Drug-Drug Interaction studies of Levocetirizine with Losartan Potassium

Khalid Aftab*, Shafaque Mehboob2, Afshan Mehboob Khan3, Najma Sultana4 and Syed Arayne4

1Department of Pharmacology & Therapeutics, Islam Medical & Dental College, Sialkot, Pakistan
2Institute of Pharmaceutical Sciences, Jinnah Sindh Medical University, Karachi, Pakistan
3Department of Physiology, Sir Syed Medical College, Karachi, Pakistan
4Department of Pharmaceutical Chemistry, University of Karachi, Karachi, Pakistan

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*Corresponding author: Khalid Aftab, Professor & HoD Pharmacology & Therapeutics, Islam Medical & Dental College, Sialkot - 51311, Pakistan, Email: khalidaftabikhan@hotmail.com

Abstract

Objective: The objective of the study was to evaluate the drug-drug interaction studies of Levocetirizine with Losartan potassium

Methodology: Calibration curve studies of working standard solutions of Levocetirizine and Losartan potassium (0.01-0.1 m Mole) were scanned. Maxima appeared at 231nm for Levocetirizine and 205 nm for Losartan potassium. The calibration curve obeyed Beer Lambert's Law. Lone availabilities of both the drugs were studied in pH 1, pH4, and pH 7.4 and pH9 at 37°C on B.P dissolution apparatus. To study the drug- drug interaction of Levocetirizine (5mg tablet) with Losartan potassium (50mg tablet), both the drugs were introduced to the dissolution apparatus at zero time and the absorbance maxima were measured at the corresponding wavelength. Graphs were plotted for % availability of drug versus time at each set of experiment.

Results: The % availability of Levocetirizine in the buffers of pH simulated to gastric juice, pH 4and pH 7.4 in the presence of Losartan potassium was 0.00%, 2676.45% and 4195.18% respectively but the availability of losartan potassium was increased up to 1960.23% in simulated to gastric pH and decreased upto and 63.07%and 0% in the buffers of pH 4, and 1 respectively. Maximum interaction is observed at pH 9 i.e., 0%.

Conclusion: On the basis of these studies, it is concluded that Levocetirizine form a charge-complex with Losartan potassium; therefore, co-administration of these drugs should be avoided.

Keywords: Levocetirizine; Losartan potassium; Drug-Drug Interactions; Absorbance Maxima

Introduction

Levocetirizine is a third generation non-sedative anti histamine, developed from the second generation anti-histamine cetirizine, works by blocking histamine receptors. It does not prevent the release of histamine from mast cell, but prevent its binding from its receptors. This in turn prevents the release of other allergic chemicals and increased blood supply to the area, and provides relief from the typical symptoms of hay fever and used to manage intermittent and persistent allergic rhinitis [1]. The qualitative assays of Levocetirizine have been performed in different subjects to determine the anti-allergic activity of the drug [2-7]. Ultraviolet (UV) detection was performed for the quantification of Levocetirizine in the tablets and for enantiomer purity testing of the drug by a validated, selective, precise and accurate method [8].

For the treatment of patients with seasonal and perennial allergic rhinitis with or without concurrent asthma, Levocetirizine was reported 5mg once daily for 32 days. Alleviation and improvement of the symptoms such as rhinorrhea, sneezing, conjunctivitis, and asthmatic symptoms were observed in over 80% of the patients at the end of the experiment [9,10]. As compared to cetirizine, Levocetirizine of 5mg dosage is Pharmacokinetically equals to 10 mg cetirizine [11]. Levocetirizine and Dextrocetirizine may have consequences for drug interactions at the renal level [12]. Levocetirizine is a
weak P-glycoprotein substrate; therefore, it should be taken with
cautions with the drugs which are either PgP substrate such as
Ketoconazole, Cyclosporine or Verapamil or PgP inducers like
rifampicin or inhibitor such as Erythromycin, Azithromycin or
Itraconazole [13,14].

