Hypertension currently affects more than 1 billion adults worldwide, and by 2025, the projected estimate is 1.5 billion.¹ In patients with hypertension, effective and long-term control of blood pressure (BP) to less than 140/90 mm Hg is expected to potentially reduce the incidence of heart failure by more than 50%, myocardial infarction (MI) by 25%, and stroke by nearly 40%.²⁻⁵ Several clinical trials show that only one-third of the patients achieve their target BP (<140/90 mm Hg, or <130/80 mm Hg if diabetes or chronic kidney disease is concomitantly present) on a single drug alone, and the remaining patients need combinations of more than 2, 3, and sometimes up to 5 drugs.⁶⁻⁹ The asymptomatic nature of hypertension, complex treatment regimens, adverse effects, unwillingness to intensify treatment (by either patient or physician), and poor compliance act as compounding factors that lead to failure of adequate BP control.¹⁰⁻¹¹ Therefore, the present hypertension management guidelines recommend an initial combination therapy with 2 or more antihypertensive agents especially for (1) stage 2 hypertension (>160 mm Hg systolic BP [SBP] and/or 100 mm Hg diastolic BP [DBP]) patients unresponsive to

The steady-state pharmacokinetic (PK) interaction potential between amlodipine (10 mg), valsartan (320 mg), and hydrochlorothiazide (HCTZ; 25 mg) was evaluated in patients with hypertension in a multicenter, multiple-dose, open-label, 4-cohort, parallel-group study. Eligible patients were randomly allocated to the dual combination of valsartan + HCTZ, amlodipine + valsartan, or amlodipine + HCTZ and nonrandomly allotted to amlodipine + valsartan + HCTZ triple combination treatment. After 6 days of treatment with a half-maximal dose of different combinations, patients were up-titrated to the maximal drug doses from day 7 through day 17. PK parameters of corresponding analytes from the triple- and dual-treatment groups were estimated on day 17 and compared. Safety and tolerability of all treatments was assessed. The Cmax and AUC0-τ values of amlodipine or HCTZ remained unaffected when administered with valsartan + HCTZ or valsartan + amlodipine, respectively. On the other hand, valsartan exposure increased by 10% to 25% when coadministered with HCTZ and amlodipine, which is not considered clinically relevant. In conclusion, there were no clinically relevant PK interactions with amlodipine, valsartan, and HCTZ triple combination compared with the corresponding dual combinations. All treatments were safe and well tolerated.

Keywords: Amlodipine; valsartan; hydrochlorothiazide; pharmacokinetics; drug: interaction; hypertensive patients

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monotherapy, (2) patients with baseline SBP/DBP ≥20/10 mm Hg above the target goal, and (3) hypertensive patients with additional cardiovascular risk factors.\textsuperscript{5,12,13} The overriding message of the American Heart Association council and the Seventh Report on the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7 report) is to achieve BP goals through aggressive treatment with multiple medications if required, and this directive is fast becoming a rule rather than an exception.\textsuperscript{5,12}

Therefore, combining drugs with distinct and complementary modes of action provides a rationale for development of fixed-dose combination therapy to treat patients with hypertension. The drugs that complement each other by targeting different pathophysiological mechanisms involved in hypertension lead to prompt and sustained reductions in BP with better tolerability. Calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors, and diuretics are contenders for such combination therapies, with strong clinical data supporting the validity of combining them.\textsuperscript{14-16} A judicious approach to hypertension management is a wider use of low-dose ARB/CCB combination early on in the treatment plan.\textsuperscript{17} Diuretics are a preferred first-step antihypertensive therapy for patients with uncomplicated hypertension.\textsuperscript{18} Thus, these 3 classes of drugs stand a valid chance of being prescribed together for the current treatment regimen for stage 2 hypertension or even earlier. However, physicians are wary to use combination therapy due to concerns that it may lead to overexposure to drugs and/or increased adverse events (AEs). Hence, ruling out pharmacokinetic (PK) interactions and establishing safety and tolerability of combination therapies becomes increasingly imperative.

