Investigation of Drug Interaction Studies of Levocetirizine with HMG-CoA Reductase Inhibitors

Saeed Arayne M¹, Najma Sultana² and Nawaz M**
¹Department of Chemistry, University of Karachi, Karachi-75270, Pakistan
²Research Institute of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Karachi, Karachi-75270, Pakistan

Abstract

The aim of present work is to study the in-vitro drug-drug interaction studies of levocetirizine with HMG-CoA reductase inhibitors (atorvastatin, simvastatin and rosuvastatin) in different pH environments in simulated gastric juice (pH 1) simulating full stomach juice (pH 4), blood pH (pH 7.4) and simulated GI (pH 9) at physiological temperature (37°C). The interactions were carried out using dissolution apparatus and drug contents were analyzed by UV-Visible spectrophotometry. The availability of levocetirizine in the presences of HMG-CoA reductase inhibitors were determined by deriving a simultaneous equation for two component system through modification of Beer’s law. It was observed that availability of levocetirizine after interaction with MG-CoA reductase inhibitors was increased or decreased due to the formation of charge transfer complexes between them.

Keywords: Levocetirizine; HMG-CoA reductase inhibitors; Atorvastatin, Simvastatin; Rosuvastatin; Interactions

Introduction

Levocetirizine (Figure 1) or 2-[2-[4-[(R)-(4-chlorophenyl)-phenyl-methyl] piperazin-1-yl] ethoxy] acetic acid, is a non-sedative anti-allergic drug. It is used to manage intermittent and persistent allergic rhinitis by inhibits binding of histamine to its receptor [1]. Levocetirizine is prescribed to relieve runny nose, sneezing and redness and itching caused by hay fever and also seasonal allergies. As levocetirizine is a weak permeability glycoprotein (PgP) substrate, therefore, it should be taken with caution with the drugs which are either PgP substrate such as ketoconazole, cyclosporine or verapamil or Pgp inducers like verapamil or rifampicin or inhibitor such as azithromycin, erythromycin, verapamil or iraconazole [2-4].

HMG-CoA reductase inhibitors (Figure 1) inhibit cholesterol synthesis in the liver by blocking 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), induce osteoblast activity and lead to bone formation [5-11]. They are the most commonly prescribed agents for the treatment of hypercholesterolemia because of their efficacy in reducing low density lipoprotein and their excellent tolerability and safety [12-14]. Simvastatin is administered in the lactone form, after absorption, the lactone ring opens in the liver by chemical or enzymatic hydrolysis and the active hydroxy acid is generated. Pravastatin is administered as an acid and is present in the active form. HMG-CoA reductase inhibitors may also alter the concentrations of other drugs, such as warfarin or digoxin, leading to alterations in effect or requiring clinical monitoring [15].

The combination of HMG-CoA reductase inhibitors with certain drugs that are CYP3A4 inhibitors or substrates increases the risk of myopathy, presumably by inhibiting the metabolism of the HMG-CoA reductase inhibitors and increasing its blood concentration. These drugs include cyclosporine [16], erythromycin [17,18], clarithromycin [19] and mibebradil [20]. Fibrates and niacin also increase the risk of statin-induced myopathy via a mechanism that does not increase plasma statin concentrations [21,22]. Myopathy has been reported with pravastatin even though it is not metabolized significantly by CYP [23]. The interaction of levocetirizine has also been reported with gliclazide [24] and human serum albumin as well [25].

Before, our research group explored a number of drug-drug interactions of hypoglycemic agents [26], NSAIDs [27-29], statins [30], atenolol [31], NIDDM drugs [32] and H₁-antagonists [33].

The purpose of present work is to study the probable in vitro interaction of levocetirizine with HMG-CoA reductase inhibitors (atorvastatin, simvastatin and rosuvastatin) at physiological temperature (37°C) in different pH environments simulated gastric juice (pH 1), simulating full stomach juice (pH 4), blood pH (pH 7.4) and simulated GI (pH 9). The method is fast, inexpensive and comprises a simple B.P. dissolution apparatus.

