European Journal of Pharmaceutical Sciences 37 (2009) 413–417

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Pharmacokinetic drug interaction between fexofenadine and fluvastatin mediated by organic anion-transporting polypeptides in rats

Fu Qiang [a], Beom-Jin Lee [b], Wonjae Lee [a], Hyo-Kyung Han [a,*]

[a] BK21 Project Team, College of Pharmacy, Chosun University, 375 Seosuk-dong, Dong-Gu, Gwangju 501-752, Republic of Korea
[b] Bioavailability Control Laboratory, College of Pharmacy, Kangwon National University, Chuncheon 200-701, Republic of Korea

ARTICLE INFO

Article history:
Received 2 January 2009
Received in revised form 17 March 2009
Accepted 22 March 2009
Available online 1 April 2009

Keywords:
Fexofenadine
Fluvastatin
Organic anion-transporting polypeptides
Drug interaction
Rat

ABSTRACT

This study aimed to examine the transporter-mediated drug interaction between fexofenadine and fluvastatin in rats. Compared to the control group given fluvastatin alone, the concurrent use of fexofenadine (10 or 20 mg/kg) prior to the oral administration of fluvastatin (5 mg/kg) decreased the systemic exposure of fluvastatin by 17–51% in rats. Consequently, the bioavailability of oral fluvastatin was significantly lower ($p < 0.05$) in the presence of fexofenadine compared to that from the control group. Furthermore, the intravenous pharmacokinetics of fluvastatin (2 mg/kg) was significantly altered by the pretreatment with fexofenadine (20 mg/kg, p.o.). The plasma clearance of fluvastatin was reduced by 44% in the presence of fexofenadine. The effect of fluvastatin on the pharmacokinetics of fexofenadine was also investigated in rats. The pretreatment with fluvastatin (5 or 10 mg/kg) decreased AUC and C_{max} of oral fexofenadine (10 mg/kg) by 47–53% and 28–60%, respectively, while it did not affect the intravenous pharmacokinetics of fexofenadine. Given that both fluvastatin and fexofenadine can interact with organic anion-transporting polypeptides (OATPs) expressed in intestine and liver, the present results suggest the potential drug interaction between fluvastatin and fexofenadine via the competition for the OATP-mediated cellular transport pathway during intestinal absorption and/or hepatic uptake of drugs.

© 2009 Elsevier B.V. All rights reserved.

1. Introduction

Drug transporters play an important role in the absorption and elimination of many endogenous and exogenous compounds. Among various drug transporters expressed in intestine and liver, organic anion-transporting polypeptides (OATPs) form a superfamily of the sodium-independent transport system for a wide range of amphipathic organic compounds including organic dyes, steroid conjugates, anionic oligopeptides and numerous pharmaceutical drugs [1–3]. Since OATPs involved in the cellular transport of many drugs and the multiple prescriptions are increasingly common in current medical practice, there might be high potential for the OATP-mediated drug–drug interactions (DDIs). However, the preclinical and clinical significance of OATP-mediated drug interactions has not been clearly defined yet while metabolic drug interactions or P-gp mediated drug interactions have been extensively examined [4,5].

Fexofenadine is a non-sedating histamine H1-receptor antagonist and effective for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria [6]. After an oral administration of fexofenadine, the majority of the dose (>85%) was recovered as the unchanged form in urine and feces while the metabolism of fexofenadine was insignificant in vivo [7,8]. Fexofenadine is a well-known substrate of the OATP-A (OATP1A2) and OATP-B (OATP2B1) as well as P-gp [9–12]. Therefore, the modulation of those transporter activities could result in the altered pharmacokinetics of fexofenadine. In fact, the fruit juice decreased the oral bioavailability of fexofenadine by inhibiting the OATPs in both rat and humans [13–15].

