PHARMACOKINETICS OF DIFFERENT FORMULATIONS OF TELMISARTAN/AMLODIPINE FIXED-DOSE COMBINATION IN HYPERTENSIVE PATIENTS

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Abstract: *Introduction: Fixed-dose combinations represent options for treating hypertension. We investigated whether the fixed combinations of telmisartan/amlodipine followed dose-dependent kinetics. Additional factors were considered. Material and methods: This open-label, single-center, non-randomized clinical trial included adult hypertensive patients using fixed-dose combinations of telmisartan/amlodipine for at least 4 weeks. Non-compartmental pharmacokinetic analysis was employed to determine the parameters of telmisartan and amlodipine. To compare pharmacokinetics between different multiple-dosing regimens and assessing the impact of other factors upon the pharmacokinetics, ANOVA test was used. Results: Amlodipine displayed dose-proportional pharmacokinetics, reflected by approximately doubling the values for C_{max} and AUC in response to dosage doubling. For telmisartan, pharmacokinetics may not necessarily follow a linear pattern. Except for BMI, there were no statistically significant differences for amlodipine's and telmisartan's pharmacokinetic parameters between subgroups. Conclusions: Amlodipine presents linear pharmacokinetics; additional studies are needed before concluding which pharmacokinetics are attributed to telmisartan within the study dose range. BMI influences amlodipine and telmisartan pharmacokinetic parameters.*

INTRODUCTION

Blood pressure values are a great contributor to the individual's total cardiovascular risk and anti-hypertensive treatment strategies, including the use of drug combinations, are chosen depending on the individual cardiovascular risk factors.(1) Among the available anti-hypertensive strategies, the combination of telmisartan with amlodipine provided greater blood pressure lowering effect than either monotherapy.(2)

Telmisartan is a nonpeptide angiotensin II antagonist that blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT (1) receptors in many tissues, including the vascular smooth muscle. Amlodipine besylate is a long-acting dihydropyridine calcium channel blocker that exerts its effect by blocking the transmembrane influx of calcium ions into vascular smooth muscles favouring a peripheral arterial vasodilator activity, which causes a reduction in peripheral vascular resistance.(3)

The bioavailability after oral administration is 64%-90% for amlodipine and 42-58% for telmisartan, with reduced food effects on AUC and C_{max} for telmisartan and absent in the case of amlodipine. Protein binding is extensive for both molecules (93% for amlodipine and 99.5% for telmisartan). Hepatic metabolism to inactive metabolites for amlodipine is extensive and CYP3A4 mediated, being eliminated from plasma in a biphasic manner and having a terminal half-life of about 30 to 50 hours. Telmisartan is metabolized by glucuronidation and it exhibits biexponential decay kinetics with a terminal elimination half-life of approximately 24 hrours.(4) It does not undergo significant first-pass metabolism, and the majority (approximately 97%) is eliminated by biliary-fecal excretion as the parent compound.(5)

A series of factors like age, gender or disease state can influence drug pharmacokinetics and consequently, may lead to a variable drug response.(6) In practice, the antihypertensive effect can be influenced by the patient's clinical status, as renal or hepatic disease influence drug metabolism, transport and elimination, while comorbidities and their associated therapies, age and even body weight, can contribute to clinically significant drug interactions.(7,8,9)

PURPOSE

Therefore, the objective of the study was to investigate whether the pharmacokinetics of amlodipine and telmisartan was or was not linear and also, to analyze the influence exerted by factors like dose, demographic (gender, age) and clinical (body mass index – BMI), glomerular filtration rate (eGFR) characteristics of the study population upon the pharmacokinetic parameters of both drugs.

MATERIALS AND METHODS

The study was conducted in full conformity with the Declaration of Helsinki (1964) and its amendments (Tokyo 1975, Venice 1983, Hong Kong 1989) and Good Clinical Practice (GCP) rules. The clinical protocol was reviewed and approved by the Ethics Committee of the University of Medicine and Pharmacy of Tîrgu-Mureş, Romania and all volunteers gave their written informed consent prior to any study procedure.

