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Research Article

Effect of ramipril on glycosylated hemoglobin and liver function test in patients of diabetic nephropathy

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ABSTRACT

Background: Diabetic nephropathy (DN) is a chronic complication of diabetes mellitus with a growing incidence. Therefore, it is essential to have a better understanding of it, especially in relation to prevention and aggressive management to avoid progression to end-stage renal disease.
Methods: This prospective randomized study represented the effects of ramipril on glycosylated hemoglobin (HbA1c), liver function tests (LFT), mean arterial blood pressure, and serum potassium level in patients diagnosed with DN, with concomitant mild to moderate hypertension. 135 diagnosed patients with DN treated with ramipril 5 mg daily for 3 months were involved in this study. Blood samples were taken from all patients and analyzed for HbA1c, LFT including alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum alkaline phosphatase (ALP), and bilirubin with serum potassium level. After 3 months of treatment with ramipril (5 mg daily), blood samples were collected and analyzed again to determine the same parameters.
Results: Ramipril produced a significant reduction in (HbA1c) of hypertensive patients ($p<0.05$), whereas, serum levels of ALT, AST, ALP, and bilirubin were significantly elevated. The results indicated that ramipril may cause liver injury. Meanwhile, the mean arterial pressure was decreased significantly by ramipril ($p<0.05$).
Conclusion: The present study concluded that: ramipril significantly reduced the percentage of HbA1c but may cause liver injury, monitoring of liver enzymes is advisable for patients on ramipril.

Keywords: Ramipril, Glycosylated hemoglobin, Liver function test, Diabetic nephropathy.

INTRODUCTION

The renin-angiotensin-aldosterone system plays a key role in the regulation of fluid and electrolyte balance.[1] In addition, the involvement of the renin-angiotensin system (RAS) in the occurrence of atherosclerotic plaque instabilization has already been addressed.[2,3]

Angiotensin-converting enzyme inhibitors (ACEIs) inhibit ACE and have been shown to be effective in many cardiovascular diseases.[4] Furthermore, they are the first line drugs that are used for the treatment of hypertension in patients with diabetic Type I nephropathy.[5] Lisinopril, enalapril, benazepril, fosinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril are long acting members of the class. All are prodrugs and converted to the active agents by hydrolysis primarily in the liver.[6] Hepatotoxicity, usually cholestatic in nature, has been reported with captopril, enalapril, and lisinopril use. Apparent cross-reactivity has been reported twice. Potential

mechanisms of injury include idiopathic hypersensitivity and modulation of eicosanoid metabolism by inhibition of kininase II and subsequent increased hepatic bradykinin activity. There now exists excellent clinical trial evidence that ACEIs have benefit in diabetes beyond blood pressure lowering. Much of this has come from the diabetic subset of the heart outcomes prevention evaluation study.[7] A number of clinical trials utilizing ACEIs have shown that their use was associated with a reduction in the development of diabetes.[8] Many clinical studies have documented that treatment with ACEIs or angiotensin receptor blockers decreased the incidence of Type 2 diabetes.[9] It has been shown that they reduced morbidity and mortality, also quite independently of lowering elevated blood pressure. Ramipril is one of the ACEI, widely used in the treatment of hypertension, heart failure, diabetic nephropathy, and myocardial infarction.[10]

METHODS

The present study was undertaken to investigate the effect of ramipril on potassium level, glycosylated hemoglobin (HbA1c), liver function, of hypertensive patients in Shri Ram Murti Institute of Medical Sciences, a tertiary care, 950 bedded teaching hospital. This study was carried out July 2012-October 2012 with proper protocol approval from Institutional Ethical Committee. The present study included 135 hypertensive patients receiving ramipril 5 mg of both sexes, their age ranges were between 35 and 65 years (mean±standard error, 54.9±2.8). Blood samples had been taken 2 times from that group (before starting the treatment with ramipril (zero time) and after 3 months of treatment.

