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Oral Pharmacokinetics of Felodipine in Mexican Healthy Volunteers: Evidence for Interethnic Differences

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ABSTRACT

Felodipine is an inhibitor of the calcium entry channels which is indicated for hypertension and chest angina disorders. The oxidative biotransformation of felodipine is mediated primarily by CYP3A4. Interethnic differences in the pharmacokinetics of drugs metabolized by CYP3A4 have been reported, being Mexicans a population endowed reduced metabolism by this pathway. Due to the relevance of this enzyme in our population and the fact that until our knowledge no pharmacokinetic data of felodipine in Mexican population is available, the purpose of this study was to evaluate the oral pharmacokinetics of felodipine in Mexican healthy subjects and compare with those reported in Caucasians subjects. Thirty volunteers received an oral dose of 5 mg of felodipine after a fasting period of 10 h. Plasma levels were determined by a high performance liquid chromatography method coupled to tandem mass spectrometry. Pharmacokinetic parameters were obtained by non-compartmental techniques. The results obtained (Mean±SEM) were: maximal concentration (C_{max}) 4.63 ± 0.40 nmol L⁻¹, time to reach this concentration (t_{max}) 3.63 ± 0.28 h, area under the plasma concentration against time curve (AUC) 59.53 ± 6.44 nmol h L⁻¹ and half-life ($t_{1/2}$) 16.62 ± 1.25 h. The results obtained were compared with those values reported in other populations under similar conditions. The bioavailability of felodipine observed in this study was higher than that reported for Caucasians. Since felodipine is eliminated primarily by CYP3A4 metabolism, our data provide an additional evidence of reduced activity of this enzymatic pathway in Mexican population.

Key words: Felodipine, CYP3A4, pharmacokinetics, Mexican population

INTRODUCTION

Felodipine, a dihydropyridine class drug is an inhibitor of the calcium entry channels which is indicated for hypertension and chest angina disorders (Todd and Faulds, 1992). Since several years, the extended-release formulation is used in clinical practice due it allows the once-daily administration (Carruthers and Vint-Reed, 1993; Hsiao *et al.*, 2011). After an

oral administration, felodipine is well absorbed from gastrointestinal tract, however, this compound undergoes an extensively first-pass metabolism resulting in low oral bioavailability (16%) (Edgar *et al.*, 1985). Oxidative biotransformation of felodipine is mediated primarily by CYP3A4, a coenzyme of CYP450 system (Guengerich *et al.*, 1991). Several reports have evidenced the influence of CYP3A4 in the metabolism of felodipine by

using inhibitors of this enzyme (Bailey *et al.*, 1996; Lundahl *et al.*, 1997).

Additionally to felodipine, CYP3A4 plays a relevant role in the metabolism of several drugs. This enzyme metabolizes a major part of drugs that are used in clinical practice (Li *et al.*, 1995). It is largely expressed in the liver and duodenal wall, which can contribute to the first pass-effect of drugs, as well as, the inter-individual variation with major impact when drugs are administered by oral route (Dorne, 2004). For felodipine, it has been estimated that 80% is extracted from blood passing through the liver (Todd and Faulds, 1992). In that sense, it is well established that the ability of organs in the body to clear a drug is directly proportional to the activity of the metabolic enzymes in the organs (Fan and de Lannoy, 2014). An important factor that determines the drug metabolism and therefore the interindividual variability, is the genetic characteristics of individuals. The main consequence of this is the modification of drug disposition and possible unexpected side effects at theoretical therapeutic doses. Previously, our group reported interethnic differences in the pharmacokinetics of several drugs metabolized by CYP3A4. An increased bioavailability for nifedipine, midazolam, cyclosporine, sildenafil and meloxicam in Mexican healthy subjects in comparison with those results obtained in Caucasian populations under similar conditions have been reported (Castañeda-Hernández *et al.*, 1996; Palma-Aguirre *et al.*, 1997; Chávez-Teyez *et al.*, 1999; Flores-Murrieta *et al.*, 2000; Carrasco-Portugal *et al.*, 2005). Due to the relevance of this enzyme in our population and the fact that until our knowledge no pharmacokinetic data of felodipine in Mexican population is available, the objectives of this study were to evaluate its oral pharmacokinetics after an oral single dose in healthy Mexican volunteers and to compare the pharmacokinetic results obtained in this study with those reported in other populations.