Materials and Methods

Materials

Levocetirizine was a kind gift from Hilton Pharma. Atorvastatin, simvastatin and rosuvastatin were obtained from PharmEvo (Pvt.) Ltd. The dosage forms of levocetirizine (Leozin® 5 mg), atorvastatin (Derot® 10mg), simvastatin (Limitrol® 10mg) and rosuvastatin (X-plended® 5mg) and were purchased from the pharmacy. Potassium chloride, potassium dihydrogen orthophosphate, disodium hydrogen orthophosphate, ammonia solution and hydrochloric acid were purchased from Merck, Darmstadt, Germany. All the reagents used were of analytical grade and double distilled deionized water was used throughout

Instrumentation

Electrical balance (Mettler Toledo # AB54), pH meter (Mettler Toledo MP220), UV-Visible 1601 Shimadzu double beam spectrophotometer, 1 cm rectangular quartz cells, Quick fit ground glass distillation assembly, water bath, Deionizer (Sterdec CSW-300), distillation unit (GFL Type 2001/2). Drug interactions were carried out by using dissolution equipment was manufactured to the B. P 2007 standards [34]. It consisted of dissolution motor and a variable speed controller with stainless steel basket assembly. The rotation speed of the
basket assembly was fixed ± 0.5 rpm throughout the experiment. The dissolution assembly was immersed in a water bath at 37°C ± 0.1°C. The drug was analyzed by measuring absorbance of the aliquots on a UV/VIS spectrophotometer (Shimadzu 1601).

**Preparation of buffers solutions**

Simulated gastric juice (pH 1) buffer was prepared by taking appropriate amount of hydrochloric acid into 500 mL of water and volume was made with deionized water in one liter volumetric flask. Buffer of pH 4.0 was prepared by taking 3.725 g of potassium chloride in deionized water in one liter; the pH was adjusted to 4 with 0.1 N hydrochloric acid. pH 7.4 buffer was prepared by taking 0.6 g potassium dihydrogen orthophosphate, 6.4 g disodium hydrogen orthophosphate and 5.85 g sodium chloride in 1000 mL deionized water and pH was adjusted if necessary. Similarly, pH 9 buffer was prepared by dissolving 4.98 g of ammonium chloride in 1000 mL of deionized water and pH was adjusted to 9 with ammonia solution.

**Calibration curve**

For calibration curve, working standard solutions of each concentration ranging from 0.01 to 0.055 mMole for HMG-CoA reductase inhibitors and 0.01-0.09 mMole for levocetirizine were prepared in simulated gastric juice (pH 1) and buffers pH 4, 7.4 and 9. The absorbance maxima were scanned in the region of 200-700 nm for these solutions against the reagent blank. Graph was plotted for absorbance against concentration and straight line was obtained which obeyed Beer Lambert's Law. Epsilon values of all drugs were calculated in all these buffers at their respective $\lambda_{\text{max}}$.

**Invitro availability studies**

The invitro availabilities of levocetirizine and HMG-CoA reductase inhibitors (atorvastatin, simvastatin and rosuvastatin) were studied at physiological temperature (37°C) in individual dosage formulation in simulated gastric juice (pH 1) and buffers of pH 4, 7.4 and 9 using B.P dissolution apparatus. 5 mg of levocetirizine was introduced in 1 liter dissolution fluid and kept on water bath maintained at 37°C. 5 mL aliquots were taken every 15 minutes for 2 hours and volume was maintained by adding an equivalent amount of fluid withdrawn. The sample was scanned in the range of 200-700 nm beside reagent blank. Same procedure was adopted for invitro availability studies of HMG-CoA reductase inhibitors.

**Drug-drug interactions studies**

The invitro interaction studies of levocetirizine with HMG-CoA reductase inhibitors in simulated gastric juice (pH 1), buffers pH 4, 7.4 and pH 9 were carried out at 37°C on a B.P 2007 dissolution apparatus. In this set of experiments levocetirizine 5 mg with statins (rosuvastatin 5 mg, simvastatin 10 mg and atorvastatin 10 mg) were added to the dissolution medium (pH 1, 4, 7.4 and pH 9) at zero time. Aliquots of 5 mL were withdrawn intermittently at 15 minutes time interval for 180 minutes and assayed for the drug content after appropriate dilution. The volume of dissolution fluid was maintained by adding an equivalent amount of dissolution fluid withdrawn, which has been previously maintained at same temperature in the same bath. The samples were scanned in the range of 200-700 nm against reagent blanks. Graphs were plotted for % availability of drug versus time in each set of experiment.