Very few reported drug-interaction studies cater to the PK and safety profiling of more than 2 antihypertensives being prescribed together. Moreover, many clinical studies are conducted in healthy volunteers assuming similarities in PK, pharmacodynamics, and safety profiles between healthy volunteers and patients with hypertension. To avoid safety risks to healthy volunteers due to a potential significant drop in BP and to simulate potential clinical use of coadministration of amlodipine, valsartan, and hydrochlorothiazide (HCTZ), this study was conducted in patients with hypertension to evaluate their PK drug interactions after multiple-dose administration. The doses used in the current study (amlodipine 10 mg, valsartan 320 mg, and HCTZ 25 mg) represent the highest approved doses for amlodipine + valsartan and valsartan + HCTZ when used as double combinations or as monotherapies.\textsuperscript{19-21}

**METHODS**

**Study Design**

This was a multicenter, multiple-dose, open-label, 4-cohort, parallel-group study in patients with hypertension (Figure 1). The study employed a parallel study design as the subjects enrolled were hypertensive patients, and a washout between the treatments...
in the crossover design may have caused potential safety concerns. This multicenter study was conducted in India after obtaining approval from the Health Authority and respective ethics committees or institutional review board for each participating center and was carried out according to the ethical principles of the Declaration of Helsinki. All patients provided written informed consent before entering the trial and participated in a screening period (day –21 to day –2), a baseline period (day –1), a treatment period (day 1 to day 17), PK sampling (complete profile was on day 17 to day 18), and study completion (day 18).

Study Population

A total of 111 patients were enrolled in the study, of which 101 patients completed the trial and the data from 94 patients were used to assess PK interaction. Patients eligibility was assessed from background and demographic and laboratory assessments at screening and baseline, which included relevant medical history, current medical conditions, date of birth, sex, race, height, weight, routine clinical chemistry, hematology, urinalysis and serology (hepatitis B and C, HIV), and pregnancy status (females). Patients were also screened for drugs of abuse. In the study, male or female patients known to be hypertensive (SBP consistently greater than 140 mm Hg or DBP consistently greater than 90 mm Hg as per JNC-7), tensive (SBP consistently greater than 140 mm Hg or DBP consistently greater than 90 mm Hg as per JNC-7), patients with SBP >140 mm Hg at screening; patients taking 4 or more antihypertensive drugs at screening; patients with a history of secondary hypertension, diabetes mellitus, angina/MI, arrhythmias, autonomic dysfunction (eg, a history of fainting, orthostatic hypotension, sinus arrhythmia), or electrocardiogram (ECG) abnormalities; patients with a hypersensitivity to drugs (especially ARBs), thiazide diuretics, dihydropyridine calcium antagonists, or drugs with similar chemical structures; patients with atopic/respiratory allergies; patients with pancreatic, hepatic, or renal dysfunctions; patients with hyponatremia or hypokalemia; and patients with any surgical or medical conditions that might significantly alter the absorption, distribution, metabolism, or excretion of drugs.

Treatment Cohorts

Treatment cohorts and the dosing scheme are given in Figure 1. The 4 treatment cohorts were cohorts 1, valsartan + HCTZ; cohort 2, amlodipine + valsartan; cohort 3, amlodipine + HCTZ; and cohort 4, amlodipine + valsartan + HCTZ. Patients were assigned to cohort 1, 2, 3, or 4 based on the inclusion criteria. Patients in cohorts 1, 2, and 3 were randomized, whereas patients in cohort 4 were nonrandomized.

To qualify for cohorts 1, 2, and 3 (2-drug coadministration groups) patients were either (1) drug-naive, requiring 2-drug therapy as per JNC-7 criteria (stage 2), (2) stabilized on 2-drug therapy, or (3) those with uncontrolled BP on monodrug therapy. To qualify for cohort 4 (3-drug coadministration group), patients were either (1) those with uncontrolled BP (consistent SBP >140 mm Hg or DBP >90 mm Hg) on 2-drug therapy or (2) those with controlled BP on 3-drug therapy.

In each treatment cohort, from day 1 to day 6, patients received a starting dose (half-maximal study dose) of trial medication as per their assigned treatments, and the patient visited the center on an outpatient department basis. Patients were admitted to the respective clinics on the night of day 6 and remained domiciled until 48 hours postdose on day 7 (ie, until day 9). From day 7 to day 17, the doses were up-titrated to the maximum study dose of amlodipine (10 mg), valsartan (320 mg), and HCTZ (25 mg). From day 10 to day 16, the patients continued to visit the respective centers to take the study medication under supervision. On day 16, patients were again domiciled in their respective clinical centers until study completion (day 18). Patients enrolled in each cohort were dosed approximately at the same time in the morning for all treatment days, and the study medication was taken with approximately 240 mL of water after an overnight fasting.
Safety and Tolerability Assessments

As part of the safety and tolerability assessments, AEs, vitals, ECGs, and laboratory assessments were monitored. Chest X-ray was performed as part of the screening phase unless a 3-month-old X-ray was available at the time of screening. Body weight, temperature, and ECG were monitored at screening; baseline; days 3, 6, 10, and 16; and end of study (on day 18).