Subjects:

Adult patients diagnosed with essential arterial hypertension, Caucasian males and females who were under

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treatment with a fixed dose combination of telmisartan and amlodipine for at least 4 weeks and with a good adherence to therapy (administered doses - at least 80 %), were included in the present study. They were considered eligible for inclusion irrespective of blood pressure status and whether they were using other therapies, including antihypertensive agents. The exclusion criteria included the following conditions: patients with suspected/known secondary arterial hypertension, congestive heart failure (New York Heart Association functional class III or IV), bilateral renal artery stenosis, clinically significant hepatic (liver transaminase elevations more than two times the upper limit of normal) or renal failure (serum creatinine > 2.3 mg/dl), biliary obstruction, hypo- and hyperkaliemia, clinically relevant cardiac arrhythmias (e.g., ventricular tachycardia, atrial fibrillation or atrial flutter), unstable or uncontrolled diabetes (HbA1C $\geq$ 10% within the 3 months prior to the study), patients with a history of drug or alcohol dependency within the 6 months prior to the study, a documented history of drug allergy or any medical history that can alter drug response, including blood pressure assessment, those receiving concomitant treatment with digoxin or other digitalis-like compounds, aliskiren or angiotensin-converting-enzyme (ACE) inhibitors, as well as patients enrolled in another study. Subjects were categorized according to the following parameters: the administered dosage of telmisartan and amlodipine fixed-dose combination and general characteristics like systolic and diastolic blood pressure, gender, age, BMI and renal function assessment (eGFR). All volunteers gave their written informed consent prior to any study procedure.

Study design:

The study was designed as an open-label, single-center, non-randomized clinical trial. All subjects received a fixed-dose combination individualized regimen of telmisartan and amlodipine (40/5 mg, 80/5 mg or 80/10 mg). The pharmaceutical product used was Twynsta® (tablets, producer Boehringer Ingelheim Pharma GmbH & Co. KG, Germany).

Venous blood was drawn into heparinized tubes before dosing and at the following times: 1, 2, 4, 6, 8, 10, 12, 24, 36, 48 and 72 hours after drug administration. The separated plasma was stored frozen (-20°C) until analysis.

Bioanalytical study:

Amlodipine and telmisartan plasma concentrations were determined by a validated liquid chromatography–mass spectrometry method. The HPLC system was an Agilent 1100 series (binary pump, autosampler, thermostat) (Agilent Technologies, Santa Clara, CA, USA) and was coupled with a Bruker Ion Trap SL (Bruker Daltonics GmbH, Bremen, Germany). A Zorbax SB-C18 chromatographic column (100x3.0 mm, 3.5µm) (Agilent Technologies) was used. The mobile phase consisted of 0.1% (V/V) formic acid in water and acetonitrile, and gradient elution was as follows: start with 37 % acetonitrile, at 1.1 min 37 % acetonitrile and 2.5 min 55 % acetonitrile. The flow rate was 1 mL/ min, and the thermostat temperature was set at 40°C. The mass spectrometry detection was in multiple reactions monitoring mode, positive ions, using an electrospray ionization source. The ion transitions monitored were m/z 238.2 and 294.2 from m/z 410.2 for amlodipine and m/z 497.4 from m/z 515.4 for telmisartan. With the purpose of extracting amlodipine and telmisartan from the human plasma, each sample preparation was submitted to the following procedure in an Eppendorf tube: 0.5 mL methanol was added to 0.2 mL plasma, after adding 01 mL valsartan solution – internal standard (methanolic solution, 25 ng/mL). Afterwards, the tube was vortexed for 10s, then centrifuged for 5 minutes at 12 000 rotations per minute (rpm).The supernatant was transferred to an autosampler vial, and 0.3 mL was injected into the chromatographic system.

The calibration curves were linear at a concentration range of 1-64 ng/mL plasma for amlodipine and 11.5-736 ng/mL for telmisartan.

