Liver and GI Review – Issue 10-July.

2- Werth B, Kuhn M, Hartmann K, Kobler E, Reinhart WH. Drug-induced liver disease: Experiences of the Swiss center for Adverse Drug Effect 1989-1991. J. Suisse Med 1993; 123:1203-1204.

3-Sturgill MG, Lambert GH. Xenobiotic induced hepatotoxicity: mechanism of liver injury and method of monitoring hepatic function. Clin. Chemist 1997; 43:1512-26.

4- Schattner A, Kozak N, Friedman J. Captopril induced cholestatic jaundice: report of 2 cases and a review of additional reports in the literature. Am J Med Sci 2001; 322:236-40.

5-Myhr K (2002). Drug induced jaundice.www. Essentialdrug Org/indices/archive / 200204 / msg 00001.php.Web.

6-Yeung E, Wong FS, Wanless IR, Guindi M. Ramipril associated hepatotoxicity. Arch Path Lab Med 2003; 127:1493-1497.

7-Palla R, Marchitiello ME, Sassano P, Salvetti A. Effect of captopril on renal function in patients with essential hypertension. Am J Cardiol 1982; 21:49 (6): 1577 - 1579.

8-Materson B, Freis E, Neal W, Borreson R , Tagushi J, Perry H, *et al*. Low dose captopril for the treatment of mild to moderate hypertension. A result of 14-week trial. Arch Intern Med 1984; 144:1947-1953.

9-Bolterman RJ, Manriquez MC, Ruiz CR, Juncos LA, Romero JC. Effects of captopril on the renin angiotensin system, oxidative stress and endothelin in normal and hypertensive rats. Hypertens Canad J 2005; 46:943-7.

10-Pechánová O. Contribution of captopril thiol group to the prevention of spontaneous hypertension. Physiol Rev 2007; 86:747-803.

11- Rahmat J, Gelfand RL, Gelfand MC, Winchester JF, Schreiner GE, Zimmerman HJ. Captopril associated cholestatic jaundice, Ann Intern Med 2000; 102: 56-58.

12- Jabar RK (2009). Effects of certain antihypertensive drugs on some biochemical parameters. MSc Thesis in Biochemistry. College of Medicine, University of Mosul.

13- Lee W. Acute liver failure. New Engl J Med 1993**;** 329: 1826-1872

14- Lee W. *Drug* – induced hepatotoxicity. N Engl J Med 2003; 349 (5): 474 – 485.

15-Crantock L, Prentice R, Powell L. Cholestatic jaundice associated with captopril therapy. J Gastroenterol Hepatol 1991; 6:528-530.

16- Green R, Flamm S. AGA technical review on the evaluation of liver chemistry tests. Gastroenterol 2002; 123(4):1367-1384.

17- Hall KE, Proctor DD, Fisher L, Rose S. American Gastroenterology Association Future Trends Committee Report: Effects of aging of the population on gastroenterology practice, education, and research. Gastroenterology 2005; 129:1305-38.

18- Dong M H, Bettencourt R, Barrett-Connor E, Loomba R. Alanine Aminotransferase Decreases with Age: The Rancho Bernardo Study. PLoS One J 2010; 5(12): e14254.

* *Pharmacist, Student of MSc Pharmacology, College of Pharmacy- University of Mosul – Iraq*

** *Assist. Prof. Dept. of Pharmacology, College of Medicine-University of Mosul-Iraq.*