BP and pulse were assessed at screening, at baseline (day –1, day 6, day 16), predose all days, and at 2, 4, 12, and 24 hours postdose on days 7, 8, and 17. Hematology, blood chemistry, serology (screening), and urinalysis were performed at screening, baseline, days 6 and 16, and at the study end.

Blood Sampling

For PK assessments, 5 mL of venous blood was collected by either direct venipuncture or an indwelling cannula on days 6, 10, 15, 16, and 17 as predose (trough). A complete PK profiling was done on day 17, with samples collected at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose. Plasma was separated and stored below 20°C until analyzed.

Analytical Methods

Plasma concentrations (ng/mL) of amlodipine, valsartan, and HCTZ were determined simultaneously using a validated LC-MS-MS method with a limit of quantification of 0.025, 5.00, and 1.00 ng/mL, respectively, using 0.1 mL of human plasma. The assay consisted of solid-phase extraction on Oasis MCX, 10 mg solid extraction plates using an automated MultiPROBE II EX HT system followed by LC-MS/MS using ESI source, positive (amlodipine and valsartan) and negative (HCTZ) ion mode. The method consisted of an automated solid-phase extraction of human lithium heparinized plasma samples followed by evaporation of the extracts to dryness and analysis of the reconstituted sample by HPLC-MS/MS in selected reaction monitoring mode using TIS as an interface. The selected masses amlodipine, valsartan, and HCTZ were precursor ion m/z 409, product ion m/z 238; precursor ion m/z 436, product ion m/z 291; and precursor ion m/z 296, product ion m/z 269, respectively. The internal standards used for amlodipine, valsartan, and HCTZ were D₆-amlodipine besylate, D₆-valsartan, and D₆¹⁵N₂-HCTZ, respectively. The linearity was established between 0.025 and 10.0 ng/mL for amlodipine, 5.00 and 5000 ng/mL for valsartan, and 1.00 and 200 ng/mL for HCTZ. The method was suitable for simultaneous determination of amlodipine, valsartan, and HCTZ in human plasma with interday accuracy within the range of –4.8% to 1.2% and the precision within the range of 5.4% to 12.0% for amlodipine, interday accuracy within the range of –12.6% to 0.0%, and the precision within the range of 2.6% to 5.4% for valsartan, and interday accuracy within the range of –6.3% to 8.8% and the precision within the range of 2.6% to 6.3% for HCTZ. Any values that were not within the accuracy ranges were appropriately diluted as per the standard operating procedure, and corresponding factors were applied for reporting the concentration values for PK analysis.

PK Assessments

The following PK parameters were determined using noncompartmental method(s) using WinNonlin Pro (version 5.2): area under the plasma concentration-time profile during dosing interval (AUC₀₋ₜ), the maximum (peak) observed steady-state drug concentration (Cₚₛₘₐₓ), the minimum (trough) observed steady-state drug concentration (Cₚₛₘᵢₙ), the average steady-state drug concentration (Cₛₛₐᵥₑ₉), and the time to reach maximum (peak) concentration following drug administration at steady state (tₛₛₘₐₓ).

Statistical Analyses

Descriptive statistics of PK parameters were presented, which included mean, SD, coefficient of variation (CV), min, median, and max. Geometric means have been stated wherever presented. As tₛₛₘₐₓ was evaluated by a nonparametric method, the median values and ranges were reported. An analysis of variance (ANOVA) was performed on log-transformed AUC₀₋ₜ and Cₛₛₘₐₓ data using the PROC MIXED SAS procedure. The sources of variation for the ANOVA model were treated as fixed effect. As the number of concomitant hypertensive pretreatments and whether the patient was BP controlled or not determined the eligibility of the patient to be included in a particular treatment cohort, these 2 factors were included in the ANOVA model. Number of concomitant hypertensive pretreatments was nested within treatment. Using the ESTIMATE statement of the PROC MIXED SAS procedure, a contrast was constructed between the test and the reference treatments to obtain the P value, the estimated mean difference, and 90% confidence interval (CI) for the log scale test-reference difference. The antilogs of
the estimated mean difference and the 90% CI constitute the ratio of geometric means and the 90% CI for the true test: reference ratio. The following treatment contrasts were performed (test:reference) – amlodipine + valsartan + HCTZ (cohort 4): valsartan + HCTZ (cohort 1); amlodipine + valsartan + HCTZ (cohort 4): amlodipine + valsartan (cohort 2); and amlodipine + valsartan + HCTZ (cohort 4): amlodipine + HCTZ (cohort 3).

