International Journal of Pharmacology

ISSN 1811-7775

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Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2016.101.107

Research Article

Evaluation of the Possible Pharmacokinetic Interaction Between Amlodipine, Losartan and Hydrochlorothiazide in Mexican Healthy Volunteers

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Abstract

The fixed-dose combinations of drugs are alternatives for a major control of chronical diseases such hypertension. Amlodipine, losartan and hydrochlorothiazide are widely used as pharmacological treatment of this cardiovascular disorder. Since these drugs have different mechanism of action, it could be assumed that a fixed-dose combination containing them will provide therapeutic advantages and greater adherence to the treatment. However, firstly is necessary to verify a possible pharmacokinetic interaction between the components. In this study, the oral pharmacokinetics of amlodipine, losartan and hydrochlorothiazide in a fixed-dose combination formulation were evaluated and compared against the individual components in 26 healthy volunteers. After an overnight fast subjects received an oral dose of losartan (50 mg), hydrochlorothiazide (12.5 mg), amlodipine (5 mg) or the same doses in fixed-dose combination formulation in four periods according to a randomized crossover design. Blood samples were obtained at selected times for a period of 72 h. Plasma was obtained and stored frozen at -80°C until analyzed by ultra performance liquid chromatography coupled with tandem mass spectrometry. The treatments were well tolerated. No changes were observed in the pharmacokinetic parameters of amlodipine. For losartan and losartan acid the plasma levels were slightly higher whereas for hydrochlorothiazide greatly increase more than twice their plasma levels with fixed-dose combination formulation. These results suggest pharmacokinetic interactions between these compounds. Further studies are necessary in order to establish the mechanisms of these interactions, however, clinical relevance should be evaluated in clinical studies in patients in which this fixed-dose combination formulation could be a therapeutic alternative.

Key words: Amlodipine, losartan, hydrochlorothiazide, fixed-dose combination, pharmacokinetic interaction

Received: September 15, 2015 Accepted: December 22, 2015 Published: January 15, 2016

Citation: Noemí Santos-Caballero, Lina Marcela Barranco-Garduño, José Carlos Aguilar-Carrasco, Miriam del Carmen Carrasco-Portugal and Francisco Javier Flores-Murrieta, 2016. Evaluation of the Possible Pharmacokinetic Interaction Between Amlodipine, Losartan and Hydrochlorothiazide in Mexican Healthy Volunteers. Int. J. Pharmacol., 12: 101-107.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Raised blood pressure or hypertension is one of the most critical risk factors in the development and progressive cardiovascular disease (Weber *et al*., 2004; Yusuf *et al*., 2004; WHO., 2011). Hypertension is an haemodynamic disorder in which the blood pressure values are ≥140/90 mm Hg for systolic/dyastolic blood pressures and it is classified in different grades in function of the value measured (WHO., 2011; Stephan *et al*., 2015). This disorder leads to an increase in morbility and mortality of patients not adequately controlled (James *et al*., 2014). There are several classes of drugs designed to maintain blood pressure values lower. In order to arrive to this goal, it has been suggested to start with an antihypertensive drug, if the goal is not reached, addition of another antihypertensive drug is recommended and if the blood pressure is not controlled with the use of two antihypertensive drugs, three agents should be used (Amar *et al*., 2002; Mancia *et al*., 2004; James *et al*., 2014). Under these situation, in order to achieve a therapeutic synergism it has been recommended that agents producing their antihypertensive action through different mechanisms of action should be employed (Sever and Messerli, 2011; Wang *et al*., 2014). A rationale combination may include a calcium antagonist, an angiotensin II receptor antagonist and a diuretic (Waeber *et al*., 2009). That is why, a new fixed dose combination has been developed, including amlodipine (AML), losartan (LOS) and hydrochlorothiazide (HCTZ).

Amlodipine produces its vasodilatation effect through the inhibition of calcium channels on vascular smooth muscle cells. After an oral administration, its bioavailability is high due to a lower hepatic extraction ratio, the maximum plasma concentration (C_{max}) is reached between 6 and 12 h, it is extensively metabolized by the liver (90%) to inactive metabolites and it has a long elimination half-life (30-50 h) (Beresford *et al*., 1988; Haria and Wagstaff, 1995).