MATERIALS AND METHODS

Subjects: A total of thirty (16 men, 14 women) young Mexican healthy volunteers of 26.27 ± 1.35 years of age (Mean \pm SEM), 165.67 ± 1.24 cm in height and weighing 64.04 ± 1.19 kg, participated in this study. All subjects were fit according to a medical history, clinical examination and suitable laboratory tests. The volunteers gave written informed consent for participation in the study, according to the protocol approved by the Institutional Ethics Committee. After an overnight fast, an indwelling cannula was inserted in a suitable forearm vein. Then, subjects received an oral dose of 5 mg of felodipine extended-release (Plendil®) with 250 mL of water. Heparinized blood samples (10 mL) were obtained 30 min before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48 h after drug administration. Plasma was obtained by centrifugation of blood samples and stored frozen at -70°C until analyzed for felodipine concentrations determination.

Determination of felodipine in plasma: Felodipine plasma levels were determined by a high performance liquid

chromatographic method coupled to tandem mass spectrometry. Briefly, 1 mL of plasma samples were placed in conical tubes and added with 2.5 ng of nimodipine as internal standard, 100 μL of 0.1 M sodium hydroxide and 2 mL of acetonitrile. Then, mixture was agitated in a vortex mixer at maximal speed for 1 min and centrifuged at 2500 rpm for 10 min. Upper layer was transferred to another tube and evaporated to dryness at 60°C under nitrogen stream. Dry residue was dissolved in 150 mL of mobile phase (see under). Aliquots (10 μL) of the reconstituted extract were injected into the chromatographic system, which was formed by an Acquity ultra performance liquid chromatograph (Waters, Assoc, Milford, MA, USA) coupled to an API-3200 mass/mass spectrometer (Applied Biosystems, Inc.). Separations of compounds was carried out using a Waters Acquity UPLC BEH C18, 50 mm length \times 2.1 mm i.d. of 1.7 μm particle size column eluted with a mixture of ammonium acetate 1 mM and acetonitrile (30:70 v/v, respectively) as mobile phase, at a flow rate of 0.2 mL min^{-1} . The detection of felodipine and internal standard was made by mass spectrometry with an ESI source and then quantified by multiple reaction monitoring. The precursor-product ion combinations of m/z were 384.0/338.0 and 419.1/343.0, for felodipine and internal standard, respectively. No interferences were observed at the retention times of felodipine and the internal standard. The method was linear in the range of 0.13-26.04 nmol L^{-1} , with intra and inter-day accuracy between 98.00 and 103.67%, whereas the coefficient of variation was lower than 9%. All tests were carried out in accordance to the Mexican Official Norm (1998).

Pharmacokinetic analysis: Individual plasma-level time curves were constructed and maximal concentration (C_{max}) and time to reach this maximum (t_{max}) were directly obtained from these curves. The area under the plasma concentration versus time curve (AUC_{0-t}) was obtained by the trapezoidal rule up to the last measurable time (Rowland and Tozer, 1989). Extrapolation to infinite (AUC_{∞}) was determined by dividing the last concentration by the elimination rate constant. The elimination half-life ($t_{1/2}$) was obtained by log-linear regression of the terminal decay phase. All pharmacokinetic analysis was carried out using WinNonlin Professional software ver. 2.1 (Pharsight, Palo Alto, CA, USA).

Pharmacokinetic parameters obtained in this study were compared with those reported by other authors. No formal statistical analysis was carried out. Data obtained in other populations is given for informative purposes.

RESULTS

Felodipine oral pharmacokinetics was characterized in Mexicans. All the subjects enrolled completed the study and no important adverse events were observed. After administration of the drug, plasma levels increased reaching a maximum in about 2.5-3 h. Then, plasma levels decayed with a half-life of about 17 h (Fig. 1). Pharmacokinetic parameters obtained by non-compartmental analysis are shown in Table 1. In order to explore possible differences between

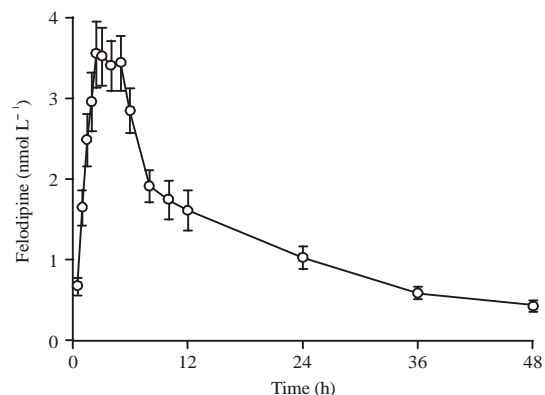


Fig. 1: Plasma concentrations against time curve of felodipine after the administration of a single oral dose of felodipine (5 mg) extended-release tablet in healthy Mexican volunteers, values are Mean±SEM

Table 1: Pharmacokinetic parameters of felodipine obtained after an oral administration of extended-release oral formulation (5 mg) in Mexican healthy volunteers.

