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THE INFLUENCE OF CERTAIN MOLECULAR DESCRIPTORS OF FECAL ELIMINATION OF ANGIOTENSIN II RECEPTOR ANTAGONISTS

Jasna B. Trbojević-Stanković[1,2], Jadranka V. Odović[3], Ratomir M. Jelić[4], Dejan M. Nesić[5,*] and Biljana B. Stojimirović[1,6]

[1] *School of Medicine, University of Belgrade,* Belgrade, Serbia
[2] *Department of Dialysis, Clinical Hospital Center "Dr Dragiša Mišović",* Belgrade, Serbia
[3] *Department of Analytical Chemistry, Faculty of Pharmacy, University of Belgrade,* Belgrade, Serbia
[4] *Faculty of Medicinal Science, University of Kragujevac,* Kragujevac, Serbia
[5] *Institute of Medical physiology, School of Medicine, University of Belgrade,* Belgrade, Serbia
[6] *Clinic of Nephrology, Clinical Center of Serbia,* Belgrade, Serbia

[*]Corresponding author: drdejannesic@yahoo.com; dejance@med.bg.ac.rs

Abstract - Angiotensin II receptor antagonists (ARBs) modulate the function of the renin-angiotensin-aldosterone system and are commonly prescribed antihypertensive drugs, especially in patients with renal failure. In this study, the relationship between several molecular properties of seven ARBs (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan) and their fecal elimination data obtained from the literature were investigated. The ARB molecular descriptors were calculated using three software packages. Simple linear regression analysis showed the best correlation between fecal elimination data and lipophilicity descriptor, Clog*P* values (R^2 = 0.725). Multiple linear regression was applied to examine the correlation of ARBs' fecal elimination data with their lipophilicity and one additional, calculated descriptor. The best correlation (R^2 = 0.909 with an acceptable probability value, P <0.05) was established between the ARB fecal elimination data and their lipophilicity and aqueous solubility data. Applying computed molecular descriptors for evaluating drug elimination is of great importance in drug research.

Key words: angiotensin II receptor antagonists; lipophilicity; aqueous solubility; fecal elimination

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INTRODUCTION

Angiotensin II receptor antagonists, also known as angiotensin receptor blockers (ARBs), AT_1-receptor antagonists or sartans, are a group of drugs that modulate the function of the renin-angiotensin-aldosterone system by antagonizing the vasoconstrictive and proinflammatory/pro-proliferative effects of angiotensin II (Csaba, 2011). They were introduced into clinical practice three decades ago and today are commonly prescribed for the treatment of hypertension, congestive heart failure and diabetic nephropathy. They reduce cardiovascular risk and mortality, abate the level of albuminuria and exert beneficial renoprotective effect on the progression of diabetic kidney disease (Csaba, 2011; Lemke and Williams,

2008; Stella et al., 2007; Sweetman, 2009; Beale and Block, 2011).

There are eight currently available ARBs on the market: azilsartan, candesartan eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan. Although they all have the same indications for usage, they demonstrate differences in their pharmacology, pharmacokinetic and pharmacodynamic properties, which may affect their clinical efficacy. They are generally well tolerated and side effects, including cough, hyperkalemia, hypotension, dizziness, headache, drowsiness, diarrhea, abnormal taste sensation and rash are rare. They are contraindicated in pregnancy as they may cause birth defects (Lemke and Williams, 2008; Beale and Block, 2011; Moffat et al., 2011).

All ARBs are acidic drugs that will mostly be ionized in physiological conditions. Most share a common tetrazole-biphenyl structure based on losartan. Telmisartan, in contrast, has a novel bisbenzimidazole structure, while eprosartan is a non-biphenyl non-tetrazole ARB (Csaba, 2011). They all have adequate lipophilicity and their plasma protein binding values are relatively similar and high, ranging from 95 to 100%. Candesartan cilexetil and olmesartan medoxomil differ from the other compounds since they are rapidly and completely hydrolyzed to their active metabolites, candesartan and olmesartan, respectively, in the intestinal wall (Lemke and Williams, 2008; Sweetman, 2009). Also, approximately 14% of losartan oral dose is oxidized to more potent metabolites and none of the other ARBs are converted to active metabolites. The ARBs have a dual route of elimination, renal and fecal, which may be of importance for patients with renal failure. According to data obtained from the relevant literature, their major route of elimination is fecal, ranging from 42-97% (Lemke and Williams, 2008; Sweetman, 2009).