**Results and Discussion**

**Quantification of drugs**

The interaction studies between levocetirizine and HMG-CoA reductase inhibitors (simvastatin, atorvastatin and rosuvastatin) were conducted in buffers of pH 1, pH 4, 7.4 and 9 at physiological temperature (37°C). Simultaneous equation was used to measure...
the quantities of levocetirizine and HMG-CoA reductase inhibitors present in the same solution. This equation can be written as follows for levocetirizine and atorvastatin simultaneous determination:

\[ C_a = \frac{A_{231} \cdot a_1 - A_{241} \cdot a_2}{a_1 \cdot b_2 - a_2 \cdot b_1} \]

Similarly,

\[ C_s = \frac{A_{231} \cdot b_1 - A_{241} \cdot b_2}{a_1 \cdot b_2 - a_2 \cdot b_1} \]

Where \( C_a \) and \( C_s \) were the concentration of levocetirizine and simvastatin, \( a_1 \) and \( a_2 \) were the molar absorptivities of levocetirizine at 231 and 241 nm, while \( b_1 \) and \( b_2 \) were the molar absorptivities of simvastatin at 231 and 241 nm. These equations were used to measure the quantities of levocetirizine and HMG-CoA reductase inhibitors simultaneously present in solution. Prior to these studies, the validity of the spectrophotometric assay methods for individual drugs was checked with the reference drugs, and molar absorptivities of both the interacting drugs at the \( \lambda_{max} \) of each drug were calculated. Similarly, atorvastatin and rosuvastatin were determined along with levocetirizine in solutions using these equations.

**Interaction studies**

The interaction studies of levocetirizine with HMG-CoA reductase inhibitors were carried out in buffer of pH 1, 4, 7.4 and 9 at 37°C simulating body environment. The results of the interaction of levocetirizine with HMG-CoA reductase inhibitors are plotted in Figures 2a-2d and difference in the extent of drug interaction has been observed.

The interaction study of levocetirizine with atorvastatin almost resulted in a significant effect on the availabilities of levocetirizine as well as atorvastatin in pH 4. At the end of the experiment 16.87% and 22.19% of levocetirizine and atorvastatin were available respectively. In pH 1, 7.4 and 9, levocetirizine availabilities were 105.47%, 134.88% and 81.38% respectively. Retardation in the availability of atorvastatin was observed in pH 9 which is 60.77%. On the other hand, 154.79% and 168.65% of atorvastatin was available in pH 1 and 7.4 respectively (Figures 2a-2d).

The availability of levocetirizine increased significantly in buffer pH 1 and 7.4 when there was an interaction with simvastatin. In pH 1, 608.83% of levocetirizine was initially available that reached to 340.61%
at 120 minutes. In buffers of pH 7.4 levocetirizine showed 287.90% availability. In pH 4, interaction between levocetirizine and simvastatin was occurred because zero% levocetirizine was available and increased quantity of simvastatin i.e, 522.93% was available. 92.46% levocetirizine and 59.86% simvastatin were available in pH 9. Simvastatin showed 88.15% and 79.25% availability in pH 1 and 7.4 respectively. These results are shown in Figures 2a-2d.

The interaction of levocetirizine with rosuvastatin in buffers of pH 4 increase the availability of levocetirizine upto 281.38% but 104.07% and 100.90% of the drug was available in pH 7.4 and 9 respectively; where as increased availability of rosuvastatin was observed in pH 7.4 and 9 i.e, 455.01% and 264.47% whereas only 60.77% of rosuvastatin was available in pH 4 (Figures 2a-2d).

The high availability of levocetirizine or HMG-CoA reductase inhibitors in the presence of each other is ascribed to the formation of charge transfer complex between them. As this charge transfer complex has high molar absorptivity as a result availability was perceived higher. On the other hand, low availability of levocetirizine or HMG-CoA reductase inhibitors is because of formation of charge transfer complex of low molar absorptivity or suppression of levocetirizine availability by HMG-CoA reductase inhibitors [26].

