THE EVALUATION OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN RENAL ELIMINATION WITH SELECTED MOLECULAR DESCRIPTORS

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PROCENA RENALNE ELIMINACIJE INHIBITORA ENZIMA KOJI KONVERTUJE ANGIOTENSIN SA ODABRANIM MOLEKULSKIM DESKRIPTORIMA

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ABSTRACT

Angiotensin-converting enzyme (ACE) inhibitors modulate the function of the renin-angiotensin-aldosterone system, and they are commonly prescribed antihypertensive drugs especially in patients with renal failure. In this study, the relationships between several molecular properties of eight ACE inhibitors (enalapril, quinapril, fosinopril, ramipril, benazepril, perindopril, moexipril, trandolapril) and their renal elimination data, from relevant literature, were investigated. The 'molecular descriptors of the ACE inhibitors, which included aqueous solubility data (logS); an electronic descriptor, polar surface area (PSA);, a constitutional parameter, molecular mass (Mr); and a geometric descriptor, volume value (Vol), as well as lipophilicity descriptors (logP values), were calculated using different software packages. Simple linear regression analysis showed the best correlation between renal elimination data and lipophilicity descriptor AClogP values (R^2 = 0.5742). In the next stage of the study, multiple linear regression was applied to assess a higher correlation between the ACE inhibitors' renal elimination data and lipophilicity, AClogP, with one additional descriptor as an independent variable. Good correlations were established between renal elimination data from the literature and the AClogP lipophilicity descriptor using the constitutional parameter (molecular mass (R^2 = 0.7425)) or the geometric descriptor (volume value (R^2 = 0.7224)) as an independent variable. The application of computed molecular descriptors in evaluating drug elimination is of great importance in drug research.

Keywords: *Angiotensin-converting enzyme inhibitors; lipophilicity; molecular mass; elimination.*

SAŽETAK

Inhibitori enzima koji konvertuje angiotenzin (ACE) modifikuju funkciju renin-angiotenzin-aldosteron sistema i predstavljaju često propisane lekova za sniženje pritiska, posebno kod pacijenata sa insuficijencijom bubrega. U ovom radu, za osam odabranih ACE inhibitora (enalapril, kvinapril, fosinopril, ramipril, benazepril, perindopril, moeksipril, trandolapril) ispitan je odnos između osobina njihovih molekula i njihove eliminacije putem bubrega. Za ispitivane inhibitore ACE korišćenjem različitih softverskih paketa izračunate su vrednosti nekoliko molekulskih deskriptora: rastvorljivost u vodi (logS), elektronski deskriptor – polarna površina molekula (PSA), molekulska masa (Mw), geometrijski deskriptor – volumen molekula (Vol) kao i deskriptor lipofilnosti (logP vrednosti). Primenom proste linearne regresione analize najbolja zavisnost dobijena je između podataka o eliminaciji inhibitora ACE putem bubrega i deskriptora lipofilnosti, AClogP vrednosti (R^2 = 0.5742). U sledećoj fazi istraživanja primenjena je metoda višestruke regresione analize (MLR) kako bi se dobila bolja zavisnost između podataka o eliminaciji ACE inhibitora putem bubrega i njihove lipofilnosti (AClogP vrednosti) uz primenu dodatnog molekulskog deskriptora kao nezavisno promenljive. Dobre korelacije su dobijene između podataka o eliminaciji putem bubrega i deskriptora lipofilnosti AClogP, uz primenu molekulske mase (R^2 = 0.7425) ili zapremine molekula (R^2 = 0.7224) kao nezavisno promenljive. Mogućnost primene izračunatih molekulskih deskriptora u proceni eliminacije lekova je od velikog značaja u njihovom istraživanju.

Ključne reči: *Inhibitori enzima koji konvertuje angiotenzin; lopofilnost; molekulska masa; eliminacija.*

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INTRODUCTION

Angiotensin-converting enzyme (ACE) inhibitors are the most commonly prescribed antihypertensive drugs today. They are a significant group of drugs widely used in the treatment of hypertension, congestive heart failure and renal failure, especially in patients with diabetes mellitus or proteinuria (1).

According their chemical structures, ACE inhibitors can be classified into three groups: sulfhydryl-containing inhibitors (exemplified by captopril), dicarboxylate-containing (exemplified by enalapril) and phosphonate-containing inhibitors (exemplified by fosinopril). The ACE inhibitors are pro-drugs, and, following administration, they undergo ester hydrolysis into their active di-acid metabolites, with the exception of lisinopril, which is already in the di-acid form (1).

