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RELATIONSHIP BETWEEN THE BIOAVAILABILITY AND MOLECULAR PROPERTIES OF ANGIOTENSIN II RECEPTOR ANTAGONISTS

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

[1] *Ivančić i sinovi d.o.o.*, Palmotićeva 13, 11000 Belgrade, Serbia

[2] *Department of Analytical Chemistry, University of Belgrade-Faculty of Pharmacy*, Belgrade, Serbia

[3] *School of Medicine, University of Belgrade*, Belgrade, Serbia

[4] *Department of Dialysis, Clinical Hospital Center "Dr Dragiša Mišović"*, Belgrade, Serbia

[5] *Institute of Medical Physiology, School of Medicine, University of Belgrade*, Belgrade, Serbia

[6] *Faculty of Medicinal Science, University of Kragujevac*, Kragujevac, Serbia

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

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Abstract: In the present study, we investigated the relationships between several molecular properties and bioavailability data for seven of the most commonly prescribed angiotensin II receptor antagonists (also known as angiotensin II receptor blockers (ARBs) or sartans), candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan. The molecular descriptors of ARBs are:, aqueous solubility (log*S* values), polar surface area (PSA), molecular weight (Mw), volume value (Vol), lipophilicity (log*P* values) and the acidity descriptor (pK_{a1}). The respective descriptors were calculated using four different software packages. The relevant bioavailability data were obtained from literature. Among calculated molecular descriptors, simple linear regression analysis showed the best correlation between bioavailability data and the lipophilicity descriptor, log*P* (R^2=0.568). Multiple linear regression established good correlations between bioavailability and the lipophilicity descriptor, log*P*, using the molecular weight, Mw, or the acidity descriptor, pK_{a1}, as an additional, independent variable (with R^2=0.661 and 0.682, respectively). Finally, excluding candesartan from the calculations resulted in a very good correlation (R^2=0.852) between the remaining ARB bioavailability and molecular descriptors Mlog*P* and Mw as independent variables, determined by multiple linear regression.

Key words: angiotensin II receptor antagonists; lipophilicity; bioavailability; molecular properties

INTRODUCTION

The ARB were introduced into clinical practice three decades ago and today are commonly prescribed for the treatment of hypertension, congestive heart failure and diabetic nephropathy [1]. ARBs are acidic drugs that are mostly ionized at physiological conditions [1]. In contrast to other ARBs, candesartan cilexetil and olmesartan medoxomil are rapidly and completely hydrolyzed in the intestinal wall into their active metabolites, candesartan and olmesartan, respectively. Approximately 14% of ingested losartan is oxidized to a more potent metabolite, while other ARBs are not converted to active metabolites. Although all ARBs have the same indications for usage, they demonstrate certain differences in pharmacological, pharmacokinetic and pharmacodynamic properties, which may affect their clinical efficacy. They have relatively high plasma protein binding (PPB) values (95-100%). With the exception of irbesartan with an oral bioavailability (BA) of 60-80% and telmisartan with BA of 42-58%, all other ARBs have lower (15-33%), but adequate values of oral bioavailability. Most of these compounds are excreted unchanged. They have a dual route of elimination, renal and fecal, which may be of importance for patients with renal failure [2-4].

Molecular properties such as lipophilicity, acidity, molecular weight, molecular volume, polar surface area and water solubility, play an important role in drug absorption, penetration into tissues, degree of distribution, degree of PPB, bioavailability and route of elimination [5-9]. Several authors have investigated the pharmacological properties of ARBs [10-12]. The drugs' lipophilicity, solubility and absorption were evaluated with computer software based on the drugs' molecular structure [7-9]. Also, various authors suggested several assays that could be employed in investigating the elimination of different drugs [13-16].