The LOS is an angiotensin II receptor antagonist (Wong *et al*., 1991). Angiotensin II is involved in blood pressure control, cardiovascular functions as well as sodium and water homeostasis (Meredith, 2005). Blocking the binding of angiotensin II to its receptor in the vascular smooth muscle avoid the vasoconstriction (Keating, 2009). After its oral administration the bioavailability of LOS is close to 33%, is metabolized to losartan carboxylic acid (LOS-A) through CYP2C9 and CYP3A4 enzymes, this metabolite possess major therapeutic activity than parent compound (Lo *et al*., 1995). The mean time to reach C_{max} of LOS and LOS-A are about 1 h and 3-4 h after its administration, respectively (Ohtawa *et al*., 1993; Lo *et al*., 1995; Stearns *et al*., 1995). The terminal half life of LOS and LOS-A are around 2 and 6 to 9 h, respectively (Ohtawa *et al*., 1993; Lo *et al*., 1995; Tamaki *et al*., 1997).

Hydrochlorothiazide (HCTZ) is a diuretic widely used in clinical practice since several years ago as individual or in FDC formulation for hypertension treatment (Wellington and Faulds, 2002). This drugs acts blocking the reabsorption of sodium in the renal tubules which contributes to increase the elimination of this electrolyte and turn favors the reduction of extracellular fluid volume and peripheral resistance (Meredith, 2005). After its oral administration, it has a bioavailability ranged from 60-70%. The time to achieve peak plasma concentration occur between 1.5-4 h after the administration. This drug is excreted unchanged in the urine and its elimination half life is around 8-10 h (Welling, 1986).

Since the mentioned drugs have different mechanism of action which can considered as complementary for the treatment of hypertension, the design of a FDC formulation is an attractive alternative for therapeutic purposes. However, before the therapeutic responses are evaluated, is necessary to verify if pharmacokinetic properties of each compound are not altered in the FDC formulation. The aim of this study was to evaluate the oral pharmacokinetics of AML, LOS and HCTZ in a FDC formulation and compared against the individual components in healthy volunteers.

MATERIAL AND METHODS

Study design: This was a randomized, open-label, single-dose, four-treatment, four-periods, four-sequences study. Healthy Mexican adults aged between 18 and 55 years of either sex, with a body mass index of 20-26 kg m^{-2} and with no congenital abnormalities or chronic diseases were elegible for inclusión. Volunteers gave written informed consent for participation in the study, according to the protocol approved by the Institutional Ethics Committee and following the recommendations of the declaration of Helsinki. Physical examination, clinical history and suitable laboratory tests were carried out for each subject. Subjects were excluded if they had a history of clinically significant medical conditions, alcohol abuse or ilegal drugs use, smoked more than 10 cigarettes per day, as well as if laboratory tests values were significantly out of reference range. Volunteers selected were randomized to receive either of the four sequences established.

After an overnight fast, subjects received, alternatively, an oral single dose of FDC formulation containing AML 5 mg, LOS 50 mg and HCTZ 12.5 mg or an oral single dose of each compound alone (plus placebo) in individual formulation at the same doses of FDC formulation given with 250 mL of water.

Heparinized blood samples (12 mL) were obtained immediately before and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 24, 48 and 72 h after drugs administration. The washout period between the treatments was two weeks. Plasma was obtained by centrifugation of blood samples and stored frozen at -80°C until analyzed for drugs concentrations by high-performance liquid chromatogry coupled to mass/mass spectrometry.

Determination of drugs in plasma: Plasma levels of AML, LOS, LOS-A and HCTZ were determined by high-performance liquid chromatography coupled to a mass/mass spectrophotometer. All validation tests were carried out according to the Mexican Official Norm (1998).

Amlodipine: Firstly, plasma samples were alkalinized. Amlodipine and internal standard (dexamethasone) were extracted by liquid-liquid extraction with a mixture of diethyl ether, hexane and dichlorometane. Organic layer was evaporated to dryness and dry residue was redissolved and injected into the chromatographic system. Separation of compounds was carried out in a Gemini 5 µm C18 column eluted with a mixture of acetonitrile, methanol and aqueous solution of ammonium acetate. The method was linear in the range of 0.1-20 ng mL^{-1} and intra and inter-day accuracy (measured as absolute deviation (%)) was lower than 4.81% and coefficient of variation were lower than 9.16%.

