Arch. Biol. Sci., Belgrade, 67(3), 801-806, 2015 DOI:10.2298/ABS150127039T

THE EFFECT OF THE MOLECULAR PROPERTIES OF CALCIUM CHANNEL BLOCKERS ON THEIR ELIMINATION ROUTE

Jasna B. Trbojević-Stanković[1,2], Jadranka V. Odović[3], Ratomir M. Jelić[4], Dejan M. Nesić[5,*], 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: Calcium channel blockers (CCBs) are among the most widely used drugs in cardiovascular medicine. In this study, nine CCBs (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil and diltiazem) were investigated to assess the relationship between their molecular properties and elimination data obtained from literature. The descriptors of the molecular properties of CCBs were calculated using three software packages. The relationship between computed molecular properties and elimination data collected from relevant literature, initially investigated with simple linear regression analysis, showed poor correlation (R^2 <0.25). Application of molecular weight or volume data as additional independent variable, multiple linear regression (MLR) revealed better correlations (R^2 ~ 0.38) between CCB renal and fecal elimination data and their lipophilicity. Excluding nimodipine from the calculations resulted in more acceptable correlations. The best correlations were established after computed lipophilicity descriptor and molecular weight were applied (R^2 = 0.66 with acceptable probability value).

Keywords: Calcium channel blockers; lipophilicity; molecular weight; elimination route; nimodipine

Received January 27, 2015; **Revised** February 18, 2015; **Accepted** February 26, 2015

INTRODUCTION

Calcium channel blockers (CCBs), also known as calcium antagonists, are commonly prescribed drugs for the treatment of various conditions of the heart and blood vessels, such as hypertension, angina pectoris, supraventricular dysrhythmias, after myocardial infarction and in migraine prophylaxis. They support vasodilator activity and reduce blood pressure by decreasing calcium influx into vascular smooth muscle cells (Stella et al., 2007; Lemke and Williams, 2008; Sweetman, 2009; Beale and Block, 2011; Mofat et al., 2011).

Most CCBs, with the exception of amlodipine (64-90%) and nifedipine (45-70%), have variable oral bioavailability because of extensive first-pass metabolism. Their half-life is relatively short – usually shorter than 12 hours, with the exception of amlodipine which, although extensively metabolized, has half-life of 35-50 hours. According to the available literature data, CCBs have a dual route of elimination, renal and fecal. The lowest values for renal and highest values for fecal elimination of CCBs was found for diltiazem, while for nimodipine renal elimination is the major route of elimination. CCBs combine well with antihypertensive

drugs that block the rennin-angiotensin system, ACE inhibitors and angiotensin receptor blockers (Stella et al., 2007; Lemke and Williams, 2008; Sweetman, 2009; Beale and Block, 2011; Mofat et al., 2011).

According to their structural and functional distinctions, CCBs can be subdivided into three groups: dihydropyridine derivatives (amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine and nisoldipine), phenylalkylamine (verapamil) and benzothiazepine derivatives (diltiazem) (Lemke and Williams, 2008). Dihydropyridine derivatives have pronounced peripheral vasodilator properties; their eflex cardiac stimulation overcomes direct cardiac effects; verapamil and diltiazem are vasodilators, but with more noticeable cardiac effects, including reduced heart rate (Stella et al., 2007; Lemke and Williams, 2008; Sweetman, 2009; Beale and Block, 2011; Mofat et al., 2011).

The clinical success of drugs mostly depends on their absorption, distribution, metabolism or route of elimination (Di and Kernsy, 2003). Lipophilicity is one of the most important molecular properties that influences these values, but a number of other molecular properties, such as molecular weight (Mw), molecular volume (Vol), polar surface area (PSA) and solubility data (logS), also play an important role 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 antihypertensive drugs including those belonging to the CCB group, their design and synthesis (Christiaans et al., 1993; Kalavagunta et al., 2014), as well as pharmacokinetics, pharmacodynamics and efficacy (Pozo and Baeyens, 1986; Sepehr-Ara et al., 2011; Ian Whyte et al., 2012; Mayama, 2014). Their acidity, lipophilicity, solubility or absorption were evaluated together with large groups of different drugs based on their molecular structure with the application of computer programs (Remko et al., 2006; Remko, 2007; Zhao, 2001).

The aim of this study was to compare the different molecular properties of nine CCBs (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil and diltiazem) and their elimination data.

