

Pharmacokinetics of fexofenadine in healthy Taiwanese volunteers

Yen-An Chen^{1,2} and Kuang-Yang Hsu^{1*}

¹College of Pharmacy, Taipei Medical University, Taiwan, R.O.C

²Protech Pharmservices Corporation, Taiwan, R.O.C

Abstract: The aim of presented study was to assess pharmacokinetic properties of fexofenadine in Taiwanese volunteers. Thirty-three healthy male subjects received 180mg fexofenadine. Blood samples were drawn at appropriate times. Drug concentrations of fexofenadine were measured by a LC/MS/MS method. Non-compartmental models were applied to describe the pharmacokinetic characters of fexofenadine. After oral administration of fexofenadine, the T_{max} was 1.90 ± 0.81 h. The C_{max} was 703.76 ± 298.94 ng/mL and $AUC_{0-\infty}$ was 4582.52 ± 1812.59 h $\times$ ng/mL. The elimination half-life of fexofenadine was 12.18 ± 3.61 h. One of the most important determinants was to prove the similar results in the pharmacokinetics of fexofenadine in Taiwan subjects compared with the reported data of other ethnic origin.

Keywords: Fexofenadine; Pharmacokinetics; LC/MS/MS.

INTRODUCTION

Fexofenadine, an antihistamine, is prescribed to alleviate allergic rhinitis and chronic urticaria. The drug neither inhibits potassium channels nor extends the QT interval in cardiology. Further, it cannot penetrate into the brain and does not cause sedation (Markham and Wag staff, 1998; Simpson and Jarvis, 2000; Nimje *et al.*, 2012). Fexofenadine also has fewer anti-cholinergic effects than other H_1 -antihistamines. These unique properties make it an optimal choice for patients (Zafar *et al.*, 2011; Nimje *et al.*, 2012).

Recent studies have shown that transporters are important for the pharmacokinetics in various drugs. Both organic anion transporting polypeptide (OATP) and P-glycoprotein (P-gp) transporters are located on the luminal membrane, resulting in opposing mechanisms for uptake into the circulation and for efflux back into the bowel (Cvetkovic *et al.*, 1999; Kim *et al.*, 1999; Dresser and Bailey, 2003; Smith and Gums, 2009). Fexofenadine is not only OATP substrate but also P-gp substrate. The drug substrates of OATP1B1 overlap with those of OATP1B3, and fexofenadine may also be a relatively specific substrate for OATP1B3. Fexofenadine has not been associated with severe side effects. Thus, it may be a good probe drug for evaluating the function of OATP1B3 in clinical trials (Shimizu *et al.*, 2005; Matsushima *et al.*, 2008 (A); Matsushima *et al.*, 2008 (B)). The implications of transporter-eliciting interactions have been reported (Dresser and Bailey, 2003; Shon *et al.*, 2005).

Pharmacokinetics of fexofenadine has been investigated in healthy volunteers. Previous studies have indicated that fexofenadine is rapidly absorbed after administration followed by a rapid distribution phase and a prolonged terminal phase. Only 5% of the dosage of fexofenadine

undergoes hepatic metabolism. Approximately 80% of fexofenadine is excreted unchanged form in faeces (Simons *et al.*, 1999; Chen, 2007; Miura and Uno, 2010). However, some issues remain controversial, such as the variation in plasma half-life, which ranges from 2.6 to 17.6h (Chen, 2007; Smith and Gums, 2009). The reasons for this variability are complicated and include assay methods, blood sampling schedules, individual differences, and effect of transporters. Recently, the effects of transporter inhibitors or inducers on fexofenadine pharmacokinetics have been examined (Hamman *et al.*, 2001; Dresser and Bailey, 2003). However, other factors that influence the pharmacokinetics of fexofenadine are less discussed.

Therefore, the present study characterizes the pharmacokinetics of fexofenadine in Taiwanese volunteers. The variables that affect these pharmacokinetic properties which provide detailed information about fexofenadine for clinical applications have also been studied.

EXPERIMENTAL

Chemicals and reagents

Standard Reference fexofenadine was purchased from Morepen Laboratories Limited (New Delhi, India). Losartan which was used as an internal standard (IS; 99.4%) was purchased from Rockville (Maryland, USA). Acetonitrile and methanol were of HPLC grade (Mallinckrodt Baker, Inc, New Jersey, USA).

