Research Article

Effect Of Enalapril On Hepatic And Renal Function Parameters In Patients With Essential Hypertension: A Prospective, Randomised, Open-Label Study

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Abstract

Background: Angiotensin-converting enzyme (ACE) inhibitors such as enalapril are first-line agents for essential hypertension, but their long-term effect on hepatic and renal function in routine clinical use is incompletely characterised. Objective: To study the effect of enalapril on hepatic (alkaline phosphatase [ALP], serum glutamic oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], total bilirubin) and renal (blood urea, serum creatinine) function parameters in patients with essential hypertension. Methods: In a prospective, randomised, open-label study conducted over 12 months (1 August 2021 to 31 July 2022) in a tertiary care hospital, Ongole, newly diagnosed patients with essential hypertension aged 25–65 years with normal baseline hepatic and renal function were randomised to enalapril maleate 5 mg or telmisartan 40 mg once daily; this report presents the enalapril arm. Hepatic and renal parameters and blood pressure were recorded at baseline, 6th month and 9th month. Intragroup comparison used the paired t-test/repeated-measures ANOVA; $p<0.05$ was considered significant. Results: Forty-six patients (mean age 43.56±8.37 years; 60.87% male) completed 9 months of enalapril therapy. Mean systolic and diastolic blood pressure fell from 142.60±9.41/87.93±5.82 mmHg to 117.93±8.98/75±5.86 mmHg ($p<0.0001$ for both). ALP rose from 79.36±19.22 to 95.28±28.04 IU/L ($p<0.0001$) and SGOT rose from 19.63±7.99 to 36.76±12.71 U/L ($p<0.0001$). SGPT (32.5±11.05 to 38.63±17.30 U/L, $p=0.0533$) and total bilirubin (0.68±0.23 to 0.64±0.26 mg/dL, $p=0.0810$) did not change significantly. Blood urea (14.86±3.80 to 14.50±3.76 mg/dL, $p=0.5536$) and serum creatinine (0.83±0.15 to 0.88±0.12 mg/dL, $p=0.5055$) remained stable. Mild adverse effects (headache, nausea, dry cough) occurred in 6/46 (13.04%) patients and resolved with continued treatment. Conclusion: Nine months of enalapril therapy produced effective blood pressure control together with a small but statistically significant rise in ALP and SGOT, without significant change in SGPT, bilirubin, or renal indices. Periodic monitoring of liver enzymes, rather than routine avoidance, appears appropriate during long-term enalapril therapy.

Keywords: enalapril; angiotensin-converting enzyme inhibitor; essential hypertension; hepatotoxicity; liver function tests; renal function.

1. Introduction

Hypertension is one of the leading risk factors for global mortality and disability, contributing to a large proportion of cardiovascular, cerebrovascular and renal disease worldwide. In India, pooled estimates suggest a prevalence of essential hypertension of approximately 29.8%, with a higher burden among urban than rural populations [1]. Current international guidelines define hypertension as a systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥80 mmHg [2], and recommend timely pharmacological treatment to reduce the long-term risk of cardiac, cerebrovascular, hepatic and renal complications [3]. In the Indian context, the Association of Physicians of India has similarly emphasised early pharmacological treatment of essential hypertension to limit target-organ damage in a population with a disproportionately high cardiovascular and renal disease burden [4].

Pharmacological blockade of the renin–angiotensin–aldosterone system (RAAS), using either angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), is well established as an effective strategy for blood pressure control, but debate persists over the comparative long-term safety of these two drug classes [5]. Unlike ACE inhibitors, ARBs selectively block the angiotensin II type-1 receptor without affecting bradykinin metabolism, a pharmacological distinction proposed to underlie differences in adverse-effect profile, including cough and, potentially,

hepatic tolerability, between the two classes [6]. Enalapril, a prodrug ACE inhibitor that is bioactivated by hydrolysis of its ethyl ester to enalaprilat, blocks the conversion of angiotensin I to angiotensin II and thereby reduces aldosterone secretion and systemic vascular resistance [7].