Losartan potassium is antihypertensive drug belongs to
Angiotensin receptor antagonist. It produces its action by
blocking angiotensin subtype [1]. Its adverse effects include
headache, upper respiratory infections, dizziness, fatigue, and
cough [15,16]. Many sensitive methods are reported for the
quantitative determination of losartan in different dosages as
well as samples including spectrofluorometric method, Reverse
Phase-High Performance Liquid Chromatography method, APCI
method and RP-HPLC method [17,18]. Losartan interact with
Ritonavir and Nelfinavir. It has also tendency to interact with H2
receptor antagonists proton pump inhibitor and Atorvastatin
[19,20]. The object of present work is to evaluate the possible
drug-drug interactions of Levocetirizine with Losartan
potassium if used co-administered.

Methodology

To study drug interactions, reported methods were followed
[21]. Reference standard of Levocetirizine was gifted by Hilton
Pharma (Pvt.), Karachi, whereas, Losartan potassium was given
by Zafa Pharmaceutical Laboratories (Pvt.) Ltd, Karachi. Each
product was labeled properly and expiry dates checked and they
were not earlier than two years old at the time of study. All the
reagents used were of analytical grade and all the glassware
were used of Pyrex brand.

Equipment: Using the following calibrated equipment’s,
analytical measurements were carried out. Electrical balance
[Mettler Toledo AB54], pH meter [Mettler Toledo MP220], UV
visible spectrophotometer [Model 1606, Shimadzu, Japan] with
10 mm path length connected to a P-IV computer loaded with
Shimadzu UVPC version 3.9 software was used in these studies,
1 cm rectangular quartz cells, ground glass distillation assembly,
water distillation unit [GEL type 2001/2, No. 10793600G],
melting point apparatus [Gallenkamp] and deionizer [Stedec
CSW-300] were used. The dissolution equipment was
manufactured to the B.P 2007 standard.

Preparation of solutions: Levocetirizine 0.04254 gm and
Losartan potassium 0.0461gm weighed accurately and each
drug was dissolved in one liter of buffers of pH 1-9 to get primary
solution of 1 m Mole, from that the stock solution of 0.1 m Mole
was prepared by diluting 25 ml of primary solution into 250 ml
volumetric flask containing corresponding buffers. Different
dilutions ranging from 0.01 to 0.1 m Mole were prepared by
diluting the stock solutions (0.1 m Mole) with different buffer
solutions of pH 9. For this purpose 5, 10, 15, 20, 25, 30, 35, 40
and 45 ml of stock solutions were separately pipette out in nine
different 50 ml volumetric flasks and diluted with individual
buffer solutions up to the mark to prepare the working solutions
of 0.01-1.0mMole. These solutions were used for calibration
curve studies.

Calibration curve studies: working standard solutions
of both the drugs of 0.01-0.1 m Mole were prepared for this
purpose. The absorbance maxima were scanned in the region
of 200-700 nm against the reagent blank. Maxima appeared at
231 nm for Levocetirizine and 205 nm for Losartan potassium.
The calibration curve was plotted for absorbance against
concentration and straight lines were obtained which obeyed
Beer Lambert’s Law. Epsilon value was also calculated from these
observations. In vitro availability studies: the in vitro availability
of Levocetirizine was studied in simulated gastric juice (pH 1),
pH 4, pH 7.4 and in pH 9 at 37°C on B.P dissolution apparatus.
5mg of Levocetirizine was introduced in 1 liter dissolution
medium. Aliquots of 5 ml were withdrawn intermittently at 15
minutes time intervals for 120 minutes and assayed for the drug
contents. The volume of the dissolution fluid was maintained by
adding an equivalent amount of dissolution fluid withdrawn in
the same bath at the same temperature. The sample was scanned
in the region 200-700 nm against blank. The same procedure
was adopted to calculate the availability of 50mg of Losartan
potassium tablet.

