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CHEMICAL INTERACTIONS BETWEEN MOLECULES OF BOTH ALISKIREN AND NEBIVOLOL IN COMBINED APPLICATION

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ABSTRACT

Few data are available in regards to utility of fixed combinations of antihypertensive drugs in hypertensive patients. European Society of Hypertension Working Group is recommended for use similar approach for all hypertensive individuals irrespectively severity of blood pressure elevation. Whether fixed combination constructed from the direct rennin inhibitor and beta-adrenoblocker is useful for hypertensive subjects is still not clear. To solve the question it has been used semi empirical docking method that allows us to propose any perspectives for the application of aliskiren and nebivolol in fixed combination. We assayed possible molecular interaction between aliskiren and nebivolol using emi empirical quantum chemistry program based on Dewar and Thiel's NDDO approximation. Obtained results have shown that that interaction between protonated aliskiren and nebivolol within combined application might lead to labile complex without creating novel compounds that could induce an appearance of unusual pharmacological effects. Moreover, the interaction between both molecules and their cations did not lead to the formation of covalent chemical bonds. This interaction was able to construct the formation of unstable compounds that are easily

dissociated at normal temperature and under real conditions of salvation in the aquatic environment. In conclusion, we suggest that similar fixed combination might discuss to create new antihypertensive drug.

KEYWORDS: hypertension; antihypertensive drugs, aliskiren; nebivolol; fixed combination; molecular interaction.

INTRODUCTION

Hypertension remains a leading cause of cardiovascular complications worldwide[1]. The use of antihypertensive drugs added to life style modification is known as fundamental approach in target pressure achieving and improving clinical outcomes[2]. Utility of fixed combinations of antihypertensive drugs are discussed widely, although European Society of Hypertension Working Group is recommended for use similar approach for all hypertensive individuals irrespectively severity of blood pressure elevation[3]. Theoretically the direct rennin inhibitors and beta-adrenoblockers might be used in combination. In this context all compounds for the drug combination should not lead to creating novel chemical complexes with unusual pharmacological potencies that might be harm for patients. To solve the question it has been used semi empirical docking method that allows us to propose any perspectives for the application of aliskiren and nebivolol in fixed combination.

METHODS

The possible molecular interaction between aliskiren and nebivolol, and their protonated forms (cations) was assay using semi empirical quantum chemistry program based on Dewar and Thiel's NDDO approximation. The obtained data were stored in space of Program MORAS 2012[4]. To manage the process of calculation and visualization program used Facio v. 16.4.1[5].

To determine the global energy minimum corresponding to the most stable conformers we have been performed Hartree-Fock method based on full geometry optimization of molecular structures[6]. After that we have been found and analyzed all stationary points on the potential energy surface (PES)[7]. Criterion of self-consistent field was chosen equal to 0.00001. To search for minimum PES was used Polak-Ribera algorithm graduated at 0.001 kcal / (Å × mol)[8]. Thermodynamic properties and thermal effects of chelation were calculated for the well balanced energetically favorable conformers of individual molecules and their aggregates.

RESULTS

In the first phase study we have investigated the possibility of chemical interaction of neutral substances - aliskirena A (0), nebivolol H (0), and their protonated forms (respectively A (H +) and N (H +)), since these molecules are cations (used aliskirena hemifumarat and nebivolol hydrochloride). Figure 1 shows that the composition of each molecule is only one amino group that is able to be subjected to protonation. Thus, one may be four types of molecules in the wild in vivo within pH ≈ 6-8 at a temperature of 36-38 ° C, i.e. two "neutral" molecules (aliskiren A (0) and nebivolol H (0)) and two molecules constructed from their protonated forms (A (H +) and N (H +)).

This leads to the formation of four types of complexes, i.e. A (0) // H (0); A (H +) // H (0); A (0) // H (H +) and A (H +) // H (H +). It should be noted that the latter complex was considered as the most typical (close to real conditions) because it includes appropriate pharmacological form.

