

Role of triple fixed combination valsartan, amlodipine and hydrochlorothiazide in controlling blood pressure

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Abstract: Hypertension is one of the main risk factors for the development of cardiovascular diseases and the search for new therapeutic strategies aimed at optimizing its control remains an ongoing research and clinical challenge. In recent years, there has been a marked increase in the use of combinations of antihypertensive drugs with complementary mechanisms of action, with the aims of reducing blood pressure levels more rapidly and vigorously than strategies employing monotherapy and improving treatment compliance and adhesion. Therefore, as recommended by the 2009 reappraisal of the European Society of Hypertension/European Society of Cardiology Guidelines, the use of a triple combination that combines a calcium channel blocker, an angiotensin II receptor blocker and a thiazide diuretic seems a reasonable and efficacious combination for the management of hypertensive patients with moderate, high or very high risk. This article reviews the clinical trials carried out with the fixed combination of amlodipine/valsartan/hydrochlorothiazide at the doses recommended for each drug in monotherapy. The data show that this combination achieved greater reductions in mean sitting diastolic and systolic blood pressure than amlodipine, valsartan or hydrochlorothiazide in monotherapy, with favorable pharmacodynamic and pharmacokinetic profiles. The triple combination at high single doses should be used with caution in elderly patients and those with renal or liver failure. Although the tolerability and safety of the triple combination are good, the most-frequently reported adverse effects were peripheral edema, headache and dizziness. Analytical alterations were consistent with the already-known biochemical effects of amlodipine, valsartan or hydrochlorothiazide in monotherapy. In summary, triple-therapy with amlodipine/valsartan/hydrochlorothiazide in a single pill contributes additional advantages to fixed-combinations of two drugs, achieving a greater and more rapid reduction in blood pressure levels in a safe, well-tolerated manner.

Keywords: hypertension treatment, antihypertensive fixed-dose triple-therapy, blood pressure control

Introduction

Hypertension affects millions of people worldwide and in developed countries the progressive aging of the population is increasing its prevalence even more. Hypertension is a determining risk factor for the development of cardiovascular diseases such as myocardial infarction, stroke, renal disease and heart failure and correct blood pressure (BP) control reduces cardiovascular morbidity and mortality.¹ However, in spite of the many therapeutic options available and the social and health consequences associated with inadequate BP control, only one-third of hypertensive patients achieve correct BP levels according to their total cardiovascular risk.¹

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Because the etiopathogenesis of hypertension is multifactorial, most patients require more than one antihypertensive drug to achieve correct BP control² and the most common therapeutic strategy is a fixed or free combination of two antihypertensive drugs.³ In patients with high or very high cardiovascular risk, such as diabetics or those with renal failure, a combination of three or more antihypertensive drugs with differing mechanisms of action is required to reach the BP objective recommended by the European Guidelines on Hypertension (BP < 130/80).⁴ The use of antihypertensive combinations with complementary mechanisms of action results in greater BP reductions than those achieved by the sum of each drug in monotherapy. Therefore, the European guidelines consider the combined use of a calcium channel blocker, an angiotensin II receptor blocker and a thiazide diuretic a reasonable combination⁴ for patients with very-high baseline BP values or those at high cardiovascular risk.

Calcium channel blockers prevent the entry of calcium to the cellular cytosol in arteriolar smooth muscle cells. Angiotensin II receptor blockers impede the activation of angiotensin II AT₁ receptors, preventing the vasoconstriction induced by angiotensin II, while blockade of the receptor in the renal cells helps prevent the renal retention of sodium. Thiazide diuretics reduce intravascular volume and total body sodium. The final effect of the combination of these three different mechanisms of action not only provides antihypertensive synergy but simultaneously counteracts or attenuates the possible adverse effects of each drug in monotherapy, particularly the hypokalemia induced by the diuretic and the peripheral edema induced by the calcium antagonist. The different available fixed combinations of valsartan/hydrochlorothiazide (HCTZ) and valsartan/amlodipine have been shown to be efficient and safe in reducing BP levels in patients in whom monotherapy is not sufficient to achieve BP control.^{5,6} The possible use of triple therapy with amlodipine, valsartan and HCTZ in a single pill represents a step forward in improving the control of hypertension by making treatment simpler and thereby improving long-term adhesion and treatment persistence.⁷

This review briefly and concisely explains some pharmacodynamic and pharmacokinetic aspects of this triple therapy and synthesizes the results of the different clinical trials carried out using this fixed combination.