Drug-drug interaction studies of Levocetirizine and
Losartan potassium: To study the drug-drug interaction of
Levocetirizine (5 mg tablet) and Losartan potassium (50 mg
tablet), both the drugs were introduced to the dissolution
medium at zero time. Same procedure was adopted to measure
the absorbance maxima of both the drugs at the corresponding
wavelength. (Figures 1 & 2) were also plotted for % availability
of drug versus time at each set of experiment.
**Results**

Levocetirizine and Losartan potassium interfere at each other’s wavelength. The lone availability of both the drugs in all the pH calculated not more than 115%. After the interaction, availabilities of Levocetirizine as well as Losartan potassium increased in the presence of each other in simulated gastric juice and the rest of the buffers. At the start of experiment in simulated gastric juice, 61.95% of the drug was available which exceeded to 436.78% till the end of the experiment. Similarly, in the buffers of pH 4, 7.4 and 9, an increased availability of Levocetirizine was observed i.e., 376.90%, 436.78% and 436.78% respectively. The availability of Losartan potassium was increased up to 2395.95%, 4195.18% 1960.23 and 61.90% in simulated to gastric pH and in the buffers of pH 4, pH 7.4 and pH 9 respectively (Figure 3)(Tables 1-3).

![Figure 3: Relative percent availability of Levocetirizine and Losartan potassium in different pH before and after interaction.](image)

**Table 1:** Concentration and corresponding absorbance of Levocetirizine in different pH.

<table>
<thead>
<tr>
<th>Conc.</th>
<th>pH1</th>
<th>pH4</th>
<th>pH7.4</th>
<th>Ph9</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.1675</td>
<td>0.1431</td>
<td>0.1278</td>
<td>0.1414</td>
</tr>
<tr>
<td>0.02</td>
<td>0.327</td>
<td>0.2711</td>
<td>0.25</td>
<td>0.2843</td>
</tr>
<tr>
<td>0.03</td>
<td>0.4965</td>
<td>0.4159</td>
<td>0.3739</td>
<td>0.4274</td>
</tr>
<tr>
<td>0.04</td>
<td>0.6499</td>
<td>0.5604</td>
<td>0.4697</td>
<td>0.5695</td>
</tr>
<tr>
<td>0.05</td>
<td>0.8054</td>
<td>0.7032</td>
<td>0.6152</td>
<td>0.7112</td>
</tr>
<tr>
<td>0.06</td>
<td>0.969</td>
<td>0.8503</td>
<td>0.739</td>
<td>0.8602</td>
</tr>
<tr>
<td>0.07</td>
<td>1.1246</td>
<td>0.9906</td>
<td>0.8638</td>
<td>0.986</td>
</tr>
<tr>
<td>0.08</td>
<td>1.439</td>
<td>1.1398</td>
<td>0.9844</td>
<td>1.1398</td>
</tr>
<tr>
<td>0.09</td>
<td>1.4498</td>
<td>1.2775</td>
<td>1.1123</td>
<td>1.2853</td>
</tr>
<tr>
<td>0.10</td>
<td>1.6012</td>
<td>1.4381</td>
<td>1.235</td>
<td>1.4541</td>
</tr>
</tbody>
</table>

**Table 2:** Concentration and corresponding absorbance of Losartan potassium in different pH.

<table>
<thead>
<tr>
<th>Conc.</th>
<th>pH0.1</th>
<th>pH4</th>
<th>pH7.4</th>
<th>Ph9</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.2000</td>
<td>0.2054</td>
<td>0.1782</td>
<td>0.6936</td>
</tr>
<tr>
<td>0.02</td>
<td>0.3650</td>
<td>0.4005</td>
<td>0.3882</td>
<td>0.7976</td>
</tr>
<tr>
<td>0.03</td>
<td>0.5914</td>
<td>0.5928</td>
<td>0.5980</td>
<td>0.9266</td>
</tr>
<tr>
<td>0.04</td>
<td>0.7848</td>
<td>0.7859</td>
<td>0.8307</td>
<td>1.0333</td>
</tr>
<tr>
<td>0.05</td>
<td>0.9788</td>
<td>0.9716</td>
<td>1.0310</td>
<td>1.1447</td>
</tr>
<tr>
<td>0.06</td>
<td>1.1735</td>
<td>1.1722</td>
<td>1.2615</td>
<td>1.2589</td>
</tr>
<tr>
<td>0.07</td>
<td>1.3707</td>
<td>1.3607</td>
<td>1.4535</td>
<td>1.3552</td>
</tr>
<tr>
<td>0.08</td>
<td>1.5671</td>
<td>1.5660</td>
<td>1.6790</td>
<td>1.4702</td>
</tr>
<tr>
<td>0.09</td>
<td>1.7548</td>
<td>1.777</td>
<td>1.8981</td>
<td>1.5786</td>
</tr>
<tr>
<td>0.10</td>
<td>1.9225</td>
<td>1.9556</td>
<td>2.0964</td>
<td>1.6799</td>
</tr>
</tbody>
</table>

**Table 3:** Maximum Availability of Levocetirizine and Losartan potassium in simulated gastric juice, pH 4, pH 7.4 and pH 9 after interaction.