In our recently published paper we assessed the correlation of the degree of PPB and the elimination of a selected ARBs with their molecular properties, molecular weight and volume using multiple regression (MLR) analysis [17,18]. In our previous studies, the correlation between ACE inhibitor lipophilicity and PPB data [19,20] or absorption [21] were studied and suitable models were presented. Following on from this work, the aim of our present study was to investigate the relationship between the different molecular properties of seven ARBs, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, and their BA.

MATERIALS AND METHODS

Software

The seven most frequently prescribed ARB were investigated: candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan. The software package Molinspiration Depiction Software (Molinspiration Cheminfirmatics) was used for the calculation of the "electronic" descriptors, polar surface area (PSA), constitutional parameter, molecular weight (Mw), and the geometric descriptor, volume value (Vol). The ARB 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 [http://www.vcclab.org]. Chemdraw ultra 12.0 was used for the calculation of another lipophilicity parameter, Clog*P*, while the software package DrugBank [http: //www.drugbank.ca] was used for the calculation of the acidity descriptor pK_a of the selected ARB. Microsoft Excel 2003 and Origin 7.0 PRO (Origin Lab Corporation, USA) were used to perform statistical analysis of regression. The selected molecular descriptors are presented in Table 1; the provided oral bioavailability data were obtained from the relevant literature [2].

RESULTS

According to data from the relevant literature, the degrees of ARB BA vary from 15% to about 70% (Table 2) and [3]. Eprosartan has the lowest oral BA (15%), while the highest were recorded for telmisartan and irbesartan (about 50% and 70%, respectively). The ARB molecular descriptors PSA, Mw, Vol, log*S*, log*P* and pK_a values, were calculated using four different software packages.

The correlations between ARB oral BA data obtained from the literature and all calculated descrip-

Table 1. Data of ARB oral bioavailability collected from relevant literature and calculated molecular descriptors.

ARB	BA%*	MlogP	pK_{a1}	Mw	PSA	Vol	logs
1. Candesartan	15	4.55	2.97	440	119	382	-5.30
2. Eprosartan	15	3.42	3.63	424	92	381	-3.60
3. Irbesartan	70	5.11	7.40	428	87	400	-5.28
4. Losartan	33	4.55	7.40	422	92	374	-4.63
5. Olmesartan	26	4.01	0.91	446	130	403	-4.68
6. Telmisartan	50	5.70	3.65	514	73	475	-5.72
7. Valsartan	25	4.15	4.37	435	112	408	-4.86

*BA values were obtained from the literature [3]

Table 2. Data of ARB oral bioavailability collected from relevant literature (*) and predicted from **(A)** Mlog*P* and Vol; **(B)** Mlog*P* and PSA; **(C)** Mlog*P* and Mw; **(D)** Mlog*P* and pK_{a1} values.

ARB	BA %*	BA % (A)	BA % (B)	BA % (C)	BA % (D)
1. Candesartan	15	36	29	36	30
2. Eprosartan	15	11	18	9	13
3. Irbesartan	70	47	47	55	53
4. Losartan	33	37	36	40	44
5. Olmesartan	26	23	18	19	15
6. Telmisartan	50	55	60	48	52
7. Valsartan	25	25	24	26	28

*BA values were obtained from the literature [3]

tors were investigated by simple linear regression. The oral BA data and the ARB molecular descriptors, Vol, Mw, log*S* and pK_{a1}, displayed low correlations (R^2<0.3) and only PSA had a slightly stronger correlation (R^2=0.361) with ARB oral BA data. The relationship between all ten lipophilicity descriptors, log*P* values and oral BA data were examined, and mostly provided low correlations (R^2<0.3). The strongest, but not sufficiently high correlation was established between Mlog*P* and oral BE data (R^2=0.567).