Parameter	Obtained value
C_{max} (nmol L ⁻¹)	4.63±0.40 (1.40-9.24)
t_{max} (h)	3.63±0.28 (1.5-6.0)
AUC_{0-1} (nmol•h L ⁻¹)	59.53±6.44 (21.24-159.04)
AUC_{∞} (nmol•h L ⁻¹)	69.85±7.83 (23.60-206.18)
$t_{1/2}$ (h)	16.62±1.25 (8.25-34.47)

Data is expressed as Mean of thirty subjects±SEM (Minimum-maximum values)

populations, AUC normalized by the administered dose AUC/D was calculated and compared with those reported in other populations. Figure 2 shows such AUC/D observed in several populations (Canadians, Swedishes, Danishes, Turkishes and Mexicanes). Although no statistical analysis was conducted, since data was taken from other reports, it can be seen that Mexicans reached higher AUC/D, indicating an increased bioavailability than the observed in other populations.

DISCUSSION

In this study, the pharmacokinetics of felodipine after the administration of a single oral dose of 5 mg extended-release formulation was evaluated. Since previous reports have evidenced increased plasma levels of some drugs metabolized by CYP3A4 in Mexicans (Castañeda-Hernández *et al.*, 1996; Palma-Aguirre *et al.*, 1997; Chávez-Teyez *et al.*, 1999; Flores-Murrieta *et al.*, 2000; Carrasco-Portugal *et al.*, 2005), such behavior could be expected for other drugs with the same biotransformation route as felodipine. In that sense, the results obtained in this study were compared with those previously reported for felodipine in other populations in order to establish if our results are similar.

Felodipine, a dihydropyridine calcium antagonist drug, is extensively metabolized by CYP3A4 enzymes, causing a presystemic elimination and low bioavailability (Edgar *et al.*, 1985). It is well established that CYP3A4 is expressed at intestinal and hepatic tissues. In the case of

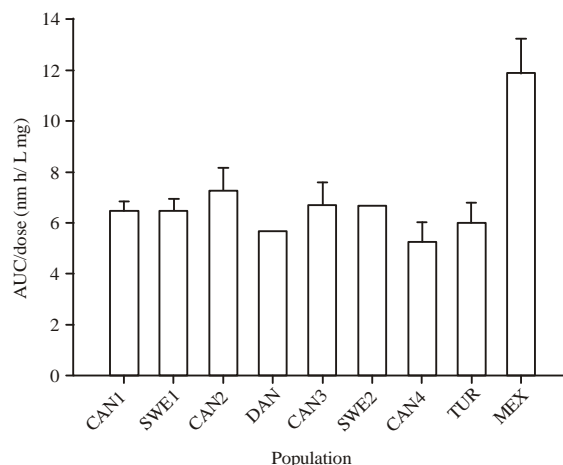


Fig. 2: Comparative oral bioavailability reported for different populations expressed as the AUC and normalized in function of dose administered. Data are expressed as Mean±SEM when provided. CAN1: Canadian subjects from the study by Hardy *et al.* (1988), SWE1: Swedish subjects from the study by Hasselgren *et al.* (1990), CAN2: Canadian subjects from the study by Bailey *et al.* (1995), DAN: Danish subjects from the study by Madsen *et al.* (1996), CAN3: Canadian subjects from the study by Bailey *et al.* (1996), SWE2: Swedish subjects from the study by Lundahl *et al.* (1997), CAN4: Canadian subjects from the study by Bailey *et al.* (1998), TUR: Turkish subjects from the study by Gelal *et al.* (2005), MEX: Mexican subjects from this study

felodipine, initially it was suggested that the major site for presystemic elimination was the liver and alternatively the intestinal metabolism contributes partially in this process (Edgar *et al.*, 1985; Regardh *et al.*, 1989). However, additional studies have demonstrated that intestinal CYP3A4 plays a major role on first-pass effect of felodipine (Lown *et al.*, 1997; Wilkinson, 2005). In that sense, assuming a diminished activity of CYP3A4 in Mexican subjects, it was expected to observe an increase in the bioavailability parameters of felodipine in our population when compared with the values reported in other populations. As it was observed, only the AUC values were considerably higher in Mexicans when compared with European and Canadian subjects. The C_{max} values obtained had a minor magnitude in differences. In this regard, it is probable that interethnic differences in the metabolism of felodipine are mainly due to a slow hepatic drug elimination.