The renin–angiotensin system is also expressed locally within the liver, where angiotensin II contributes to hepatic stellate cell activation, fibrogenesis and portal hypertension, providing a plausible biological basis for hepatic effects of RAAS-acting drugs [8]. While ACE inhibitors are generally well tolerated, case reports and pharmacovigilance data have described idiosyncratic and dose-related hepatocellular or cholestatic injury with several agents of this class [9], and experimental models have reproduced enalapril-induced hepatocyte injury with oxidative and immune-mediated mechanisms [10]. Renal effects of ACE inhibition are comparatively well characterised in diabetic and proteinuric kidney disease, but the trajectory of routine hepatic and renal biochemistry during long-term enalapril therapy for uncomplicated essential hypertension is less well documented [11].

Although previous studies have established the antihypertensive and cardiovascular benefits of ACE inhibitors and ARBs [5], their contribution to understanding hepatic and renal biochemical safety has been comparatively limited. Most trials have focused on blood-pressure efficacy, cardiovascular events, or long-term renal outcomes, while hepatic safety information has largely originated from case reports and pharmacovigilance data [12]. The few prospective studies assessing liver and renal biochemical parameters have generally involved selected populations, including patients with diabetic nephropathy, thereby limiting their applicability to individuals with uncomplicated essential hypertension [13]. Consequently, there remains a paucity of prospective evidence evaluating simultaneous hepatic and renal biochemical changes following initiation of enalapril in patients with essential hypertension. The present study addresses this gap by prospectively assessing baseline and follow-up hepatic and renal function parameters in patients initiated on enalapril for essential hypertension, as part of a larger prospective, randomised, open-label study comparing enalapril and telmisartan; this article reports the first objective of that study, namely the effect of enalapril, in isolation, on hepatic and renal function parameters over nine months of therapy.

Objective
To study the effect of enalapril on hepatic and renal function parameters in patients suffering from essential hypertension.

2. Materials and Methods

This report is prepared and structured in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for cohort studies [14].

Study design and scope

This was a prospective, randomised, open-label study. Eligible patients were randomised to receive either enalapril maleate or telmisartan, an angiotensin receptor blocker with well-characterised pharmacokinetic and pharmacodynamic properties in hypertension [15]; the present report addresses the first objective of the parent study and therefore describes only the enalapril treatment arm and its outcomes.

Setting and duration

The study was conducted in the outpatient Department of General Medicine in a tertaiary care hospiatl Ongole, in collaboration with the Department of Pharmacology, Government Medical College, Ongole, over a period of 12 months, from 1 August 2021 to 31 July 2022. Each enrolled patient was followed for 9 months from the date of enrolment.

Participants

The study will include newly diagnosed patients with essential hypertension aged 25–65 years, of either sex, with normal baseline hepatic and renal function. Patients previously treated with antihypertensive drugs, pregnant or lactating women, and those with abnormal baseline liver or renal parameters will be excluded. Patients with diabetes mellitus, thyroid disorders, chronic bronchitis/COPD, heart disease, phaeochromocytoma, aldosteronism, hyperlipidaemia, chronic alcohol use, or chronic use of corticosteroids, NSAIDs, or oral contraceptive pills will also be excluded to minimize potential confounding factors.

Intervention

Patients allocated to the enalapril arm received enalapril maleate 5 mg orally once daily for 9 months. Systolic and

diastolic blood pressure were recorded at each visit in the sitting position after 10 minutes of rest, using a mercury sphygmomanometer by the auscultatory method.

Outcome variables and measurement

Hepatic function (serum ALP, SGOT, SGPT and total bilirubin) and renal function (blood urea and serum creatinine) were measured at baseline (day 0), 6th month and 9th month by standard laboratory assay. Safety was assessed at every visit through directed enquiry for subjective symptoms (headache, dizziness, fatigue, back pain, dyspepsia, myalgia, pruritus, nausea, dry cough) and clinical examination for objective signs (rash, hypotension).