Pharmacodynamic profile

Valsartan is a powerful, specific angiotensin II AT₁ receptor antagonist. In hypertensives, administration of a single oral dose of valsartan produces a reduction in BP that begins

2 hours after administration and reaches a peak at 4 to 6 hours. The antihypertensive effect persists for 24 hours after administration. When repeated doses are administered, the maximum reduction in BP is usually achieved in 2 to 4 weeks.⁸

Amlodipine inhibits the entry of calcium ions to the vascular smooth muscle of the resistance arterioles. The antihypertensive mechanism of action of amlodipine is due to a direct relaxant effect on the vascular smooth muscle, causing reductions in peripheral vascular resistance and BP. These effects are dependant on the movement of extracellular calcium ions to the interior of smooth muscle cells through specific ion channels. After administration of therapeutic doses to hypertensives, amlodipine causes vasodilation that induces a reduction in BP levels with no significant changes in the heart rate or plasma catecholamine levels. In hypertensive patients with normal kidney function, therapeutic doses of amlodipine are associated with a reduction in renal vascular resistance and increased glomerular filtration and renal plasma flow, with no modifications in the filtration rate or proteinuria.⁸

HCTZ is a diuretic that reduces the reabsorption of electrolytes in the renal tubule, increasing the excretion of sodium and chloride and, consequently, increasing plasma renin activity and aldosterone secretion, increasing urinary potassium loss and reducing serum potassium.⁸ Currently, no specifically designed studies have evaluated the pharmacodynamic characteristics of the triple combination. However, in spite of the lack of specific pharmacodynamic studies, the use of the fixed combination of amlodipine/valsartan/HCTZ is accepted, as the three products are all approved by the European Medicines Agency (EMA) to treat hypertension in monotherapy and pharmacodynamic studies show no unfavorable interactions.⁹

Pharmacokinetic profile

The pharmacokinetic characteristics of amlodipine, valsartan or HCTZ in monotherapy or in combination at fixed doses (amlodipine/valsartan or valsartan/HCTZ) are well known.^{10,11} The three drugs exhibit linear pharmacokinetics.⁸

Pharmacokinetics of the drugs in monotherapy

The absorption of oral amlodipine is practically total and plasma concentrations increase gradually to reach a peak at 6 to 9 hours. Its bioavailability is 64% to 80%, which is not modified by food ingestion. Ninety-four percent binds with plasma proteins.¹² It is metabolized in the liver by CYP 3A4.

The elimination of amlodipine from plasma occurs in two phases, with a half-life of 30 to 50 hours. Ten percent of the original amlodipine and 60% of amlodipine metabolites are excreted in urine.⁸

The absorption of oral valsartan is approximately 23%, reaching a peak at 3 hours. Ninety percent binds with plasma proteins, mainly serum albumin. Valsartan does not transform extensively since only approximately 20% of the dose is recovered as metabolites. It is mainly eliminated unaltered in the feces (83%) and the urine (13%).⁸ The half-life of valsartan is 6 hours.⁶

The absorption of oral HCTZ is rapid, with a maximum serum concentration (C_{max}) of approximately 2 hours. The increase in mean area under the serum concentration-time curve during the dosing interval (AUC) is linear and dose-dependent within the therapeutic range. The bioavailability is 65% to 75%. Food ingestion reduces bioavailability by 10% and peak concentration by 20%, increasing the maximum time from 1.6 hours to 2.9 hours. More than ninety percent is eliminated unaltered in the urine.