Chromatographic conditions

The HPLC system (Agilent-1100, Wilmington, DE, USA) contains a Binary pump, an auto sampler and an Eclipse C₈ column (4.6 $\times$ 50 mm, 5 μ m). Chromatography was performed at 35°C. The mobile phase was 55% methanol in 1M ammonium acetate solution (v/v) and the flow rate was set at 1.0mL/min. The tandem mass spectrometry

*Corresponding author: e-mail: kyhsu@tmu.edu.tw

detection system was assayed using the API 4000 model. Ion transition m/z values for fexofenadine and losartan were 502.80 $\rightarrow$ 466.90 and 423.40 $\rightarrow$ 207.10, respectively.

Sample preparation

A 200 μ L aliquot of human plasma was spiked with 500 μ L of acetonitrile that comprised 2ng/mL IS and was vortexed for 1min. The mixture was centrifuged at 3,000 rpm for 10min; the organic layer was transferred into a fresh tube and evaporated to dryness under a stream of nitrogen. The residues were resolved into 400 μ L of the mobile phase, and a 10 μ L aliquot was injected into the HPLC and subjected to analysis.

Method validation

The retention times for fexofenadine and losartan were 1.76 and 2.65 min, respectively, without significant interfering peaks. The calibration curves of fexofenadine showed a linear relationship over a concentration range of 1-1000ng/mL. The regression equation for fexofenadine was $y=0.0144x-0.000904$ and the correlation coefficient (r^2) was 0.9980. The mean relative error ranged from 3.0 % to 6.0%, and the coefficients of variance were all less than 15.4%.

Subjects

The study protocol was approved by the Institutional Review Board of Mackay Memorial Hospital. All subjects signed the informed consent. Thirty-three healthy male volunteers completed this study. The clinical characteristics of the volunteers were as follows (mean $\pm$ SD): Age, 23.5 $\pm$ 2.9 years; height, 172.5 $\pm$ 6.2 cm; and body weight, 65.9 $\pm$ 6.3kg. The volunteers were free from diseases and routine examinations were within reference value.

Study design

The study subjects were fasted overnight and administered a single fexofenadine tablet at a dose of 180 mg with 240mL water. Allegra[®] tablets were used as an investigation drug. Blood samples (10mL) were drawn in heparinised tubes before dosing (0h) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 36, 48 and 60h post administration. After centrifugation, plasma was transferred to labelled tubes and stored at a temperature of -20°C until further assays. The time between blood collection and freezer storage was not more than 1.5h.

Data analysis

Individual fexofenadine plasma concentration data were analysed by the WinNonlin[®] (Pharsight, Cary, NC) program. Pharmacokinetic parameters: peak concentration (C_{max}) and time to achieve peak concentration (T_{max}), were noted from plasma profiles. Half-life ($t_{1/2}$) and area under the concentration-time curve (AUC) were obtained by calculating.

RESULTS

Representative plasma concentrations against time profiles for fexofenadine is shown in fig 1. The concentrations of fexofenadine were determined in all the samples. In previous studies, the methods used to quantify fexofenadine concentrations were of limited value because of their poor sensitivity (Coutant *et al.*, 1991; Russel *et al.*, 1998). However, the results indicated that the method developed in this study was suitable for pharmacokinetic studies.

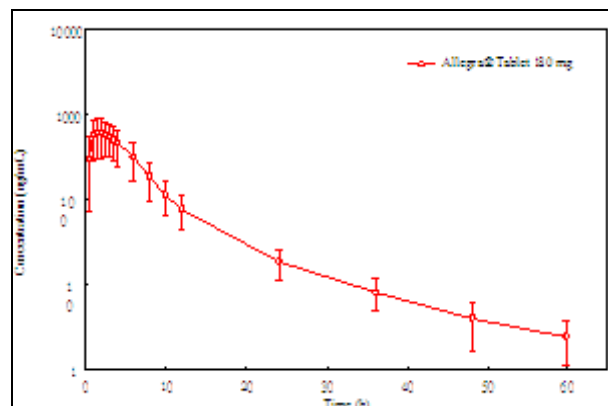


Fig. 1: Representative plasma concentration-time curves for fexofenadine.

