



A possible role for hydrochlorothiazide (HCTZ) as “enhancer” of zofenopril activity at the tissue level

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Abstract

Background: Combination therapy with an angiotensin-converting enzyme (ACE) inhibitor and a thiazide diuretic has proven to be effective in the treatment of hypertension with or without end-organ damage.

Discussion: The mechanism of action of such a combination therapy may involve a opposite effect on the renin-angiotensin-aldosterone system (RAAS) with possible “functional” synergistic effects. Indeed, while diuretics can initially reduce intravascular volume leading to an activation of the RAA system with consequent vasoconstriction and salt and water retention, the concomitant presence of an ACE inhibitor may prevent such a counterregulatory response on neurohumoral system. This creates the conditions for the achievement of a maximal antihypertensive effect for both the ACE inhibitor and the diuretic. In recent years, however, experimental evidence has suggested that in addition to the above described mechanism of action, which is common to all the combinations of ACE-inhibitors and diuretics, it can be possible to identify some additional and peculiar mechanisms involving some selected drugs. Such additional mechanisms would be essentially related to some differences in the pharmacokinetic profiles of ACE inhibitors. In particular, the extent of lipophilicity could play an important role in membrane penetration and tissue accumulation and has been correlated with the overall ACE-inhibitory activity of various compounds, *eg.*, tissue ACE inhibitory activity could increase with the increase of lipophilicity. For instance, in rats with myocardial infarction, volume depletion induced by concomitant administration of HCTZ can increase the tissue levels of zofenoprilat (the active metabolite of zofenopril, an highly lipophilic ACE inhibitor), but not those of the highly hydrophilic lisinopril. An interesting hypothesis is that associating HCTZ to a highly lipophilic ACE inhibitor translates into peculiar clinical profiles, therefore we suggest further studies on this matter.

Conclusion: Experimental models have shown that hydrochlorothiazide (HCTZ) could act like a “tissue levels enhancer” of lipophilic ACE-inhibitors, *eg.*, can increase tissue concentrations of zofenoprilat (active metabolite of zofenopril, an highly lipophilic compound), and consequently induce an enhancement of its tissue ACE inhibition. On the basis of available experimental data, we suggest a peculiar interaction between zofenopril and HCTZ, *i.e.*, HCTZ could act as a “tissue levels enhancer” of zofenopril. This hypothesis, if confirmed, could imply a relevant therapeutic advantage for the treatment of arterial hypertension.

Keywords: ACE inhibitors, zofenopril, thiazide diuretics, hydrochlorothiazide, lipophilicity, ACE tissue inhibition, hypertension, combination therapy, enhancer

Introduction

Hypertension is the most common independent risk factor for cardiovascular (CV) diseases and responsible for a large proportion of morbidity and mortality in developed countries [1].

It has been recognized that the activation of the renin-angiotensin-aldosterone system (RAAS) plays a relevant role in the pathophysiological mechanisms of essential hypertension [2,3]. Angiotensin II has been shown to have a deleterious effect at different levels including the cardiac, vascular and renal tissues [4]. Pharmacological agents such as ACE inhibitors, that actively prevent the formation of angiotensin II, may therefore have favourable effects in terms of end-organ protection, beyond their activity on blood pressure (BP) [5].

Furthermore, it is now recognized that to achieve optimal BP control the majority of patients will require at least two antihypertensive drugs, belonging to different pharmacologic classes [6].

Discussion

Combination therapy with an ACE inhibitor plus a thiazide diuretic

Combination therapy with an angiotensin-converting-enzyme (ACE) inhibitor plus a low-dose thiazide diuretic (*eg.*, hydrochlorothiazide - HCTZ) has many advantages in the treatment of hypertension, *i.e.*, it can effectively reduce BP levels, prevent end-organ damage and reduce the probability of adverse metabolic effects often caused by the administration of an high dose of diuretic therapy [7,8].