Preliminary analysis has showed that molecules have the appropriate reactive amine groups (CH3O-; -O-; -OH; -CONH-; -CONH2; -NH2; -NH-) that are able to easily protonate (in acid environment - pH <7) and deprotonate (alkaline - pH> 7). However, these reactions do not lead to the formation of chemical bonds between the studied molecules. But this fact does not preclude the physical and chemical (intermolecular) interactions (van der Waals, electrostatic, hydrophobic, hydrogen bonds) as a part of the molecules present electron and electron acceptor centers, which form the local areas of high and low electron density.

Table 1 shows some common characteristics of both molecules (aliskiren, nebivolol), as well as their cations and complexes based on the results of the calculations in RM7approximation. One can see that the cations of both molecules and their complexes have demonstrated high dipole moments that could lead to strong interaction with water molecules in solution. It promotes dissociation of complexes on separate parts. Values of orbital energies (HOMO and LUMO) testify to opportunity weak donor-acceptor interactions of molecules and their protonated forms.

It is possible to put a conclusion on force of such interaction, analyzing results of thermodynamic calculations (for aliskiren and nebivolol values of heat of formation (Hf), standard enthalpies (ΔH0298), standard entropies (ΔS0298), Gibbs energy (ΔG0298)) which have been carried out on the base of the optimized geometry of compounds and their

complexes (Table 2). Higher ΔH0298 and lower ΔG0298 have demonstrated the stable the complex, which is stronger intermolecular linkage between molecules of a complex. Values of entropy ΔS0298 do not give the appreciable contribution to the general energy of system and do not influence a qualitative situation of the investigated molecular systems.

The results have shown that the interaction between both molecules and their cations did not lead to the formation of covalent chemical bonds. This interaction was able to construct the formation of unstable compounds that are easily dissociated at normal temperature and under real conditions of salvation in the aquatic environment. The structure of intermolecular complex A(H+)//H(H+), calculated in quantum-chemical approximation PM7 (full optimization of geometry) is shown in Figure 2.

The further assessment of strength of complexes was performed on the basis of thermodynamic parameters of the formation of the starting compounds (heat generation and energy Gibbs) using the following formula:

$$Q = H^{f}_{(A(0)\ або\ A(H^{+}))} + H^{f}_{(H(0)\ або\ H(H^{+}))} - H^{f}_{((A(0\ або\ A(H^{+}))//((H(0)\ або\ H(H^{+}))};$$

$$\Delta G^{0}_{298\ (A(0))} = \Delta H^{0}_{298\ (A(0))} - T\cdot\Delta S^{0}_{298\ (A(0))};$$

$$\Delta G^{0}_{298\ (A(H^{+}))} = \Delta H^{0}_{298\ (A(H^{+}))} - T\cdot\Delta S^{0}_{298\ (A(H^{+}))};$$

$$\Delta G^{0}_{298\ (H(0))} = \Delta H^{0}_{298\ (H(0))} - T\cdot\Delta S^{0}_{298\ (H(0))};$$

$$\Delta G^{0}_{298\ (H(H^{+}))} = \Delta H^{0}_{298\ (H(H^{+}))} - T\cdot\Delta S^{0}_{298\ (H(H^{+}))};$$

$$\Delta\Delta G^{0}_{298} = \Delta G^{0}_{298\ (A(0)\ або\ A(H^{+}))} + \Delta G^{0}_{298\ (H(0)\ або\ H(H^{+}))} -$$

$$\Delta G^{0}_{298\ ((A(0\ або\ A(H^{+}))//((H(0)\ або\ H(H^{+}))}.$$

The results of calculations regarding thermodynamic characteristics of complex formation are given in Table 3. In fact, the complex, which was formed protonated aliskiren and nebivolol, was found the least strong pharmacological compound.

