Paper

Short-term effects of angiotensin receptor blockers on blood pressure control, and plasma inflammatory and fibrinolytic parameters in patients taking angiotensin-converting enzyme inhibitors

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Abstract

Introduction. Angiotensin-converting enzyme (ACE) inhibitors reduce cardiovascular events in patients with established vascular disease and heart failure (HF). ACE-inhibitors have important effects on fibrinolytic balance, which may be the underlying mechanism for a reduction in cardiovascular events. Although angiotensin-receptor blockers (ARBs) offer greater tolerability than ACE-inhibitors, the major ARB trials have demonstrated a lack of reduction in myocardial infarction (MI) occurrence and mortality in contrast to ACE-inhibitors. In this study, we investigated the combined effects of ARBs and ACE-inhibitors on fibrinolytic and inflammatory parameters in patients with uncontrolled hypertension.

Methods. Twenty-four patients with uncontrolled hypertension despite taking adequate doses of ACE-inhibitor therapy were selected. Patients were started on Candesartan 16 mg once a day. Plasma plasminogen activator inhibitor (PAI-1) antigen (Ag), tissue plasminogen activator (t-PA) Ag, thrombin-activatable fibrinolysis inhibitor (TAFI) % activity and high sensitivity C-reactive protein (hsCRP) levels, were measured during low salt intake at baseline and two weeks after therapy with an ARB.

Results. Addition of ARB to the regimen reduced systolic (155±17 *vs.* 139±13, p<0.001), and diastolic (91±9 *vs.* 81±8, p<0.001) blood pressures (BP). No significant changes were observed in PAI-1 Ag (66±51 *vs.* 68±52, p=0.9), t-PA Ag (12.6±5.3 *vs.* 13.3±4.7, p=0.3), TAFI % activity (119±30 *vs.* 118±32, p=0.9) and hsCRP (3.9±3.4 *vs.* 3.6±3.6, p=0.7) levels after adding an ARB.

Conclusions. Combined ARB and ACE-inhibitor use provide better BP control without any detrimental effect in plasma inflammatory and fibrinolytic parameters.

Introduction

An impressive amount of experimental and clinical evidence has defined a role for the renin-angiotensin system (RAS) in the development of hypertension, atherosclerosis and ischaemic cardiovascular disease. It is now widely accepted that the activation of the RAS is associated with vascular toxicity and cardiovascular events that are independent of its effects on blood pressure (BP). These observations have fuelled the hypothesis that pharmacological interruption of the RAS particularly reduces the risk of cardiovascular events in hypertensive patients. Therefore, blockade of the RAS has been an important target in the treatment of hypertension.

Until recently, the angiotensin-converting enzyme (ACE) inhibitors were the only class of medications to block RAS and they have played a pivotal role in the treatment of hypertension and cardiovascular disease. Now, a relatively new class of medications that can block the angiotensin II type I (AT_1) receptor are available. Mechanistically, angiotensin-receptor blockers (ARB) inhibit the RAS by blocking the AT_1-receptor. Several survival studies have investigated the effects of ACE-inhibitors in patients with high vascular risk.[1-7] These comprehensive investigations showed a substantial benefit from ACE-inhibitors with a reduction in the risk of myocardial infarction (MI) and cardiovascular events by approximately 8% per year of treatment. Relatively fewer studies were conducted or completed with ARBs.

Although ARBs offer greater tolerability than ACE-inhibitors, the major ARB trials have demonstrated lack of reduction in MI and mortality in contrast to ACE-inhibitors. In the Losartan Intervention For End point reduction in hypertension (LIFE) and Study on COgnition and Prognosis in Elderly (SCOPE) trials, long-term treatment with ARBs in hypertension was associated with an increase of MI which however was statistically not significant.[8,9] On the other hand, Valsartan Antihypertensive Long-term use Evaluation (VALUE) trial recruited 'high-risk' patients with hypertension, 80% of whom had symptomatic vascular disease. Treatment with valsartan was associated with a statistically significant increase (19%; p=0.02) in total MI (fatal and non-fatal MI) compared with amlodipine 10 mg.[10] These observations fuelled the discussion that ARBs might actually increase risk of MI.[11]

The pharmacological and biological differences in the actions of these separate classes of drugs

