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Drug-Drug Interaction Studies of Levocetirizine with Atenolol

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Abstract: The objective of the study was to evaluate the drug-drug interaction studies of levoceterizine with atenolol. Calibration curve studies of working standard solutions of levocetirizine and atenolol (0.01~0.1 mmol) were scanned. Maxima appeared at 231 nm for levocetirizine and 224 nm for atenolol. The calibration curve obeyed Beer Lambert's Law. Lone availabilities of both the drugs were studied in pH 1, pH 4, pH 7.4 and pH 9 at 37 °C on B.P. (British Pharmacopoeia) dissolution apparatus. To study the drug-drug interaction of levocetirizine (5 mg tablet) and atenolol (100 mg tablet), both the drugs were introduced to the dissolution apparatus in simulated gastric juice (pH 1), pH 4, pH 7.4 and pH 9 at 37 °C at zero time and measured the absorbance maxima of both the drugs at the corresponding wavelength. Graphs were plotted for availability percentage (%) of drug versus time at each set of experiment. The availability percentage (%) of levocetirizine in the buffers of pH simulated to gastric pH 4, pH 7.4 and pH 9 in the presence of atenolol was 436.78%, 376.90%, 436.78% and 436.78%, respectively, but the availability of atenolol was increased up to 214.80%, 212.96%, 214.93% and 231.51% in simulated to gastric pH and in the buffers of pH 4, pH 7.4 and pH 9, respectively. On the basis of these studies, it is concluded that levocetirizine forms a charge-complex with atenolol; therefore, co-administration of these drugs should be avoided.

Key words: Levocetirizine, atenolol, drug-drug interactions, absorbance maxima.

1. Introduction

Levocetirizine is a third generation non-sedative anti-histamine, developed from the second generation anti-histamine cetirizine and works by blocking histamine receptors. It does not prevent the release of histamine from mast cells, but prevents 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]. UV (ultraviolet) detection was performed for the quantification of levocetirizine in the tablets and for enantiomeric 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 5 mg 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 5 mg dosage is pharmacokinetically equal to 10 mg cetirizine [11].

Levocetirizine and dextrocetirizine may have consequences for drug interactions at the renal level

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[12]. Levocetirizine is a weak PgP (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].

Atenolol is a β-adrenolytic, cardio-selective drug efficient in cases of arterial hypertension and cardiac arrhythmias. Its adverse effects include fatigue, sleep disturbance and depressions. Many sensitive methods are reported for the quantitative determination of atenolol in different dosages, as well as samples including spectroflurometric method, RP-HPLC (reverse phase-high performance liquid chromatography) method, APCI (atmospheric pressure ionization interface) method and RP-HPLC method [15-18].

Many drug interactions of atenolol have been reported. Enalapril and atenolol give less hypotensive effects when given together, with attenuation of the potential additive response by 30~50%.

Atenolol acted synergistically only at a low hydralazine dose. Moreover, it interfered with the vasodilator response of hydralazine in the heart, skeletal muscles and the arteriovenous anastomosis and abolished the negative effect of hydralazine on this parameter. It also interacts with metal [19].

The object of present work is to evaluate the possible drug-drug interactions of levoceterizine with atenolol if co-administered.

2. Methodology

To study drug interactions, reported methods were followed [20]. Reference standard of levocetirizine was gifted by Hilton Pharma (Pvt.), Karachi, whereas, atenolol 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 at the time of study. All the reagents used were of analytical grade and all the glassware were used of Pyrex brand.

2.1 Equipments

Using the following calibrated equipments, 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.

2.2 Preparation of Solutions

Levocetirizine 0.04254 gm and atenolol 0.0266 gm were weighed accurately and each drug dissolved in one liter of buffers of pH 1~9 to get primary solution of 1 mmol, from that the stock solution of 0.1 mmol 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 mmol were prepared by diluting the stock solutions (0.1 mmol) 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 0.01~0.09 mmol. These solutions were used for calibration curve studies.

