A comparison of the effects of valsartan and captopril monotherapy on hepatic enzymes activities

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*(Ann. Coll. Med. Mosul 2006; **32(1&2)**: 63-66)*
Received: 12th Sep, 2006; Accepted: 17th Jan, 2007

ABSTRACT

Objective: This study was conducted to assess the effect of valsartan and captopril, each as monotherapy in hypertensive patients, on hepatic enzymes activities including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP).

Patients and methods: Thirty nine hypertensive patients were included in the study, 20 of them using captopril and 19 using valsartan. Serum ALT, AST, and ALP activities were measured before and after 2 months of starting treatment.

Results: Patients on captopril showed significantly increased mean level of ALT and AST ($P<0.001$),(although still within normal limits) while mean ALP levels showed no significant difference. In the valsartan group, mean ALT, AST and ALP values showed insignificant differences.

Conclusion: In hypertensive patients with liver disease, valsartan may be more suitable than captopril for the potential influence of the latter on serum transaminase levels.

Keywords: captopril, valsartan, hepatic enzymes activities.

الخلاصـــة

أهداف البحث: أجريت هذه الدراسة لمقارنة تأثير عقا ري الكابتوبريل والفالسارتان كعلاج أحادي لمرضى ارتفاع ضغط الدم الشرياني على فعاليات أنزيمات الكبد، الالنين امينو ترانسفيريز، الاسبارتيت امينو ترانسفيريز والأنزيم الفوسفاتي القاعدي.

المشاركون: أجريت الدراسة على 39 مريضا مصابين بارتفاع ضغط الدم الشرياني ، 20 مريضا منهم يستخدمون عقار الكابتوبريل كعلاج أحادي و 19 منهم يستخدمون عقار الفالسارتان كعلاج أحادي. تم قياس فعاليات أنزيمات الكبد الثلاثة قبل وبعد شهرين من بدء العلاج بالعقارين.

النتائج: اظهرت نتائج الدراسة وجود ارتفاع معنوي في مستوى فعاليات أنزيمي الالنين امينو ترانسفيريز والاسبارتيت امينو ترانسفيريز (مع بقاء القياسات ضمن الحد الطبيعي) لدى المرضى المستخدمين لعقار الكابتوبريل كعلاج أحادي (ب $< 0,001$) مع عدم ظهور أي فرق معنوي في مستوى فعالية الأنزيم الفوسفاتي القاعدي. أما المرضى المستخدمين لعقار الفالسارتان فلم يظهر لديهم أي فرق معنوي في مستويات فعاليات الأنزيمات الثلاثة المقاسة في الدراسة الحالية.

الاستنتاج: عقار الفالسارتان ملائم للمرضى المصابين بارتفاع ضغط الدم والذين يعانون من مرض في الكبد اكثر من عقار الكابتوبريل بسبب تأثير الأخير على مستوى أنزيمي الالنين امينو ترانسفيريز والاسبارتيت امينو ترانسفيريز.

The liver is the principal organ that is capable of converting drugs into forms that can be readily eliminated from the body. Many drugs may affect the liver adversely in more than one way[1]. The importance of investigating the hepatic adverse effects of drugs on the liver lies in the fact that drug induced hepatotoxicity has become an important public health problem, contributing to more than 50 % of acute liver failure cases[2].

Captopril is an angiotensin converting enzyme (ACE) inhibitor widely used for congestive heart failure and arterial

hypertension. Adverse hepatic events especially cholestasis, have rarely been reported with the use of captopril[3]. Valsartan is a new angiotensin II antagonist (ARA) licensed for the treatment of hypertension. The advantage of angiotensin II receptor antagonists is their low incidence of side effects. Dry cough which is a common side effect of ACE inhibitors is not a problem with ARA therapy[4,5]. In addition, compared with ACE inhibitors, ARA are associated with a much lower incidence of angioedma[6]. Throughout the life cycle of modern medicine there is a continuous process of risk identification, assessment and management[7]. The present study was conducted to investigate the effect of valsartan on hepatic enzymes activities including ALT, AST and ALP in hypertensive patients, comparing it with captopril.

Patients and methods

This study was conducted between April 2005 and August 2006 on a number of newly diagnosed hypertensive patients referred from specialists in the field of Medicine. Inclusion criteria included:

Newly diagnosed hypertensive patients who did not previously start any antihypertensive therapy. They should be free from other organic diseases especially hepatic and renal diseases. Patients with history of heart failure, ischemic heart diseases, diabetes as well as smokers and alcoholics were excluded from the study. Their treating physicians should decide that they need no other drug apart from the antihypertensive agents. Careful follow up made sure that no drug was added during the two months of study (especially considering the last 2 weeks).

Because of the above restricted criteria, only 39 hypertensive patients were finally selected and included in this study. They were divided into two groups:

Group 1: This group included 20 hypertensive patients on captopril as monotherapy for a period of 2 months. They were 14 males and 6 females with a mean age of 49.9±10.13 years, and a range of 29 -65 years. The captopril daily dose was between 50-100mg. **Table 1**.

Group 2: This group included 19 patients, who were treated with valsartan as monotherapy for a period of 2 months. They were 13 males and 6 females with a mean age of 53.78 ±10.44 years, and a range of 39-75 years. The valsartan daily dose was 126.31 ± 40.58 mg/d, ranged from 80- 160 mg. **Table 1**.