A drug's clinical success mostly depends on its absorption, distribution, metabolism or route of elimination (Di and Kernsy, 2003). Lipophilicity is one of the most important molecular properties that influence these values, but a number of other molecular properties - molecular weight (Mw), molecular volume (Vol), polar surface area (PSA) and solubility data (logS), also play important roles in drug absorption, penetration into tissues, degree of distribution, degree of plasma protein binding and route of elimination (Hartman and Schmitt, 2004; Remko et al., 2006; Remko, 2007; Zhao, 2001). According to the available literature, a number of authors investigated drugs belonging to the ARBs group, their pharmacological properties as well as their similarities and differences (Cheung, 2004; Zwieten, 2006; Husain et al., 2011). Their acidity, lipophilicity, solubility or absorption was evaluated based on their molecular structure with the application of computer programs (Remko et al., 2006; Remko, 2007; Zhao, 2001).

In our previous studies, we investigated the lipophilicity of several ACE inhibitors under different chromatographic conditions (Odovic et al., 2005; Odovic et al., 2006; Odovic et al., 2009) and the correlation between ACE inhibitor lipophilicity data with their protein binding (PPB) data (Odovic and Trbojevic-Stankovic, 2012) or absorption (Odovic et al. 2012). In a recently published paper, the molecular properties (molecular weight and volume values) of a selected group of ARBs were correlated in multiple linear regression (MLR) analysis with their PPB data (Odovic and Trbojevic-Stankovic, 2014). In continuation to these studies, the aim of this study was to compare the different molecular properties of seven ARBs (eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan) and their fecal elimination data.

MATERIALS AND METHODS

The seven most often prescribed ARBs, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan, were investigated (Table 1). The fecal elimination data of the investigated ARBs (Table 2) were obtained from the relevant literature (Lemke and Williams, 2008). The software package Molinspiration Depiction Software (Molinspiration Cheminfirmatics) was used for the calculation of electronic descriptor - polar surface area (PSA); constitutional parameter - molecular weight (Mw);

and geometric descriptor - volume value (Vol). The ARBs 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), as well as their aqueous solubility data (log*S*) were calculated using the software package Virtual Computational Chemistry Laboratory. Chemdraw ultra 12.0 was used for the calculation of another lipophilicity parameter, the Clog*P* values.

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

RESULTS

According to the available literature data, the degree of ARBs fecal elimination varied from 42% to 97% (Table 2). The lowest values of fecal elimination were found in olmesartan medoxomil (around 42%), losartan (60%) and candesartan cilexetil (67%).

The five ARBs' molecular descriptors (PSA, Mw, Vol, log*P*, log*S*) were calculated using different software packages. The correlations between the ARBs elimination data obtained from relevant literature and the calculated descriptors were investigated by simple linear regression. Fecal elimination data and ARBs molecular descriptors (Vol, Mw and log*S*) showed low correlations with correlation coefficients (R^2) around 0.2. The relationship between fecal elimination and values of PSA provided correlation with R^2 = 0.552., The relationship between different lipophilicity descriptors, log*P* values, and fecal elimination data were examined. The strongest correlation was found between Clog*P* and fecal elimination data (R^2 = 0.725).

In the next stage of the study, the relationship between fecal elimination data and two different ARB molecular descriptors were investigated with multiple linear regression (MLR). Clog*P* was chosen as the first independent variable since it showed the best correlations with ARB fecal elimination data. Solubility data (logS) was chosen as the second independent variable, since the correlations between Clog*P* values and all other calculated molecular descriptors (Vol, Mw and PSA) provide R^2>0.3.

The values of predicted fecal elimination were calculated according to the following equation:

$$\text{Fecal el.}_{\text{pred}}\ (\%) = 14.431\ (\pm 2.294)\text{Clog}P + 14.206(\pm 4.993)\log S + 69.673(\pm 20.779) \quad \text{Eq. 1.}$$

where R^2 = 0.909; S.D. = 7.030; F = 19.963.