Losartan and losartan acid (metabolite): Plasma samples were acidified and drugs were extracted through a solid phase technique. Tolmetin was used as internal standard. Compounds were eluted with a mixture of methanol, acetonitrile and ammonium acetate and injected into the chromatographic system. Separation of compounds was carried out in a Polaris 5 µm C18 column eluted with a mixture of acetonitrile and methanol with an aqueous solution of ammonium acetate and formic acid. The method was linear in the ranges of 5-900 and 15-1500 ng mL^{-1} for LOS and LOS-A, respectively. The intra and inter-day accuracy (measured as absolute deviation (%)) for LOS was lower than 11.47% and coefficient of variation were lower than 6.82%, whereas for LOS-A were lower than 11.09% and coefficient of variation were lower than 5.94%, for intra and inter-day accuracy and coefficient of variation, respectively.

Hydrochlorothiazide: For the analysis of HCTZ, plasma samples were previously acidified and paracetamol was used as internal standard. Drugs were extracted through a liquid-liquid technique using a mixture of diethyl ether and dichlorometane. Organic layer was evaporated to dryness and dry residue was redissolved and injected into the chromatographic system. Separation of compounds was carried out in a Sielc Primesep D 100 Å column eluted with a mixture of acetonitrile and aqueous mixture solution of formic acid and ammonium acetate. Under these conditions, the method was linear in the range of 1-400 ng mL^{-1} and intra and inter-day accuracy (measured as absolute deviation (%)) was lower than 5.98% and coefficient of variation was lower than 6.85%.

Under these conditions, each analytical method was suitable for conducting pharmacokinetic studies of AML, LOS, LOS-A and HCTZ.

Pharmacokinetic and statistical analysis: Individual plasma-level time curves were constructed for each formulation. The maximal concentration (C_{max}) and time to reach this maximum (t_{max}) were directly obtained from these curves. Area under the plasma concentration against time curve until the last sampling time (AUC_t) was obtained by the trapezoidal rule (Rowland and Tozer, 1989). Area under the curve extrapolated to infinity (AUC_∞) was obtained by the sum of AUC_t plus extrapolation to infinity, obtained by dividing the last concentration by the terminal elimination rate constant (Ke). Half-life ($t_{1/2}$) was obtained by diving ln2/ke. All parameters were obtained using the WinNonlin Professional ver. 2.1 software (Pharsight, Palo Alto, CA and USA).

RESULTS

A total of twenty-eight Mexican healthy male and female were enrolled. Among them, two volunteers abandoned the study. The study was completed by twenty-six subjects weighing (Mean±S.D) 66.03±10.71 kg, 1.62±0.09 m in height and 35.48±9.52 years of age were included in the study. Treatments were well tolerated and no important adverse events were observed.

The mean (s.e.m.) drug plasma concentration-time profiles obtained after the oral administration of the formulations in study are shown in Fig. 1-4. Figure 1 shown similar pharmacokinetic profile of AML between both formulations. Plasma levels are kept very close both absorption and elimination phases. As Fig. 2 showed the profiles obtained for LOS. It can be seen that during absorption phase the plasma levels from both formulations reaches its C_{max} in similar manner. However, the profiles change during decay phase in which the plasma levels are

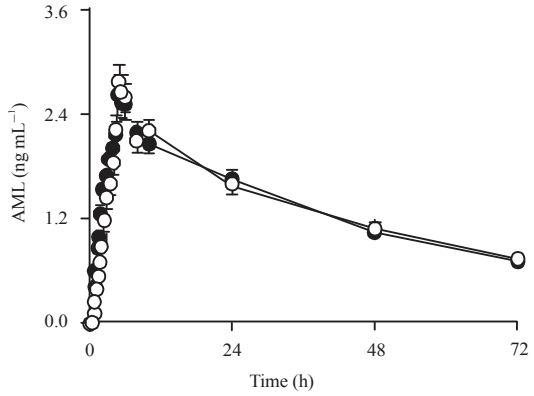

Fig. 1: Amlodipine (AML) plasma concentration against time curves after administration of an oral dose of 5 mg in two pharmaceutical formulations. Individual tablets of amlodipine 5 mg (black circles) and FDC formulation of amlodipine 5 mg, losartan 50 mg and hydrochlorothiazide 12.5 mg (white circles) to 26 healthy volunteers. Data are expressed as Mean±SEM