In the next stage, the relationship between BA data and two different ARB molecular descriptors as independent variables were investigated with MLR. Mlog*P* was chosen as the first independent variable since it showed the best correlation with ARB oral BA data in simple linear regression. The solubility data could not be used as the second independent variable since log*S* provided good correlation with Mlog*P* values (R^2=0.805). Therefore, PSA, Mw, Vol and pK_{a1} were chosen as possible, secondary independent variables, besides MlogP. The following correlations were obtained:

Eq.1:

$$\mathbf{BA_{pred}(\%)}=22.43(\pm11.96)\mathbf{Mlog}\boldsymbol{P}-0.70(\pm0.26)\mathbf{Vol}-39.36(\pm79.01)$$

(R^2=0.574; n=7; S.D.=16.03; F=2.70);

Eq.2:

$$\mathbf{BA_{pred}(\%)}=16.33(\pm10.13)\mathbf{Mlog}\boldsymbol{P}-0.26(\pm0.38)\mathbf{PSA}-13.78(\pm74.21)$$

(R^2=0.613; n=7; S.D.=15.29; F=3.170);

Eq.3:

$$\mathbf{BA_{pred}(\%)}=27.80(\pm10.61)\mathbf{Mlog}\boldsymbol{P}-0.26(\pm0.24)\mathbf{Mw}-24.45(\pm85.68)$$

(R^2=0.661; n=7 S.D.=14.30; F=3.90);

Eq.4:

$$\mathbf{BA_{pred}(\%)}=16.98(\pm8.05)\mathbf{Mlog}\boldsymbol{P}+3.07(\pm2.55)\mathbf{pK_{a1}}-56.26(\pm34.50)$$

(R^2=0.682; n=7 S.D.=13.85; F=4.29).

The best correlation was established between ARB BA data obtained from the literature and the Mlog*P* lipophilicity descriptor, using Mw or the acidity descriptor pK_{a1} as additional, independent variables with R^2=0.661 and 0.682, respectively. The obtained results are presented in Table 2. It can be noticed that among the investigated ARB candesartan's predicted BA values were twice as high as those found in the available BA data for all obtained calculations. Therefore, it was decided to repeat calculations after excluding candesartan, and a significantly higher correlation was found in the first stage in simple linear regression between ARB BA data and Mlog*P* values with R^2=0.702. Subsequently, MLR analysis also provided a much better relationship between available BA data for ARB in the literature and all the calculated molecular descriptors, PSA, Mw, Vol and pK_{a1} (R^2>0.70). The best MLR analysis was established with the application of Mlog*P* and Mw as independent variables:

Eq.5:

$$\mathbf{BA_{pred}(\%)}=29.42(\pm7.44)\mathbf{Mlog}\boldsymbol{P}-0.30(\pm0.17)\mathbf{Mw}+39.75(\pm60.18)$$

(with R^2=0.852; n=6; S.D.=9.98; F=8.63).

The established correlation is presented in Fig.1.

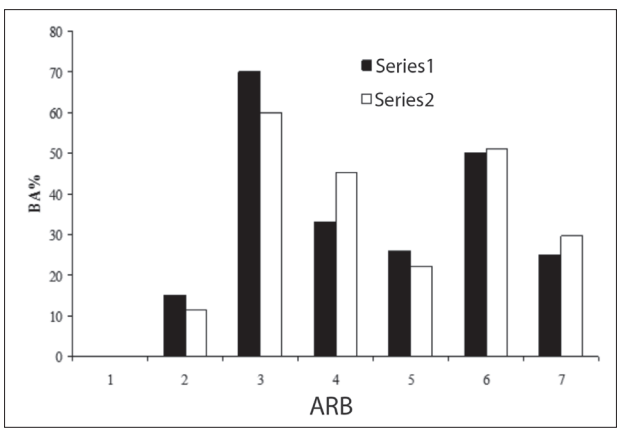

Fig. 1. The relationship between ARB oral bioavailability data collected from the literature [3] (Series 1) and predicted in MLR, using Mlog*P* and Mw, after candesartan exclusion (Series 2). The numbers denote ARB as presented in Table 1.