The plasma concentration data were fit using the compartment pharmacokinetic model to describe the disposition of fexofenadine. There were large variations in the concentration profiles. The time-concentrations profiles did not fit well to either one- or two-compartment model. Therefore, a non-compartmental model was applied to describe the pharmacokinetic properties of fexofenadine in the present study. It was corresponded with the results from previous researches (Uno *et al.*, 2004; Boyle *et al.*, 2005). Pharmacokinetic parameters of fexofenadine are summarized in table 1. After fexofenadine administration, the AUC_{0-t} and $AUC_{0-\infty}$ were 4537.65 $\pm$ 1794.69 and 4582.52 $\pm$ 1812.59 h $\times$ ng/mL, respectively. The mean ratio of AUC_{0-t} to $AUC_{0-\infty}$ was over 80%, which represented a suitable sampling schedule.

DISCUSSION

Pharmacokinetic characters of fexofenadine appeared to be dose proportional in published investigations (Russel *et al.*, 1998). However the variability in the pharmacokinetic characteristics of fexofenadine were not exhaustively discussed. In this study, fexofenadine was rapidly absorbed and reached T_{max} at 1.90 $\pm$ 0.81h after administration. The average T_{max} observed in a former research was 1.0 to 3.9h (Smith and Gums, 2009). The C_{max} was 703.76 $\pm$ 298.94ng/mL and $AUC_{0-\infty}$ was 4582.52 $\pm$ 1812.59h $\times$ ng/mL. These results were similar to the results obtained by Hofmann *et al.*, (2002) who reported a C_{max}

Table 1: Comparison of pharmacokinetic parameters of fexofenadine in different ethnic healthy volunteers

Population	Parameters	Dosage (mg)	T _{max} (h)	C _{max} (ng/mL)	AUC _{0-∞} (h×ng/mL)	t _{1/2} (h)
Chinese		60	4.1±0.88	152.62±74.18	978.19±411.06	11.14±4.95
Chinese		120	3.58±1.17	365.98±168.02	2437.5±885.9	9.29±3.61
Japanese		120	2.1±0.9	610±222	3808±1266	9.6±2.9
Germany		180	1.5±0.6	734.5±261.3	4107.5±1837.4	19.1±7.0
Taiwanese (present study)		180	1.90±0.81	703.76±298.94	4582.52±1812.59	12.18±3.61

of 734.5±261.3ng/mL and AUC_{0-∞} of 4107.5±1837.4 h×ng/mL after administration of 180 mg fexofenadine in humans.

The t_{1/2} of fexofenadine was 12.18±3.61 h. However, the t_{1/2} of fexofenadine ranged from 2.6 to 17.6 h in previous studies (Chen, 2007; Smith and Gums, 2009). Factors affecting the plasma half-life of fexofenadine could be complex. The sensitivity of the analytical methods, length of blood sampling, influence of transporters and individual variation might also alter pharmacokinetic results. After administration of fexofenadine, plasma concentrations at 24h were under 10ng/mL. HPLC methods with lower limit of quantification (LLOQ) values of 5 to 8.2ng/mL were not sensitive enough to detect the drug in the elimination phase (Coutant *et al.*, 1991; Surapaneni *et al.*, 1994; Shon *et al.*, 2005). The pharmacokinetics of single oral doses of fexofenadine ranging from 10 to 280mg was investigated could not estimate the terminal t_{1/2} because of low sensitivity (Russell *et al.*, 1998). Hofmann *et al.*, (2002) developed a specific assay for fexofenadine with LLOQ of 0.5ng/mL which was a significant improvement over that achieved with published methods and the t_{1/2} of fexofenadine was 19.1±7.0h. Uno *et al.*, (2004) also explored an LC method for determination of fexofenadine and achieved an LLOQ value of 1.0ng/mL and t_{1/2} was 9.6±2.9h. These improvements in assay sensitivity resulted in the similarity obtained in the pharmacokinetic parameters in previous studies.