Pharmacokinetics of the triple combination

After oral administration of the fixed combination of amlodipine/valsartan/HCTZ in fasting conditions, the peak plasma level of valsartan is reached in 3 to 4 hours, that of HCTZ in 1 to 3 hours and that of amlodipine in 6 to 9 hours.⁹ The elimination half-lives of valsartan, HCTZ and amlodipine are 13 to 23 hours, 10 to 12 hours and 41 to 47 hours, respectively.⁹

The absorption of amlodipine/valsartan/HCTZ is similar to the individual administration of each of its components in terms of bioequivalence and bioavailability. Five studies have evaluated the bioavailability and bioequivalence of amlodipine/valsartan/HCTZ and the effect of food ingestion on them.⁸ The VEA489A2305 study analyzed the bioequivalence of amlodipine/valsartan/HCTZ at doses of 5/160/12.5 mg, respectively. With a confidence interval (CI) of 90% the ratio of the geometric mean for AUC_{0-t} , $AUC_{0-\infty}$, C_{max} was 0.8 to 1.25 indicating that the rate and extent of absorption of amlodipine/valsartan/HCTZ are similar to administration of each drug in monotherapy. Likewise, the VEA489A2306 study, which analyzed the bioequivalence of a dose of 5/160/25 mg, respectively, found a similar range of bioequivalence. The subsequent VEA489A2105 and VEA489A2106 studies analyzed the bioequivalence of 5 and 10 mg of amlodipine in the United States formulation versus the Norvasc[®] formulation, and both studies found a

range of AUC_{0-t} , $AUC_{0-\infty}$, C_{max} of 0.8 to 1.25. Comparison between amlodipine/valsartan/HCTZ 10/160/25 mg and amlodipine/valsartan/HCTZ 10/160/12.5 mg showed no differences in bioequivalence and bioavailability. The combination of amlodipine/valsartan/HCTZ at a maximum dose of 10/320/25 mg showed similar linear and dose proportional pharmacokinetics to the dose of 5/160/12.5 mg, whose bioequivalence was clearly established in the previous trials.

The effect of ingestion on the bioavailability of amlodipine/valsartan/HCTZ 10/320/25 mg at fixed doses in healthy subjects was evaluated in the CVEA 489A2310 clinical trial, a randomized, open-label, single-dose, two-period crossover study. Eighteen subjects were randomized to the fixed combination of a single oral dose of amlodipine/valsartan/HCTZ administered under fasting or fed conditions. The results showed that the C_{max} of valsartan increased by 12% and AUC_{0-t} , $AUC_{0-\infty}$, C_{max} increased by 14% after ingestion in comparison with fasting conditions. The upper limit of 90% CI for both C_{max} and AUC was between 1.25 and 1.32. Likewise, the bioavailability of amlodipine, valsartan and HCTZ is similar under fed and fasting conditions following a single oral dose administration of 10 mg/320 mg/25 mg of the amlodipine/valsartan/HCTZ fixed combination tablet. With respect to the pharmacokinetic interaction between amlodipine, valsartan and HCTZ, the VEA489A2104 study in hypertensive patients found that the addition of valsartan to the amlodipine/HCTZ combination increased the AUC of HCTZ by 8% and decreased the C_{max} by 17%. The addition of valsartan to the amlodipine/HCTZ fixed combination increased the AUC and C_{max} of amlodipine by 9% and 10%, respectively, with a CI of 80% to 125%.

The addition of HCTZ to the fixed combination of amlodipine/valsartan increased the AUC and C_{max} of valsartan by 25% and 22%, respectively, although the geometric mean ratios for amlodipine exposure were not within the 80% to 125% range. Finally, the addition of amlodipine to the valsartan/HCTZ fixed combination increased the AUC of valsartan by 10% and the C_{max} by 15% and increased the AUC of HCTZ by 3% and the C_{max} by 2%, with 90% CI within the 80%–125% range. In conclusion, there are no pharmacokinetic interactions and therefore the safety and efficacy of the triple fixed dose combination of amlodipine/valsartan/HCTZ is sufficiently demonstrated in phase III efficacy studies.

Special subgroups

Children and adolescents

There are no pharmacokinetic data for people aged <18 years.

Elderly patients (≥ 65 years)

The peak plasma concentration time of amlodipine is similar in young patients and the elderly, although in the elderly amlodipine clearance tends to decline, causing an increase in AUC of around $>70\%$; therefore, caution should be used when increasing the dose.⁸ The systemic exposure of valsartan is slightly higher in the elderly in comparison with young people, although no clinical significance has been demonstrated. There is little data on the systemic clearance of HCTZ, which decreases in both the healthy and hypertensive elderly.

