REVISTA CIENTÍFICA ISSN: 0004-2927

Ars Pharmaceutica

Ars Pharm. 2012; 53(4)

FACULTAD DE FARMACIA. UNIVERSIDAD DE GRANADA. ESPAÑA

http://farmacia.ugr.es/ars

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Binding of desloratadine and atenolol with bovine serum albumin and their in-vitro interactions

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Original Paper
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Competing interest / Conflicto de interes:
Author declares no conflict of interest.

Received: 3/05/2012
Accepted: 12/09/2012

RESUMEN

Objetivo: Unir atenolol, antagonista selectivo de los receptores β_1, y desloratadina, antagonista de los receptores H_1, a albúmina sérica bovina.

Método: El análisis de la unión se analizó mediante diálisis de equilibrio utilizando ranitidina y diazepam como sondas específicas para el sitio I y sitio II respectivamente

Resultados: Los resultados sugirieron dos conjuntos de constantes de asociación. Para el atenolol: constante de asociación con afinidad elevada (k_1 = 5 x 10-5 M-1) con baja capacidad (n_1 = 2) y constante de asociación con afinidad baja (k_2 = 5 x 10-5 M^{-1}) con alta capacidad (n_2 = 5), mientras que para la desloratadina: constante de afinidad de asociación elevada (k_1 = 45 x 10-5 M^{-1}) con baja capacidad (n_1 = 1,3) y constante de afinidad de asociación baja (k_2= 5 x 10-5 M^{-1}) con alta capacidad (n_2 = 2,5), a un pH 7,4 y 27 °C. Tras la administración conjunta de atenolol y desloratadina en presencia o ausencia de ranitidina o diazepam, la desloratadina provocó la liberación del atenolol de su sitio de unión a la albúmina sérica bovina, provocando una disminución de la unión del atenolol a la albúmina sérica bovina. La fracción libre de atenolol incrementó del 84,1% al 99% y la concentración de la desloratadina de 0 x 10^{-5} M a 14 x 10^{-5} M. En presencia de diazepam como sonda específica para el sitio II, la desloratadina incrementó la fracción libre de atenolol del 0,45% to 14,3%.

Conclusión: Los datos obtenidos indican la interacción de concentraciones elevadas de desloratadina a los sitios de unión de la albúmina sérica bovina modificando las propiedades farmacocinéticas del atenolol.

PALABRAS CLAVE: Atenolol, desloratadine, drug-drug interaction, bovine serum albumin, equilibrium dialysis

ABSTRACT

Aims: The binding of atenolol a selective β_1 receptor antagonist and desloratadine, an H_1 receptor antagonist, to bovine serum albumin.

Methods: The analysis of binding was studied by equilibrium dialysis method (ED) using ranitidine and diazepam as site-1 and site-2 specific probe, respectively.

Results: The study suggested two sets of association constants, for atenolol: high affinity association constant (k_1 = 5 x 10-5 M^{-1}) with low capacity (n_1 = 2) and low affinity association constant (k_2 = 2.5 x 10-5 M^{-1}) with high capacity (n_2 = 5), while for desloratadine: high affinity association constant (k_1 = 45 x 10-5 M^{-1}) with low capacity (n_1 = 1.3) and low affinity association constant (k_2 = 5 x 10-5 M^{-1}) with high capacity (n_2 = 2.5) at pH 7.4 and 27 °C. During concurrent administration of atenolol and desloratadine in presence or absence of ranitidine or diazepam, desloratadine causes the release of atenolol from its binding site on BSA resulting reduced binding of atenolol to BSA. The increment in free fraction of atenolol was from 84.01% to 99 % upon the addition of increased concentration of only desloratadine at a concentration of 0 x 10^{-5} M to 14 x 10^{-5} M. In presence of diazepam as site-II specific probes, desloratadine further increases the free fraction of atenolol was from 0.45% to 14.3%.

Conclusion: These data were indicative for the interaction of higher concentration of desloratadine at the binding sites on BSA changing the pharmacokinetics properties of atenolol.

KEY WORDS: Atenolol, desloratadine, drug-drug interaction, bovine serum albumin, equilibrium dialysis

INTRODUCTION

Atenolol, a selective β_1 receptor antagonist, is used in the management of hypertension[1-3]; while desloratadine, a tricyclic H_1-antagonist, is a drug used to treat allergic and other related symptoms[4-6]. This is a very used practice to co-prescribe atenolol and desloratadine for the patient. Hence, the concurrent administration of these two drugs is supposed to modulate the pharmacokinetic profiles such as protein binding, volume of distribution, elimination of each other.