Fluvastatin is a lipid-lowering agent and a potent inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the rate-limiting enzyme in cholesterol biosynthesis [16,17]. Fluvastatin is readily and extensively absorbed from the gastrointestinal tract following an oral administration, but it undergoes the extensive first-pass metabolism [18,19]. Previous studies have indicated the OATP1B1-, OATP2B1-, and OATP1B3-mediated fluvastatin transport [20,21]. Since both fexofenadine and fluvastatin can interact with OATPs expressed in intestine and liver, the coadministration of both drugs may change the systemic exposure of each drug via the competition for the common cellular transport pathways and consequently alters the therapeutic risk–benefit ratio of each drug. As a result, the drug interaction potential between fexofenadine and fluvastatin is of great importance for the clinical safety of both drugs but so far it has not been evaluated yet. Therefore, the present

* Corresponding author. Tel.: +82 62 230 6364; fax: +82 62 222 5414.
E-mail address: hkhan@chosun.ac.kr (H.-K. Han).

0928-0987/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejps.2009.03.012

study investigated the potential pharmacokinetic drug interaction between fluvastatin and fexofenadine after the concomitant use of those drugs in rats.

2. Materials and methods

2.1. Materials

Fluvastatin sodium was purchased from Biocon Chemical Co. (Electronic city, Bangalore, India). Fexofenadine, atorvastatin, piroxicam were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Triethylamine was obtained from Junsei Chemical Co. (Tokyo, Japan). Acetonitrile, methanol, ethanol and acetic acid were obtained from Merck Co. (Darmstadt, Germany). All other chemicals were of analytical grade and all solvents were of HPLC grade.

2.2. Animal studies

Male Sprague–Dawley rats (280–300 g) were purchased from Samtako Bio Co. (Osan, Korea). All animal studies were performed in accordance with the "Guiding Principles in the Use of Animals in Toxicology" adopted by the Society of Toxicology (USA). Rats were divided into ten groups ($n = 6$ per each group). Groups 1–3: 10 mg/kg of fexofenadine (p.o.) + 0, 5 or 10 mg/kg of fluvastatin (p.o., 15 min prior to fexofenadine administration), Groups 4 and 5: 5 mg/kg of fexofenadine (i.v.) + 0 or 10 mg/kg of fluvastatin (p.o., 15 min prior to fexofenadine administration), Groups 6–8: 5 mg/kg of fluvastatin (p.o.) + 0, 10 or 20 mg/kg of fexofenadine (p.o., 15 min prior to fluvastatin administration) and Groups 9 and 10: 2 mg/kg of fluvastatin (i.v.) + 0 or 20 mg/kg of fexofenadine (p.o., 15 min prior to fluvastatin administration). A single dose of approximately 10 mg/kg fexofenadine is comparable to the clinical dose of 120 mg in humans [14,15]. Also, the doses for fluvastatin used in the present study were selected based on the previous report [22] as well as assay sensitivity. Fexofenadine was dissolved in ethanol and water (1:10) for oral administration and in saline (0.9%) for i.v. administration. Fluvastatin was dissolved in the distilled water for oral administration and in saline (0.9%) for i.v. administration. Blood samples were collected from the femoral artery at 0, 0.05, 0.16, 0.25, 0.5, 1, 2, 4, 8, 12, 24 h following an intravenous administration. Blood samples were also collected from the femoral artery at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8, 12, 24 h following an oral administration. Blood samples were centrifuged and the obtained plasma was stored at $-70\,^{\circ}\mathrm{C}$ until analyzed.

2.3. HPLC assay

2.3.1. Fexofenadine

Plasma concentration of fexofenadine was determined by the HPLC method described as follows. In brief, 10 μl of piroxicam (10 μg/ml) as an internal standard was added to 90 μl of each plasma sample and then the mixture was deproteinized by adding 200 μl of acetonitrile. After centrifugation of the samples at 13,000 × g for 10 min, the supernatant was evaporated and the residue was reconstituted with 120 μl of the mobile phase, and then 50 μl of aliquots were injected directly into the HPLC system (Perkin Elmer Series 200; Waltham, MA, USA). The octadecylsilane column (Gemini C18, 4.6 mm × 150 mm, 5 μm; Phenomenex, Torrance, CA, USA) was eluted with the mobile phase consisting of 0.1 M triethylamine:acetonitrile:methanol (61:19.5:19.5, v/v/v%, pH 4.4 adjusted with phosphoric acid) at a flow rate of 1.0 ml/min. The UV detector set at 195 nm. The calibration curve from the standard samples was linear over the concentration range of 0.01–0.5 μg/ml. The detection limit of fexofenadine was 0.01 μg/ml.