Bias

Randomisation to treatment arm limited selection bias in treatment allocation; the open-label design was chosen because enalapril and telmisartan differ in formulation and dosing schedule, but outcome assessment relied on objective laboratory values, which limits observer-related measurement bias for the hepatic and renal endpoints reported here.

Study size

Sample size was estimated using the standard formula for prevalence-based studies, $N = (Z^2\alpha/2 \times p \times q)/d^2$ [16], with $Z\alpha/2 = 1.96$ (95% confidence), an expected proportion of hepatic/renal adverse change of 7%, q = 93 and an allowable error (d) of 5%, giving a minimum estimated requirement of 100 patients for the parent comparative study. For the objective reported here, 49 patients were allocated to enalapril; 46 completed 9 months of follow-up and were analysed.

Statistical methods

Data were entered and analysed using Microsoft Excel 2016 and Epi Info. Continuous variables are expressed as mean ± standard deviation and categorical variables as frequencies and percentages. Change from baseline to 6th and 9th month within the enalapril group was analysed using the paired Student's t-test or one-way repeated-measures analysis of variance (ANOVA) for matched observations. A two-sided $p<0.05$ was considered statistically significant.

Ethical considerations

Institutional ethics committee clearance was obtained prior to initiation of the study, and written informed consent was obtained from all participants before enrolment.

3. Results

Participant flow

Of 256 patients screened for the parent study, 159 did not meet the eligibility criteria, leaving 97 eligible patients who were randomised to enalapril (49 patients) or telmisartan (48 patients). In the enalapril arm, 3 patients were lost to follow-up during the 9-month study period; 46 patients completed follow-up and were included in the analysis reported below.

Baseline characteristics

The baseline demographic and clinical characteristics of the 46 patients who received enalapril are summarised in Table 1. The majority of patients (43.48%) were aged 41–50 years, and 60.87% were male.

Table 1. Baseline demographic and clinical characteristics of the enalapril group.

Characteristic	Enalapril (n=46)
Age, years	43.56 ± 8.37
Age group, n (%)	
25–40 years	16 (34.78)
41–50 years	20 (43.48)
51–65 years	10 (21.74)
Male, n (%)	28 (60.87)
Female, n (%)	18 (39.13)
Blood pressure, mmHg	
Systolic BP	142.60 ± 9.41
Diastolic BP	87.93 ± 5.82

Hepatic parameters	
ALP, IU/L	79.36 ± 19.22
SGOT, U/L	19.63 ± 7.99
SGPT, U/L	32.50 ± 11.05
Total bilirubin, mg/dL	0.68 ± 0.23
Renal parameters	
Blood urea, mg/dL	14.86 ± 3.80
Serum creatinine, mg/dL	0.83 ± 0.15

Effect on blood pressure

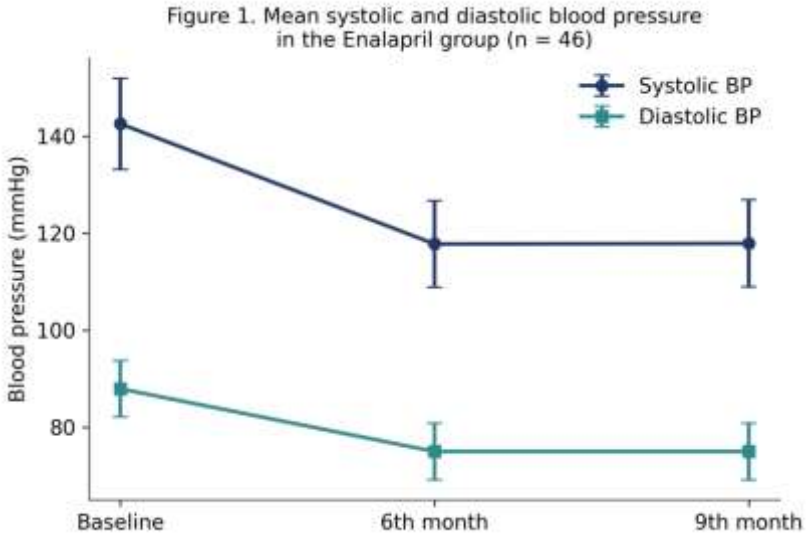
Mean SBP fell from 142.60±9.41 mmHg at baseline to 117.82±8.92 mmHg at 6 months and 117.93±8.98 mmHg at 9 months (p<0.0001). Mean DBP fell from 87.93±5.82 mmHg at baseline to 75±5.86 mmHg at both 6 and 9 months (p<0.0001) (Table 2, Figure 1).