Pharmacokinetic study:

The following pharmacokinetic (PK) parameters of amlodipine and telmisartan were analyzed by non-compartmental pharmacokinetic methods, following the same protocol: maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), observed area under the concentration-time curve (AUC_{0-t}, t=72 h), total area under the concentration-time curve ($AUC_{0-\infty}$, extrapolated to infinite time), elimination rate constant (k_{el}), plasma terminal half-life ($t_{1/2}$), peak trough fluctuation within dosing interval (%PTF), clearance (Cl), volume of distribution (Vd) and accumulation ratio (AR).

The maximum plasma concentration (C_{max}, ng/ml) and the time to reach the peak concentration (t_{max}, h) were obtained directly by visual inspection of each subject's plasma concentration-time profile. The area under the concentration-time curve (AUC_{0-t}) was estimated by integration using the trapezoidal rule from time zero to the last measurable concentration at time t. The area was extrapolated to infinity ($AUC_{0-\infty}$) by the addition of C_t/ k_{el} to AUC_{0-t} where C_t is the last quantifiable drug concentration and k_{el} is the elimination rate constant. The elimination rate constant k_{el} was estimated by the least-square regression of plasma concentration-time data points lying in the terminal region by using semi-logarithmic dependence that corresponds to first-order kinetics and the half-life ($t_{½}$) was calculated as $0.693/k_{el}$.

Statistical analysis:

Analysis of variance (ANOVA) was used to evaluate potential differences in PK parameters (log transformed) of amlodipine and telmisartan between different dosage regimens. One-way ANOVA was also employed to compare the pharmacokinetic parameters of amlodipine and telmisartan between different groups considering variables like gender, age, BMI and renal function in order to assess their influence upon the pharmacokinetic parameters of the aforementioned drugs. All statistical analysis was performed using Phoenix® WinNonlin 6.1 (Pharsight, Princeton, NJ 08540, USA) software. Differences were regarded as statistically significant for $p<0.05$.

RESULTS

Subjects:

The study population included 22 hypertensive patients that received different formulations of a fixed dose combination containing telmisartan and amlodipine (40/5 mg – 8 subjects, 80/5 mg – 6 subjects, 80/10 mg – 8 subjects). A summary of the general characteristics (demographic and clinical data) of the study patients is presented in table no. 1:

Table no. 1. Demographic and clinical data of study sample

Variables	Age category		Gender		BMI Assessment			Renal function	
	Adult	*Elderly*	*Male*	*Female*	*Normal*	*Overweight*	*Obese*	*Normal*	*Renal impairment*
No. of subjects	16*	6	6	16	4	6	12	13	9

Age category: adult <65 years (*majority: 50-60 years old); elderly ≥65 years old; Body mass index (BMI) assessment: normal - BMI<25 kg/m^2, overweight - 25 ≤BMI<30 kg/m^2, obese - BMI≥30 kg/m^2); Renal function: normal (eGFR>90

mL/min/1.73 m^2), renal impairment (eGFR<90 mL/min/1.73 m^2); eGFR = estimated glomerular filtration rate

Pharmacokinetic study;

The mean plasma concentration–time curve of telmisartan and amlodipine, corresponding to different doses of each drug included in the fixed dose drug combination are depicted in figure no. 1 (amlodipine, 5 mg vs 10 mg) and figure no. 2 (telmisartan, 40 mg vs 80 mg).

Figure no. 1. Mean (±SD) plasma concentrations of amlodipine, following oral administration in hypertensive patients of a fixed dose combination containing 5 mg or 10 mg amlodipine (left – linear scale (Cartesian) graph, right - semi-logarithmic presentation).