2.3 Calibration Curve Studies

Working standard solutions of both the drugs of 0.01~0.1 mmol 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 224 nm for atenolol. 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.

2.4 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. 5 mg of levocetirizine was introduced in 1 L dissolution medium. Aliquots of 5 mL were withdrawn intermittently at 15 min time intervals for 120 min 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 100 mg of atenolol tablet.

2.5 Drug-Drug Interaction Studies of Levocetirizine and Atenolol

To study the drug-drug interaction of levocetirizine (5 mg tablet) and atenolol (100 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. Figs. 1 and 2 (Tables 1 and 2) were also plotted for availability percentage (%) of drug versus time at each set of experiment.

3. Results

Levocetirizine and atenolol 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 atenolol, increased in the presence of each other in simulated gastric juice and the rest of the buffers. At

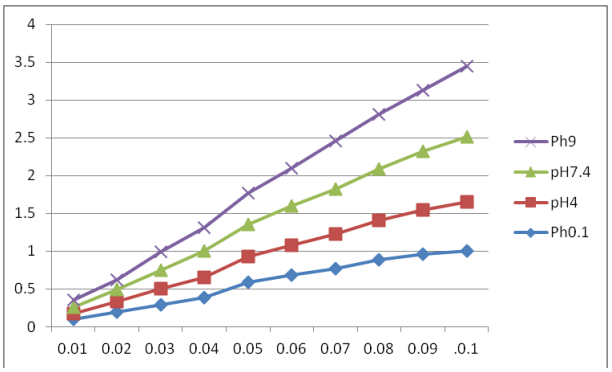

Fig. 1 Concentration (mmol) and corresponding absorbance graph of levocetirizine in different pH.

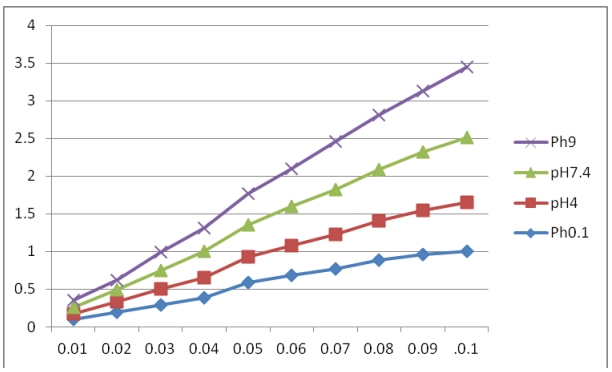

Fig. 2 Concentration (mmol) and corresponding absorbance graph of Atenolol in different pH.

Table 1 Concentration and corresponding absorbance of levocetirizine in different pH.

Concentration (mmol)	pH 1	pH 4	pH 7.4	pH 9
0.01	0.1675	0.1431	0.1278	0.1414
0.02	0.327	0.2711	0.25	0.2843
0.03	0.4965	0.4159	0.3739	0.4274
0.04	0.6499	0.5604	0.4697	0.5695
0.05	0.8054	0.7032	0.6152	0.7112
0.06	0.969	0.8503	0.739	0.8602
0.07	1.1246	0.9906	0.8638	0.986
0.08	1.439	1.1398	0.9844	1.1398
0.09	1.4498	1.2775	1.1123	1.2853
0.10	1.6012	1.4381	1.235	1.4541

Table 2 Concentration and corresponding absorbance of atenolol in different pH.

Concentration (mmol)	pH 1	pH 4	pH 7.4	pH 9
0.01	0.1034	0.0753	0.0856	0.0936
0.02	0.1914	0.1372	0.1667	0.1236
0.03	0.2877	0.2125	0.2528	0.2421
0.04	0.3843	0.2682	0.3457	0.3131
0.05	0.5907	0.3342	0.4322	0.4167
0.06	0.6842	0.3937	0.5183	0.5038
0.07	0.7704	0.4572	0.5981	0.6361
0.08	0.8817	0.5269	0.6803	0.7241
0.09	0.9626	0.5818	0.7727	0.8160
0.1	1.0028	0.6473	0.8600	0.9357

Table 3 Availability (%) of levocetirizine and atenolol in simulated gastric juice after interaction.