Renal failure

The pharmacokinetics of amlodipine are not significantly affected by renal failure and therefore patients with a glomerular filtration rate >30 mL/minute may receive the normal starting dose.⁸

Liver failure

Patients with liver failure have reduced clearance of amlodipine, increasing the AUC by 40% to 60%. The mean half-life of valsartan in patients with mild-to-moderate chronic liver disease is double that found in healthy volunteers. Therefore, it should be used with caution in patients with liver failure.

Clinical efficacy studies

Clinical trials in patients with hypertension and other cardiovascular risk factors or comorbidities have shown the efficacy of strategies based on amlodipine,¹⁰ valsartan¹¹ or HCTZ in the reduction of cardiovascular morbidity and mortality. Two completed clinical trials, the VEA A2302 and VEA ABR01 studies, were designed to evaluate the efficacy and safety of amlodipine/valsartan/HCTZ in combination, although the VEA ABR01 study found no significant evidence with respect to clinical efficacy. The most representative trial is the recently published Triple Antihypertensive Therapy with Amlodipine, Valsartan and Hydrochlorothiazide: A randomized clinical trial (VEA A2302).¹³

VEA A2302 study¹³

This was a multinational, randomized, double-blind study in parallel groups. Patients aged 18 to 85 years with moderate-severe hypertension (grades 2–3) with mean sitting diastolic blood pressure (MSDBP) ≥ 100 mmHg and mean sitting systolic blood pressure (MSSBP) ≥ 145 mmHg were included. Patients had to discontinue antihypertensive treatment for one week, during which they received placebo. Patients with severe hypertension

(MSSBP ≥ 180 mmHg or MSDBP ≥ 110 mmHg) were randomized immediately to active treatment. Patients who did not fulfil inclusion criteria 7 days after ceasing previous treatment continued with placebo for 2 to 3 weeks and were randomized if MSSBP ≥ 145 mmHg and MSDBP ≥ 100 mmHg were achieved. Patients with MSSBP ≥ 200 mmHg or MSDBP ≥ 120 mmHg were excluded. Patients receiving ≥ 4 antihypertensive drugs in the screening visit, or ≥ 3 antihypertensive drugs with MSSBP/MSDBP $\geq 140/90$ mmHg, or ≥ 2 antihypertensive drugs with MSSBP/MSDBP $\geq 180/110$ mmHg were also excluded.

Other exclusion criteria were a history of hypersensitivity to one of the three drugs in monotherapy, a history of hypertensive encephalopathy, stroke, transient ischemic accidents, myocardial infarction or any other type of revascularization, second or third degree heart block, angina pectoris, significant arrhythmia or valvular alteration; uncontrolled type 1 or type 2 diabetes, hepatic, renal or pancreatic disease or need for any other medication that might interfere in BP control.

Of the 4285 patients enrolled in 15 countries, only 2271 were randomized to double-blind treatment after a single-blind placebo run-in period for a maximum of 4 weeks, followed by active treatment for 8 weeks. After receiving instructions on BP self-measurement, patients were provided with a semi-automatic OMRON apparatus (model HEM705CP) for home determination of systolic BP and diastolic BP twice daily during the placebo period. Patients with MSSBP ≥ 145 mmHg and < 200 mmHg and MSDBP > 100 mmHg and < 120 mmHg were randomized (1:1:1:1) to one of the four treatment arms: amlodipine/valsartan/HCTZ 10/320/25 mg, valsartan/HCTZ 320/25 mg, amlodipine/valsartan 10/320 mg or amlodipine/HCTZ 10/25 mg all once daily.

Patients underwent a 2-stage forced-titration period starting with lower doses of study medication for the two first weeks post randomization. From the third week to the end of the study at 6 weeks, all patients reached the maximum dose to which they had been randomized.