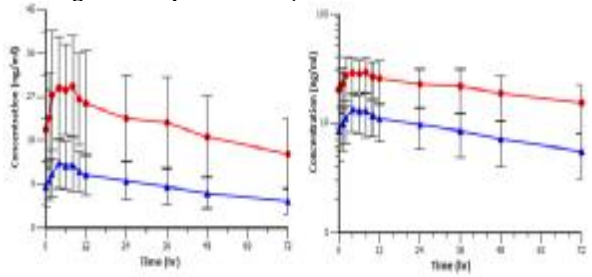
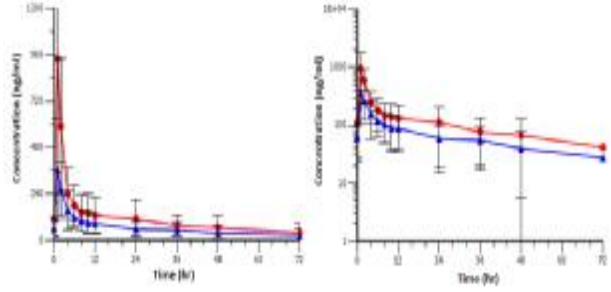


Figure no. 2. Mean (±SD) plasma concentrations of telmisartan, following oral administration in hypertensive patients of a fixed dose combination containing 40 mg or 80 mg telmisartan (left – linear scale (Cartesian) graph, right - semi-logarithmic presentation)



The variation of telmisartan and amlodipine mean pharmacokinetic parameters according to each dose given was presented in table no. 2 (amlodipine) and table no. 3 (telmisartan). The results of the statistical analysis employed in order to establish if statistical significant differences were present between the pharmacokinetic parameters of each drug, between the two different dosage regimens, were also included in the tables mentioned above.

Table no. 2. Pharmacokinetic parameters of amlodipine after administration of 10 mg-dose and 5 mg-dose (as a fixed dose combination with amlodipine) to hypertensive patients and the results of statistical analysis test

Pharmacokinetic parameters[a]	Amlodipine dosage regimen (mg)				
	5	CV (%)	10	CV (%)	p[b] value
C_{max} (ng/ml)	14.05 ± 5.21	37.06	31.92 ± 12.71	39.80	0.0001, S
t_{max} (hr)	5.71 ± 2.33	40.86	5.00 ± 1.85	37.03	0.5422, NS
AUC_{0-t} (hr*ng/ml)	622.10 ± 254.43	40.90	1529.20 ± 631.80	41.32	0.0001, S
$AUC_{0-\infty}$ (hr*ng/ml)	1160.40 ± 590.18	50.86	3203.20 ± 1599.43	49.93	0.0002, S
k_{el} (1/hr)	0.01 ± 0.00	35.94	0.01 ± 0.00	22.54	0.2235, NS
$t_{1/2}$ (hr)	63.85 ± 22.92	35.90	73.11 ± 14.83	20.29	0.2235, NS
Cl (L/hr)	21.61 ± 9.82	45.45	18.72 ± 7.69	41.06	0.4400, NS
Vd (L)	1983.00 ± 1233.97	62.23	1896.71 ± 666.72	35.15	0.8545, NS
%PTF	54.40 ± 19.87	36.52	45.92 ± 10.33	22.49	0.3915, NS
AR	4.36 ± 1.37	31.40	4.91 ± 0.89	18.05	0.2331, NS

[a]Data are presented as mean ± standard deviation; CV (%) – coefficient of variation

[b]p< 0.05 – statistically significant (S); NS – statistically non-significant

Table no. 3. Pharmacokinetic parameters of telmisartan after administration of 80 mg-dose and 40 mg-dose (as a fixed dose combination with amlodipine) to hypertensive patients and the results of statistical analysis test

Pharmacokinetic parameters[a]	Telmisartan dosage regimen (mg)				
	40	CV (%)	80	CV(%)	p[b] value
C_{max} (ng/ml)	402.98 ± 238.94	59.29	1002.62 ± 785.67	78.36	0.0278, S
t_{max} (hr)	1.50 ± 1.07	71.27	1.36 ± 0.84	62.03	0.7636, NS
AUC_{0-t} (hr*ng/ml)	4755.58 ± 2914.99	61.30	8144.10 ± 5708.88	70.10	0.1173, NS
$AUC_{0-\infty}$ (hr*ng/ml)	7444.28± 8607.45	115.62	10743.21± 8707.99	81.06	0.2053, NS
k_{el} (1/hr)	0.02 ± 0.01	36.36	0.02 ± 0.01	40.25	0.7999, NS
$t_{1/2}$ (hr)	37.12 ± 28.48	76.73	36.25 ± 15.04	41.49	0.7999, NS
Cl (L/hr)	17.95 ± 8.11	45.18	24.46 ± 18.68	76.39	0.4672, NS
Vd (L)	827.21 ± 377.37	45.62	1194.19 ± 821.02	68.75	0.4040, NS
%PTF	336.78 ± 208.22	61.83	445.97 ± 202.26	45.35	0.1423, NS
AR	2.78 ± 1.70	61.05	2.72 ± 0.89	32.57	0.8293, NS