It has been established that variability in drug metabolism is clearly associated with interindividual and interethnic variation in pharmacokinetics (Kim *et al.*, 2004). Although felodipine is widely used in therapeutics, information on the pharmacokinetics of this drug in different population is scarce. The studies selected for comparison were conducted with a single oral administration; subjects receiving 5 or 10 mg of felodipine extended-release formulation. Our results exhibited

higher AUC values than Caucasian individuals. However, this is not the first report that evidenced a lower CYP3A4 activity to metabolize felodipine. Hsiao *et al.* (2011) studied the pharmacokinetics of felodipine in healthy male Taiwanese subjects after the administration of felodipine extended-release tablets at doses of 5 mg once daily for six days. They compared the results obtained with respect the values of Canadian, Swedish, Danish, German and Turkish subjects in studies under comparable conditions and similar design. Similarly to our results, an increase in bioavailability of felodipine was observed for Taiwanese subjects. Moreover, felodipine was well tolerated and no serious adverse events were observed.

Interestingly, a similar activity of CYP3A4 in the metabolism of drugs was detected previously between Mexicans and Taiwanese subjects. This was reported for nifedipine (Chien *et al.*, 2004), another dihydropyridine calcium antagonist drug. Moreover, the fact that adverse events related to the vasodilator activity of felodipine were not present during our study, as well as Taiwanese subjects study, could be due to the extended-release formulation properties (Todd and Faulds, 1992), since baroreceptors are more sensitive to speed of reduction in blood pressure than the total effect of the drug.

CONCLUSION

In summary, the present study is the first to report an increased bioavailability of felodipine after the oral administration of a single standard dose of this drug in Mexican subjects. Our findings suggest that the higher levels of felodipine may be due to a slow drug elimination. Since some evidence exists for reduced CYP3A4 activity in Mexican population, our results provide an additional evidence of this phenomenon. Moreover we found a similar behavior to with Taiwanese subjects as was previously observed for nifedipine. Further studies are necessary in order to evaluate different factors that may influence the interethnic differences in the oral pharmacokinetics of felodipine.

REFERENCES

- Bailey, D.G., J.M.O. Arnold, J.R. Bend, L.T. Tran and J.D. Spence, 1995. Grapefruit juice-felodipine interaction: Reproducibility and characterization with the extended release drug formulation. *Br. J. Clin. Pharmacol.*, 40: 135-140.
- Bailey, D.G., J.R. Bend, J.M.O. Arnold, L.T. Tran and J.D. Spence, 1996. Erythromycin-felodipine interaction: Magnitude, mechanism and comparison with grapefruit juice. *Clin. Pharmacol. Ther.*, 60: 25-33.
- Bailey, D.G., J.H. Kreeft, C. Munoz, D.J. Freeman and J.R. Bend, 1998. Grapefruit juice-felodipine interaction: Effect of naringin and 6',7'-dihydroxybergamottin in humans. *Clin. Pharmacol. Ther.*, 64: 248-256.
- Carrasco-Portugal, M.D.C., J.C. Aguilar-Carrasco, M. Lujan, G. Reyes-Garcia, R. Medina-Santillan and F.J. Flores-Murrieta, 2005. Further evidence for interethnic differences in the oral pharmacokinetics of meloxicam. *Clin. Drug Invest.*, 25: 307-313.
- Carruthers, S.G. and C. Vint-Reed, 1993. Antihypertensive effect and tolerability of felodipine Extended Release (ER) tablets in comparison with felodipine Plain Tablets (PT) and placebo in hypertensives on a diuretic. Canadian study group. *Clin. Invest. Med.*, 16: 386-394.
- Castañeda-Hernández, G., J.A. Palma-Aguirre, M.A. Montoya-Cabrera and F.J. Flores-Murrieta, 1996. Interethnic variability in nifedipine disposition: Reduced systemic plasma clearance in Mexican subjects. *Br. J. Clin. Pharmacol.*, 41: 433-434.
- Chávez-Teyes, L., G. Castaneda-Hernandez and F.J. Flores-Murrieta, 1999. Pharmacokinetics of midazolam in Mexicans evidence for interethnic variability. *Clin. Drug Invest.*, 17: 233-239.
- Chien, S.C., Y.S. Uang, H.Y. Lin and K.Y. Hsu, 2004. Pharmacokinetics of nifedipine in Taiwanese. *Biopharmaceut. Drug Dispos.*, 25: 77-84.
- Dorne, J.L.C.M., 2004. Impact of inter-individual differences in drug metabolism and pharmacokinetics on safety evaluation. *Fundam. Clin. Pharmacol.*, 18: 609-620.
- Edgar, B., C.G. Regardh, G. Johnsson, L. Johansson, P. Lundborg, I. Lofberg and O. Ronn, 1985. Felodipine kinetics in healthy men. *Clin. Pharmacol. Ther.*, 38: 205-211.
- Fan, J. and I.A. de Lannoy, 2014. Pharmacokinetics. *Biochem. Pharmacol.*, 87: 93-120.
- Flores-Murrieta, F.J., G. Castaneda-Hernandez, V. Granados-Soto and J.E. Herrera, 2000. Increased bioavailability of sildenafil in Mexican men. *J. Am. Med. Assoc.*, 283: 1825-1826.
- Galal, A., D. Balkan, D. Ozzeybek, Y.C. Kaplan, S. Gurler, H. Guven and N.L. Benowitz, 2005. Effect of menthol on the pharmacokinetics and pharmacodynamics of felodipine in healthy subjects. *Eur. J. Clin. Pharmacol.*, 60: 785-790.
- Guengerich, F.P., W.R. Brian, M. Iwasaki, M.A. Sari, C. Baeaeernhielm and P. Berntsson, 1991. Oxidation of dihydropyridine calcium channel blockers and analogs by human liver cytochrome P-450 IIIA4. *J. Med. Chem.*, 34: 1838-1844.
- Hardy, B.G., W.R. Bartle, M. Myers, D.G. Bailey and B. Edgar, 1988. Effect of indomethacin on the pharmacokinetics and pharmacodynamics of felodipine. *Br. J. Clin. Pharmacol.*, 26: 557-562.
- Hasselgren, B., O. Ronn, B. Edgar, P. Johansson and B. Wall, 1990. Pharmacokinetics and hemodynamic and diuretic/natriuretic effects of felodipine administered as an extended-release tablet. *Cardiovasc. Drugs Ther.*, 4: 1495-1500.