Pharmacokinetic studies revealed that atenolol is incompletely absorbed from oral dosage forms and the bioavailability is approximately 50% due to reduced absorption. After oral administration peak blood levels are observed at 2-4 h and elimination half life of atenolol is calculated from 6 to 9 h by different authors. In plasma only 3% of atenolol are protein-bound[7-9]. Although marked interactions of atenolol are found when calcium or aluminium hydroxide are concurrently administered with the beta blocker[10]. Rifampicin has also reported to affect the pharmacokinetics slightly by a slight reduction in its bioavailability[11]. Orange juice moderately reduce the bioavailability of atenolol by interfering with its absorption from the gastrointestinal tract[12]. Another studies showed that amlodipine displaces atenolol in-vitro from its binding sites[13]. Interactions of valsartan and atenolol have also been reported following single doses[14].

On the other hand it has been reported that the protein binding of desloratadine is 85-89%. The mean elimination half-life of Desloratadine was 27 hours[15-17]. No significant interactions of desloratadine with food materials are reported[18]. However, there is lack of sufficient reports on pharmacokinetic interactions of B-blockers with antihistaminic drugs administered concurrently.

Since, plasma protein binding properties are primarily determinants of the pharmacokinetic properties of most of the drugs, such as plasma clearance, half-life, apparent volume of distribution and the duration and intensity of pharmacologic effect[19,20]. Drug displacement also affects other aspects of drug deposition, such as, metabolism and excretion[21]. Therefore, the present study was undertaken to characterize the binding profiles of atenolol as well as to notify the interaction of desloratadine with atenolol at its binding site on albumin using bovine serum albumin employing equilibrium dialysis methods.

Our studies revealed that binding of atenolol with two sets of association constant: high affinity association constant with low capacity and low affinity association constant with high capacity. Site specific probe displacement study implied that atenolol bind to site II, the diazepam site. However, it has low binding affinity to site I on BSA. While, concurrent administration of desloratadine significantly modulates binding of atenolol to BSA. Desloratadine displaced Atenolol from its binding site of BSA.

MATERIALS AND METHODS

Materials and instruments

Dialysis membrane (molecular weight cut off at 3500 Daltons) and bovine serum albumin (fatty acid free, fraction V, 96-98%) used in the experiment were purchased from Medicell International Ltd., UK and Sigma Chemical Co., USA, respectively. Atenolol, desloratadine, ranitidine hydrochloride and diazepam were kind gift from a local pharmaceutical company of Bangladesh. Disodium hydrogen phosphate (Na_2HPO_4), potassium dihydrogen phosphate (KH_2PO_4), were obtained from Glaxo; U.K. High-resolution UV-VIS spectrophotomer (SP8-400 UV/ VIS Spectrophotometer, Thermospectronic, England.) and Metabolic Shaking Incubator (Clifton Shaking Bath, Nickel Electro Ltd., England.) were used in the experiment. All other chemicals used in the experiment were of commercial grade. Equilibrium Dialysis method was employed in this study. Dialysis membrane used in the experiment was cut into small pieces and was boiled for 8 hours at 65-70 °C in de-ionized water to remove sulfur.

Preparation of standard curve

Standard calibration curve was prepared following the methods reported before[19]. Briefly, for the preparation of standard curves of ranitidine hydrochloride, diazepam, atenolol, desloratadine, solutions of different concentrations (0×10^{-5} M to 10×10^{-5} M) of these drugs were prepared in phosphate buffer of 7.4 and taking absorbance values at determined λ_{max} 318 nm, 235 nm, 273 nm and 242 nm, respectively. Standard curves were obtained by plotting the absorbance values against the corresponding the concentrations.

Estimation of association constant

To determine the association constant of atenolol, different concentrations (2×10^{-5} M to 8×10^{-5} M) of atenolol solutions were mixed with prepared BSA solution (2×10^{-5} M in phosphate buffered saline, pH 7.4) to get a final volume of 5 ml each. These solutions were allowed to stand for sometime for the maximum binding of atenolol to BSA. From each mixture, 3.5 ml of solution was withdrawn and poured into previously prepared semi-permeable membrane tubes and both sides of the membranes were sealed properly as there was no leakage. The membrane tubes containing drug-protein mixture were immersed in conical flasks containing 30 ml of phosphate buffer (pH 7.4)

and were placed in a metabolic shaker for dialysis for 12 hours (27 °C, 20 rpm). Buffer samples were collected from each conical flask after dialysis and free fraction of atenolol was measured by UV spectrophotometer (λ_{max} 273 nm).