Exclusion criteria

Patients with severe or chronic cardiovascular disease that might affect the medical evaluation of this study were excluded. In addition to that patients receiving any other medication rather than ramipril were also excluded.

Blood samples

For the liver function tests (LFT) and potassium measurement, 4 ml of the blood sample was collected from each population treated with ramipril for 3 months by venipuncture under basal conditions with vacutainer system. The blood was transferred into a disposable plain tube without anticoagulant. The blood was allowed for 30 mins to clot and after centrifugation for 5 mins at 3000 rpm; the serum was collected in a well-defined plain tube and kept frozen immediately for analysis of potassium and liver function. For the HbA1c measurement, 2 ml of the blood sample was collected from each patient. The blood was transferred into a disposable plain tube with anticoagulant (EDTA). Any hemolytic sample was excluded for the measurement of HbA1c.

Statistical analysis

All the results were expressed as mean±standard error mean. The significance of differences between the patients before and after treatment with ramipril was determined using paired t-test. $p<0.05$ were considered significant.

RESULTS

Effect of ramipril on LFTs, before and after 3 months of the treatment

Administration of ramipril for 2 months produced statistically significant ($p<0.05$) elevation in total serum bilirubin (TSB), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), and serum alkaline phosphatase (ALP) concentrations of hypertensive patients, as shown in Table 1.

Administration of 5 mg daily dose of ramipril for 3 months to hypertensive patients caused a significant ($p<0.05$) reduction in the percentage of HbA1c ($p<0.05$).

The mean arterial pressure (MAP), systolic and diastolic pressure were decreased significantly ($p<0.05$) in hypertensive patients after treatment with ramipril in comparison with the same group of patients before starting treatment Table 2.

Table 1: The effect of ramipril on LFTs and HbA1c in DN with concomitant mild to moderate patients treated with ramipril (5 mg daily).

Parameters	Before treatment	After 3 months of treatment
Serum bilirubin (mg/dl)	8.26±0.4	9.6±0.36*
ALT (U/L)	9.96±0.54	12.43±0.71*
AST (U/L)	12.38±0.74	14.68±0.9*
Serum ALP (U/L)	102.6±5.6	117±8.9*
Serum HbA1c	8.28±0.76	7.82±0.39

*$p<0.05$. Data are represented by mean±standard error of the mean n=135. LFT: Liver function tests, HbA1c: Glycosylated hemoglobin, DN: Diabetic nephropathy, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase

Table 2: Systolic, diastolic and MAP before and after 3 months of treatment with ramipril (5 mg), daily.

Blood pressure (mmHg)	Before the treatment with ramipril	After 3 months of treatment with ramipril
Systolic blood pressure	158.38±3.86	136.93±1.87*
Diastolic blood pressure	95.64±2.35	85.16±0.75
MAP	117.8±2.2	102.4±1*

*$p<0.05$, Data are represented by mean±standard error of the mean n=135. MAP: Mean arterial pressure