- Hsiao, C.L., Y.C. Wu and K.Y. Hsu, 2011. Pharmacokinetics of felodipine extended-release tablets in healthy Taiwanese subjects: A retrospective review. *Arzneimittelforschung*, 61: 444-451.0
- Kim, K., J.A. Johnson and H. Derendorf, 2004. Differences in drug pharmacokinetics between east asians and caucasians and the role of genetic polymorphisms. *J. Clin. Pharmacol.*, 44: 1083-1105.
- Li, A.P., D.L. Kaminski and A. Rasmussen, 1995. Substrates of human hepatic cytochrome P450 3A4. *Toxicology*, 104: 1-8.
- Lown, K.S., D.G. Bailey, R.J. Fontana, S.K. Janardan and C.H. Adair *et al.*, 1997. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. *J. Clin. Invest.*, 99: 2545-2553.
- Lundahl, J., C.G. Regardh, B. Edgar and G. Johnsson, 1997. Effects of grapefruit juice ingestion-pharmacokinetics and haemodynamics of intravenously and orally administered felodipine in healthy men. *Eur. J. Clin. Pharmacol.*, 52: 139-145.
- Madsen, J.K., J.D. Jensen, L.W. Jensen and E.B. Pedersen, 1996. Pharmacokinetic interaction between cyclosporine and the dihydropyridine calcium antagonist felodipine. *Eur. J. Clin. Pharmacol.*, 50: 203-208.
- Mexican Official Norm, 1998. Tests and procedures to prove that a medication is interchangeable. Mexican Official Norm, NOM-177-SSA1-1998, Requirement 9.1, Official Journal of the Federation, May 7, 1999, Mexico City, Mexico. <http://www.salud.gob.mx/unidades/cdi/nom/177ssa18.html>
- Palma-Aguirre, J.A., J. Gonzalez-Llaven, F.J. Flores-Murrieta and G. Castaneda-Hernandez, 1997. Bioavailability of oral cyclosporine in healthy Mexican volunteers: Evidence for interethnic variability. *J. Clin. Pharmacol.*, 37: 630-634.
- Regardh, C.G., B. Edgar, R. Olsson, M. Kendall, P. Collste and C. Shansky, 1989. Pharmacokinetics of felodipine in patients with liver disease. *Eur. J. Clin. Pharmacol.*, 36: 473-479.
- Rowland, M. and T.N. Tozer, 1989. *Clinical Pharmacokinetics: Concepts and Applications*. 3rd Edn., Lea and Febiger, Philadelphia, USA.
- Todd, P.A. and D. Faulds, 1992. Felodipine. A review of the pharmacology and therapeutic use of the extended release formulation in cardiovascular disorders. *Drugs*, 44: 251-277.
- Wilkinson, G.R., 2005. Drug metabolism and variability among patients in drug response. *N. Eng. J. Med.*, 352: 2211-2221.