Even though they have the same usage indications, they demonstrate differences in their pharmacokinetic and pharmacodynamic properties, which may affect their clinical efficacy. The ACE inhibitors demonstrate their antihypertensive effect through their active metabolites by modulation of the renin-angiotensin-aldosterone enzymatic system and selective dilation of efferent renal arterioles. In hypertensive patients with renal failure, particularly of diabetic aetiology, ACE inhibitors are used as the drug of choice because, in addition to their antihypertensive effects, they slow the progression of microalbuminuria and proteinuria (2-5).

Some ACE inhibitors have dual routes of elimination, renal and faecal, which may be important for patients with renal failure. They can be applied in patients with end-stage renal failure who are treated with renal replacement therapy, haemo or peritoneal dialysis (1).

ACE inhibitor's pharmacological properties (absorption, protein binding, distribution, activity, duration of action and elimination) and their relationship with lipophilicity were investigated in numerous studies by chromatographic methods, spectrophotometry, capillary electrophoresis or spectrofluorimetry. ACE inhibitors were determined in pharmaceutical formulations and biological material. There are few data on the elimination of ACE inhibitors by peritoneal dialysate (6-17).

In our previous studies, we investigated the lipophilicity of several ACE inhibitors under different chromatographic conditions (18-20) and the correlation between ACE inhibitors' chromatographic or *in silico* lipophilicity data and with their protein binding (PPB) data (21) or absorption (22). In continuation of these studies, our aim was to correlate ACE inhibitors' molecular descriptors (electronic descriptor - polar surface area (PSA); constitutional parameter - molecular weight (Mw); geometric descriptor - volume value (Vol); aqueous solubility data (log*S*)) with their renal elimination data to determine a reliable relationship appropriate for evaluating renal elimination of the investigated group of drugs. The selection of appropriate molecular descriptors was established.

MATERIALS AND METHODS

The eight most often prescribed ACE inhibitors were investigated.

1. **enalapril maleate**, (*S*)-1-[*N*-[1-(ethoxycarbonyl)-3-phenylpropyl]-*L*-alanyl]-*L*-proline maleate;
2. **quinapril hydrochloride,** [3*S*-[2[*R**(*R**)],3*R**]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl] amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid hydrochloride;
3. **fosinopril sodium,** (4*S*)-4-cyclohexyl–1-[[(*R*)-[(1*S*)-2-methyl-1-(1-oxopropoxy)- propoxy](4-phenylbutyl) phosphinyl]acetyl]-*L*-proline, sodium salt;
4. **ramipril,** (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3–phenylpropyl]amino]-1–oxopropyl] octahydrocyclopenta[b]pyrrole–2–carboxylic acid;
5. **benazepril hydrochloride**, (3*S*)-3-[[1-(ethoxycarbonyl)-3–phenylpropyl]amino]-2,3,4,5–tetrahydro–2-oxo–1*H*-1–benzazepine–1–acetic acid hydrochloride;
6. **perindopril erbumin,** 2-methylpropan-2-amine (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxopentan-2-yl]amino]propanoyl]-2,3,3a,4,5,6,7,7a-octahydroindole-2-carboxylic acid;
7. **moexipril,** (3*S*)-2-[(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline-3-carboxylic acid**;**
8. **trandolapril,** [2*S*-[1[*R**(*R**)],2*α*,3a*α*,7a*β*]]-1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-1*H*-indole-2-carboxylic acid.

The software package Molinspiration Depiction Software (Molinspiration Cheminfirmatics) (23) was used for the calculation of the electronic descriptor polar surface area (PSA), the constitutional parameter molecular weight (Mw) and the geometric descriptor volume value (Vol) (Table 1). The ACE inhibitors' lipophilicity descriptors, different log*P* values (Alog*Ps,* AClog*P,* AB/log*P,* milog*P,* Alog*P,* Mlog*P,* KOWWINlog*P,* XLOG*P*2*,* XLOG*P*3), and aqueous solubility data (log*S*), were calculated using the Virtual Computational Chemistry Laboratory software package (24).

The elimination data of the investigated compounds (Table 1) were obtained from the relevant literature (1) and using software package DrugBank (25).

Microsoft Excel 2003 and Origin 7.0 PRO (Origin Lab Corporation, USA) were used to perform the statistical analysis of the regression.

RESULTS

In this paper, the correlations between renal elimination data of selected ACE inhibitors and their calculated molecular properties were examined.