RESULTS

Patient Disposition and Demographics

A total of 111 patients were enrolled, and 101 patients completed all the requirements of the trial. Ten enrolled patients were discontinued from the study. Four of them were withdrawn because of AEs (2 AEs out of these were suspected to be study drug related), 3 patients were withdrawn as they were not able be up-titrated as per protocol (due to their BP being ≤110/70 mm Hg with the half-maximal dose), and 3 patients were dropped due to administrative reasons (1 withdrew consent and the other 2 were lost to follow-up). For the PK evaluation, 94 patients were assessed, as 7 patients were excluded due to noncompliance with the protocol (n = 6) and due to vomiting event before 2× median $t_{\text{a(max)}}$ (n = 1). Patient disposition is depicted in Figure 1, and patient demographics are summarized in Table I.

Pharmacokinetic Analyses

Effect of valsartan on amlodipine and HCTZ PK. The effect of valsartan on the exposure to amlodipine and HCTZ was determined by comparing the PK of respective analytes between patients treated with amlodipine + valsartan + HCTZ (test) and amlodipine + HCTZ (reference). Examination of predose levels on day 15, day 16, and day 17 suggested that steady state was reached with multiple dosing for amlodipine and HCTZ by day 15 and valsartan did not influence the predose drug levels at steady state. The plasma concentration-time profile of amlodipine and HCTZ on day 17 in the presence and absence of valsartan is presented in Figure 2, and the corresponding mean PK parameters
and the statistical analyses are summarized in Table II. Coadministration of valsartan with amlodipine and HCTZ increased $C_{\text{ssmax}}$ and $AUC_{0-\tau}$ of amlodipine by 10% and 9%, respectively, and decreased $C_{\text{ssmax}}$ of HCTZ by 17% and increased $AUC_{0-\tau}$ of HCTZ by 8%. The median $t_{\text{ssmax}}$ for both amlodipine and HCTZ was not altered in the presence of valsartan (Table II). The elimination profile for both amlodipine and HCTZ remained similar when administered with and without valsartan.

**Effect of HCTZ on amlodipine and valsartan PK.**

The effect of HCTZ on exposure to amlodipine and valsartan was determined by comparing the PK exposure to the respective analytes between patients treated with amlodipine + valsartan + HCTZ (test) and amlodipine + valsartan (reference). Examination of predose levels on day 15, day 16, and day 17 suggested that steady state was reached for both amlodipine and valsartan with multiple dosing by day 15 and HCTZ did not influence predose drug levels at steady state. The day 17 plasma concentration-time profile of amlodipine and valsartan in the presence and absence of HCTZ is presented in Figure 3, and the corresponding mean PK parameters and the statistical analyses are summarized in Table III. Coadministration of HCTZ with amlodipine and valsartan increased both $C_{\text{ssmax}}$ and $AUC_{0-\tau}$ of amlodipine by 10% and increased $C_{\text{ssmax}}$ and $AUC_{0-\tau}$ of valsartan by 22% and 25%, respectively. The median $t_{\text{ssmax}}$ for both amlodipine and valsartan was not altered in the presence of HCTZ (Table III). The elimination profile for both amlodipine and valsartan remained similar when administered with and without HCTZ.

**Effect of amlodipine on valsartan and HCTZ PK.**

The effect of amlodipine on exposure to valsartan and HCTZ was determined by comparing the PK exposure to the analytes between patients treated with amlodipine + valsartan + HCTZ (test) and valsartan + HCTZ (reference). Examination of predose
levels on day 15, day 16, and day 17 suggested that steady state was reached with multiple dosing for valsartan and HCTZ by day 15 and that amlodipine did not influence predose drug levels at steady state. The day 17 plasma concentration-time profile of valsartan and HCTZ in the presence and absence of amlodipine is presented in Figure 4, and the corresponding mean PK parameters and the statistical analyses are summarized in Table IV. Coadministration of amlodipine with valsartan and HCTZ increased \( C_{\text{ssmax}} \) and \( \text{AUC}_{0-\tau} \) of valsartan by 15% and 10%, respectively, and marginally increased \( C_{\text{ssmax}} \) and \( \text{AUC}_{0-\tau} \) of HCTZ by 2% and 3%, respectively. The median \( t_{\text{ssmax}} \) for both valsartan and HCTZ was not altered in the presence of amlodipine (Table IV). The elimination profile for both valsartan and HCTZ remained similar when administered with and without amlodipine.