The primary study objective was to evaluate the efficacy and safety of the “high-dose” triple combination amlodipine/valsartan/HCTZ 10/320/25 mg in comparison with each of the components in double therapy (valsartan/HCTZ 320/25 mg, amlodipine/valsartan 10/320 mg or amlodipine/HCTZ 10/25 mg) in patients with severe-moderate hypertension. The secondary objectives were to evaluate the number of patients who achieved MSSBP/MSDBP $< 140/90$ mmHg, the number of responders for diastolic BP (MSDBP < 90 mmHg and/or ≥ 10 mmHg with

respect to baseline DBP values), the number of responders for SBP (MSBPP < 140 mmHg and/or ≥ 15 mmHg with respect to baseline SBP, and the reduction in systolic and diastolic mean BP by 24 hour ambulatory BP monitoring (ABPM).

Of the 2271 randomized patients, 2060 completed the study. The main causes of discontinuation in the placebo run-in period were not to require the study drug any longer (28.1%), abnormal test procedure results (6.9%) and withdrawal of consent (5.3%). In the randomized group, the main causes of discontinuation were adverse effects (3.1%), withdrawal of informed consent (2.5%) and loss to follow-up (1.5%).

There were no differences in baseline characteristics between the two groups. Nearly 72% of randomized patients were Caucasians and 55% were male, with a mean age of 53 years (14% aged ≥ 65 years). Baseline MSSBP/MSDBP was 169.9/106.5 mmHg. Approximately 10% of patients were diabetic. Previous hypertensive treatment included angiotensin converting enzyme inhibitors in 30.2%, dihydropyridine derivatives in 18.1%, thiazide diuretics in 17.3%, angiotensin II receptor blockers in 16.4% and beta-blockers in 12.5%.

Table 1 summarizes the results of the primary objective. Significant reductions in MSDBP and MSSBP were observed in comparison with baseline values in the four treatment arms, although the greatest reductions were observed in the amlodipine/valsartan/HCTZ group. The greatest antihypertensive effect was observed from the third week of treatment onwards in all treatment arms. Comparison of the antihypertensive efficacy of the four pharmacological combinations showed that amlodipine/valsartan/HCTZ 10/320/25 mg achieved significantly higher reductions than those obtained

with valsartan/HCTZ 320/25, amlodipine/valsartan 10/320 and amlodipine/HCTZ 10/25 (Table 2). These differences were maintained after adjustment for race, sex and age.

With respect to the secondary objectives, significantly higher proportions of patients treated with triple therapy reached overall BP control (defined as MSSBP/MSDBP < 140/90 mmHg), diastolic control rates and systolic control rates. Likewise, the rate of responders for both SBP and DBP was also significantly higher in patients randomized to the triple therapy. Finally, reductions in BP measured by ABPM were clinically and statistically higher in the triple therapy arm compared with all three dual therapies.

VEA ABR01 study⁹

This was a multicenter, randomized, parallel double-blind study which included hypertensive patients aged ≥ 18 years in stable treatment with >2 antihypertensive drugs during the last two months. The main end point of the study was to evaluate the proportion of patients who reached BP control after 12 weeks of treatment. Of the 264 patients who received amlodipine/valsartan/HCTZ, 61% reached the control objective (intention-to-treat). The percentage of control was similar in the treatment arms: 43.9% for amlodipine/valsartan/HCTZ 10/160/12.5 mg and 45.8% for amlodipine/valsartan/HCTZ 5/160/25 mg. However, the main limitation of this study was that it was not designed to compare antihypertensive strategies.⁹

VAA A2201EI study⁹

This was a multicenter, double-blind, open label extension study lasting 52 weeks in 2201 patients with mild-moderate

Table 1 Within-treatment analyses for change from baseline to endpoint in mean sitting BP (ITT population)

Treatment	N	Mean change from baseline (SE)	95% CI for mean change from baseline	P value
Diastolic BP				
AML/VAL/HCTZ 10/320/25	571	-24.57 (0.395)	(-25.348–23.797)	<0.0001*
VAL/HCTZ 320/25	553	-19.40 (0.431)	(-20.250–18.558)	<0.0001*
AML/VAL 10/320	558	-21.41 (0.394)	(-22.186–20.639)	<0.0001*
AML/HCTZ 10/25	554	-19.60 (0.407)	(-20.399–18.801)	<0.0001*
Systolic BP				
AML/VAL/HCTZ 10/320/25	571	-39.37 (0.962)	(-40.725–38.08)	<0.0001*
VAL/HCTZ 320/25	553	-31.81 (0.739)	(-33.265–30.362)	<0.0001*
AML/VAL 10/320	558	-33.37 (0.660)	(-34.668–32.077)	<0.0001*
AML/HCTZ 10/25	554	-31.86 (0.710)	(-33.264–30.475)	<0.0001*

*Indicates statistical significance ≤ 0.05 .