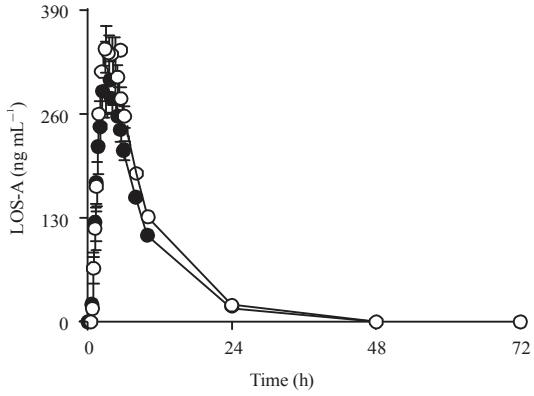

Fig. 3: Losartan acid (LOS-A) plasma concentration against time curves after administration of an oral dose of 50 mg of losartan in two pharmaceutical formulations. Individual capsules of losartan 50 mg (black circles) and FDC formulation of amlodipine 5 mg, losartan 50 mg and hydrochlorothiazide 12.5 mg (white circles) to 26 healthy volunteers. Data are expressed as Mean±SEM

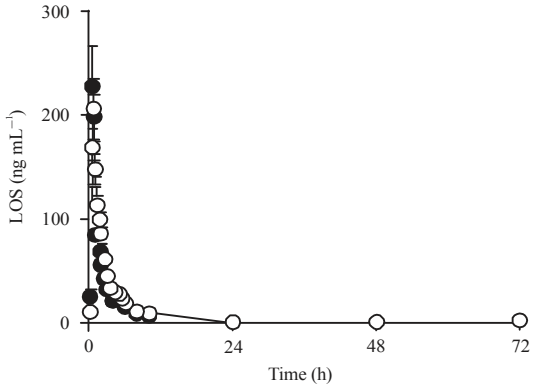

Fig. 2: Losartan (LOS) plasma concentration against time curves after administration of an oral dose of 50 mg in two pharmaceutical formulations. Individual capsules of losartan 50 mg (black circles) and FDC formulation of amlodipine 5 mg, losartan 50 mg and hydrochlorothiazide 12.5 mg (white circles) to 26 healthy volunteers. Data are expressed as Mean±SEM

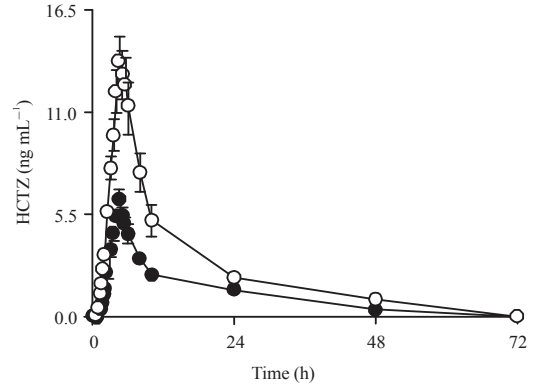

Fig. 4: Hydrochlorothiazide (HCTZ) plasma concentration against time curves after administration of an oral dose of 12.5 mg in two pharmaceutical formulations. Individual capsules of hydrochlorothiazide 12.5 mg (black circles) and FDC formulation of amlodipine 5 mg, losartan 50 mg and hydrochlorothiazide 12.5 mg (white circles) to 26 healthy volunteers. Data are expressed as Mean±SEM

slightly higher for FDC formulation. Similarly, LOS-A from the FDC formulation achieves higher concentrations than LOS alone formulation which are more evident at t_{max} and in the initial decay phase as shown in Fig. 3. Finally, the pharmacokinetic profiles of HCTZ are depicted in Fig. 4. In this case the co-administration of this compound with AML and LOS greatly increase more than twice their plasma levels. The mean pharmacokinetic parameters of each compound by formulation are shown in Table 1.