Table 1. The ACEi calculated molecular descriptors and renal elimination data collected from relevant literature (*); predicted from (A) AClogP and Vol; (B) AClogP and Mw values.

ACEi	Ren. el.*	AC logP	Vol	Mw	logS	PSA	Ren. el.A	Ren. el.B
1	100	1.52	357	376	-2.92	96	101	101
2	96	2.08	411	439	-3.81	96	77	78
3	50	3.05	539	564	-4.70	110	45	44
4	60	2.07	396	417	-3.58	96	73	72
5	88	2.09	395	424	-4.24	96	71	73
6	100	1.58	358	368	-2.63	96	97	94
7	100	1.87	462	499	-4.21	114	109	111
8	33	2.39	413	430	-3.98	96	54	53

*Ren. El. values obtained from literature (Lemke and Williams, 2013)
The numbers denote ACEi.

The five molecular descriptors (PSA, Mw, Vol, log*P*, log*S*) of the ACE inhibitors were calculated using different software packages as well as elimination data of investigated compounds from the relevant literature are shown in Table 1.

In the first stage of the investigation, correlations between the renal elimination data and calculated molecular descriptors of the ACE inhibitors were investigated using simple linear regression analysis. The renal elimination data and the 'molecular descriptors, (Vol, Mw and log*S*) of the ACE inhibitors showed correlations with correlation coefficients (R^2) lower than 0.2. Next, the relationship between different lipophilicity descriptors, log*P* values and renal elimination data were examined. The strongest correlation was found between AClog*P* and the renal elimination data (R^2 = 0.5742).

Following these results, in the next stage of the study, the relationship between renal elimination data and two different molecular descriptors of the ACE inhibitors were investigated using multiple linear regression (MLR) analysis. The AClog*P* was chosen as the first independent variable since it showed the best correlations with the ACE inhibitors' renal elimination data. The application of five calculated molecular descriptors (PSA, Mw, Vol, log*P* and log*S*) of ACE inhibitors was investigated by MLR analysis.

Good correlations were established between renal elimination data obtained from the literature and the AClog*P* lipophilicity descriptor using the constitutional parameter molecular mass (R^2 = 0.7425) or the geometric descriptor volume value (R^2 = 0.7224) as an independent variable. The values of predicted renal elimination were calculated according to the following equations:

$$\text{Renal el.}_{\text{pred 1}}\,(\%) = 101.1189(\pm 48.0996) - 74.9464(\pm 24.0853)\text{AClog}P + 0.3199(\pm 0.1957)\text{Vol}$$

with n = 8; R^2 = 0.7224; S.D. = 16.6729; F = 6.5073 Eq. 1.

$$\text{Renal el.}_{\text{pred 2}}\,(\%) = 102.1234(\pm 44.0093) - 73.0586(\pm 21.3470)\text{AClog}P + 0.2918(\pm 0.1614)\text{Mw}$$

with n = 8; R^2 = 0.7425; S.D. = 16.0606; F = 7.2073 Eq. 2.

The results obtained using MLR analysis by applying two different descriptors as independent variables are presented in Table 1 and in Fig. 1.

DISCUSSION

The clinical success of drugs depends mostly on their absorption, distribution, metabolism or route of elimination (ADME) (26). Lipophilicity is one of the most important molecular properties that influence these values, but a number of other molecular properties (such as molecular

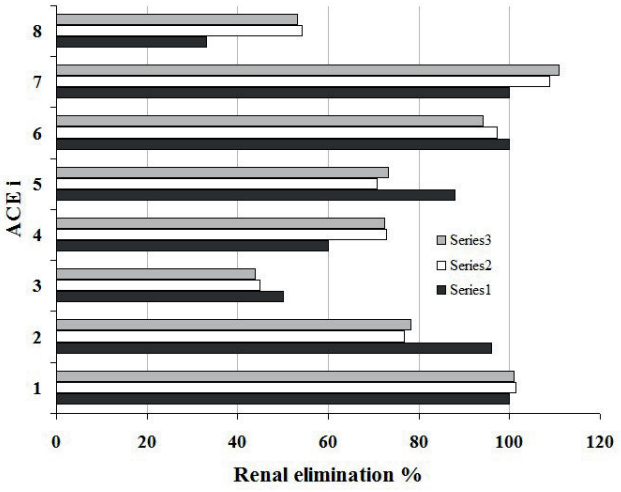

Fig. 1. The relationship between ACEi renal elimination collected from relevant literature and (Lemke and Williams, 2013) (Series 1) and predicted in MLR using AClogP and Vol (Series 2); AClogP and Mw values (Series 3). The numbers denote ACEi.

weight (Mw), molecular volume (Vol), polar surface area (PSA) and solubility data (logS)) also play important roles in drug absorption, tissue penetration, degree of distribution, degree of plasma protein binding and route of elimination (27-29).