2.3.2. Fluvastatin

Plasma concentration of fluvastatin was determined by the HPLC method as follows. Briefly, 15 μl of atorvastatin (10 μg/ml) as an internal standard was added to 85 μl of each plasma sample and then the sample was deproteinized by adding 200 μl of acetonitrile. After centrifugation of the samples at 13,000 × g for 10 min, the supernatant was evaporated and the residue was reconstituted with 200 μl of the mobile phase, and then 50 μl of aliquots were injected directly into the HPLC system (Perkin Elmer Series 200, USA). An octadecylsilane column (Gemini C18, 4.6 mm × 250 mm, 5 μm; Phenomenex, Torrance, CA, USA) was eluted with the mobile phase of 0.1 M acetic acid:acetonitrile:methanol (34.5:4.0:61.5, v/v/v%) at a flow rate of 1.0 ml/min. The UV detector set at 235 nm. The calibration curve from the standard samples was linear over the concentration range of 0.01–1 μg/ml. The detection limit of fluvastatin was 0.01 μg/ml.

2.4. Pharmacokinetic data analysis

Noncompartmental pharmacokinetic analysis was performed using the WinNonlin® version 5.2 (Pharsight Corporation, Mountain View, CA, USA). The elimination rate constant (K_{el}) was estimated from the slope of the terminal phase of the log plasma concentration–time points fitted by the method of least-squares and the terminal half-life ($T_{1/2}$) was calculated by $0.693/K_{el}$. The peak concentration (C_{max}) and the time to reach peak concentration (T_{max}) of drug in plasma were obtained by visual inspection of the data from the concentration–time curve. The area under the plasma concentration–time curve (AUC_{0-t}) from time zero to the time of last measured concentration (C_{last}) was calculated by the linear trapezoidal rule. The AUC from time zero to infinite ($AUC_{0-\infty}$) was obtained by the addition of AUC_{0-t} and the extrapolated area determined by C_{last}/K_{el}. Total plasma clearance (CL) was calculated by dose/AUC. The absolute bioavailability (A.B.) of drug was calculated by $AUC_{p.o.}/AUC_{i.v.} \times dose_{i.v.}/dose_{p.o.} \times 100$. The relative bioavailability (R.B.) of fexofenadine was estimated by $AUC_{fexofenadine\ with\ fluvastatin}/AUC_{fexofenadine} \times 100$ and the R.B. of fluvastatin was estimated by $AUC_{fluvastatin\ with\ fexofenadine}/AUC_{fluvastatin} \times 100$.

2.5. Statistical analysis

All mean values were presented with their standard deviation (mean ± S.D.). Statistical analysis was conducted using a one-way ANOVA followed by a posteriori testing with Dunnett correction. A p value less than 0.05 was considered statistically significant.

3. Results

3.1. Altered pharmacokinetics of fexofenadine in the presence of fluvastatin

The mean plasma concentration–time profiles of fexofenadine in the presence and the absence of fluvastatin were characterized in rats and illustrated in Figs. 1 and 2. The mean pharmacokinetic parameters of fexofenadine were also summarized in Tables 1 and 2. As shown in Table 1, the pretreatment with fluvastatin (5 or 10 mg/kg) significantly altered the oral exposure of fexofenadine compared to the control group given fexofenadine alone. The C_{max} and AUC of fexofenadine decreased by 28–60% and 47–53%, respectively via the concurrent use of 5 or 10 mg/kg of fluvastatin. Consequently, the absolute and relative bioavailability values of fexofenadine decreased significantly ($p < 0.05$) under the pretreatment with fluvastatin. However, there was no significant change in T_{max} and terminal plasma half-life ($T_{1/2}$) of fexofenadine in the presence

Download English Version:

https://daneshyari.com/en/article/2481698

Download Persian Version:

https://daneshyari.com/article/2481698

Daneshyari.com