The mechanism of action of such a combination therapy may involve a synergistic and opposite effect on the renin-angiotensin-aldosterone system (RAAS) [9]. Diuretic therapy can initially reduce plasma volume with a consequent increase in plasma renin activity, aldosterone secretion and urinary potassium loss [9]. Conversely, ACE inhibitors block the production of angiotensin II while counteract the reactive

hyperreninemia that may reduce the antihypertensive effect of diuretics. Therefore the combination of the two drugs seems specifically designed to promote the maximal antihypertensive effect of both classes of drugs [9].

Because of this combined effect, the dosages of each agent needed to achieve adequate blood pressure control are less than those required in monotherapy; this may improve tolerability, reducing adverse effects of single components [10].

In recent years, however, some experimental evidences have suggested that, in addition to the above reported mechanism of action which is common to all ACE inhibitors/diuretics combinations, it might be possible to identify some additional pharmacological mechanisms that are peculiar of some of these combinations [11]. Such additional mechanisms would be essentially related to the pharmacological characteristics of ACE inhibitors, particularly in terms of their different profile of lipophilicity [11].

Impact of lipophilicity on tissue concentrations of ACE inhibitors

Lipophilicity plays a relevant role in membrane penetration and tissue accumulation, and has been correlated with activity of various drugs, *eg.*, tissue ACE inhibitory activity could be higher for lipophilic compounds [11,12].

The lipophilicity of various ACE inhibitors has been evaluated *in vitro* by determining octanol-water distribution coefficients (the higher the value of the coefficient, the greater the lipophilicity of the drug) [12]. ACE inhibitors show a wide spectrum of lipophilicity. Zofenopril, for example, is a highly lipophilic ACE inhibitor, showing an octanol-water distribution coefficient 35 at pH 7, while lisinopril is a very hydrophilic ACE inhibitor, showing an octanol-water distribution coefficient <0.001 at pH 7 [12].

Zofenopril is chemically characterized by the presence of a sulphhydryl (SH) group [13]. Zofenopril and its active metabolite zofenoprilat are highly lipophilic, more than other ACE inhibitors [14]. The high lipophilicity of zofenopril allows effective and long-lasting tissue penetration [15-17]; furthermore, zofenopril has a sustained activity on cardiac ACE inhibition, antioxidant properties and remarkable tissue protective effect [18] and can improve oxidative stress in patients with essential hypertension [19].

Effect of HCTZ administration on ACE inhibitors pharmacokinetics

Volume depletion induced by concomitant administration of HCTZ can significantly influence steady-state plasma and tissue levels of ACE inhibitor [11]. The effect of concomitant administration of HCTZ could differ, however, depending on the lipophilicity of the ACE inhibitor, *i.e.*, resulting in increased plasma ACE inhibitor levels in case of hydrophilic compounds (*eg.*, lisinopril) versus increased tissue ACE inhibitor levels in case of lipophilic compounds (*eg.*, zofenopril) [11].

Interestingly, an experimental study on rats showed

remarkable different pharmacokinetics of two ACE inhibitors, lisinopril and zofenopril, in condition of volume depletion induced by concomitant administration of HCTZ [11]. The main hypothesis of this study is that sodium and water depletion induced by diuretic therapy can increase the efficacy of ACE inhibitor in the treatment of hypertension and renal dysfunction. The same mechanism might apply to the treatment of left ventricular dysfunction after myocardial infarction [11].