Data obtained from the VEA A2302 Study.¹³

Abbreviations: ITT, intention to treat; AML, amlodipine; VAL, valsartan; HCTZ, hydrochlorothiazide.

Table 2 Between-treatment comparisons for change from baseline to endpoint in mean sitting BP (MSBP) (mmHg)

Treatment	LSM change from baseline	LSM difference in change from baseline (SE)	P value	Hochberg adjusted P value
Diastolic BP				
AML/VAL/HCTZ 10/320/25	-24.74			<0.0001*
VAL/HCTZ 320/25	-19.69	-5.05 (0.539)	<0.0001	
AML/VAL 10/320	-21.49	-3.25 (0.537)	<0.001+	
AML/HCTZ 10/25	-19.46	-5.28 (0.539)	<0.0001	
Systolic BP				
AML/VAL/HCTZ 10/320/25	-39.68			<0.0001*
VAL/HCTZ 320/25	-32.04	-7.64 (0.848)	<0.0001	
AML/VAL 10/320	-33.5	-6.18 (0.846)	<0.001**	
AML/HCTZ 10/25	-31.48	-8.20 (0.848)	<0.0001	

Notes: The Hochberg adjusted P values are based on the maximum P value for the three comparisons in MSDBP and the maximum P value for the three comparisons in MSSBP.

*Indicates statistical significance $P \leq 0.05$.

**Maximum P values of the three comparisons.

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Abbreviations: LSM, least squares mean; AML, amlodipine; VAL, valsartan; HCTZ, hydrochlorothiazide.

hypertension who were randomized to receive amlodipine/valsartan 2.5/80 mg or 5/80 mg for 8 weeks. The dose was later increased to amlodipine/valsartan 5/160 or 10/160 mg, with the option of adding HCTZ 12.5 mg if BP control was inadequate. However, since the number of patients who required HCTZ was far below those who received dual therapy, this study can only be used for safety evaluation but does not support the efficacy of the triple combination of amlodipine/valsartan/HCTZ.⁹

Safety and tolerability studies

Although a reasonable number (1789) of patients have been treated with the triple combination of amlodipine/valsartan/

HCTZ, most information on safety and tolerability comes from the VEA A2302 study.¹³ The number of patients treated with high doses of this combination or treated for more than 6 months is limited. There are also few data on people aged >65 years and subgroups such as type 1 diabetics, badly controlled type 2 type diabetics, and patients with pre-existing heart disease or renal failure (creatinine ≥ 1.5).¹³

In the VEA A2302 study, the frequency of patients with >1 adverse effect (AE) was similar in the four treatment arms, with a proportion of between 45% and 48%. Most adverse effects were classified as mild-moderate. The

Table 3 Adverse events, regardless of study drug relationship, by preferred term and treatment

	AML/VAL/HCTZ 10/320/25 mg (n = 582)	VAL/HCTZ 320/25 mg (n = 559)	AML/VAL 10/320 (n = 566)	AML/HCTZ 10/25 mg (n = 561)	Total (n = 2268)
Preferred term	N (%)	N (%)	N (%)	N (%)	N (%)
Any preferred term	263 (45.2)	253 (45.3)	254 (44.9)	271 (48.3)	1041 (45.9)
Dizziness	45 (7.7)	39 (7)	13 (2.3)	22 (3.9)	119 (5.2)
Peripheral edema	26 (4.5)	5 (0.9)	48 (8.5)	50 (8.9)	129 (5.7)
Headache	25 (4.3)	30 (5.4)	28 (4.9)	39 (7)	122 (5.4)
Dyspepsia	13 (2.2)	5 (0.9)	6 (1.1)	2 (0.4)	26 (1.1)
Fatigue	13 (2.2)	15 (2.7)	12 (2.1)	8 (1.4)	48 (2.1)
Muscle spasms	13 (2.2)	7 (1.3)	7 (1.2)	5 (0.9)	32 (1.4)
Back pain	12 (2.1)	13 (2.3)	5 (0.9)	12 (2.1)	42 (1.9)
Nasopharyngitis	12 (2.1)	13 (2.3)	13 (2.3)	12 (2.1)	50 (2.2)
Nausea	12 (2.1)	7 (1.3)	10 (1.8)	12 (2.1)	41 (1.8)