DISCUSSION

Oral BA is one of the most important pharmacologic properties in drug design and development. It is a subcategory of absorption and represents the fraction of administered drug dose that reaches systemic circulation. High oral BA reduces the amount of an administered drug needed to achieve the desired pharmacological effect, thereby reducing the risk of side effects and toxicity, while poor oral BA can result in low efficacy and lead to unpredictable response to a drug. BA for intravenously administered drugs is 100%. However, for orally administered drugs, BA usually decreases due to incomplete absorption and first-pass metabolism as well a high degree of plasma protein binding. Various physiological factors may reduce the bioavailability of drugs prior to their entry into the systemic circulation. Furthermore, drug administration with or without food also affects absorption. Concurrent intake of other drugs may alter absorption and first-pass metabolism, while intestinal motility alters the dissolution and may affect the degree of chemical degradation of the drug by intestinal microflora. Diseases affecting liver metabolism or gastrointestinal function will also have an effect on BA. A drug's physical properties (hydrophobicity, acidity, solubility, molecular mass, volume and polar surface area) or its formulation as well as the age and gender of the patients and the dosing scheme also exert important influences on its BA.

Previous studies evaluated the acidity, lipophilicity, solubility and absorption of different drugs based on their molecular structure with the application of computer programs [7-9]; they also evaluated the influence of molecular properties on drug BA [22,23], but ARB were not included in these studies. According to the available literature, the ARB pharmacokinetics and pharmacodynamics, including their effects and duration of action, were investigated by several authors [24-29]. However, most of these methods had certain limitations and a new approach for a fast, easy and reliable evaluation of ARB oral BA was necessary.

The central aim of the study was to establish a high throughput approach for evaluating the oral BA data of selected ARB using simple or multiple linear regression analyses. 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 ARB oral BA data were investigated. Of all log*P* values, only Mlog*P* provided relatively good correlation (R^2=0.567) with ARB oral BA. The methods used for lipophilicity descriptor calculation provided ten different log*P* values. They can be divided into substructure-based and property-based methods, and the substructure-based methods can be additionally subclassified into fragmental and atom-based [30]. The lipophilicity descriptor Mlog*P* was calculated with the property-based method based on topological descriptors [30].

Secondly, the relationship between ARB and BA data and calculated molecular descriptors was investigated using MLR analysis with the application of two independent variables, Mlog*P* and one of the following: PSA, Mw, Vol or pKa. Although the best correlation was established between ARB BA data and the Mlog*P* lipophilicity descriptor, using the molecular weight (R^2=0.661) or acidity (R^2=0.682) as independent variables it was observed that the calculated BA values for candesartan differed notably from its literature available BA values (Table 2). Candesartan is actually an active metabolite and its prodrug form is candesartan cilexetil. Candesartan cilexetil is absorbed after oral administration and hydrolyzed during absorption to form candesartan. An absolute bioavailability for candesartan is about 15% following its oral administration. Peak plasma concentration occurs after 3 to 4 h. Candesartan has very high degree of plasma protein binding (PPB), higher than 99%. The high values of candesartan's PPB, together with incomplete absorption and first-pass metabolism may be some of the reasons for its low BA values.

Following this observation, candesartan was excluded from further investigation resulting in much higher correlation (R^2=0.702) between ARB BA data and Mlog*P* values calculated using simple linear regression. MLR analysis of ARB BA data and the lipophilicity descriptor Mlog*P*, with the application of different molecular descriptors established satisfactory

correlations (R^2>0.70), the best (R^2>0.852) being Mw as an independent variable, confirming the important influence of ARB molecular properties on their oral BA. The results obtained can be considered as good considering the limited number of compounds and since values of R^2 higher than 0.81 are proposed as very high correlation by Asuero et al. [31].