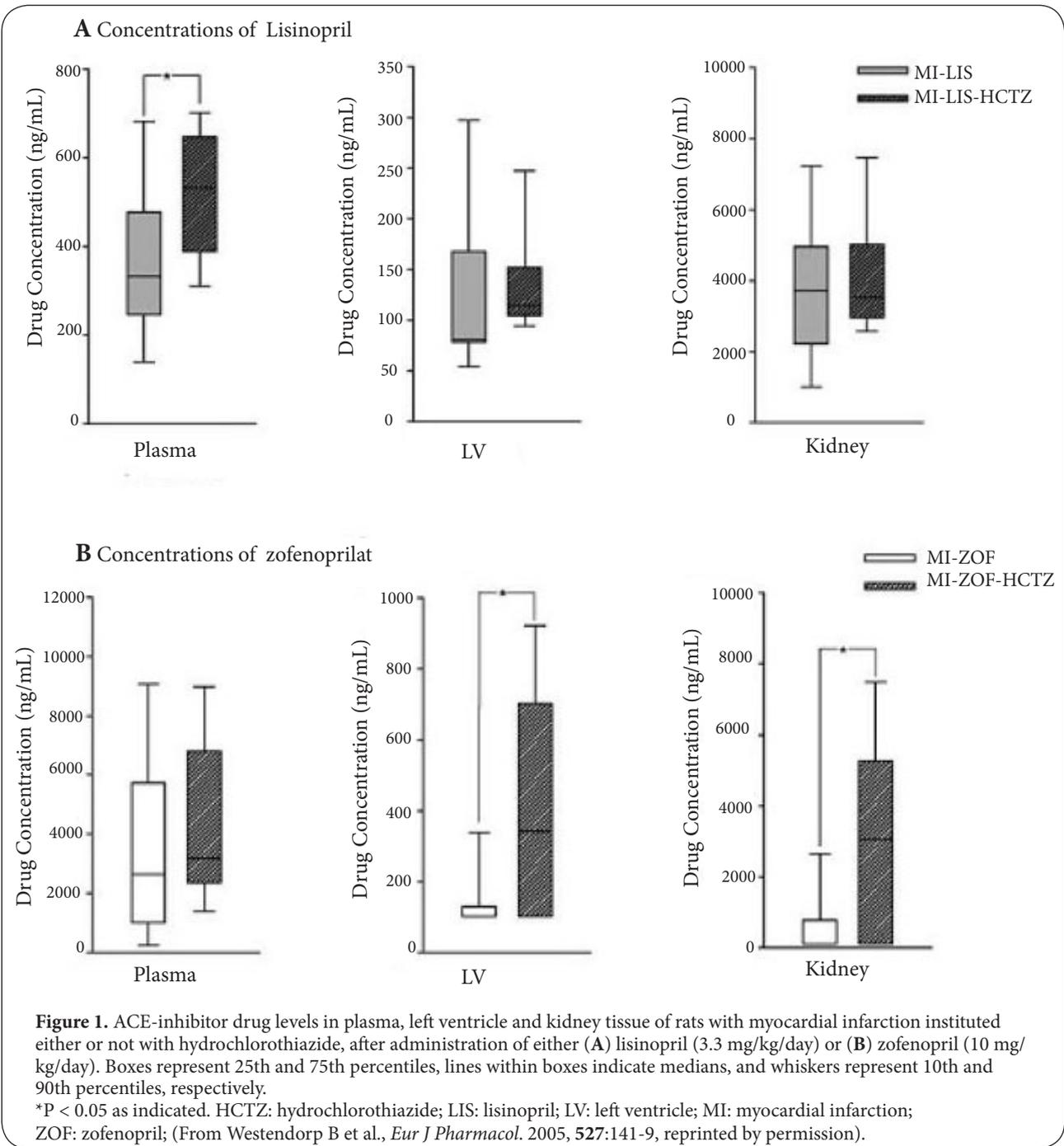
In the above mentioned study, myocardial infarction was induced in rats through coronary ligation; after 1 week, they were randomized to 50 mg/kg/day hydrochlorothiazide or to control treatment for 3 weeks. The last week, the animals received lisinopril or zofenopril in equipotent dosages (3.3 and 10 mg/kg/day, respectively). They were sacrificed after the last dose of ACE inhibitor and tissues were collected to evaluate drug concentrations. Lisinopril concentrations in plasma were significantly increased by HCTZ, whereas lisinopril tissue levels remained unchanged; on the contrary, plasma concentrations of zofenoprilat (the active metabolite of zofenopril) were only marginally increased by HCTZ, whereas zofenoprilat accumulation in both cardiac and renal tissues was markedly increased (Figure 1) [11].