[a]Data are presented as mean ± standard deviation; CV (%) – coefficient of variation

[b]p< 0.05 – statistically significant (S); NS – statistically non-significant

The pharmacokinetic evaluation also included the assessment of factors that may influence telmisartan and amlodipine pharmacokinetics like gender (male or female), age (adult or elderly), BMI (normal, overweight, obese) and renal function (normal or renal impairment).

There were no statistically significant differences regarding the pharmacokinetic parameters of telmisartan and amlodipine between genders (male vs. female) and different age categories (adult vs. elderly (p<0.05 for all pharmacokinetic parameters, data not shown).

The variation of telmisartan and amlodipine pharmacokinetic parameters within the study population, when considering factors like BMI and renal function, was presented in table no. 4 (BMI assessment) and table no. 5 (renal function). Also, those tables included the results of statistical analysis performed in order to investigate whether statistically significant

differences exist between the different groups that resulted after variable classification (table no. 1).

Table no. 4. Assessment of the impact of BMI upon amlodipine and telmisartan pharmacokinetics

Amlodipine				
Pharmacokinetic parameters[a]	**BMI assessment***			
	Normal	**Overweight**	**Obese**	**p[b] value**
C_{max} (ng/ml)	19.22 ± 6.89	12.78 ± 7.14	24.88 ± 13.87	0.0522, NS
t_{max} (hr)	5.50 ± 1.91	5.67 ± 2.94	5.33 ± 1.97	0.9745, NS
AUC_{0-t} (hr*ng/ml)	897.24 ± 308.69	539.69 ± 296.23	1176.38 ± 704.86	0.0405, S
$AUC_{0-\infty}$ (hr*ng/ml)	2003.28 ± 669.12	868.56 ± 461.37	2387.34 ± 1705.50	0.0226, S
k_{el} (1/hr)	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00	0.0358, S
$t_{1/2}$ (hr)	88.93 ± 18.98	53.53 ± 12.98	66.83 ± 18.77	0.0358, S
Cl (L/hr)	16.86 ± 4.15	25.98 ± 13.77	19.09 ± 6.43	0.3291, S
Vd (L)	2178.86 ± 770.84	2170.11 ± 1789.84	1766.64 ± 620.89	0.7274, NS
%PTF	44.03 ± 15.85	61.49 ± 19.62	48.67 ± 15.52	0.2017, NS
AR	5.86 ± 1.14	3.74 ± 0.77	4.54 ± 1.12	0.0317, S
Telmisartan				
Pharmacokinetic parameters[a]	**BMI assessment***			
	Normal	**Overweight**	**Obese**	**p[b] value**
C_{max} (ng/ml)	449.75 ± 179.20	611.01 ± 592.48	982.96 ± 814.75	0.2270, NS
t_{max} (hr)	1.75 ± 1.50	1.50 ± 1.22	1.25 ± 0.45	0.8127, NS
AUC_{0-t} (hr*ng/ml)	5885.43 ± 3576.79	3363.01 ± 1872.75	9028.52 ± 5658.16	0.0086, S
$AUC_{0-\infty}$ (hr*ng/ml)	10770.17 ± 11801.98	4132.52 ± 2607.22	11840.28 ± 8857.24	0.0307, S
k_{el} (1/hr)	0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.4616, NS
$t_{1/2}$ (hr)	49.73 ± 37.97	35.01 ± 11.44	32.96 ± 15.89	0.4616, NS
Cl (L/hr)	17.21 ± 9.60	37.67 ± 22.62	15.93 ± 5.82	0.0112, S
Vd (L)	960.10 ± 310.02	1722.53 ± 854.96	763.39 ± 502.09	0.0111, S
%PTF	345.20 ± 294.11	518.69 ± 276.59	370.40 ± 115.90	0.3292, NS
AR	3.53 ± 2.27	2.65 ± 0.68	2.53 ± 0.94	0.4651, NS