### Safety and Tolerability

Administration of the dual combinations of valsartan + HCTZ, amlodipine + valsartan, amlodipine + HCTZ, and of the triple combination of amlodipine + valsartan + HCTZ was safe and well tolerated. Eighteen of 111 (16.22%) subjects reported a total of 30 AEs. Most AEs reported during the study were of mild-to-moderate intensity, transient in nature, and were not suspected to be drug related. Events determined by the investigator to be related to study treatment included hypokalemia (1.8%), increased blood glucose (0.9%), dizziness (0.9%), increased serum amylase (0.9%), increased lipase (0.9%), and atrial fibrillation (0.9%). One serious adverse event, atrial fibrillation, was reported for a patient treated in cohort 4, and according to the investigator, the serious AE was suspected to be related to trial medication.

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**Table III**  Effect of Hydrochlorothiazide on the Pharmacokinetics of Valsartan and Amlodipine

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Valsartan</th>
<th>Amlodipine</th>
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</thead>
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<tr>
<td></td>
<td>A+V+H</td>
<td>A+V</td>
</tr>
<tr>
<td>Subjects, n</td>
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<td>23</td>
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<td>( \text{AUC}_{0-\tau} ), ng·h/mL</td>
<td>82687 ± 43225</td>
<td>61652 ± 28718</td>
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<tr>
<td>( C_{\text{ssmax}} ), ng/mL</td>
<td>10777 ± 4145</td>
<td>8348 ± 3125</td>
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<tr>
<td>( T_{\text{ssmax}} ), h (^2)</td>
<td>3 (2-6)</td>
<td>3 (1-4.5)</td>
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<tr>
<td>( C_{\text{ssmin}} ), ng/mL</td>
<td>444 ± 356</td>
<td>336 ± 188</td>
</tr>
<tr>
<td>( C_{\text{ssavg}} ), ng/mL</td>
<td>3445 ± 1801</td>
<td>2569 ± 1197</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. A+V+H, amlodipine + valsartan + hydrochlorothiazide; A + V, amlodipine + valsartan. a. Median (range) was presented.

---

**Figure 4.** Effect of amlodipine (A) on plasma concentration-time profiles of (a) valsartan (V) and (b) hydrochlorothiazide (HTCZ, H). Data are presented as arithmetic mean (SD).
The patient was withdrawn from the trial and treated for atrial fibrillation. The patient completely recovered with no further episodes and was subsequently discharged. In total, there were 4 patients who discontinued the study drug due to AEs. These included 1 patient from cohort 1 (predose tachycardia and extra systoles not related to the study medication) and 3 patients from cohort 4 (preexisting impaired glucose tolerance, elevated amylase levels related to study medication, and atrial fibrillation as stated previously). There were no deaths in the study. No apparent differences in the AE profiles were observed among the 4 treatment cohorts.

DISCUSSION

Keeping in view the current therapeutic options of empirically adopting rational combinations of 2 or more drugs with different and complementary modes of action as the first-line treatment of hypertension, PK interactions have to be considered and assessed due to potential safety/tolerability concerns. As very few studies report probable PK interactions and associated safety and tolerability profiles of various antihypertensives given together,\textsuperscript{19,20,22,23} it becomes vital that these are established using the most desired combinations. The current study is aimed to determine steady-state drug interaction potential when amlodipine, valsartan, and HCTZ are combined to treat hypertension.

The study was not conducted in healthy volunteers, as treatment to steady-state with triple combination of amlodipine, valsartan, and HCTZ can cause a significant drop in BP. Furthermore, conducting a drug-drug interaction study in patients with hypertension reflects the intent-to-treat target patient population who have not been controlled well with the dual-combination treatment earlier and hence rendering the results more relevant to the clinical application. Earlier data indicate no PK interaction between valsartan and amlodipine or between valsartan and HCTZ.\textsuperscript{19,20} No PK interaction has yet been reported for the amlodipine and HCTZ combination, but none is anticipated based on their different metabolism and clearance pathways. Few studies that exist on the amlodipine and HCTZ combination report no increase in adverse drug events.\textsuperscript{24-26} In the current study, the influence of adding a third drug on the PK of double combinations of valsartan + HCTZ or amlodipine + valsartan or amlodipine + HCTZ was evaluated, making this study especially useful for the subset of patients who are nonresponsive to treatment with any of the dual combinations.