DISCUSSION

ACEIs are prescribed for many cardiovascular and renal diseases, adverse hepatic events especially cholestasis have rarely been reported with captopril, lisinopril, and fosinopril. In this study, ramipril significantly elevated the liver function parameters (TSB, ALT, AST, and ALP), prolonged cholestatic hepatitis, and biliary cirrhosis may result from the use of ramipril. Monitoring of liver enzymes is advisable for patients starting on ramipril.[11] Cross-reactivity between enalapril and captopril are documented. Therefore in patients who developed hepatotoxicity while taking one ACEI, other agents in this class should be avoided.[12] In spite of that there is no previous reports of ramipril-induced liver injury, at least 32 cases of captopril-induced liver injury have been reported, and 12 additional cases involving enalapril, lisinopril, and fosinopril have also been reported. The majority of cases had cholestatic liver tests with clinical findings of jaundice and pruritus.[13] Complete recovery occurred in the majority of cases from days to months after discontinuing the offending agent.[14] There are no available experimental models to study ACEIs - associated hepatotoxicity. It is not known if a common mechanism exists or if each ACEI produces hepatotoxicity via a separate mechanism. It's known that ACEIs can result in greater hypotension in the presence of hepatotoxicity. Therefore, it's possible that hypotension secondary to ACEI administration decreases liver perfusion, causing secondary hypoxia and exacerbating the hepatotoxicity. Moreover, it has been suggested that hypersensitivity may be a mechanism of injury, as supported by the low incidence, occurrence at low dosages, and the clinical features of fever, rash, myalgias, or eosinophilia. In the biopsies from hepatic injured cases, eosinophils were seen in small numbers. Another case had peripheral eosinophilia. Another mechanism suggested is that of a metabolic idiosyncrasy involving the sulfhydryl group of ACEIs,[14] or the terminal proline ring shared by captopril, lisinopril, and enalapril,[13] mediating bile stasis. The final mechanism suggests that its relates to the intrinsic property of ACEIs to inhibit the inactivation of bradykinin, causing increased conversion of arachidonic acid to prostaglandins.[15,16]

Certain prostaglandins, such as 16, 16-dimethyl prostaglandin E, decrease bile flow rates in humans. In individuals with unusual variations in hepatic prostaglandin metabolism, exposure to ACEIs may lead to increased production of specific prostaglandins that favor bile stasis. Bile stasis may then increase leukotriene levels, with resulting hepatocellular and biliary tract toxicity, as seen in animal models of bile duct ligation. According to most cases reported, there has been an increase in ALP in references,[15] which is coincide with our results. It was shown that high ramipril dose elevated serum ALP in a time-dependent manner, drugs, sometimes, may cause serious injuries to the livers of patients who take them, with loss of function leading to illness, disability, hospitalization, and even life-threatening liver failure and death.[10] The widespread use of ramipril and other ACEIs may cause an increased frequency of hepatotoxicity. Because in all the liver injured cases, the liver enzymes (AST, ALT, ALP) with TSB was raised and because of the possibility for prolonged severe cholestatic jaundice, cirrhosis, and death from hepatic failure following the use of ACEIs, monitoring of liver enzymes should be considered when prescribing an ACEI.[16,17] The fact that ramipril-induced hepatitis can occur without causing any symptoms suggests the clinicians should start monitoring liver enzymes as soon as ramipril is prescribed. Clinicians should be aware that ACEI-induced cholestasis may mimic extrahepatic bile duct obstruction and may cause a delay in diagnosis. Because of the potential cross-reactivity between ACEIs, using a different ACEI may not be advisable.[13] In the present study, oral administration of ramipril for 3 months caused slight but statistically significant elevation in serum potassium level. Angiotensin II (Ang II) is a potent constrictor of vascular smooth muscle and also stimulates the synthesis and release of aldosterone from the adrenal cortex. Aldosterone acts on the distal tubules and collecting ducts of nephrons in the kidney to increase the absorption of sodium and excretion of potassium. By inhibiting the formation of Ang II, ACEIs indirectly reduce aldosterone secretion and thereby suppress the reabsorption of sodium and excretion of potassium in the distal tubule.[18] ACEIs will increase the potassium levels; this problem is more likely to occur in people with advanced kidney disease. Taking potassium supplements or potassium-containing salt substitutes.[19] In this study, HbA1c, a useful measure of the efficacy of glucose-lowering treatment,[20] had been significantly decreased in hypertensive patients receiving ramipril. Physical activity, weight loss, and some glucose-lowering agents (Diabetic Prevention Program, 2002); reduce the incidence of diabetes in people with elevated glucose levels that are just below the diagnostic threshold for diabetes. Several trials involving people with hypertension or cardiovascular disease have suggested that any agents that block or inhibit the RAS may also prevent diabetes.[21] Recent clinical trials suggest that blockade of the RAS, either by inhibiting the ACE,[22] or by blocking the angiotensin Type 1 (AT1) receptor, may substantially lower the risk for Type 2 diabetes. On the other hand, the use of up to 15 mg of ramipril daily for 3 years does not significantly prevent diabetes or death in people without cardiovascular disease who have impaired fasting glucose levels or impaired glucose tolerance. However, significantly more participants receiving ramipril had normal fasting glucose levels and glucose tolerance than those receiving placebo, and the distribution of the glucose levels had shifted downward in the ramipril group. Whether this apparent late divergence between the ramipril group and the placebo group is real (or simply due to chance) can be reliably ascertained only by further follow-up.[23] Therefore, a modest reduction in glucose levels resulting from the use of ramipril would allow more participants to cross into the normal range rather than into the more distant diabetic range, and there would be more power to detect an effect on regression to normal levels than progression to diabetic levels. Furthermore, DREAM trial suggest that drugs that block the RAS may have a modest, favorable[24] effect on glucose metabolism.[23] These