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will ultimately affect the long-term outcomes. Benefits of ACE-inhibition appear to be independent of the haemodynamic effects. Recent research has demonstrated an interesting interaction between the RAS and the fibrinolytic system.[12] The fibrinolytic system serves as one of the main endogenous defence mechanisms against intravascular thrombus formation. The effects of the fibrinolytic system are mediated by plasmin, the protease generated by the action of plasminogen activators on the inactive precursor plasminogen. Tissue plasminogen activator (t-PA) is considered to be the primary plasminogen activator in the blood. Vascular fibrinolysis is largely regulated by the balance between the plasminogen activators and a specific rapidly acting plasminogen activator inhibitor (PAI-1).[13] Accumulated data suggest that in addition to its well-known vasoconstrictor effects, angiotensin II (Ang II) modulates fibrinolysis.[12-14] ACE inhibitors and ARBs exhibit differences in modulation of the interaction between the RAS and the fibrinolytic system.[15] Treatment with ACE-inhibitors, but not with ARB, was associated with a decrease in PAI-1 antigen (Ag) and activity. In contrast, plasma t-PA Ag was reduced during treatment with ARB.[15,16] Despite the activating effects of ACE-inhibitors on the fibrinolytic system caused by reducing the PAI-1 and PAI-1/t-PA balance, ARBs were associated with a concerning decrease in t-PA Ag levels in clinical and experimental models.[15-17] Ang IV, bradykinin, and aldosterone may have a role in defining contrasting effects of ACE-inhibitor and ARB on plasma fibrinolytic balance.[15-18]

Patients with hypertension frequently require combined drug therapy.[19,20] Whether simultaneous use of RAS cascade blockade by ACE-inhibitors and ARBs maintain or improve the outcome benefit of ACE-inhibition is a subject for clinical long-term studies. In this study, we investigated the combined effects of ARBs and ACE-inhibitors on fibrinolytic and inflammatory parameters such as: PAI-1, t-PA, thrombin-activatable fibrinolysis inhibitor (TAFI) Ag and high sensitivity C-reactive protein (hsCRP) levels in high vascular risk patients with uncontrolled hypertension.

Methodology

Twenty-four patients (mean age 58±8) with uncontrolled hypertension (diastolic blood pressure [DBP] > 85 mmHg and/or systolic blood pressure [SBP] > 135 mmHg), despite receiving adequate doses of ACE-inhibitor therapy, were selected. Subjects with known renal insufficiency, renal artery stenosis or serum creatinine over 2 mg/dL were excluded. Compliance with antihypertensive medications was assessed at the beginning of the study and non-compliant patients were not included in the study. Informed consent was obtained from all patients, and the study protocol was approved by the local ethics committee.

All patients were on low salt diet regimen. Plasma PAI-1, t-PA Ag, and TAFI % activity levels (TAFI was measured for the last 12 consecutive patients), and hsCRP (for the first 12 consecutive patients) levels were measured at baseline. All patients were started on an ARB (Candesartan 16 mg per oral once a day). They returned to the cardiology clinic after two weeks. Patients were examined and BP levels were recorded. Plasma PAI-1 Ag (n=24), t-PA Ag (n=24), TAFI % activity (n=12) and hsCRP (n=12) levels were measured again two weeks after starting ARB treatment. Blood samples were collected at 9 am in order to avoid the effect of diurnal variation on plasma fibrinolytic parameters.[21] PAI-1, t-PA Ag levels were determined using a two-site enzyme-linked immunosorbent assay (Diagnostica Stago). The PAI-1 and t-PA mass ratio was determined by dividing plasma concentrations (ng/ml) by the molecular weights of the two proteins (70 kD for t-PA and 50 kD for PAI-1).

Statistical analysis

Previous studies revealed that ARB lowered t-PA Ag levels by 10% with a standard deviation of nearly 1 ng/ml at the end of two weeks in normotensive subjects.[15] For power of 80% at two-sided 5% significance, sample size was calculated to be 24. The primary outcome was the change in plasma fibrinolytic parameters (t-PA and PAI-1) at the end of two weeks. Previous studies revealed that ACE-inhibition lowered PAI-1 and ARBs lowered t-PA Ag levels at the end of two weeks in normotensive subjects.[15] Therefore, we measured fibrinolytic parameters at two weeks after adding ARB to an ACE-inhibitor. Given the small sample size, the non-parametric Wilcoxon Signed Rank test was used to test the difference of the parameters before and after Candesartan treatment. Results are presented as means. Statistical significance was accepted as $p<0.05$.

Results

Twenty-four patients (mean age was 58±8, 75% female) were included in the study. Baseline characteristics of the patients are listed in table 1. All patients had a diagnosis of hypertension on treatment with an antihypertensive regimen. Patients had uncontrolled BP (mean SBP and DBP were 155±17 and 91±9 mmHg respectively) despite taking adequate doses of ACE-inhibitors (14 patients were on lisinopril 20 mg once a day, three patients were on lisinopril 10 mg once a day, five patients were on ramipril 10 mg once a day, two patients were on perindopril 4 mg once a day). Most patients were requiring combined antihypertensive regimen at baseline (16 patients were on diuretics, eight patients were on

Table 1
Baseline characteristics of the patients.