The study results indicate that valsartan did not influence predose drug levels at steady state for either amlodipine or HCTZ, and the rate of absorption ($t_{\text{ssmax}}$) of both was unaltered. The increase in exposure to amlodipine and HCTZ when coadministered was lower than the total variability estimated with PK exposure to amlodipine (21%-37%) and HCTZ (29%-44%); hence, these are not considered clinically relevant (Table II). The observed increase in amlodipine and valsartan exposure in the presence of HCTZ (Table III) is less than the estimated CV% for exposure of amlodipine (24%-25%) and valsartan (37%-52%). Hence, the observed increase in amlodipine and valsartan exposure is also not considered clinically relevant. Furthermore, amlodipine did not affect HCTZ exposure (Table IV). The observed increase in valsartan exposure in the

Table IV Effect of Amlodipine on the Pharmacokinetics of Valsartan and Hydrochlorothiazide

<table>
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<tr>
<th>PK Parameter</th>
<th>Valsartan</th>
<th>Hydrochlorothiazide</th>
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<td>Subject, n</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>AUC$_{0-\tau}$, ng·h/mL</td>
<td>82687 ± 43225</td>
<td>68188 ± 33241</td>
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<td>$C_{\text{ssmax}}$, ng/mL</td>
<td>10777 ± 4145</td>
<td>8677 ± 3255</td>
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<td>$T_{\text{ssmax}}$, h&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (2-6)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>$C_{\text{ssmin}}$, ng/mL</td>
<td>444 ± 356</td>
<td>26 ± 26</td>
</tr>
<tr>
<td>$C_{\text{ssavg}}$, ng/mL</td>
<td>3445 ± 1801</td>
<td>82 ± 36 (44%)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. A+V+H, amlodipine + valsartan + hydrochlorothiazide; V+H, valsartan + hydrochlorothiazide.

\(a\). Median (range) was presented.
presence of amlodipine is not considered clinically relevant as it is within the CV% estimated for valsartan exposure.

The lack of clinically significant PK interactions between these 3 antihypertensive drugs can be attributed to their different PK disposition and elimination pathways. Amlodipine is extensively (~90%) metabolized by liver enzymes to inactive metabolites that are eliminated via renal route.\(^{19}\) Valsartan is mainly excreted via biliary route, and hepatic metabolism is minimal with about 15% to 20% excreted as inactive metabolites and 75% to 80% excreted unchanged through feces.\(^{19,20}\) HCTZ is eliminated rapidly via the renal route, with at least 55% to 77% of the administered dose being eliminated unchanged within 24 hours.\(^{20}\) The lack of a clinically relevant PK interaction indicates that the combination of these 3 antihypertensive agents may not translate into decreased efficacy or increased drug-related adverse effects. Indeed, the triple combination of amlodipine, valsartan, and HCTZ resulted in improved BP control compared with any of the dual combinations in patients with moderate to severe hypertension and was well tolerated.\(^ {27}\)

The improved efficacy of the combination of amlodipine, valsartan, and HCTZ may be attributed to the complementary mode of action that potentiates efficacy by acting through different pathophysiological pathways and may also potentially offset each drug’s side effects.\(^{12,26,28}\) HCTZ, a diuretic, leads to volume depletion, electrolyte balance, and smooth muscle cell relaxation. However, the volume-depleting action activates the renin-angiotensin aldosterone system that is blocked by valsartan, an ARB. In turn, the ARB that spares potassium from being excreted renally can potentially reduce hypokalemia, a common side effect of the diuretic therapy.\(^ {16}\)

Conversely, hyperkalemia, a side effect observed with ARBs, can be reduced by diuretics. Furthermore, coadministration of amlodipine, a CCB, with an ARB and/or a diuretic has been observed to result in less CCB-induced edema.\(^ {2}\) Thus, the combination of amlodipine, valsartan, and HCTZ complements each individual drug by improving potency and reducing side effects.

Overall, administration of the dual combinations of valsartan + HCTZ, amlodipine + valsartan, and amlodipine + HCTZ and of the triple combination of amlodipine + valsartan + HCTZ was safe and well tolerated in patients with hypertension. Most of the observed AEs during the study were of mild-to-moderate intensity, and transient in nature, and not suspected to be drug related. No apparent differences in the AE profiles of the 4 treatment cohorts were observed.

**CONCLUSION**

No clinically relevant PK interaction between amlodipine, valsartan, and HCTZ was observed when coadministered. All treatments in this study were well tolerated and safe.

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