[a]Data are presented as mean ± standard deviation; CV (%) – coefficient of variation

[b]p< 0.05 – statistically significant (S); NS – statistically non-significant

*Body mass index (BMI) assessment: normal - BMI<25 kg/m^2, Overweight - 25 ≤BMI<30 kg/m^2, Obese - BMI≥30 kg/m^2)

Table no. 5. Assessment of the impact of renal dysfunction upon amlodipine and telmisartan pharmacokinetics

Amlodipine			
Pharmacokinetic parameters[a]	**Renal function***		
	Normal	**Renal impairment**	**p[b] value**
C_{max} (ng/ml)	20.91 ± 13.70	20.30 ± 11.57	0.0808, NS
t_{max} (hr)	4.67 ± 2.24	6.00 ± 2.00	0.3695, NS
AUC_{0-t} (hr*ng/ml)	920.62 ± 613.79	973.70 ± 632.26	0.0529, NS
$AUC_{0-\infty}$ (hr*ng/ml)	1780.84 ± 1331.63	1988.07 ± 1561.65	0.0524, NS
k_{el} (1/hr)	0.01 ± 0.00	0.01 ± 0.00	0.2874, NS
$t_{1/2}$ (hr)	64.28 ± 19.09	69.25 ± 21.91	0.2874, NS
Cl (L/hr)	19.17 ± 4.47	21.53 ± 11.26	0.4303, NS
Vd (L)	1732.84 ± 525.97	2103.10 ± 1291.07	0.9492, NS
%PTF	53.17 ± 17.17	50.04 ± 17.88	0.0537, NS
AR	4.39 ± 1.14	4.69 ± 1.31	0.3087, NS
Telmisartan			
Pharmacokinetic parameters[a]	**Renal function***		
	Normal	**Renal impairment**	**p[b] value**
C_{max} (ng/ml)	757.39 ± 556.57	803.39 ± 804.44	0.3598, NS
t_{max} (hr)	1.22 ± 0.44	1.54 ± 1.13	0.4325, NS
AUC_{0-t} (hr*ng/ml)	6631.56 ± 4460.39	7106.00 ± 5636.66	0.5315, NS
$AUC_{0-\infty}$ (hr*ng/ml)	8089.48 ± 5527.66	10550.30 ± 10340.67	0.6901, NS
k_{el} (1/hr)	0.03 ± 0.01	0.02 ± 0.01	0.3078, NS
$t_{1/2}$ (hr)	30.98 ± 14.54	40.44 ± 23.20	0.3078, NS
Cl (L/hr)	21.22 ± 13.47	22.70 ± 17.68	0.3616, NS
Vd (L)	939.78 ± 598.93	1144.48 ± 782.78	0.1194, NS
%PTF	401.46 ± 194.94	409.58 ± 222.04	0.4876, NS
AR	2.41 ± 0.86	2.97 ± 1.38	0.3580, NS

[a]Data are presented as mean ± standard deviation; CV (%) – coefficient of variation

[b]p< 0.05 – statistically significant (S); NS – statistically non-significant

*Renal function: normal (eGFR>90 mL/min/1.73 m^2), renal impairment (eGFR<90 mL/min/1.73 m^2); eGFR = glomerular filtration rate