Conclusions

The interaction results between levocetirizine and HMG-CoA reductase inhibitors reveal that levocetirizine has tendency to bind with the mentioned interacting drugs. This results in significant change in the availability of not only levocetirizine but also of interacting drugs in most of the cases. These interactions reveal that charge transfer complexes are formed in between levocetirizine and HMG-CoA reductase inhibitors. This may affect the availability of levocetirizine and interacting drugs. On the basis of these findings, it is anticipated that availability of levocetirizine can be affected by the co-administration of these classes of drugs, leading to decrease or loss of therapeutic efficacy of these drugs. Therefore, for the co-administration of these two classes of drugs, a proper interval should be maintained.

References

1. Block JH, Beale JM (2011) Wilson and Givold’s Textbook of Organic Medicinal and Pharmaceutical Chemistry 10, 11th Editions, Volume 10, Lippincott-Raven Publishers, USA.
2. Strolin Benedetti M, Whomsley R, Mathy FX, Jacques P, Eспie P, et al. (2008) Stereospecific renal tubular secretion of levocetirizine and dextrocetirizine, the two enantiomers of the H1-antihistamine cetirizine. Fundam Clin Pharmacol 22: 19-23.
3. Strolin Benedetti M, Whomsley R, Baltes E (2004) Pharmacokinetic drug-drug interactions involving H1 antihistamines in humans. Marone G (Editor), Clinical immunology and allergy in medicine (Proceedings EAACI 2002 congress), JGC Editions, Napplse, Italy, 625-632.
4. Whomsley R, Gerim B, Brochot A, Strolin BM, Baltes E (2003) Transport characteristics of cetirizine and levocetirizine in CaCO₂ cell monolayers. Allergy 58: 274.
5. Banu J, Kalu DN (2002) Effects of cerivastatin and parathyroid hormone on the lumbar vertebra of aging male Sprague-Dawley rats. Bone 31: 173-179.
6. Mundy G, Garrett R, Harris S, Chan J, Chen D, et al. (1999) Stimulation of bone formation in vitro and in rodents by statins. Science 286: 1946-1949.
7. Meier CR, Schlienger RG, Kraendlin ME, Schlegel B, Jick H (2000) HMG-CoA reductase inhibitors and the risk of fractures. JAMA 283: 3205-3210.
8. Oxlund H, Dalstra M, Andreassen TT (2001) Statin given perorally to adult rats increases cancellous bone mass and compressive strength. Calcif Tissue Int 69: 299-304.
9. Skoglund B, Forslund C, Aspenberg P (2002) Simvastatin improves fracture healing in mice. J Bone Miner Res 17: 2004-2008.
10. Whang K, Zhao M, Qiao M, Rossini G, Horn D, et al. (2000) Administration of lovastatin locally in low doses in a novel delivery system induces prolonged bone formation. Journal of Bone & Mineral Research 15(Suppl): S225.
11. Kwak B, Muhlaupt F, Myli S, Mach F (2000) Statins as a newly recognized type of immunomodulator. Nat Med 6: 1399-1402.
12. Bakker-Arkema RG, Davidson MH, Goldstein RJ, Davignon J, Isaacschoin JL, et al. (1998) Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. JAMA 275: 128-133.
13. Stein EA, Lane M, Laskarzewski P (1998) Comparison of statins in hypertriglyceridemia. Am J Cardiol 81: 686-698.
14. Marais AD, Naoumova RP, Firth JC, Penny C, Neuwirth CK, et al. (1997) Decreased production of low density lipoprotein by atorvastatin after apheresis in homozygous familial hypercholesterolemia. J Lipid Res 38: 2071-2078.
15. Bredie SJ, de Bruin TW, Demacker PN, Kastelein JJ, Stalenhoef AF (1995) Comparison of gemfibrozil versus simvastatin in familial combined hyperlipidemia and effects on apolipoprotein-B-containing lipoproteins, low-density lipoprotein subfraction profile, and low-density lipoprotein oxidizability. Am J Cardiol 75: 348-353.