Gender (% women)	75
Age (years)	58±8
Hyperlipidaemia (%)	79
History of smoking (%)	50
LVEF (%)	56±7
Obesity (%)	29
Diabetes mellitus (%)	42
Vascular disease (%)	58
Creatinine (mg/dL)	0.9±0.2
Number of antihypertensive medications	2.4±0.8

Key: LVEF = left ventricular ejection fraction.

β-blockers, six patients were on calcium channel blockers, two patients were on long-acting nitrate preparations in addition to an ACE-inhibitor). Average number of antihypertensive medications were 2.4±0.8 at baseline. All patients had a high vascular risk profile, 58% had prior history of vascular disease (coronary artery disease and/or peripheral arterial disease and/or cerebrovascular disease), and 42% had diabetes mellitus. Patients had normal left ventricular systolic function (mean ejection fraction 56±7%) and renal function (mean creatine levels were 68.63±15.25 mmol/L) As already noted, all patients were started on an ARB (Candesartan 16 mg once a day) for BP control, and they returned to the cardiology clinic after two weeks for a repeat examination and BP check.

All patients tolerated adding ARB to their regimen with no discernible side effects. Addition of an ARB to an ACE-inhibitor provided better BP control (SBP [155±17 *vs.* 139±13, p<0.001], and DBP 91±9 *vs.* 81±8, p<0.001). Eight patients with high vascular risk were able to achieve the suggested target BP of 130/80 mmHg after adding an ARB. A higher BP goal of 140/90 was achieved in 20 patients and four patients remained to have poorly controlled hypertension two weeks after ARB treatment.

We measured plasma Ag levels of the fibrinolytic variables (PAI-1 Ag, t-PA Ag, PAI-1/t-PA molar ratio) in all patients. TAFI levels were measured for the last 12 consecutive patients and hsCRP levels were measured for the first 12 consecutive patients. No significant changes were observed in hsCRP (3.9±3.4 *vs.* 3.6±3.6, p=0.7), PAI-1 Ag (66±51 *vs.* 68±52 ng/ml, p=0.9), t-PA Ag (12.6±5.3 *vs.* 13.3±4.7 ng/ml, p=0.3), PAI-1/t-PA molar ratio (7.5±4.7 and 6.7±4.2, p=0.4) and TAFI % activity levels (119±30 *vs.* 118±32, p=0.9) BP and plasma fibrinolytic parameters (table 2).

Discussion

This pilot study shows that even though ARBs reduced t-PA in normotensive subjects,[16] combined adding ARB to ACE-inhibitor in patients with uncontrolled hypertension provide better BP control without any detrimental effect in plasma inflammatory and fibrinolytic parameters in the short term. ACE-inhibitor use at baseline might have suppressed the effects of ARB on fibrinolytic parameters.

It is now widely accepted that the activation of the RAS is associated with vascular toxicity and cardiovascular events that may be independent of its effects on BP. A long-term prospective trial by Alderman *et al.* examined the relationship between the renin-sodium profile and subsequent MI in > 1,700 patients entering the hypertension control programme. After an average of 8.3 years of follow-up the risk of MI increased nearly five-fold in patients with a high renin-sodium profile at baseline compared to those with a low profile, despite equivalent success in managing hypertension.[22] Further studies demonstrated that plasma renin activity (PRA), without monitoring urinary sodium, also predicted the risk of MI in 2,902 hypertensive patients during an average of 3.6 years follow-up.[23] There was for every two unit increase in PRA an overall 25% increase in MI incidence. Therefore, optimal blockade of RAS has long been a target in preventing vascular complications in hypertensive patients.[24]

Table 2
Systolic and diastolic blood pressure, inflammatory and fibrinolytic markers before and after adding ARB to the antihypertensive regimen.

	Before ARB treatment	After ARB treatment	p
hsCRP (n=12) (mg/dL)	3.9	3.6	0.2
PAI-1 Ag (ng/ml)	66	68	0.8
t-PA Ag (ng/ml)	12.6	13.3	0.4
PAI-1/t-PA molar ratio	7.5	6.7	0.7
TAFI (n=12) (% activity)	119	118	0.6

Key: ARB = angiotensin-receptor blockers; hsCRP = high sensitivity C-reactive protein; PAI-1 Ag = plasminogen activator inhibitor antigen; t-PA Ag = tissue plasminogen activator antigen; TAFI = thrombin-activatable fibrinolysis inhibitor.