DISCUSSIONS

Telmisartan/amlodipine is a dual antihypertensive single pill combination approved by the US Food and Drug Administration (FDA) in 2009 and by the European Medicines Agency (EMA) the following year.(5) According to clinical trial

data, the fixed dose combination of amlodipine and telmisartan is a safe and useful option in particular for the long-term treatment of moderate to severe hypertension, as complementary mechanisms of action potentiate the antihypertensive effect.(5,10) This combination may be a good therapeutic option especially for patients with diabetes and/or metabolic syndrome considering that these drugs do not worsen metabolic complications, which can be considered an important advantage.(5) By using the bioequivalence methodology, the effect of telmisartan and amlodipine coadministration on the other pharmacokinetic profile was reported to be equivalent to the individually administered compounds (90% confidence intervals: 80%–125%).(11) Another drug interaction (open-label, randomized, two-sequence, two-period crossover) study demonstrated that telmisartan 120 mg had no effect on the steady-state pharmacokinetics of amlodipine 10 mg.(12)

Considering the important place of this fixed dose combination for the hypertension treatment, the present study was conducted with the objective of investigating the pharmacokinetic profile of different formulations of this combination (40/5 mg, 80/5 mg, 80/10 mg). A secondary objective consisted of analyzing the influence of gender, age, BMI and renal function upon amlodipine and telmisartan pharmacokinetics.

The analysis of telmisartan and amlodipine mean plasma concentrations corresponding to different doses for each drug included in the drug combination (40 mg vs. 80 mg for telmisartan and 5 mg vs. 10 mg for amlodipine) revealed that doubling the dose of either telmisartan or amlodipine resulted in approximately double plasma levels, which was more noticeable for amlodipine than for telmisartan. More precisely, the linear pharmacokinetics was more evident for amlodipine, as proven by the C_{max} variation. By doubling the administered dose of amlodipine (5 mg to 10 mg), the same effect was reflected in C_{max}, which was also doubled (14.05 to 31.92 ng/ml). The small differences observed when comparing the pharmacokinetic parameters calculated for the 10 mg dose vs. the 5 mg dose can be attributed to the interindividual variability, which in the case of C_{max} was approximately 37% to 39%. Another pharmacokinetic parameter that supports the linearity of pharmacokinetics is AUC. For this parameter also, the values corresponding to the 10 mg dose were approximately double in comparison to the ones calculated for the 5mg dose (AUC_{0-t}: 622.10 vs. 1529.20 hr*ng/ml; $AUC_{0-\infty}$: 1160.40 vs. 3203.20 hr*ng/ml) and the variability associated was about 40% to 50%. The following pharmacokinetic parameters were dose-independent and presented similar values between the two subgroups (5 mg and 10 mg): $t_{1/2}$, k_{el}, Cl, Vd, %PTF and AR. Other studies have concluded that amlodipine shows linear dose-related pharmacokinetic characteristics.(13)

By comparing telmisartan pharmacokinetics corresponding to the two administered doses (40 mg and 80 mg), similar aspects to the previous amlodipine pharmacokinetic analysis can be observed. After doubling the dose, from 40 mg to 80 mg telmisartan, C_{max} and AUC values were also approximately doubled (C_{max}: 402.98 vs 1002.62 ng/ml; AUC_{0-t}: 4755.58 vs 8144.10 hr*ng/ml). However, the interindividual variability was much larger than the one recorded for amlodipine, with CV (%) values of up to 115% for $AUC_{0-\infty}$ in the 40mg dose subgroup. This variability can be explained by considering telmisartan elimination route, respectively biliary excretion. In this case, telmisartan dose eliminated via the biliary tract can be followed by reabsorption of the active compound (enterohepatic cycle), which can be considered an important factor in explaining the large variability observed for this drug.

The influence exerted by dose upon amlodipine and telmisartan pharmacokinetics was evaluated by using the ANOVA test. For amlodipine, statistically significant differences were determined for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. These results confirmed the remarks presented earlier concerning the linearity of amlodipine pharmacokinetics. As for the other pharmacokinetic parameters, the lack of significance was predictable taking into account the fact that parameters like $t_{1/2,}$ Cl, Vd, %PTF and AR are dose-independent, being considered “intrinsic” properties of the drug.