results suggest that ramipril may have favorable effects on glucose metabolism, a finding that is constant with other reports on studies of ACEIs (when used for established indications). Recent data's indicated that the use of ACEIs in hypertensive patients at high risk of developing diabetes is best anti-hypertensive drug to protect against diabetes. 22% fewer people developed diabetes if they were on ACEIs than a similar group of people at high risk of diabetes, who were not on ACEIs.[23] Also ACEIs, provide cardiovascular protection for people with diabetes.[25] However, for now, the routine use of ramipril for the express purpose of preventing diabetes is not indicated.[26] These significant effects suggest that a longer or larger study would be needed to detect a reduction in the rate of newly diagnosed diabetes in this population. After 2 months of the treatment with ramipril, the blood pressure was successfully controlled. ACEIs act on the RAS, which is a cascade of hormones contributing to the regulation of blood pressure and blood volume. They suppress the RAS pathway by inhibiting ACE, which in turn decreases the formation of a potent vasoconstrictor Ang II, and slows the degradation of the potent vasodilator, bradykinin.[27] In the present study, the MAP was significantly decreased. The MAP is a term used in medicine to describe average blood pressure in an individual. It is defined as the average arterial pressure during a single cardiac cycle.[28] MAP is considered to be the perfusion pressure seen by organs in the body. Furthermore, it is believed that a MAP that is >60 mmHg is enough to sustain the organs of the average person, If the MAP falls significantly below this number for an appreciable time, the end organ will not get enough blood flow, and will become ischemic.[29] ACEIs are highly effective antihypertensive drugs that lower blood pressure and help reverse left ventricular hypertrophy. Based on recent observation that Ang II inhibits adipogenic differentiation of human adipocytes via the AT1 receptor[30] that expression of Ang II - forming enzymes in adipose tissue is inversely correlated with insulin sensitivity the hypothesis proposed that RAS blockade prevents diabetes by promoting the differentiation of adipocytes.[31] Increased formation of Ang II by large insulin-resistant adipocytes inhibits recruitment of preadipocytes, resulting in increased storage of lipids in muscle and other tissues, thereby increasing insulin sensitivity. In contrast, RAS blockade promotes recruitment of preadipocytes, thereby increasing the number of small insulin-sensitive adipocytes.[32] Redistribution of lipids from muscle and other tissues to adipose tissue would result in improved insulin sensitivity. However, in our recent study, body mass indexes (BMI) were not changed significantly after the treatment with ramipril.[33]

CONCLUSION

The present study concluded the following:

1. Ramipril significantly reduced the percentage of HbA1c after starting treatment, which means that ramipril is a good choice for hypertensive patients at high risk of developing diabetes
2. Ramipril significantly induced an increase in the level of liver function parameters (bilirubin, ALT, AST, and ALP), which means that ramipril may cause liver injury, monitoring of liver enzymes is advisable for patients on ramipril
3. There was no significant change in the BMI, after starting treatment with ramipril.

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