CONCLUSION

The results of the present paper have confirmed that the molecular properties, especially lipophilicity, acidity and molecular weight of angiotensin II receptor blockers, are of considerable importance and that their calculation can be considered as a high-throughput screening for evaluation of the oral bioavailability of the selected compounds. For the selected group of angiotensin II receptor blockers, simple linear regression analysis provided a correlation (R^2=0.568) between the calculated lipophilicity descriptor and bioavailability data. However, in multiple linear regression, better correlations were established between the bioavailability and lipophilicity descriptor, using the molecular weight or the acidity descriptor as additional, independent variables (with R^2=0.661 and 0.682, respectively). Candesartan exclusion from multiple linear regression analysis resulted in very good correlation (R^2=0.852) between the remaining angiotensin II receptor blockers' bioavailability, lipophilicity and molecular weight descriptors as independent variables. Since bioavailability affects drug action and activity and is considerably influenced by molecular properties, the examination of its relationship with computed molecular descriptors can be of great importance, especially in the development of newly synthesized drugs.

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REFERENCES

1. Csaba F. Indications for and utilization of angiotensin receptor II blockers in patients at high cardiovascular risk. Vasc Health Risk Manag. 2011;7:605-622.
2. Lemke TL, Williams DA, Roche VF, Zito SW, editors. The Foye's Principles of Medicinal Chemistry. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2008. 1377 p.
3. Stella VJ, Borchardt RT, Hageman MJ, Oliyai R, Maag H, Tilley JW. Biotechnology: Pharmaceutical Aspects, Prodrugs: Challenges and Rewards. 18th ed. New York: Springer Science, Business Media; 2007. 1464 p.
4. Sweetman SC. Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009. 805 p.
5. Di L, Kernsy EH. Profiling drug - like properties in discovery research. Curr Opin Chem Biol. 2003;7:402-8.
6. Hartmann T, Schmitt J. Lipophilicity - beyond octanol/water: a short comparison of modern technologies. Drug Discov Today Techn. 2004;1(4):431-9.
7. Remko M, Swart M, Bickelhaupt FM. Theoretical study of structure, pKa, lipophilicity, solubility, absorption and polar surface area of some centrally acting antihypertensives. Bioorg Med Chem. 2006;14:1715-28.
8. Remko M. Acidity, lipophilicity, solubility, absorption, and polar surface area of some ACE inhibitors. Chem Pap. 2007;61(2):133-41.
9. Zhao YH, Le J, Abraham MH, Hersey A, Eddershaw PJ, Luscombe CN, Boutina D, Beck G, Sherbone B, Cooper I, Platts JA. Evaluation of human intestinal absorption data and subsequent derivation of a quantitative structure-activity relationship (QSAR) with the Abraham descriptors. J Pharm Sci. 2001;90:749-84.
10. Cheung BMY. Sartans for hypertension – implications of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial. Hong Kong Med J. 2004;10(5):359.
11. Zwieten van PA. Angiotensin II receptor antagonists (AT1 blockers, ARBs, sartans): similarities and differences. Netherlands Heart J. 2006;14(11):381-7.
12. Husain A, Md Mitra SAM, Bhasin PS. A review of pharmacological and pharmaceutical profile of irbesartan. Pharmacophore. 2011;2(6):276-86.
13. Hellstern A, Hildebrand M, Humpel M, Hellenbrech D, Saller R, Madetzki C. Minimal biliary excretion and enterohepatic recirculation of lormetazepam in man as investigated by a new nasobiliary drainage technique. Int J Clin Pharmacol Ther Toxicol. 1990;28(6):256-61.
14. Kullak-Ublick GA, Becker MB. Regulation of drug and bile salt transporters in liver and intestine. Drug Metab Rev. 2003;35(4):305-17.
15. Verho M, Luck C, Stelter WJ, Rangoonwala B, Bender N. Pharmacokinetics, metabolism and biliary and urinary excretion of oral ramipril in man. Curr Med Res Opin 1995;13(5):264-73.
16. Martin PD, Warwick MJ, Dane AL, Hill SJ, Giles PB, Phillips PJ, Lenz E. Metabolism, excretion, and pharmacokinetics of rosuvastatin in healthy adult male volunteers. Clin Ther. 2003;25(11):2822-35.