<table>
<thead>
<tr>
<th>Buffers</th>
<th>% available Levocetirizine(231 nm)</th>
<th>% available Losartan potassium(205nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 1</td>
<td>0.00</td>
<td>1960.23</td>
</tr>
<tr>
<td>pH 4</td>
<td>2676.45</td>
<td>63.07</td>
</tr>
<tr>
<td>pH 7.4</td>
<td>4195.18</td>
<td>0.00</td>
</tr>
<tr>
<td>pH 9</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Discussion

This procedure was design to simultaneously measure the quantities of two drugs present in the same solution without separating them. This was accomplished by developing the mathematical relationship between Levocetirizine and interacting drug because both the drugs have interfered at each other’s wavelength which gave the concentration of two drugs simultaneously, when maxima measured at their absorption. Molar absorptivities were used in calculating the quantities of these drugs in a solution of unknown concentration.

According to Beer’s law; \[A = \varepsilon b c \] (1)

Where, \(A\) = absorbance, \(\varepsilon\) = molar absorptivity or epsilon, \(b\) = path length of the cell (1cm) & \(c\) = concentration of the solution.

If more than two components are present in the solution which was absorbing at the same wavelength, the above equation (1) can be written as;

\[A = \varepsilon b Ca + \varepsilon'BbCb \]  

(2)

Where, \(Ca\) and \(Cb\) were concentrations of the two components present in the solution and \(\varepsilon\) and \(\varepsilon'\) were the absorptivities of the two components obtained from the absorbance of the standard solution. Similarly, this equation could be derived for the absorbance taken at another wavelength.

Levocetirizine absorbs maximum at 231nm and Losartan Potassium at 205respectively. Let \(Ca\) be the concentration of Levocetirizine and \(Cb\) is of Losartan potassium. Now equation (2) can be written as;

\[A_{231} = a_{231}b_{231}Ca + a_{b2}b_{b2}Cb \]  

(3)

\[A_{224} = a_{224}b_{224}Ca + a_{b1}b_{b1}Cb \]  

(4)

Where, \(b\) is 1, and \(a_1\) and \(a_2\) were absorptivities of Levocetirizine at 231nm and 205nm and \(b_1\) and \(b_2\) were of Losartan Potassium at 231nm and 205nm. By multiplying equation (3) with \(a_2\) and equation (4) with \(a_1\), we get;

\[Cb = \frac{A_{231} - A_{205}a_{1}}{a_{b1}a_{1b2}} \]  

(5)

\[Cb = \frac{A_{231}b_{2} - A_{205}b_{2}}{a_{b1}a_{1b2}} \]  

(4)

The above equations (5) and (6) were used to calculate % availabilities of Levocetirizine and Losartan potassium in the presence of each other [22]. Both the drugs showed more than 200% availability that is impossible. This may be due to the formation of charge-transfer complex. Therefore, the resultant chelate proved the drug-drug interaction of Levocetirizine with Losartan potassium in different pH. Therefore, precaution should be taken by a hypertensive patient while using Levocetirizine (an anti-allergic drug) with Losartan Potassium. In vivo and large scale studies are highly recommended because as a result of interaction both the drugs can either decrease or even lose their therapeutic effects.

Conclusion

Several studies are reported which indicate that Levocetirizine dihydrochloride has tendency to form complex with other drugs or substances [22,23]. On the other hand, availability of Losartan Potassium has also been observed to be influenced in the presence of other drugs [24,25]. Keeping this fact in view, current study is conducted which also supports the drug-drug interactions of Levocetirizine and Losartan Potassium. On the basis of these studies, it is concluded that Levocetirizine is a form of charge-complex with Losartan potassium; therefore the co-administration of these drugs should be avoided.

References


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