The results obtained using MLR analysis applying two different descriptors as independent variables are presented in Table 3 and Fig. 1.

The correlations found can be considered as good as those proposed by Asuero et al. (2006), with acceptable P, as well as F values, due to the limited

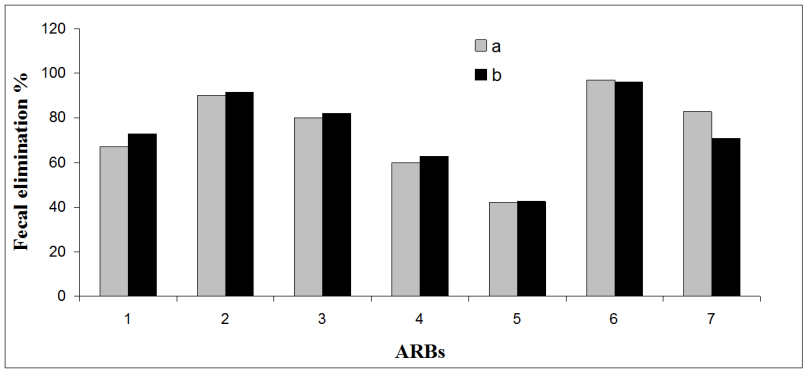
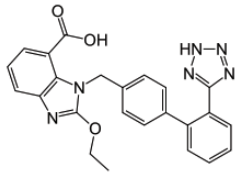
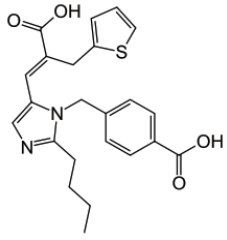
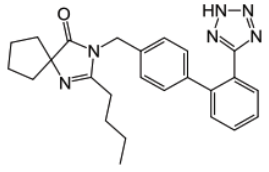
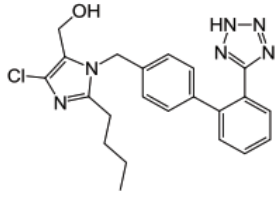
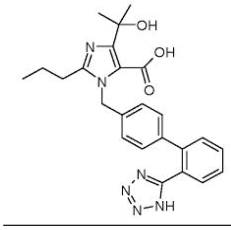
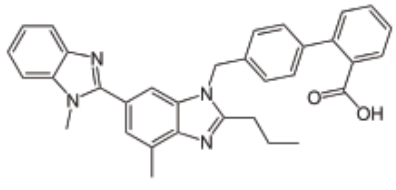
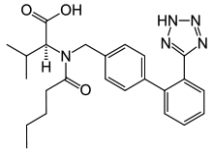


Fig. 1. The relationship between ARBs fecal elimination data from literature (a) and predicted (b) fecal elimination data (using Clog*P*, and log*S* values) (R^2 = 0.909). ARBs – Angiotensin II receptor antagonists; 1 – candesartan; 2 – eprosartan; 3 – irbesartan; 4 – losartan; 5 – olmesartan; 6 – telmisartan; 7 – valsartan.

Table 1. The structures of investigated ARBs

ARBs	
	**1. Candesartan,** 2-ethoxy-3-[[4-[2-(2H-tetrazol-5-yl)phenyl] phenyl]methyl] benzimidazole-4-carboxylic acid
	**2. Eprosartan,** 4-[[2-butyl-5-[(E)-2-carboxy-3-thiophen-2-yl-prop-1-enyl]imidazol-1-yl]methyl]benzoic acid
	**3. Irbesartan,** 2-butyl-3-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one
	**4. Losartan**, [2-butyl-5-chloro-3-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl] methyl]imidazol-4-yl]methanol
	**5. Olmesartan,** 5-(2-hydroxypropan-2-yl)-2-propyl-3-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl]imidazole-4-carboxylic acid
	**6. Telmisartan,** 2-[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl]methyl]phenyl]benzoic acid
	**7. Valsartan,** (2S)-3-methyl-2-[pentanoyl-[[4-[2-(2H-tetrazol-5-yl)phenyl] phenyl]methyl]amino] butanoic acid

ARBs - Angiotensin II receptor antagonists

Table 2. Fecal elimination data, calculated lipophilicity descriptor, ClogP values and aqueous solubility data (log*S*) of investigated ARBs.