These findings may be related to volume depletion induced in the rats by the concomitant administration of HCTZ; rather than leading to increased plasma levels, as in the case of lisinopril, the lipophilic nature of zofenopril would favor drug penetration of this ACE inhibitor into the tissue, with a subsequent tissue accumulation of the active metabolite zofenoprilat [11].

The possible interpretation of these findings is that HCTZ could act like a "tissue levels enhancer", *i.e.*, HCTZ can increase tissue concentrations of zofenopril and induce a peculiar enhancement of the tissue activity of this lipophilic ACE inhibitor [11].

Peculiar characteristics of the fixed combination zofenopril plus HCTZ

Therapy with ACE inhibitors can ameliorate myocyte contractile function [20], reduce collagen deposition and non-myocyte cellular proliferation [20,21] and prevent myocyte hypertrophic response [20,21]. In addition, it has also been demonstrated that ACE inhibitors can counteract the vasoconstriction of the atherosclerotic coronary arteries [4]. Treatment with ACE inhibitors has also prevented endothelial dysfunction both in animal [22-26] and in human experiments [27-31]. The favourable effects of ACE inhibitors seem to be related to their ability to release local vasodilators such as nitric oxide (NO) as well as to antagonize the vasoconstrictive effects of angiotensin II [32]. In addition, ACE inhibitors can counteract several atherosclerotic processes, including proliferation of vascular smooth muscle cells, low-density lipoprotein (LDL) oxidation, local accumulation of neutrophils and thrombosis [33].



The increase in tissue levels of ACE inhibitor, determined by concomitant administration of HCTZ, could contribute to the development of organ-protective effects of ACE inhibitor therapy; therefore, an highly lipophilic ACE inhibitor, such as zofenopril, would take advantage of co-administration with HCTZ, in comparison to an hydrophilic ACE inhibitor, such as lisinopril [11].

The aim of this paper is not to compare different drug combination treatments for high blood pressure, or to match

up different clinical trials; our goal is to open a debate in the specific context of the combination therapy between ACE inhibitors and thiazide diuretics. On the basis of available experimental data [11], we suggest a peculiar interaction between zofenopril and HCTZ, *i.e.*, HCTZ could act as a "tissue levels enhancer" of zofenopril.

This hypothesis, if confirmed, could imply a relevant therapeutic advantage for the treatment of arterial hypertension; therefore we would hope for other Authors' studies, so to

obtain more evidences to confirm our theory.

Conclusions

The combination of an angiotensin-converting enzyme (ACE) inhibitor and thiazide diuretic is effective in the treatment of hypertension and end-organ protection.

Mechanism of action of such a combination may involve a synergistic and contrasting effect on the renin-angiotensin-aldosterone system (RAAS).

Recent experiments, however, suggest that some of these associations may possess additional mechanisms. Experimental models, in fact, have shown that volume depletion induced by concomitant administration of HCTZ can increase tissue levels of zofenoprilat (the active metabolite of zofenopril, an highly lipophilic ACE inhibitor) but not tissue levels of lisinopril (an highly hydrophilic ACE inhibitor). Increased tissue drug levels of lipophilic ACE inhibitors may contribute to enhance their tissue activity and potentially increase their cardiovascular therapeutic effects.

On the basis of available experimental data, we suggest a peculiar interaction between zofenopril and HCTZ, *i.e.*, HCTZ could act as a “tissue levels enhancer” of zofenopril. This hypothesis, if confirmed, could imply a relevant therapeutic advantage for the treatment of arterial hypertension.

List of abbreviations

ACE: Angiotensin-Converting Enzyme
BP: Blood Pressure
HCTZ: Hydrochlorothiazide
RAAS: Renin-Angiotensin-Aldosterone System

Competing interests

CB reports lecture fees from Menarini International, which could have economic benefits from the publication of this work.

Authors' contributions

All authors contributed extensively to the work presented in this paper.
CB wrote the main paper, FMV and IP wrote some supplementary considerations, provided full bibliographic support, and edited the manuscript.
All authors discussed the results and implications and commented on the manuscript at all stages.

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