Patients with hypertension and vascular risk frequently require multi-drug regimens for a BP control goal of less than 130/80 mmHg.[19,20] Clinical trials indicate that two/three of people with hypertension and high vascular risk will require two or more different antihypertensive medications to achieve this new target.[19,20] Our group consisted of patients with moderate-to-severe hypertension that was uncontrolled despite taking 2.4±0.8 different antihypertensive medications at baseline. The majority of the patients had vascular disease and/or high vascular risk, including diabetes in 42%. Inflammatory and fibrinolytic parameters indicated an elevated vascular risk at baseline. Studies involving PAI-1 kinetics in healthy populations show a molar excess of active PAI-1 over t-PA.[25] PAI-1/t-PA ratio in our group of patients appeared to be higher than the previously reported ratio in normal populations.[26,27] despite taking adequate doses of an ACE-inhibitor, suggesting that the fibrinolytic system is inhibited in these patients with high vascular risk and poorly controlled hypertension.

In addition to their established role in heart failure and reduced left ventricular systolic function, ACE-inhibitors have provided long-term mortality reduction in patients with vascular risk and normal left ventricular function.[17,28] The mechanisms through which RAS blockade with ACE-inhibition can reduce the incidence of cardiovascular events has been an active area of research. BP reduction, reduced left ventricular remodelling, reduced sympathetic activity, reduced arterial permeability and lipoprotein entry, growth factor inhibition (Ang II, platelet derived growth factor, transforming growth factor beta etc.), bradykinin accumulation, prevention of atherosclerosis, free radical scavenging, and anti-inflammatory effects are some of the mechanisms invoked to explain this benefit. It is likely that several of these mechanisms are operative simultaneously. Importantly, ACE-inhibitors have activating effects on the fibrinolytic balance in patients with hypertension and vascular disease, which may also explain the decrease in cardiovascular events after RAS blockade with ACE inhibition.[15,16] If triggering of any or all of these mechanisms by the RAS contributes to precipitation of infarction, interruption of the RAS could theoretically reduce the risk of MI.

Since the time that ARBs were first introduced their usage has increased both because of the opinion that they have at least similar systemic effects to ACE-inhibitors, but also better tolerability. The activation of RAS is a risk indicator in hypertension, therefore the addition of an ARB to an ACE-inhibitor is theoretically an attractive strategy in patients with hypertension associated with high vascular risk. Enzymatic pathways that are not ACE related can also produce Ang II despite high-dose ACE-inhibitor treatment.[29] Adding an ARB to ACE-inhibitor can therefore provide a more efficient blockade of the RAS. Studies assessing the long-term outcome of combined ACE-inhibitor and ARB use in patients with heart failure and low left ventricular ejection fraction however display conflicting results.[30,31]

In this small pilot study, we observed that combined ARB and ACE-inhibitor use provide better BP control without any detrimental effect in plasma inflammatory and fibrinolytic parameters. We should indicate that the effects of ARB on BP control, plasma inflammatory and fibrinolytic parameters cannot be judged from this pilot study. Randomised controlled trials with long-term follow-up are necessary.

In addition to ACE-inhibitors, ARBs, aldosterone antagonists and renin inhibitors can block RAS cascade at different levels.[32] Future studies and vascular markers of risk are needed to determine the best strategy and combination to achieve the blockade of the activated RAS in hypertensive patients with increased vascular risk.

Limitations

Our sample size was small. The effects of ARBs on BP control, plasma inflammatory and fibrinolytic parameters cannot be judged from this research as a control group was not included. Randomised controlled trials (RCT) with long-term follow-up are necessary to understand the mechanisms of optimal RAS blocking regimen.

Previous studies revealed that ACE inhibition lowered PAI-1 antigen levels at the end of two weeks in normotensive subjects.[15,16] Therefore, we measured tPA, PAI-1 Ag and molar ratio two weeks after the ARB treatment. However, we do not know the long-term effects of combined ARB and ACE-inhibitor use on fibrinolytic and inflammatory parameters.

We compared tPA and PAI-1 Ag levels before and after ARB treatment, but we did not include a subgroup of patients treated without ACE-inhibitor or ARB. However, since adding ARB was the only alteration in their treatment during the two weeks, we suggest that any change in fibrinolytic parameters might be due to adding ARB to the antihypertensive regimen. Similarly, we cannot rule out diet as a confounding variable influencing the levels of PAI-1 and t-PA Ag. Given the fact study patients had a long-term diagnosis of treated hypertension, all patients were on long-term low salt diet.

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