Determination of binding site of atenolol using ranitidine as site-I specific probe

To determine the binding sites of atenolol at BSA, the concentrations of BSA and probe (ranitidine hydrochloride as site-I specific probe) were remained fixed in 1:1 ratio (2×10^{-5} M: 2×10^{-5} M) and the concentration of atenolol was added in increased concentration (0 to 16×10^{-5} M). So, the final ratio of BSA: Probe: atenolol were 1:1:0, 1:1:4, 1:1:6, 1:1:8. The dialysis was carried out as described above and free fraction of ranitidine hydrochloride was measured at λ_{max} 318 nm. Only BSA solution and mixture of BSA and atenolol were used as positive and negative control during the measurement.

Determination of binding site of atenolol using diazepam as site-II specific probe

The binding sites of atenolol at BSA, using diazepam as site-II specific probe, were determined employing the same methods as described above. Briefly, BSA: diazepam: atenolol were mixed at 1:1:0, 1:1:1, 1:1:2, 1:1:4. The dialysis was carried out as described above and free concentration of diazepam was measured at λ_{max} 235 nm. Alternatively, BSA: atenolol: diazepam were taken as 1:1:0, 1:1:1, 1:1:2, 1:1:4. After dialysis, free concentration of atenolol was measured at λ_{max} 273 nm. Negative and positive controls were maintained in both cases of measurements.

Determination of binding site of desloratadine using ranitidine as site-I specific probe

For the determination of the binding sites of desloratadine at BSA, the concentrations of BSA and probe (ranitidine hydrochloride as site-I specific probe) were remained fixed in 1:1 ratio (2×10^{-5} M: 2×10^{-5} M) and the concentration of desloratadine was added in increased concentration (0 to 12×10^{-5} M). So, the final ratio of BSA: Probe: desloratadine were 1:1:0, 1:1:2, 1:1:4, 1:1:6. The dialysis was carried out as described above and free fraction of ranitidine hydrochloride was measured at λ_{max} 318 nm. Only BSA solution and mixture of BSA and atenolol were used positive and negative control during the measurement.

Determination of binding site of desloratadine using diazepam as site-II specific probe

The binding sites of desloratadine at BSA, using diazepam as site-II specific probe, were determined employing the same methods as describe above. Briefly, BSA: diazepam: desloratadine were mixed at 1:1:0, 1:1:1, 1:1:2, 1:1:4, 1:1:6. The dialysis was carried out as described above and free concentration of diazepam was measured at λ_{max} 235 nm. Alternatively, BSA: desloratadine: diazepam were taken as 1:1:0, 1:1:1, 1:1:2, 1:1:4, 1:1:6. After dialysis, free concentration of desloratadine was measured at λ_{max} 242 nm. Negative and positive controls were maintained in both cases of measurements.

Effect of desloratadine on atenolol binding to BSA

The effect of desloratadine on atenolol, when bound to BSA was estimated in absence and in presence of site specific probes using ranitidine as site-I specific and diazepam as site-II specific probes, respectively. In absence of site specific probes, the BSA and atenolol was mixed at 1:1 ratio (2×10^{-5} M: 2×10^{-5} M) and then desloratadine was added in increasing concentration (0 to 14×10^{-5} M) to make final ratio of BSA, atenolol and desloratadine in each experiment as 1:1:0, 1:1:1, 1:1:3, 1:1:5 and 1:1:7. While in presence of probes; BSA, probe and atenolol were mixed at ratio of 1:2:1 and desloratadine was added in increasing concentration to make the final ratio of protein, probe, atenolol and desloratadine as 1:2:1:0, 1:2:1:1, 1:2:1:3, 1:2:1:5, 1:2:1:7. Dialysis was carried out and the amount of free atenolol was measured in absence and in presence of probes as described above. Only BSA was used as positive control, mixture of BSA and desloratadine, and mixture of BSA, desloratadine and probe were used as negative control.