17. Odovic J, Trbojevic-Stankovic J. In silico evaluation of angiotensin II receptor antagonist's plasma protein binding using computed molecular descriptors. Acta Medica Medianae. 2014;53(1):19-24.
18. Trbojević - Stanković J, Odović J, Jelić R, Nešić D, Stojimirović B. The influence of certain molecular descriptors of fecal elimination of angiotensin II receptor antagonists. Arch Biol Sci. 2015;67(1):103-9.
19. Odovic JV, Markovic BD, Injac RD, Vladimirov SM, Karljikovic-Rajic KD. Correlation between ultra-high performance liquid chromatography-tandem mass spectrometry and reversed-phase thin-layer chromatography hydrophobicity data for evaluation of angiotensin-converting enzyme inhibitors absorption. J Chromatogr A. 2012; 1258: 94-100.
20. Trbojević-Stanković J, Odović J, Jelić R, Nešić D, Stojimirović B. The effect of calcium channel blockers' molecular properties on elimination route. Arch Biol Sci. 2015; 67 (3): 801-6.
21. Odovic J, Trbojevic-Stankovic J. Correlation between Angiotensin-converting enzyme inhibitors lipophilicity and protein binding data. Acta Medica Medianae. 2012;51(4):13-8.
22. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drugs candidates. J Med Chem. 2002; 45:2615-23.
23. Turner JV, Glass BD, Agatonovic-Kustrin S. Prediction of drug bioavailability based on molecular structure. Anal Chim Acta. 2003;485: 89-102.
24. Sleem M, Taye A, El-Moselhy MA, Mangoura SA. Combination therapy with losartan and L-carnitine protects against endothelial dysfunction of streptozotocin-induced diabetic rats. Eur J Pharmacol. 2014;744:10-7.
25. Łukawski K, Janowska A, Jakubus T, Raszewski G, Czuczwar SJ. Combined treatment with gabapentin and drugs affecting the renin–angiotensin system against electroconvulsions in mice. Eur J Pharmacol. 2013;706(1-3):92-7.
26. Toba H, Tojo C, Wang J, Noda K, Kobara M, Nakata T. Telmisartan inhibits vascular dysfunction and inflammation via activation of peroxisome proliferator-activated receptor-γ in subtotal nephrectomized rat. Eur J Pharmacol. 2012; 685(1-3): 91-8.
27. Lacourcière Y, Asmar R. A comparison of the efficacy and duration of action of candesartan cilexetil and losartan as assessed by clinic and ambulatory blood pressure after a missed dose, in truly hypertensive patients: a placebo-controlled, forced titration study. Candesartan/Losartan study investigators. Am J Hypertens. 1999; 12(12), 1181-7.
28. Meredith P. Comparative ARB pharmacology. Br J Cardiol. 2010;17(2): s3-s5.
29. Meredith PA, Murray LS, McInnes GT. Comparison of the efficacy of candesartan and losartan: a meta-analysis of trials in the treatment of hypertension. J Hum Hypertens. 2010;24(8):525-31.
30. Mannhold R, Poda GI, Tetko IV. Calculation of molecular lipophilicity: state-of-the-art and comparison of logP methods on more than 96,000 compounds. J Pharm Sci. 2003;98:861-93.
31. Asuero AG, Sayago A, Gonzalez AG. The correlation coefficient: An overview. Crit Rev Anal Chem. 2006;36:41-59.
32. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Met. 2000;44:235-49.
33. Ghose AK, Viswanadhan VN, Wendoloski JJ. A Knowledge-Based Approach in Designing Combinatorial or Medicinal Chemistry Libraries for Drug Discovery. J Combin Chem. 1999;1:55-68.