Analytical methods with significant improvements in sensitivity also enabled longer plasma concentration–time profiles of fexofenadine (Fu *et al.*, 2004; Nirogi *et al.*, 2007). Sufficient duration of collecting samples was required for adequate calculation of the terminal elimination rate to compute the profiles. Shon *et al.*, (2005) reported the pharmacokinetics of fexofenadine in Korean volunteers 24h after drug administration and had a t_{1/2} was 5.0±1.7h, which was less than that reported previously. The pharmacokinetics of fexofenadine in Japanese volunteers was investigated by Boyle *et al.*, (2005) who reported 24h was not adequate to confirm the elimination phase. Gou *et al.*, (2009) studied the pharmacokinetics of fexofenadine for up to 48h and reported a t_{1/2} of 11.14±4.95h and 9.29±3.61h at dosage of 60 and 120mg. The AUC₀₋₄₈ and AUC_{0-∞} were 961.17 ±409.97 and 978.19±411.06h×ng/mL, respectively. The

mean ratio of AUC₀₋₄₈ divided by AUC_{0-∞} was over 80%, which represented a good fit with the sampling schedule. Taken together, these data indicated that the blood sampling duration for pharmacokinetic studies of fexofenadine should be at least 48h to capture the complete plasma-concentration profile and the true elimination half-life.

Fexofenadine was a substrate for numerous transporters systems. Co-administration with a transporters inhibitor or inducer resulted in different pharmacokinetic parameters of fexofenadine, including C_{max}, AUC, and t_{1/2}. The results of previous clinical trials demonstrated that fexofenadine administration with P-gp inhibitors significantly increased the C_{max} and AUC of fexofenadine. When fexofenadine was administered with itraconazole, the mean C_{max} of fexofenadine was 40% higher, while the AUC was 30% higher in subjects given placebo (Shon *et al.*, 2005). Conversely, administration of fexofenadine with P-gp inducers may reduce the AUC and C_{max}. Substances that inhibit or induce OATP may also significantly affect the plasma concentration levels of fexofenadine. Administration of fexofenadine with grape fruit juice, orange juice, or apple juice, which are known P-gp and OATP inhibitors, reduced the AUC of fexofenadine by 58, 31, and 22%, respectively (Dresser and Bailey, 2003; Smith and Gums, 2009).

In the present study, the pharmacokinetic parameters of fexofenadine in healthy Taiwanese volunteers was compared to the literature values obtained in similar studies on Chinese; Japanese and Germany volunteers as shown in table 1. Pharmacokinetic parameters of fexofenadine in subjects from Taiwan were consistent with those reported in subjects of other ethnic origins. However, it appeared that individual variations in fexofenadine pharmacokinetics were significant between subjects of various ethnic origins.

CONCLUSIONS

In the present study, we clarified the controversial issues associated with the pharmacokinetics of fexofenadine in humans. The results of this study conducted in Taiwanese volunteers suggested that no differences exist in the pharmacokinetic characteristics of fexofenadine between subjects of various ethnic origins.