DISCUSSION

Hypertension monotherapy may become not sufficient for some patients, being required the coadministration of two or more drugs to achieve appropriate blood pressure control. However, patient adherence during polypharmacy or complex treatment regimens are major factors to detrimental therapeutic goal among patients with

Table 1: Pharmacokinetic parameters of amlodipine (AML), losartan (LOS), losartan acid (LOS-A) and hydrochlorothiazide (HCTZ) after the administration of an oral single dose of the formulations in study to 26 healthy volunteers

	AML		LOS		LOS-A		HCTZ	
Parameters	Alone	FDC	Alone	FDC	Alone	FDC	Alone	FDC
C_{max} (ng mL^{-1})	2.86 (0.15)	3.03 (0.17)	261.24 (35.59)	268.49 (31.93)	340.62 (28.23)	391.34 (28.49)	6.70 (0.56)	14.74 (1.37)
t_{max} (h)	5.50 (0.24)	7.25 (1.68)	0.72 (0.05)	0.96 (0.09)	3.67 (0.23)	3.70 (0.21)	4.52 (0.09)	4.56 (0.10)
AUC_{0-t} (ngh mL^{-1})	96.72 (5.43)	96.99 (5.58)	379.66 (32.33)	424.89 (33.09)	2408.88 (164.16)	3022.38 (182.78)	54.82 (5.76)	137.58 (19.12)
AUC_{∞} (ngh mL^{-1})	140.10 (7.92)	137.39 (8.87)	413.67 (37.83)	456.22 (37.43)	2742.97 (144.62)	3301.51 (169.25)	82.11 (8.80)	163.58 (19.43)
$t_{1/2}$ (h)	41.96 (1.72)	39.66 (1.53)	3.30 (0.82)	2.77 (0.47)	4.67 (0.32)	4.88 (0.18)	13.33 (1.83)	10.52 (0.82)

C_{max}: Maximum plasma concentration, t_{max}: Maximum time, AUC_{0-t}: Area under the plasma concentration, AUC_{∞}: Area under curve extrapolated to infinity, $t_{1/2}$: Half-life, AML: Amlodipine, LOS: Losartan, HCTZ: Hydrochlorothiazide, FDC: Fixed dose combination, Data are expressed as Mean±SEM

hypertension (Erdine, 2010; Bangalore and Ley, 2012). This can be solved by the use of once-daily dosing containing two or more compounds, that is, by using FDC formulation. The main advantages of this type of pharmaceutical alternatives are: Improving patient adherence by regimen simplification, to reduce pill burden, optimizing care and lower medical cost (Frantz, 2006; Erdine, 2010; Angeli *et al*., 2012; Bangalore and Ley, 2012). However, in order to obtain a formulation with adequate biopharmaceutical properties, features such as solubility, drug release, reactivity and stability between the components are needed to be considered during the design and development of this type of pharmaceutical formulation (Frantz, 2006). Additionally, another aspect to be considered previous to a new FDC become available is to establish if pharmacokinetic interaction between the components is present.

This study shows that the co-administration of AML, LOS and HCTZ in a new FDC formulation causes an increase in the bioavailabilities of HCTZ and lesser extent in LOS and its metabolite, whereas for AML it was not observed any modification. Since all formulations tested in this study were manufactured with the same excipients, a possible drug-formulation interaction can be ruled out. Rather, our results suggests a possible pharmacokinetic interaction that affect the systemic exposure to HCTZ and LOS. It has been established that pharmacokinetic drug-drug interaction refers to an alteration of the concentration of one drug caused by the presence of a second drug through effects on absorption, distribution, metabolism or excretion (Grasela *et al*., 1987; Fleisher *et al*., 1999).

As it observed, HCTZ, LOS and LOS-A AUC_t and AUC_{∞} values from FDC formulation were higher in comparison with those obtained for each compound alone. According with these results, in this study faced two scenarios: (i) AML or HCTZ influence on the oral parmacokinetics of LOS and (ii) AML or LOS influences on the oral pharmacokinetics of HCTZ.