Table 1: The common molecular characteristics of aliskiren, nebivolol and their catons and complexes: Results of RM7approximation

Drug (complex)	S_c, Å^2	V_c, Å^3	Energy of MO, eB		μ, D	P_I, eB
			LUMO	HOMO		
A(0)	576.0	724.1	-8.887	0.286	6.92	8.887
A(H^+)	519.0	721.3	-11.263	-2.635	7.86	11.263
H(0)	399.8	461.7	-8.883	-0.405	3.64	8.883
H(H^+)	396.6	461.9	-11.401	-3.690	11.78	11.401
A(0)//H(0)	763.8	1200.8	-8.789	-0.285	4.02	8.789
A(H^+)// H(0)	691.8	1182.5	-10.726	-2.543	13.47	10.726
A(0)// H(H^+)	673.7	1166.5	-10.572	-2.393	9.90	10.572
A(H^+)// H(H^+)	693.4	1201.0	-12.966	-4.501	10.70	12.966

Abbreviations: Sc - size of surface of a molecule; Å – angstroms; Vc - amount of molecules (complexes); MO - molecular orbitals; HOMO - high occupied molecular orbitals; LUMO - low vacant molecular orbitals; μ - dipole moment; PI -ionization potential.

Notes: The size of surface (Sc) of a molecule (in square angstroms, Å2), available for molecules of water, that is important for an evaluation of an opportunity of interaction of compounds (nebivolol and aliskiren) with active centers of enzymes that is sutable objects of influence of pharmacological drugs. The following parameters: energies high occupied and low vacant molecular orbitals (MO) (accordingly, HOMO and LUMO, in eV), electrical dipole moment (μ, D) and potential of ionization (PI, eV) are electronic characteristics of molecules of aliskirene and nebivolol. At close values of area of surface and volume of molecules - drugs which use in a combination, these parameters will be determining. They specify polarity of moleculas, their electron-donating (HOMO) and electrophilic (LUMO) properties that determines intensity of interaction of molecules in intermolecular complexes.

Table 2: Basic thermodynamic properties of both molecules (aliskirena, nebivolol), cations and their complexes.

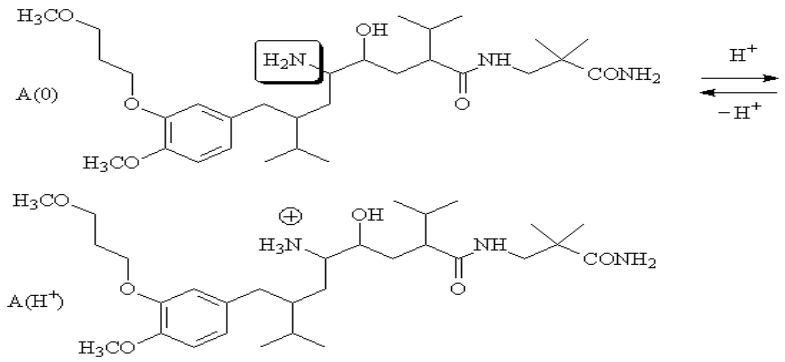
Drug (complex)	H^f, kcal/mol	ΔH^0_{298}, kcal/mol	ΔS^0_{298}, cal/(К×mol)	ΔG^0_{298}, kcal/mol
A(0)	-317.03	27.39	247.20	-46.22
A(H^+)	-212.95	26.95	239.07	-44.27
H(0)	-237.36	16.45	178.67	-36.89
H(H^+)	-90.91	15.74	164.53	-33.43
A(0)//H(0)	-583.19	44.40	372.11	-66.46
A(H^+)//H(0)	-483.24	42.53	348.75	-61.47
A(0)//H(H^+)	-476.23	42.54	346.31	-60.57
A(H^+)//H(H^+)	-307.15	42.91	352.38	-61.98

Abbreviations: Hf - heat of formation, ΔH0298 - standard enthalpies, ΔS0298 - standard entropies, ΔG0298 – Gibbs energy.

Table 3: The heat effect (Q) and total energy effect (ΔΔ G0298) the formation of complexes.