Table 2. Systolic and diastolic blood pressure in the enalapril group across visits (mean ± SD).

Parameter	Baseline	6th month	9th month	p-value*
SBP, mmHg	142.60 ± 9.41	117.82 ± 8.92	117.93 ± 8.98	<0.0001
DBP, mmHg	87.93 ± 5.82	75.00 ± 5.86	75.00 ± 5.86	<0.0001

Intragroup comparison, baseline vs 9th month.

Figure 1. Mean systolic and diastolic blood pressure in the enalapril group across visits (error bars = SD).



Effect on hepatic function parameters

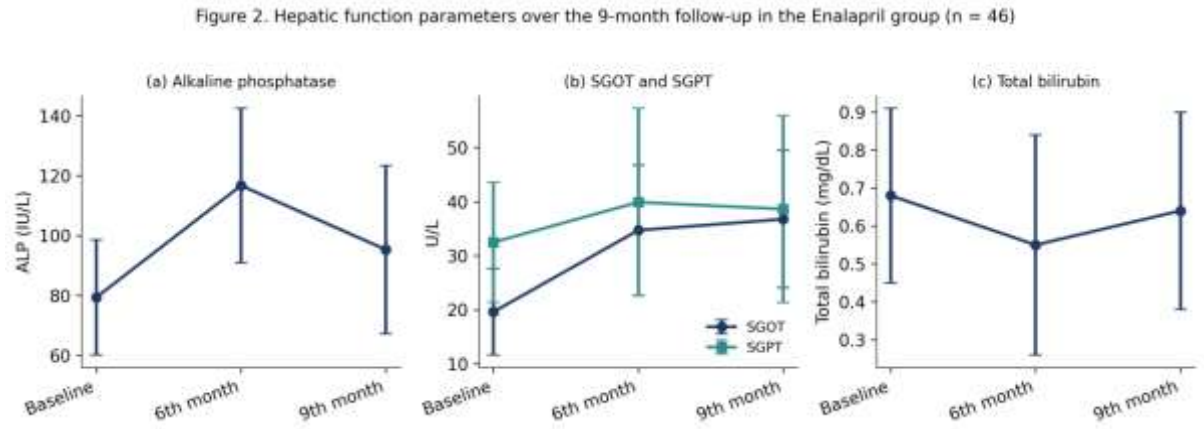
ALP rose from 79.36±19.22 IU/L at baseline to 116.71±25.77 IU/L at 6 months and 95.28±28.04 IU/L at 9 months (p<0.0001). SGOT rose from 19.63±7.99 U/L at baseline to 34.71±12.06 U/L at 6 months and 36.76±12.71 U/L at 9 months (p<0.0001). SGPT increased from 32.5±11.05 U/L at baseline to 39.91±17.36 U/L at 6 months and 38.63±17.30 U/L at 9 months, but this change was not statistically significant (p=0.0533). Total bilirubin showed no significant change from 0.68±0.23 mg/dL at baseline to 0.64±0.26 mg/dL at 9 months (p=0.0810) (Table 3, Figure 2).

Table 3. Hepatic function parameters in the enalapril group across visits (mean ± SD).