Serial No.	Levocetirizine (231 nm)	Atenolol (224nm)	Percentage of available levocetirizine (%)	Percentage of available atenolol (%)
0	0	0	0	0
15	0.0193	0.0221	17.27	2.09
30	1.4116	1.4807	376.9	51.34
45	1.4321	1.8826	397.15	208.27
60	1.4404	1.9055	401.38	210.37
75	1.4448	1.9143	406.92	211.12
90	1.4520	1.9186	413.32	211.44
105	1.46778	1.9333	418.04	213.57
120	1.4753	1.9497	436.78	214.80

Table 4 Availability (%) of levocetirizine and atenolol in pH 4 after interaction.

Serial No.	Levocetirizine (231 nm)	Atenolol (224 nm)	Percentage of available levocetirizine (%)	Percentage of available atenolol (%)
0	0.00	0.00	0.00	0.00
15	1.2935	1.7363	305.28	193.18
30	1.3365	1.8011	305.54	201.07
45	1.3699	1.8034	308.06	203.39
60	1.3726	1.8348	308.47	205.28
75	1.3743	1.8422	315.12	206.08
90	1.3799	1.8513	328.56	206.60
105	1.3844	1.8523	352.46	208.08
120	1.4089	1.8647	376.90	212.96

the start of experiment in simulated gastric juice, 17.27% of the drug was available which exceeded to 436.78% till the end of the experiment. Similarly, in the buffers of pH 4, pH 7.4 and pH 9, an increased availability of levocetirizine was observed, i.e., 376.90%, 436.78% and 436.78%, respectively. The availability of atenolol was increased up to 214.80%, 212.96%, 214.93% and 231.51% (Fig. 3 and Tables 3-6) in simulated to gastric pH and in the buffers of pH 4, pH 7.4 and pH 9, respectively.

4. Discussion

This procedure was designed 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

Table 5 Availability (%) of levocetirizine and atenolol in pH 7.4 after interaction.

Serial No.	Levocetirizine (231 nm)	Atenolol (224 nm)	Percentage of available levocetirizine (%)	Percentage of available atenolol (%)
0	0.00	0.00	0.00	0.00
15	0.0193	0.0221	17.27	2.09
30	1.4116	1.4807	376.90	51.34
45	1.4321	1.9055	397.15	210.37
60	1.4404	1.9143	398.27	208.27
75	1.4448	1.9186	406.92	211.12
90	1.4520	1.9055	413.32	211.44
105	1.4678	1.9333	418.04	213.57
120	1.4953	1.9497	436.78	214.93

Table 6 Availability (%) of levocetirizine and atenolol in pH 9 after interaction.

Serial No.	Levocetirizine (231 nm)	Atenolol (224 nm)	Percentage of available levocetirizine (%)	Percentage of available atenolol (%)
0	0.00	0.00	0.00	0.00
15	0.1293	0.0320	19.01	3.01
30	1.4116	1.4707	382.16	53.44
45	1.4304	1.9113	387.52	211.12
60	1.4382	1.9124	397.15	22146
75	1.4401	1.9221	408.34	224.91
90	1.4504	1.9355	409.91	230.35
105	1.4678	1.9381	410.78	231.25
120	1.4853	1.9451	420.31	231.51