Compound	Fecal el.	ClogP	logS
Candesartan	67	5.44	-5.30
Eprosartan	90	5.05	-3.60
Irbesartan	80	6.05	-5.28
Losartan	60	4.10	-4.63
Olmesartan	42	2.76	-4.71
Telmisartan	97	7.46	-5.72
Valsartan	83	4.87	-4.86

ARBs – Angiotensin II receptor antagonists

Table 3. Fecal elimination of ARBs obtained from relevant literature (a) and predicted (b) from the MLR relation with calculated Clog*P* and log*S* values.

ARBs	Fecal el. (a)	Fecal el. (b)
Candesartan	67	73
Eprosartan	90	91
Irbesartan	80	82
Losartan	60	63
Olmesartan	42	43
Telmisartan	97	96
Valsartan	83	71

ARBs - Angiotensin II receptor antagonists.

number of compounds. The correlation that was found between the ARB fecal elimination data and the *in silico* molecular descriptors – lipophilicity parameter (Clog*P)* and aqueous solubility data (log*S*) – confirmed the high-throughput screening technique for the evaluation of fecal elimination of the selected compounds.

DISCUSSION

The molecules with high lipophilicity show a higher degree of absorption, better penetration into tissues and distribution compared to less lipophilic ones with similar properties. Also, lipophilicity affects the duration of action of a drug, as well as the efficiency of its elimination. Namely, weakly lipophilic drugs are mostly eliminated by the urine, while highly lipophilic ones usually exhibit a high degree of fecal elimination. The drug present in the feces may represent the unabsorbed amount of an orally ingested dose, the amount of the dose that was absorbed but consequently excreted via the biliary route, or a combination of both. However, according to the available literature, it is still unclear whether ARB fecal elimination includes unabsorbed drugs (Lemke and Williams, 2008; Sweetman, 2009). This is understandable since a drug's absorption is highly affected by its lipophilicity, solubility, molecular size as well as other molecular properties. The Lipinski "rule of 5" predicts low absorption or permeation for drugs with calculated log*P* greater than 5 and the molecular weight greater than 500 (Lipinski, 2000).

In this research seven ARBs (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan) were studied in order to evaluate the correlation between their fecal elimination data (ranging from 42-97%) obtained from relevant literature and calculated molecular descriptors. The main aim was to establish a high throughput approach using simple or multiple linear regression analysis capable of predicting the fecal elimination of selected

ARBs. Several ARB molecular descriptors were calculated using three different software packages. All calculated descriptors, electronic descriptor – PSA, constitutional parameter – Mw, geometric descriptor – Vol, lipophilicity descriptors - 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), as well as aqueous solubility data – logS*,* play important roles in drug absorption, distribution, metabolism and route of elimination.

The correlations between the ARBs' calculated molecular descriptors and the fecal elimination data obtained from the relevant literature were examined. The applicability of calculated molecular descriptors in ARBs elimination evaluation was established. According to the available literature, ARB pharmacokinetics, pharmacodynamics, efficacy and duration of action were investigated by a number of authors (Lacourcière and Asmar, 1999; Meredith et al., 2010; Meredith 2010). Different authors have suggested several assays that could be employed in investigating the elimination of different drugs (Hellstern et al., 1990; Kullak-Ublick and Becker, 2003; Verho et al., 1995; Martin et al., 2003). Nonetheless, most of these methods have certain limitations and a new fast, reliable and cost-effective evaluation of ARBs' route of elimination should be developed. The rise in complexity and size of the average drug molecule, as well as its high log*P* values and low water solubility, can lead to a higher probability of drugs being rapidly cleared metabolically or via biliary excretion (Lipinski, 2000; Ghose el al., 1999). Since a drug's route and degree of elimination may affect its duration of action and activity, especially in patients with damaged kidney function, the application of computed molecular descriptors in the prediction of drug elimination are of great importance, especially for the newly synthesized drugs.

The present study presents an effective technique that could be used for the fast and easy prediction of elimination route. The proposed methodology confirmed that lipophilicity, together with other molecular properties, is essential in the route of elimination of drugs and could be regarded as a new, additional, *in vitro* approach appropriate for the modeling of elimination of the investigated group of ARBs.

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