From each patient in both groups, a venous blood sample was taken and the obtained sera were used for the measurement of ALP, AST and ALP activities as a base line measurement before initiation of antihypertensive therapy. After 2 months treatment, another venous blood sample was taken from each patient in both group and measurement of the same parameters was done.

Data were represented as mean ± SD. Paired T- test was used to compare the results. The differences were considered significant at $p \leq 0.05$[8].

Results

In the captopril group (group I). Mean AST and ALT concentrations were significantly higher after treatment (although still within normal limits). However, mean ALP value was not significantly different as shown in **Table 2.**

In hypertensive patients on valsartan, the mean values of AST, ALT and ALP were not significantly different before and after treatment as shown in **Table 2**.

Table (1): *Patients characteristic.*

	Captopril	
No.	20	-------
Age (mean±SD) years	49.9±10.13	range =29-65
Male	14	-------
Female	6	-------
Dose (mean±SD) mg	76.25±23.61	range =50-100
	Valsartan	
No.	19	-------
Age (mean±SD) years	53.78±10.44	range =39-75
Male	13	-------
Female	6	-------
Dose (mean±SD) mg	126.31±40.58	range =80-160

Table (2): *Effects of captopril and valsartan monotherapy on AST, ALT and ALP activities.*

parameters	Before treatment Mean ± SD	After treatment Mean ± SD	P value
Captopril			
AST (U/L)	10.35±1.63	10.8±1.76	<0.001*
ALT (U/L)	9.7±2.69	10.15±2.83	<0.001*
ALP (U/L	64.95±17.94	65.6±17.23	NS
Valsartan			
AST (U/L)	10.78±3.29	10.94±3.25	NS
ALT (U/L)	10.36±4.57	10.73±2.92	NS
ALP (U/L	62.05±21.95	66.84±17.01	NS

P > 0.05: Non-significant difference(NS)

Discussion

The present study revealed an elevated mean ALT and AST levels in patients using captopril monotherapy while ALP levels were not significantly changed.

Drugs are an important cause of liver injury. More than 900 drugs, toxins and herbs have been reported to cause liver injury, and drugs account for 20 -40 % of all instances of fulminant hepatic failure[9,10]. NSAIDs, metformin and valproic acid are well recognized examples. Among antihypertensive drugs, methyldopa is classically implicated in hepatotoxicity[11]. During the last two decades, ACE inhibitors have been prescribed for an increasing number of cardiovascular and renal diseases[12,13]. As a class of drugs, ACE inhibitors are well tolerated. Liver injury is rare but has been reported in patients receiving captopril[14], enalopril[15], lisinopril[16] and fosinopril[17]. The newer class of antihypertensive drugs is the angiotensin II receptor antagonists of which, valsartan is commenly used.

In this study, the isolated elevation of transaminases (ALS and ALP) in association with captopril therapy may give some evidence that captopril causes hepatocellular damage rather than cholestasis, as the measurement of the activities of ALT and AST in plasma provide a sensitive index of hepatocellular damage, while ALP is normally attached to the biliary canalicular and sinusoidal membranes of the hepatocyte and released in great amount when there is cholestasis[18]. Adverse hepatic events, especially cholestasis have rarely been reported with captopril. The hepatotoxic feature of ACE inhibitors was found to be cholestatic, mixed hepatocellular cholestatic and predominant hepatocellular in nature[19]. Schattner et al., 2001 reported a severe cholestatic jaundice in two elderly patients treated with captopril[20]. In another report, liver biopsy taken from a 50 years old black female who developed hepatic dysfunction secondary to captopril therapy showed primarily cholestasis with secondary hepatocellular elements[21]. The apparent discrepancy between the cholestatic nature of these reported cases and the results of this study which suggested hepatocelluar dysfunction can be explained by the difference in presentation. This study has included asymptomatic patients screened for hepatic dysfunction, while the other reports of cholestatic hepatic injury have included clinically jaundiced patients. It is possible that mild elevations of transaminases skip clinical detection, and the more clinically obvious cases of cholestatic jaundice are reported.

The effect of captopril on the liver is considered to be idiosyncratic, which is a bizarre and dose independent reaction that occurs in a small fraction of patients and it has no obvious relationship to the duration of therapy[22]. Yeung et al noticed that hepatotoxicity of ACE inhibitor may develop as early as 5 days to as long as 3 years after starting treatment[23], while Rhahmat et al demonstrated that the latent period for the development of abnormality lies between 21 to 300 days[24].

Up to my knowledge no study has dealt with the effect of valsartan on liver functions, so this study was done to evaluate this effect. The study showed insignificant changes in the activities of AST, ALT and ALP after 2 months of treatment. Shen et al went farther than the result of the current study when they concluded that valsartan can retard the progression of hepatic fibrosis and may provide an effective new strategy for anti-liver fibrosis therapy[25]. Despite an extensive search I could not come across a published study comparing the effect of valsartan and captopril on hepatic enzymes activities.

Drug induced hepatic injury is the most common reason cited for withdrawal of an approved drug[26]. hepatotoxicity is a well established yet rare adverse effect of captopril, however the very common use of this drug together with the severity of liver injury it may cause, calls for a high index of

suspicion and increased awareness of this phenomenon.

In conclusion, in hypertensive patients with liver disease ARA may be more suitable than ACE inhibitors for the potential influence of the latter on serum transaminases levels.

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