REFERENCES

- Boyle J, Ridout F, Mesdows R, Johnsen S and Hindmarch I (2005). Suppression of the histamine-induced wheal and flare response by fexofenadine HCl 60mg twice daily, loratadine 10mg once daily and placebo in healthy Japanese volunteers. *Curr. Med. Res. Opin.*, **21**: 1495-1503.
- Chen C (2007). Some pharmacokinetic aspects of the lipophilic terfenadine and zwitterionic fexofenadine in humans. *Drug R. D.*, **8**: 301-314.
- Coutant JE, Westmark PA, Nardella PA, Walter SM and Okerholm RA (1991). Determination of terfenadine and terfenadine acid metabolite in plasma using solid-phase extraction and high-performance liquid chromatography with fluorescence detection. *J. Chromatogr.*, **570**: 139-148.
- Cvetkovic M, Leake B, Fromm MF, Wilkinson GR and Kim RB (1999). OATP and P-glycoprotein transporters mediate the cellular uptake and excretion of fexofenadine. *Drug Metab. Dispos.*, **27**: 866-871.
- Dresser GK and Bailey DG (2003). The effects of fruit juices on drug disposition: A new model for drug interactions. *Eur. J. Clin. Invest*, **33**: 10-16.
- Fu I, Woolf EJ and Matuszewski BK (2004). Determination of fexofenadine in human plasma using 96-well solid phase extraction and HPLC with tandem mass spectrometric detection. *J. Pharm. Biomed. Anal.*, **35**: 837-846.
- Guo D, Zou J, Zhu Y, Lou S, Fan H and Qin Q (2010). Measurement of fexofenadine concentration in micro-sample human plasma by a rapid and sensitive LC-MS/MS employing protein precipitation: Application to a clinical pharmacokinetic study. *Biomed. Chromatogr.*, **24**: 335-341.
- Hamman MA, Bruce MA, Haehner-Daniels BD and Hall SD (2001). The effect of rifampin administration on the disposition of fexofenadine. *Clin. Pharmacol. Ther.*, **69**: 114-121.
- Hofmann U, Seiler M, Drescher S and Fromm MF (2002). Determination of fexofenadine in human plasma and urine by liquid chromatography-mass spectrometry. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.*, **766**: 227-233.
- Kim RB, Wandel C, Leake B, Cvetkovic M, Fromm MF, Dempsey PJ, Roden MM, Belas F, Chaudhary AK, Roden DM, Wood AJ and Wilkinson GR (1999). Interrelationship between substrates and inhibitors of human CYP3A and P-glycoprotein. *Pharm. Res.*, **16**: 408-414.
- Markham A and Wagstaff AJ (1998). Fexofenadine. *Drugs*, **55**: 269-274.
- Matsushima S, Maeda K, Hayashi H, Debori Y, Schinkel AH, Schuetz JD, Kusuha H and Sugiyama Y (2008). Involvement of multiple efflux transporters in hepatic disposition of fexofenadine. *Mol. Pharmacol.*, **73**: 1474-1483.
- Matsushima S, Maeda K, Ishiguro N, Igarashi T and Sugiyama Y (2008). Investigation of the inhibitory effects of various drugs on the hepatic uptake of fexofenadine in humans. *Drug Metab. Dispos.*, **36**: 663-669.
- Miura M and Uno T (2010). Clinical pharmacokinetics of fexofenadine enantiomers. *Expert. Opin. Drug Metab. Toxicol.*, **6**: 69-74.
- Nimje HM, Nimje ST, Oswal RJ and Bhamre ST (2012). Stability indicating RP-HPLC Method for estimation of fexofenadine hydrochloride in pharmaceutical formulation. *E-J. Chem.*, **9**: 1257-1265.
- Nirogi RV, Kandikere VN, Shukla M, Mudigonda K, Maurya S and Komarneni P (2007). Quantification of fexofenadine in human plasma by liquid chromatography coupled to electrospray tandem mass spectrometry using mosapride as internal standard. *Biomed. Chromatogr.*, **21**: 209-216.
- Russell T, Stoltz M and Weir S (1998). Pharmacokinetics, pharmacodynamics, and tolerance of single- and multiple-dose fexofenadine hydrochloride in healthy male volunteers. *Clin. Pharmacol. Ther.*, **64**: 612-621.
- Shimizu M, Fuse K, Okudaira K, Nishigaki R, Maeda K, Kusuha H and Sugiyama Y (2005). Contribution of OATP (organic anion-transporting polypeptide) family transporters to the hepatic uptake of fexofenadine in humans. *Drug Metab. Dispos.*, **33**: 1477-1481.
- Shon JH, Yoon YR, Hong WS, Nguyen PM, Lee SS, Choi YG, Cha IJ and Shin JG (2005). Effect of itraconazole on the pharmacokinetics and pharmacodynamics of fexofenadine in relation to the MDR1 genetic polymorphism. *Clin. Pharmacol. Ther.*, **78**: 191-201.
- Simons FE and Simons KJ (1999). Clinical pharmacology of new histamine H1 receptor antagonists. *Clin. Pharmacokinet.*, **36**: 329-352.
- Simpson K and Jarvis B (2000). Fexofenadine: A review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria. *Drugs*, **59**: 301-321.
- Smith SM and Gums JG (2009). Fexofenadine: Biochemical, pharmacokinetic and pharmacodynamic properties and its unique role in allergic disorders. *Expert. Opin. Drug Metab. Toxicol.*, **5**: 813-822.
- Surapaneni S and Khalil S KW (1994). A sensitive HPLC method for the determination of terfenadine and its metabolite in human plasma. *J. Liq. Chromatogr.*, **17**: 2419-2428.
- Uno T, Yasui-Furukori N, Takahata T, Sugawara K and Tateishi T (2004). Liquid chromatographic determination of fexofenadine in human plasma with fluorescence detection. *J. Pharm. Biomed. Anal.*, **35**: 937-942.
- Zafar F, Shoaib MH and Yousuf RI (2011). Development of RP-HPLC method for fexofenadine determination in tablet formulations and development of dissolution method. *Pakistan J. Pharmacol.*, **28**: 43-49.