16. Launay-Vacher V, Izzedine H, Dayer G (2005) Statins' dosage in patients with renal failure and cyclosporine drug-drug interactions in transplant recipient patients. J Int Med 101: 9-17.
17. Mück W, Ochmann K, Rohde G, Unger S, Kuhlmann J (1998) Influence of erythromycin pre- and co-treatment on single-dose pharmacokinetics of the HMG-CoA reductase inhibitor cerivastatin. Eur J Clin Pharmacol 53: 469-473.
18. Siedlik PH, Olzon SC, Yang BB, Stern RH (1999) Erythromycin coadministration increases plasma atorvastatin concentrations. J Clin Pharmacol 39: 501-504.
19. Chouhan UM, Chakrabarti S, Millward LJ (2005) Simvastatin interaction with clarithromycin and amiodarone causing myositis. Ann Pharmacother 39: 1760-1761.
20. Pruksaritnont T, Ma B, Tang C, Meng Y, Assang C, et al. (1999) Metabolic interactions between mibefradil and HMG-CoA reductase inhibitors: an in vitro investigation with human liver preparations. Br J Clin Pharmacol 47: 291-298.
21. Botbol MB (1999) Distinct drug-interaction profiles for statins. Am J Health Syst Pharm 56: 1019-1020.
22. Grauer PJ, Vega JM, Mercuri MF, Dobrinarska MR, Tober JA (1999) Concomitant use of cytochrome P450 3A4 inhibitors and simvastatin. Am J Cardiol 84: 811-815.
23. Haria M, McTavish D (1997) Pravastatin. A reappraisal of its pharmacological properties and clinical effectiveness in the management of coronary heart disease. Drugs 53: 299-336.
24. Saeed Arayne M, Sultana N, Shamshad H, Mirza AZ (2010) Drug interaction studies of glidugidone with fexofenadine, cetirizine, and levocetirizine. Med Chem Res 19: 1064-1073.
25. Liu X, Du Y, Sun W, Kou J, Yu B (2009) Study on the interaction of levocetirizine dihydrochloride with human serum albumin by molecular spectroscopy. Spectrochim Acta A Mol Biomol Spectrosc 74: 1189-1196.
26. Nawaz M, Arayne MS, Sultana N (2013) Drug interactions and synthesis of cetpirome with hypoglycemic agents. Medicinal Chemistry Research 22: 3581-3588.
27. Gul S, Sultana N, Arayne MS, Shamim S, Akhtar M (2012) New method for optimization and simultaneous determination of sparflaxin and non-steroidal anti-inflammatory drugs: Its in-vitro application. American Journal of Analytical Chemistry 3: 328-337.
28. Sultana N, Arayne MS, Shafl N (2007) In vitro interaction studies of dillazem with NSAID's using UV spectrophotometry and RP-HPLC techniques. Pak J Pharm Sci 20: 202-213.
29. Arayne MS, Sultana N, Zuberi MH, Haroon U (2010) In vitro studies of interaction between metformin and NSAIDs (Non-steroidal anti-inflammatory drugs) using spectrophotometry and RP-high performance liquid chromatography. J Chin Chem Soc 55: 206-211.
30. Arayne MS, Sultana N, Urooj H, Batool Z (2009) In vitro evidences for simvastatin and isosaratan potassium interaction and it's in vivo implications. J Chin Chem Soc 54: 432-436.
31. Sultana N, Arayne MS, Ifikhar B, Nawaz M (2008) A New RP-HPLC Method for Monitoring of Atenolol: Application to Atenolol Metal Interaction Studies. J Chin Chem Soc Pak 30: 113-118.
32. Sultana N, Arayne MS, Ahmed N (2006) In vitro availability of metformin in presence of h(2) receptor antagonists. Pak J Pharm Sci 19: 28-34.

33. Sultana N, Arayne MS, Quraish R (2007) In vitro interactions of captopril with H2-receptor antagonists. Pak J Pharm Sci 20: 132-139.

34. (2007) British Pharmacopoeia. Her Majesty's Stationary Office. 2: 248-257.