Parameter	Baseline	6th month	9th month	p-value*
ALP, IU/L	79.36 ± 19.22	116.71 ± 25.77	95.28 ± 28.04	<0.0001
SGOT, U/L	19.63 ± 7.99	34.71 ± 12.06	36.76 ± 12.71	<0.0001
SGPT, U/L	32.5 ± 11.05	39.91 ± 17.36	38.63 ± 17.30	0.0533
Total bilirubin, mg/dL	0.68 ± 0.23	0.55 ± 0.29	0.64 ± 0.26	0.0810

**Intragroup comparison, baseline vs 9th month (paired t-test/repeated-measures ANOVA).*

Figure 2. Hepatic function parameters (a) ALP, (b) SGOT and SGPT, (c) total bilirubin in the enalapril group across visits (error bars = SD*).*



Effect on renal function parameters

Blood urea did not change significantly from 14.86±3.80 mg/dL at baseline to 14.50±3.76 mg/dL at 9 months (p=0.5536). Serum creatinine likewise did not change significantly from 0.83±0.15 mg/dL at baseline to 0.88±0.12 mg/dL at 9 months (p=0.5055) (Table 4, Figure 3).

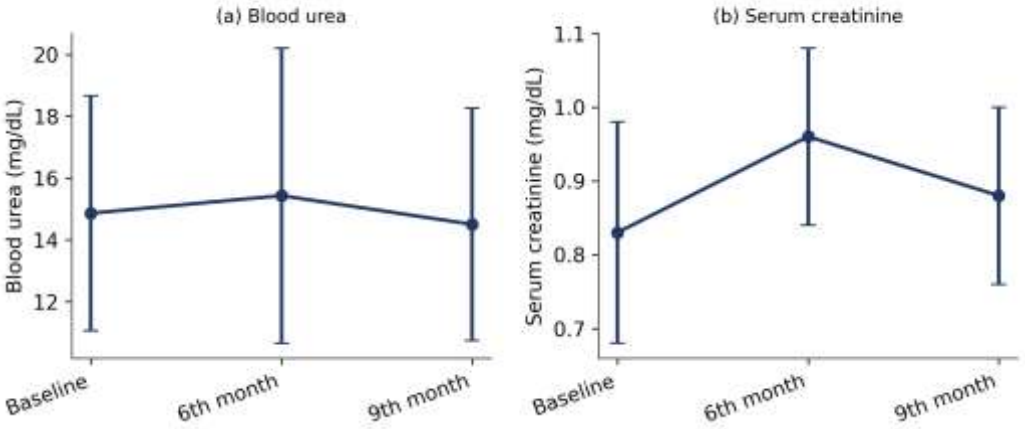
Table 4. Renal function parameters in the enalapril group across visits (mean ± SD).

Parameter	Baseline	6th month	9th month	p-value*
Blood urea, mg/dL	14.86 ± 3.80	15.43 ± 4.78	14.50 ± 3.76	0.5536
Serum creatinine, mg/dL	0.83 ± 0.15	0.96 ± 0.12	0.88 ± 0.12	0.5055

**Intragroup comparison, baseline vs 9th month.*

Figure 3. Renal function parameters (a) blood urea, (b) serum creatinine in the enalapril group across visits (error bars = SD).

Figure 3. Renal function parameters over the 9-month follow-up in the Enalapril group (n = 46)



Adverse effects

Six of 46 patients (13.04%) receiving enalapril reported mild adverse effects headache, nausea and dry cough. Treatment was continued in all cases, and the reported symptoms resolved despite continued therapy over the 9-month period. No patient discontinued enalapril for a hepatic or renal adverse event, and no case met biochemical criteria for clinically significant hepatic or renal impairment during the study.

4. Discussion

In this prospective study of 46 patients with essential hypertension treated with enalapril for 9 months, blood pressure control was effective and sustained, consistent with the established antihypertensive efficacy of ACE inhibitors reported in comparative trials of enalapril and telmisartan [17]. The principal finding relevant to the study objective was a statistically significant rise in ALP and SGOT, without significant change in SGPT, total bilirubin, blood urea or serum creatinine.