For telmisartan, the only pharmacokinetic parameter that was associated with statistically significant differences between the two dose-subgroups was C_{max} ($p< 0.05$). Unlike amlodipine, the AUC values of telmisartan were not statistically different, result that can be attributed to a reduced power analysis for ANOVA-test due to the large variability that characterized telmisartan pharmacokinetic parameters (of up to 115%). Therefore, after considering the statistical results, it is not clear whether telmisartan displayed a linear or non-linear pharmacokinetics. According to the literature, telmisartan showed a nonlinear pharmacokinetics over a dose range between 20 mg and 160 mg telmisartan.(14) Therefore, additional studies with a larger sample-size (80-100 patients) are needed in order to provide an adequate statistical power that would be sufficient for revealing any statistical significant differences between telmisartan pharmacokinetic parameters and to clearly show the effect exerted by dose on this drug pharmacokinetics.

Neither telmisartan pharmacokinetics, nor amlodipine pharmacokinetics was significantly different between different gender-groups ($p>0.05$ for all the calculated mean pharmacokinetic parameters). Similar results were obtained regarding the influence exerted by age upon the fixed dose combination of telmisartan and amlodipine. More precisely, there were no statistically significant differences between the telmisartan and amlodipine mean pharmacokinetic parameters compared between adults and elderly. Nonetheless, considering that a large proportion of the patients classified as adults were aged between 50 and 60 years, which represents an age close to the definition of elderly, the results interpretation must be made with precaution. Further investigation that presumes inclusion of adults aged between 25 and 55 years old is necessary to clearly establish if age could have a significant influence upon telmisartan and amlodipine pharmacokinetics.

Similar to the other factors investigated in the present study, the mean pharmacokinetic parameters of telmisartan and amlodipine were calculated for the three subgroups derived from the study population after BMI assessment (normal, overweight and obese) (table no. 4). As for amlodipine, the statistical analysis demonstrated that certain pharmacokinetic parameters like $t_{1/2,}$ $AUC_{0-\infty}$ and AR were significantly influenced by the BMI categories. For telmisartan, statistically significant differences between the three BMI groups were obtained for AUC_{0-t} and $AUC_{0-\infty,}$ Cl and Vd.

The last variable considered as potential influencing factor upon telmisartan and amlodipine pharmacokinetics was renal function. Whether or not renal impairment was present, the statistical analysis established that the pharmacokinetics of both investigated drugs was not influenced ($p>0.05$ for all the calculated mean pharmacokinetic parameters).

A review of the literature showed that had a modest impact upon amlodipine pharmacokinetics (15) and that there were no relevant gender-related differences in the pharmacokinetics of amlodipine.(16) Also, same as the present study, another research demonstrated that renal impairment had little effect on the pharmacokinetics of amlodipine, suggesting that dosage adjustment is not necessary in patients with renal

dysfunction.(17)

As for telmisartan, other studies revealed that female subjects generally had a two-to-three-fold higher plasma levels than male subjects, but no dose adjustment based on gender was considered necessary. Also, similar to the present investigation, the pharmacokinetics of telmisartan was not affected by age and decreased renal function as renal excretion does not contribute to the clearance of this drug.(18) Therefore, the majority of the results presented in this study were in accordance with the data mentioned in the literature.

Limits:

The small sample size included in the present study may be a potential limit because it can be a factor which reduces the statistical power of the study. Therefore, additional studies that include a larger study population are required in order to establish if the results obtained in the present study are complete or not.

CONCLUSIONS

The results demonstrated that amlodipine presented a linear pharmacokinetics within the studied dose range. In the case of telmisartan, the results suggested a potentially nonlinear pharmacokinetics, but a final conclusion cannot be reached without reducing the interindividual variability associated to the pharmacokinetic parameters and increasing the statistical power by including a larger sample-size population in additional studies.

The dose had a significant effect especially upon amlodipine pharmacokinetics, meanwhile demographic factors like gender and age had no influence on the pharmacokinetics of both drugs included in the fixed dose combination. As for the clinical variables, although eGFR value was not identified as an influencing factor, the BMI proved to be one. More specifically, there were statistically significant differences between some of the pharmacokinetic parameters of both telmisartan and amlodipine when compared between the BMI assessment subgroups (normal vs. overweight vs. obese).

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