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Abbreviations: AML, amlodipine; VAL, valsartan; HCTZ, hydrochlorothiazide.

most common adverse effects (Table 3) were peripheral edema (5.7%), headache (5.4%) and dizziness (5.2%). Dizziness occurred more frequently in the triple therapy (7.7%) and in the dual combination of valsartan/HCTZ (7%) compared with the dual combinations of amlodipine/valsartan (2.3%) or amlodipine/HCTZ (3.9%). Peripheral edema, however, was more common in patients receiving amlodipine/HCTZ (8.9%) or amlodipine/valsartan (8.5%) than in those treated with the triple combination (4.5%) or valsartan/HCTZ (0.9%) (Table 4). Three percent of adverse effects were classified as severe, and the distribution was similar in all four treatment arms. Adverse effects potentially associated with reductions in BP were very infrequent. Hypotension was most frequently reported in patients receiving triple therapy (1.5%) and the valsartan/HCTZ (1.4%) combination. Other symptoms, such as fainting ($\leq 1\%$), postural instability or orthostatic hypotension were infrequent.⁹

In the longest study (2201E1) the most common adverse effects reported were peripheral edema, nasopharyngitis, dizziness, headache and back pain. The incidence of edema was 17% for the high dose combination and 9.7% for the low dose combination.⁹ No deaths were reported in any of the studies. Seventy-six percent of patients reporting severe adverse effects required hospitalization.¹³ Analytical alterations were consistent with the known biochemical effects of amlodipine, valsartan or HCTZ. There was an increase in blood urea in all arms, which was greater in the triple combination and in the valsartan/HCTZ combination. Increased creatinine, uric acid and calcium were observed in patients who received HCTZ. Serum potassium decreased in all arms including HCTZ; the reduction was greatest in the amlodipine/HCTZ combination (-0.39 mmol/L) and smallest in the amlodipine/valsartan/

HCTZ (-0.16 mmol/L) and valsartan/HCTZ (-0.08 mmol/L) combinations.⁹

In general, there was a lower incidence of adverse effects in people aged ≥ 65 years than in younger people in the triple combination group, although only 14% of patients included in the VEA A2302 study were aged ≥ 65 and only 14 patients (2.2%) were aged > 75 years.⁹ Only 3% of patients in the VEA A2302 trial discontinued the study, mainly due to dizziness and hypotension, with an incidence of 1% and 0.7% in the triple and dual combination groups, respectively, effects that were attributed *a priori* to the greater antihypertensive efficacy of the triple combination with respect to the dual combinations.

There are no data on the amlodipine/valsartan/HCTZ fixed combination in pregnant women, although according to the recommendations for each drug in monotherapy, triple therapy is not advised in the first trimester of gestation and is contraindicated in the second and third trimesters.⁹

Future perspectives of triple fixed combinations

Currently, although there are a large number of antihypertensive drugs and fixed combinations of two drugs, there are, in general, no large differences in their efficacy in reducing BP when administered in monotherapy. Only 30% to 40% of hypertensive patients achieve BP control with a single drug.¹⁴ Many clinical trials on the efficacy of hypertensive treatment have shown the necessity to associate different antihypertensive drugs to reach BP control according to total cardiovascular risk. This evidence is collected in the 2007 Guidelines of the European Society of Hypertension/European Society of Cardiology, and is confirmed and reinforced by the very-recent reappraisal of guidelines by the European Society of Hypertension.¹⁵ The ESH/ESC guidelines promote the use of fixed combinations as the frontline antihypertensive strategy in patients with very high BP or in those with high cardiovascular risk, in whom a rapid reduction in BP is desirable.¹⁵