RESULTS

Estimation of binding parameters

Scatchard analysis of the binding of the drugs at pH 7.4 and at 27° C provided a non-liner curve, suggesting the presence of at least two classes of binding sites for the binding of atenolol and desloratadine to BSA (Figure 1A and 1B). Figure 1A shows that the number of high affinity binding site (n_1) for atenolol was approximately two (low capacity) and the number of low affinity binding site (n_2) was approximately five (high capacity). The high affinity association constant (k_1) for the atenolol binding to BSA at pH 7.4 is quite high (5.2×10^{-5} M^{-1}), while the low affinity association constant (k_2) for this drug to BSA is about 2 fold lower (2.5×10^{-5} M^{-1}) than that of primary association constant. While Figure 1B shows that the number of high affinity binding site (n_1) for desloratadine was approximately one (low capacity) and the number of low affinity binding site (n_2) was approximately two (high capacity). The high affinity association constant (k_1) for the desloratadine binding to BSA at pH 7.4 is very high (45×10^{-5} M^{-1}), while the low affinity association constant (k_2) for this drug to BSA is about 9 fold lower (5×10^{-5} M^{-1}) than that of primary

Figure 1. Scatchard plot for the binding of atenolol (A) and desloratadine (B) to BSA by equilibrium dialysis at pH 7.4 and 27 °C. The drugs [0 x 10^{-5} M to 8 x 10^{-5} M] were added to BSA [2 x 10^{-5} M] and dialyzed as described under materials and methods. Free fraction of drugs were measured by UV-spectroscopic method and analyzed.

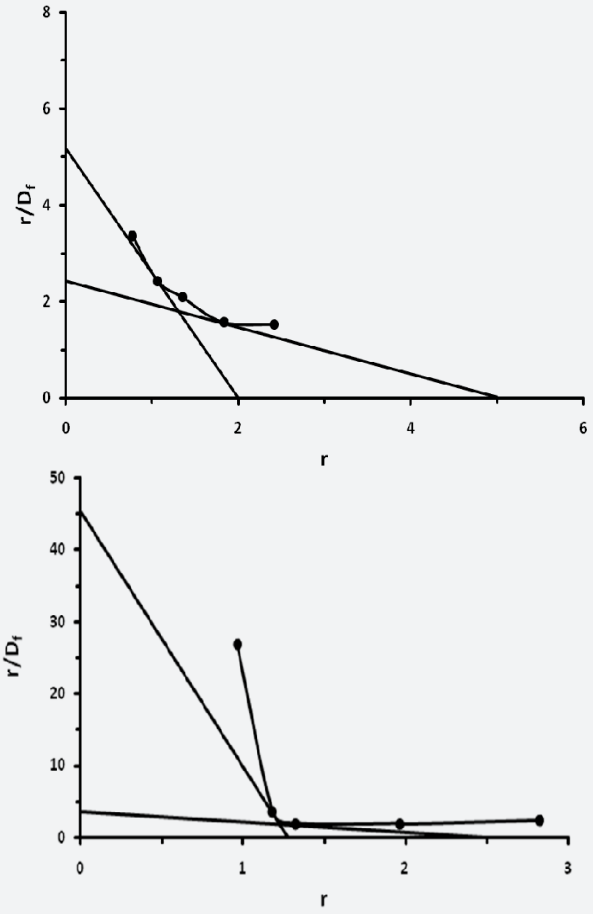

Figure 2. Free fraction of ranitidine (●) or diazepam (■) bound to BSA (1:1) as % of initial upon the addition of atenolol by equilibrium dialysis at 27 °C and pH 7.4.

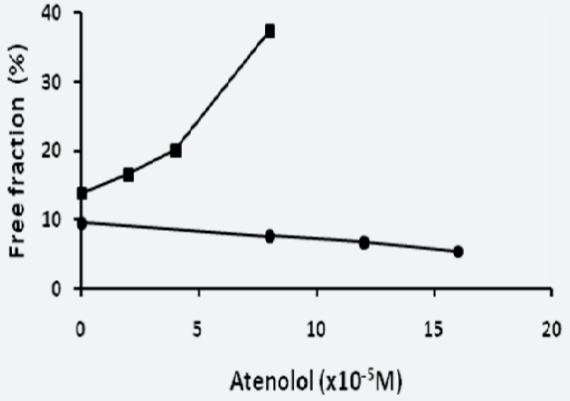

Figure 3. Free fraction of ranitidine (●) or diazepam (■) bound to BSA (1:1) as % of initial upon the addition of desloratadine by equilibrium dialysis at 27°C and pH 7.4