Complexes	Q, kcal/mol	$\Delta\Delta G^0_{298}$, kcal/mol
A(0)//H(0)	28.80	-16.65
$A(H^+)$//H(0)	32.93	-19.69
A(0)//$H(H^+)$	68.30	-19.08
$A(H^+)$//$H(H^+)$	3.29	-15.72

A



B

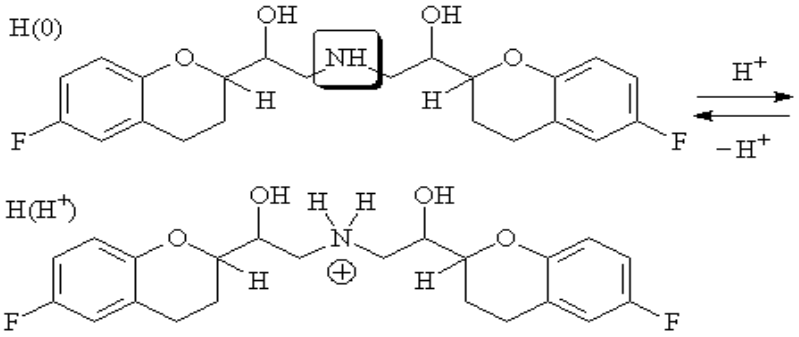


Figure 1: Neutral (A (0), H (0)) and protonated (A (H +), N (H +)) forms of both aliskiren (A) and nebivolol (B).

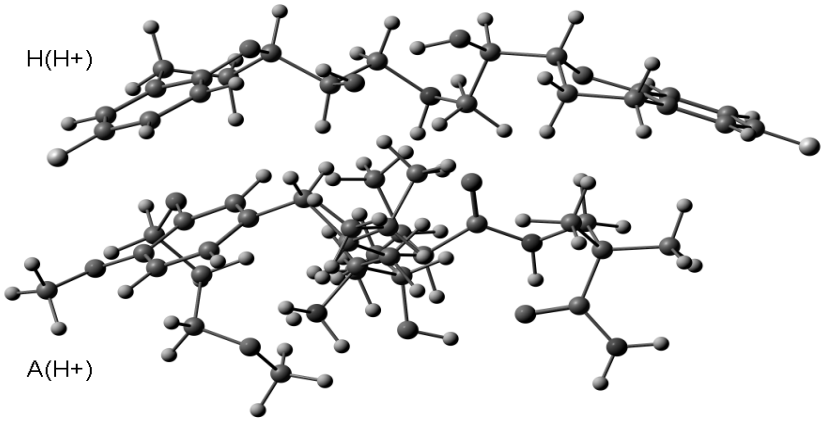


Figure 2: The structure of intermolecular complex A(H+)//H(H+), calculated in quantum-chemical approximation PM7 (full optimization of geometry).

DISCUSSION

The results of the study have shown that interaction between protonated aliskiren and nebivolol within combined application might lead to labile complex without creating novel compounds that could induce an appearance of unusual pharmacological effects. As one can see the energy of the dissociation of hydrogen it corresponds to one communication, which should lead to easy destruction of such labile structures in aqueous solution to source components (aliskiren and nebivolol). Similar weak interaction of the components in this complex can be explained by electrostatic repulsion protonated aliskirena and nebivolol that it contains. It was the toughest set of A (0) // H (H +) through the formation of strong hydrogen bonds involving groups> NH2 (+) and nebivolol groups protonated -NH2, -OH and> C = O aliskiren neutral form. However, in this case solvation of complexes in aqueous solution might lead to a significant weakening and its dissociation. We did not find any evidences regarding promptly creating of novel antihypertensive combination based on aliskiren and nebivolol. Taken into consideration contemporary technologies of drugs, similar fixed combination might be.

In conclusion, we suggest that similar fixed combination might discuss to create new antihypertensive drug. Future investigations are required to scrutiny pharmacokinetic and pharmacodynamic particularities of this combination.

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