The vast majority of essential hypertensive patients will require two or more antihypertensive drugs to achieve blood pressure targets.¹⁶ In addition, the recent ESH reappraisal of the European guidelines states that the best combinations for hypertension treatment are combinations of agents blocking the rennin-angiotensin system with thiazide diuretics or calcium channel blockers, and the combination of all three drugs when needed. Therefore, the use of these three components in a single pill taken in the morning seems a reasonable choice for many patients

Table 4 Comparison of occurrence of peripheral edema between treatment groups

Treatment comparison (A vs B)	Treatment A n/N (%)	Treatment B n/N (%)	P value
AML/VAL/HCTZ 10/320/25 vs VAL/HCTZ 320/25	26/582 (4.5)	5/559 (0.9)	0.0002
AML/VAL/HCTZ 10/320/25 vs AML/VAL 10/320	26/582 (4.5)	48/566 (8.5)	0.0057
AML/VAL/HCTZ 10/320/25 vs AML/HCTZ 10/25	26/582 (4.5)	50/561 (8.9)	0.0029

Data obtained from the VEA A2302 Study.¹³

Abbreviations: AML, amlodipine; VAL, valsartan; HCTZ, hydrochlorothiazide.

with moderate-severe high risk hypertension. An alpha or beta-blocker may be added to this baseline strategy when needed due to comorbidities or to achieve blood pressure control.¹⁵ The possibility of giving three drugs in a single tablet instead of three tablets will improve adherence to the therapeutic strategy, the quality of life and treatment persistence in the long term. In addition, the cost of the combination is often less expensive than buying each drug individually.¹⁷

Triple combination therapy with amlodipine/valsartan/HCTZ in a single tablet should be administered once daily with or without food. The highest recommended dose is 10/320/25 mg.⁸ It is contraindicated in patients with severe renal failure (creatinine clearance <30 mL/min), severe liver failure, during the second and third trimesters of pregnancy, and in cases of refractory hypokalemia, hyponatremia, hypercalcemia and symptomatic hyperuricemia. Caution is recommended in patients with mild-moderate liver failure, heart failure and coronary disease and in elderly patients in whom the maximum dose of 10/320/25 mg is not recommendable. There are no data to support the indication of amlodipine/valsartan/HCTZ in pediatric patients.⁸ Finally, drug interactions have not been explicitly evaluated, although the interactions known for the individual components are attributed to the triple combination.⁸ Logically, the triple fixed-dose combination of amlodipine/valsartan/HCTZ may increase the hypotensive effects of other antihypertensive drugs the patient may be taking.⁸

Summary and conclusions

The prevalence of hypertension in Europe is approximately 20% to 30% in the third/fourth decade of life and increases to >70% in people aged ≥ 65 years.⁹ Most patients require pharmacological combinations to achieve BP control.⁹ The combination of three drugs with synergistic and complementary mechanisms of action is a reasonable option for the management and control of moderate to severe hypertension. This article has reviewed the current evidence on the antihypertensive efficacy and safety of the triple combination of amlodipine/valsartan/HCTZ at both low and maximum doses. The efficacy of the triple combination is superior to that of its components in monotherapy or in dual combination. The tolerability and safety are good with only mild to moderate adverse effects in most cases, whose frequency is similar or inferior to that of its components in monotherapy. The main benefit of this triple combination in one tablet is to improve treatment adherence and compliance in order to achieve the therapeutic

objective rapidly and efficiently.¹² It is proven that delaying BP control by strategies of staggered dose increases is a risk factor for cardiovascular events in comparison with the initial use of combinations.¹⁶

In conclusion, the availability of a combination of three antihypertensive drugs in a single tablet contributes additional advantages to dual combinations, allowing more rapid and effective BP control in patients with moderate-severe hypertension or high cardiovascular risk. This is undoubtedly the right path to increase treatment adherence, improve compliance and reduce the morbidity and mortality associated with inadequate BP control.

Disclosures

The authors disclose no conflicts of interest.

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