Since there are not evidence about LOS or HCTZ induce or inhibit significantly the metabolism of other drugs, interaction at metabolic process due these agents is unlikely. In the case of AML, there are reports that indicate a competitive inhibition of the CYP3A4 metabolic activity (Son *et al*., 2014). Losartan (LOS) is partially metabolized by CYP3A4, if a competitive inhibition was carried out between AML and LOS, the LOS-A/LOS C_{max} and AUC_t ratios were minor for the FDC formulation in comparison with those obtained for LOS alone. In this study, they were slightly higher, which indicates that the increase in the C_{max} and AUC_t of LOS-A is a direct result due to the increase of LOS concentrations possibly related to the absorption process as reviewd below. Thus, AML does not affect the metabolic process of LOS. In the case of the greater bioavailability of HCTZ observed with FDC formulation, this can be explained by a different mechanism of metabolic process since HCTZ is excreted unchanged in the urine (Beermann and Groschinsky-Grind, 1977).

Other possible mechanism to consider in a drug-drug interaction occur during distribution pharmacokinetic process. It has been established that when a drug is displaced from its protein-binding sites, its concentration and its metabolic rate increase (Fan and de Lannoy, 2014). However, for this condition it is necessary that the coadministered drugs have higher affinity to plasma proteins. Amlodipine has a high degree of protein binding (98%) (Meredith and Elliot, 1992), whereas LOS and LOS-A are highly bound to plasmatic protein (98.8 and 99.7%, respectively), additionally, *in vitro* studies showed neither LOS or LOS-A were displaced by pharmacologically concentrations of drugs with high degree of protein binding such as non-steroidal anti-inflammatory drugs, warfarin or diazepam, thus, displacement of LOS from binding sites are unlikely (Christ, 1995). Hydrochlorothiazide has lower extent of protein binding (40-68%) (Beermann and Groschinsky-Grind, 1977), therefore, a mechanism of this type can not be ruled out since AML and LOS have high affinity to protein binding and they could displace HCTZ. However, there are previous reports were FDC formulations containing LOS and HCTZ were evaluated for safety and efficacy and were well-tolerated (McCrea *et al*., 1995; Keating, 2009) and no evidence of pharmacokinetic drug interaction was observed (McCrea *et al*., 1995). Thereby, the presence of

AML appears to play an important role in our results. However, further evaluation is thus warranted.

Regarding a possible interaction at absorption site, it has been recognized that the presence of transporters at the apical surface of small intestinal play significant roles in determining the drug bioavailability, therefore, it is necessary to consider for drug-drug interaction (You and Morris, 2007). There is evidence that calcium channel antagonists are modulators to a variable degree of P-glycoprotein efflux transporter (Sharom, 2007). In fact, it has been reported the potential of AML to inhibit the efflux activity of this transporter (Katoh *et al*., 2000; Zhou *et al*., 2013). This inhibitory activity could help to explain the increase in the bioavailabilities of LOS and HCTZ since there are evidence suggesting LOS and HCTZ are substrates of this transporter (Hayeshi *et al*., 2006; Choi *et al*., 2010, 2013; Liao *et al*., 2010; Yang *et al*., 2011). In this study the dose of AML in FDC formulation is low, according with this, is possible that the impact on the oral bioavailability of LOS is modest but significant. In the case of HCTZ the differences between the bioavailabilites are much greater, a combination of pharmacokinetic interaction at different sites could explain such differences. Moreover, it has reported the HCTZ absorption is greater at pH 6 than pH 7.4 (Liao *et al*., 2010), thus a possible alteration of physiological pH by the presence of AML and/or LOS could be not ruled out.

CONCLUSION

In conclusion, this study shows that the coadministration of AML, LOS and HCTZ in a new FDC formulation or the administration of each drug alone to healthy Mexican volunteers were well-tolerated. However, it was observed an increase in the systemic exposure to LOS and LOS-A as well as to HCTZ after the administration of FDC formulation. Further studies are necessary in order to establish the mechanisms of these pharmacokinetic drug-drug interactions.

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