According to the available literature, several authors investigated drugs belonging to the ACE inhibitor group, their pharmacological properties and their similarities or differences (6-10). Their acidity, lipophilicity, solubility and absorption were evaluated based on their molecular structures with the application of computer programs (27-29).

Various authors have also suggested several assays that could be employed in investigations of different drug eliminations (30-32). Most of these methods still have certain limitations, and a new approach for fast, reliable and cost-effective evaluation of the route of elimination of ACE inhibitors should be developed. The decrease in complexity and size of the average drug molecule, as well as its low log*P* values and high water solubility, can lead to higher probability of drugs being rapidly cleared via renal elimination (33). Since a drug's route and degree of elimination may affect a drug's duration of action and activity, the application of computed molecular descriptors in the prediction of a drug's elimination are of great importance, especially for the newly synthesized drugs.

In this study, eight ACE inhibitors—,enalapril maleate, quinapril hydrochloride, fosinopril sodium, ramipril, benazepril hydrochloride, perindopril erbumin, moexipril and trandolapril—were studied to evaluate correlations between their renal elimination data obtained from the relevant literature and calculated molecular descriptors. According to the data from the literature, the degree of renal elimination of the ACE inhibitors can vary from 33% to 100% (Table 1). The lowest values of renal elimination were found for trandolapril (approximately 33%), while enalapril, perindopril and moexipril dominantly exhibit renal elimination (approximately 100%).

The correlations between the ACE inhibitors' calculated molecular descriptors and their renal elimination data obtained from relevant literature were examined. The applicability of calculated molecular descriptors in ACE inhibitor elimination evaluation was investigated. The main topic of this study was to establish an approach using simple or multiple linear regression analysis capable of predicting the renal elimination of selected ACE inhibitors based on their molecular properties.

In the first stage of the study, the relationship between all calculated log*P* values (Clog*P*, Alog*Ps*, AClog*P*, AB/log*P*, milog*P*, Alog*P*, Mlog*P*, KOWWINlog*P*, XLOG*P*2, XLOG*P*3) and renal elimination data for ACE inhibitors was investigated. Amongst all log*P* values, only AClog*P* provided a relatively good correlation (R^2 = 0.5742) with the 'renal elimination data of the ACE inhibitors.

Second, the relationship between the renal elimination data and calculated molecular descriptors of the ACE inhibitors was investigated using MLR analysis with application of two independent variables, AClog*P* and one of the following: polar surface area (PSA), molecular weight (Mw), volume value (Vol) or solubility (logS) to assess their higher correlation. The best correlations were established between the ACE inhibitors' renal elimination data and the AClog*P* lipophilicity descriptor using the molecular weight (R^2 = 0.7425) or volume (R^2 = 0.7224) as an independent variable, indicating that these molecular properties are critical for ACE inhibitors' route of elimination. The established correlations are presented by Eq. 1 and Eq. 2. They indicate that the molecule's lipophilicity has a dominant influence on the ACE inhibitor's renal elimination, and the increase in lipophilicity led to a decrease in their renal elimination.

The correlation observed between the ACE inhibitors' renal elimination data and their *in silico* molecular descriptors (lipophilicity parameter (AClog*P)* and constitutional parameter (molecular mass) or geometric descriptor (volume value)) can be considered good, as proposed by Asuero et al. (34), due to the limited number of compounds. These correlations confirmed the calculation of descriptors as the technique suitable for evaluation of renal elimination of the selected compounds.

CONCLUSION

A relatively good correlation was obtained between the renal elimination data and the calculated molecular lipophilicity descriptor (AClogP) (R^2 = 0.5742). Furthermore, using MLR analysis with two different descriptors as independent variables and the lipophilicity descriptor (AClog*P)* and molecular mass or volume value as independent variables, better correlations were established (with R^2 = 0.7425 and R^2 = 0.7224, respectively). The possible application of computed molecular descriptors in evaluating drug routes of elimination can be highly useful in drug research.

The present study may be considered an effective assay and could be used as a fast, easy and cost-effective screening technique for route of elimination evaluation. The proposed methodology confirmed that lipophilicity, together with other molecular properties, is essential in a drug's route of elimination.

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