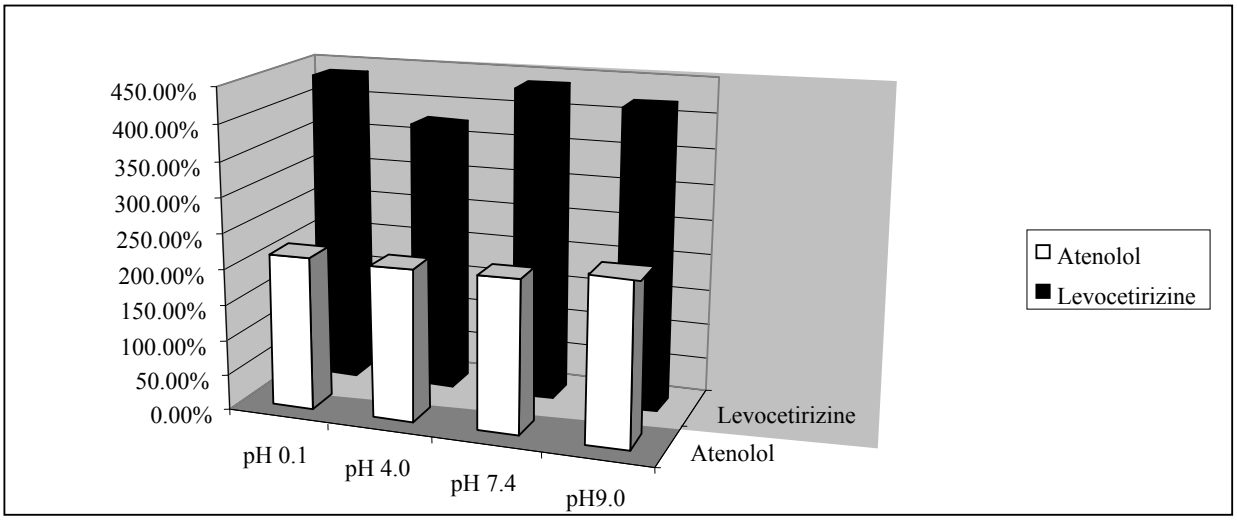

Fig. 3 Maximum percent availability of levocetirizine and atenolol in different pH after drug interactions.

their absorption. Molar absorptivities were used in calculating the quantities of these drugs in a solution of unknown concentration.

According to Beer's law:

$$A = \varepsilon bc \text{ and } \varepsilon = A/C \cdot b \quad (1)$$

where, A = absorbance, ε = molar absorptivity or epsilon, b = path length of the cell (1 cm), c = concentration of the solution.

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

$$A = \varepsilon bC_a + \varepsilon \square bC_b \quad (2)$$

where, C_a and C_b were concentrations of the two components present in the solution and ε and ε□ were the absorptivities of the two components obtained from the absorbance of the standard solution. Similarly, Eq. (2) could be derived for the absorbance taken at another wavelength.

Levocetirizine absorbs maximum at 231 nm and atenolol at 224 nm, respectively. Let C_a be the concentration of levocetirizine and C_b is of atenolol. Now Eq. (2) can be written as:

$$A_{231} = a_1bC_a + b_1bC_b \quad (3)$$

$$A_{224} = a_2bC_a + b_2bC_b \quad (4)$$

where, b is 1, a_1 and a_2 were absorptivities of levocetirizine at 231 nm and 224 nm, and b_1 and b_2 were of atenolol at 231 nm and 224 nm. By multiplying Eq. (3) with a_2 and Eq. (4) with a_1, we get:

$$C_b = \frac{A_{231}a_2 - A_{224}a_1}{a_2b_1 - a_1b_2} \quad (5)$$

$$C_a = \frac{A_{231}b_2 - A_{224}b_1}{a_2b_1 - a_1b_2} \quad (6)$$

The above Eqs. (5) and (6) were used to calculate the availabilities (%) of levocetirizine and other drug (atenolol) in the presence of each other [21]. 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 atenolol in different pH. Therefore, precaution should be taken by a hypertensive patient while using levocetirizine (an anti-allergic drug) with atenolol. *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.

5. Conclusions

On the basis of these studies, it is concluded that levocetirizine is a form of charge-complex with atenolol; therefore the co-administration of these drugs should be avoided.

Conflict of Interest

There is no conflict of interest.

Acknowledgments

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