The rise in ALP and SGOT with enalapril is biologically consistent with experimental and clinical evidence that ACE inhibitors, including enalapril, can produce hepatocellular stress in susceptible individuals [10]. Isolated case reports of ACE-inhibitor-associated liver injury, including with ramipril, describe a similar hepatocellular or mixed pattern of enzyme elevation [12], and a comparative study of enalapril and telmisartan in patients with diabetic nephropathy likewise reported rises in ALP, SGOT and SGPT with both agents [13]. Angiotensin receptor blockers have also been associated with aminotransferase elevation in some series [18], suggesting that a degree of hepatic enzyme change may be a class-related phenomenon of RAAS blockade rather than specific to any single agent, although the magnitude appeared smaller with enalapril than has been reported for some ARBs in comparable settings.

SGPT and total bilirubin did not change significantly with enalapril in the present study. This is broadly reassuring, since bilirubin elevation is more specific for clinically relevant hepatocellular dysfunction than isolated transaminase rise. In contrast, a study of antihypertensive agents in diabetic patients reported measurable increases in serum total bilirubin with both ACE inhibitors and ARBs [19]; the absence of a bilirubin signal in the present, non-diabetic essential-hypertension cohort may reflect differences in baseline hepatic risk, comorbidity profile, or drug dose between the study populations.

Renal parameters remained stable throughout follow-up, consistent with the mechanistic understanding that RAAS blockade is renoprotective, rather than nephrotoxic, in the pathogenesis and treatment of proteinuric kidney disease [20], particularly in patients without pre-existing chronic kidney disease [21]. Similar renal stability with RAAS-acting drugs has been reported in meta-analyses of ACE inhibitors and ARBs combined with calcium-channel blockers or diuretics [22], and in proteinuric diabetic populations [23]. Taken together with the present findings, these data support the continued first-line use of enalapril in essential hypertension from a renal-safety standpoint, while indicating that hepatic enzymes merit periodic monitoring, particularly beyond six months of therapy, when the rise in ALP and SGOT was most apparent.

The adverse-effect profile observed headache, nausea and dry cough in 13% of patients is consistent with the known

tolerability profile of enalapril, in which cough is a recognised, dose-independent class effect of ACE inhibition [17]. All reported symptoms were mild and did not necessitate discontinuation of therapy.

Thus this study prospectively followed a relatively homogeneous cohort of newly diagnosed, treatment-naive patients with essential hypertension for 9 months, excluding patients on multidrug antihypertensive therapy or with comorbidities that could independently affect hepatic or renal function, which strengthens the internal validity of the observed drug-related changes. Limitations include the single-centre design, the moderate sample size for the enalapril arm (n=46), the open-label design, and a follow-up period that, while longer than many prior comparative studies, may still be too short to capture rare or late-onset hepatotoxic events. As enalapril was administered at a single fixed dose (5 mg once daily) rather than across its full therapeutic range, dose-dependence of the hepatic signal could not be assessed.

Findings apply most directly to adults aged 25–65 years with newly diagnosed, uncomplicated essential hypertension and normal baseline hepatic and renal function; they should be extrapolated cautiously to patients with pre-existing hepatic or renal impairment, diabetes, or those on concurrent hepatotoxic medications, who were excluded from this study.

5. Conclusion

Nine months of enalapril therapy in patients with essential hypertension produced effective and sustained blood pressure reduction together with a small but statistically significant rise in serum ALP and SGOT. SGPT, total bilirubin, blood urea and serum creatinine did not change significantly. These findings support the continued use of enalapril as a first-line antihypertensive agent, with periodic monitoring of liver enzymes rather than routine avoidance recommended during long-term therapy, particularly in the first 6–9 months of treatment.

Declarations

Ethical approval

Institutional ethics committee approval was obtained, and written informed consent was taken from all participants prior to enrolment.

Funding

No external funding was received for this study.

Conflict of interest

The authors declare no conflict of interest.

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