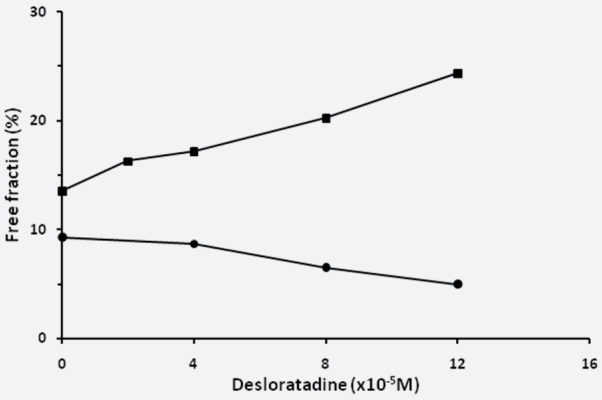

Figure 4. Free fraction of atenolol (●) and desloratadine (■) bound to BSA (1:1) as % of initial upon the addition of diazepam by equilibrium dialysis at 27°C and pH 7.4

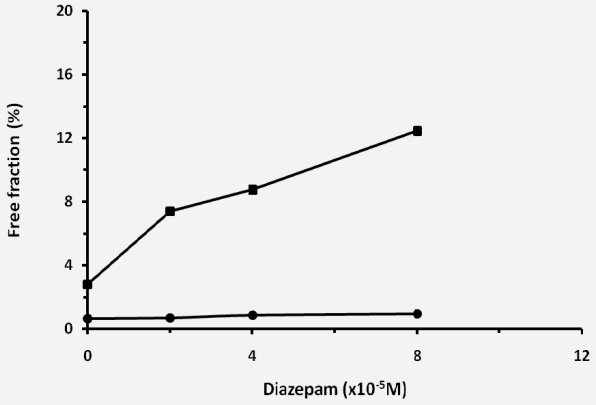

Figure 5. Free fraction of atenolol (●) and desloratadine (■) bound to BSA (1:1) as % of initial upon the addition of diazepam by equilibrium dialysis at 27°C and pH 7.4

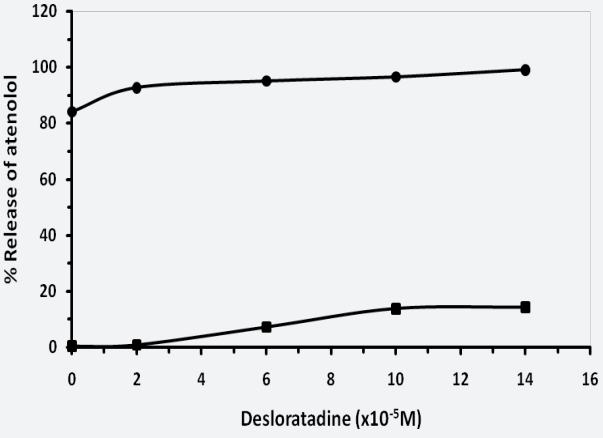

Table 1. Association constant of atenolol and desloratadine bound to BSA at pH 7.4 (27 °C)

Name of the drug	pH	Association constant	
		k_1 (high affinity)×$10^5 M^{-1}$	k_2 (low affinity)×$10^5 M^{-1}$
Atenolol	7.4	5 ± 0.07	2.5 ± 0.03
Desloratadine	7.4	45± 0.07	5 ± 0.03

Note: Value represents the mean ± SEM of three independent experiments

association constant .These findings indicate higher binding affinity of desloratadine to BSA.

Interaction of atenolol with site specific probes

The effects of atenolol on the binding of site specific probes were examined to determine whether atenolol binds preferentially with site-I or site-II on BSA. As mentioned under materials and methods, site specific probe and BSA were mixed at 1:1 molar ratio and atenolol was added in an increased concentration from 0 x 10^{-5} M to 16 x 10^{-5} M. The result showed that atenolol causes the decrement of free fraction of ranitidine from approximately 9.8% to 6% and increment of diazepam approximately from 14% to 40% (Figure 2). On the other hand diazepam increased the free fraction of atenolol from 0.65% to 0.95% (Figure 4).

Interaction of desloratadine with site specific probes

The effect of desloratadine was measured to know whether it can release the ranitidine and diazepam from their binding sites or not. It was found that desloratadine at a concentration from 0 x 10^{-5} M to 12 x 10^{-5} M decreased the free fraction ranitidine approximately from 9.32% to 4.96% and increased the free fraction of diazepam from approximately 13.52% to 24.40% (Figure 3). Alternatively diazepam increased the free fraction of desloratadine from 2.8% to 12.45% (Figure 4).

Interaction of desloratadine with atenolol at the binding sites on BSA

The interactions at bindings sites on BSA were studied between atenolol and desloratadine in the absence or in presence of site specific probes ranitidine and diazepam, respectively. In absence of both ranitidine and diazepam, desloratadine increased the free fraction of atenolol from approximately 84.01% to 99% with the addition of desloratadine from 0 x 10^{-5} M to 14 x 10^{-5} M (Figure 5). Whereas, in presence of diazepam as site specific probe, desloratadine at the same concentration, incremented the free fraction of atenolol from 0.45% to 14.3% (Figure 5).

DISCUSSION

Binding of drugs are determined by studying its ability to displace the site specific probes. In this study ranitidine hydrochloride and diazepam were used as site-I and site-II specific probes, respectively. The association constants as shown in Table: 1 indicates that atenolol binds less preferentially to BSA than desloratadine. Figure 2 shows the change in free concentration of ranitidine and diazepam by atenolol. It is seen that the free concentration of ranitidine decreased from approximately 9.8% to 6%. whereas, Whereas, the free concentration of diazepam was increased approximately from 14% to 40% by the same drug. On the other hand the association constant as shown in Table: 1 indicates that desloratadine is highly bound to BSA. Figure 3 show the change in free concentration of ranitidine and diazepam by desloratadine. It is seen that the free concentration of ranitidine decreased from approximately 9.32% to 4.96%. whereas, the free concentration of diazepam was increased from approximately from 13.52% to 24.40% by the same drug. From this observation it can be said that atenolol and desloratadine at higher concentration displaced diazepam to a greater extent as compared to ranitidine, so atenolol and desloratadine has greater affinity for site II than for site I on the BSA molecule. This implies the fact that at a lower drug to BSA ratio, atenolol binds to its high affinity site i.e., site II or the benzodiazepine site, whereas at higher ratio it does not only binds to its high affinity site but also to its low affinity site i.e., site I or the warfarin site on the BSA molecule.

The pharmacokinetic properties of drugs are influenced by exogenous as well as endogenous compounds by binding to serum albumin in a reversible manner[19]. Here we, for the first time, reported the *in vitro* interaction of desloratadine with atenolol at the binding sites on BSA. Plasma protein binding properties are considered to be the primary determinants of the pharmacokinetic properties of many drugs. Therefore any alteration or change in the serum albumin binding of these drugs might lead to a change in the pharmacokinetic properties of these drugs. Figure 5 showed the change in the free concentration of atenolol bound to BSA in the presence of desloratadine with and without diazepam, the site II specific probe at pH

7.4 and at 27°C. As observed in Figure 5, the free fraction of atenolol bound to BSA was increased from 84.01% to 99% by desloratadine in the absence of diazepam. Whereas in Figure 5, in the presence of diazepam, this increment was from 0.45% to 14.3%. This suggests that atenolol is displaced by desloratadine in the presence of diazepam.

CONCLUSION

Serum albumin, the most abundant protein in blood plasma serves as a depot and transport protein for numerous endogenous and exogenous compounds[22]. The most outstanding property of albumin is its ability to bind reversibly an incredible variety of ligands including fatty acids, amino acids (tryptophan and cysteine), steroids, metals such as calcium, copper and zinc, and numerous pharmaceuticals[23]. Hence serum binding can be one of the determinants for the pharmacokinetics of drugs[20,21]. The binding of atenolol and desloratadine, antihypertensive and anti-histaminic drugs respectively, to bovine serum albumin (BSA) has been studied by equilibrium dialysis method at pH 7.4 in order to have an insight in the binding chemistry of the drug to BSA. We found that desloratadine, displaces atenolol from its binding sites on BSA. As there is strong analogy between BSA and (human serum albumin (HSA), it is assumed that similar types of binding characteristics will be exhibited by atenolol when bound to HSA. The pharmacologic activity of a drug is related to its protein binding. If a drug shows less affinity for albumin due to any alteration in protein binding, the pharmacologic effect of the drug may be significantly altered[19,21]. The results of the present study in combination with the current advances in the binding of atenolol and interaction with desloratadine might be helpful in realizing to the overall binding behavior of the drug with HSA. However, from our limited data it is too early to draw such conclusion about the changes of pharmacokinetic/pharmacological properties of the atenolol in presence of desloratidine. Further studies are deserved to get more detailed of the pharmacokinetic interactions using *in vivo* experimental model.

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