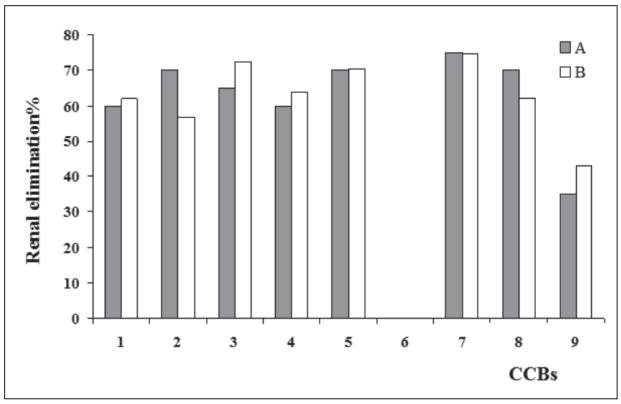

Fig. 1. The relationship between CCB renal elimination data collected from the literature (**A**) and predicted (**B**) using Clog*P* and Mw values. Numbers denote CCBs – calcium channel blockers (Table 1).

MATERIALS AND METHODS

The nine CCBs investigated were: amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil and diltiazem.

CCB aqueous solubility data (log*S*) were calculated using the software Virtual Computational Chemistry Laboratory and the software package Molinspiration Depiction Software (Molinspiration Cheminfirmatics) was used for the calculation of electronic descriptors: polar surface area (PSA); constitutional parameter (molecular weight (Mw)); geometric descriptor (volume value (Vol)). Chemdraw ultra 12.0 was used for the calculation of lipophilicity parameters, Clog*P* values. All calculated molecular descriptors are presented in Table 1. The elimination data of the investigated CCBs (Table 1) were obtained from the relevant literature (Lemke and Williams, 2008). Microsoft Excel 2003 and Origin 7.0 PRO (Origin Lab Corporation, USA) were used for statistical analysis.

RESULTS

According to the available data from literature, CCBs have a dual route of elimination, (renal and fecal) and renal elimination has been shown as the major

one. The lowest values for renal and highest for fecal elimination were found for diltiazem (35% and 65%, respectively). For nimodipine, renal elimination is the major route of elimination (Table 1).

The five CCB molecular descriptors (PSA, Mw, Vol, log*P*, log*S*) were calculated using different software packages (Table 1). The correlations between CCB elimination data obtained from the relevant literature and the calculated molecular descriptors (PSA, Mw, Vol, log*P*, log*S*) were initially investigated using simple linear regression, providing very poor correlation with coefficients (R^2) of around 0.25.

In the next stage of the study, the relationships between CCB renal and fecal elimination data and two different CCB molecular descriptors were investigated using multiple linear regression (MLR). The relationship between CCB fecal as well as renal elimination data and lipophilicity with the application of molecular weight or volume data as an additional independent variable provided similar correlations, with coefficients (R^2) around 0.38. The predicted values of CCB renal and fecal elimination data are presented in Table 2.

Finally, all relationships were investigated after nimodipine exclusion, since it was noticed that

Table 1. Data of CCBs renal and fecal elimination data collected from relevant literature and calculated molecular descriptors

CCBs	Renal el.%*	Fecal el.%*	PSA	Mw	Vol	ClogP.
1. Amlodipine	60	25	100	409	364	3.43
2. Felodipine	70	10	65	384	323	2.24
3. Isradipine	65	30	104	371	330	3.92
4. Nicardipine	60	35	114	480	437	5.23
5. Nifedipine	70	15	110	346	303	3.13
6. Nimodipine	100	0	120	418	379	4.00
7. Nislodipine	75	12	110	388	353	4.58
8. Verapamil	70	16	64	455	454	4.47
9. Diltiazem	35	65	59	415	378	1.19

(*)CCB values were obtained from Lemke and Williams (2008)

Table 2. CCB renal and fecal elimination data predicted from Clog*P* and Mw ([a]) and Clog*P* and Vol values ([b]).

CCBs	Renal el. %([a])	Renal el. %([b])	Fecal el. %([a])	Fecal el. %([b])
1. Amlodipine	66	67	25	24
2. Felodipine	59	61	31	28
3. Isradipine	76	76	12	12
4. Nicardipine	71	73	23	19
5. Nifedipine	73	72	14	15
6. Nimodipine	69	70	21	21
7. Nislodipine	79	79	9	10
8. Verapamil	68	64	25	30
9. Diltiazem	45	44	48	49

nimodipine renal elimination is the major elimination route, without values of fecal elimination data. Relatively low correlations (R^2 around 0.45) were established for the relationships between CCBs presented in the available literature and the predicted fecal elimination data.

However, for relationships between renal elimination data collected from the relevant literature and those predicted, applying computed lipophilicity descriptor (Clog*P*) and molecular weight (Mw) or molecular volume (Vol) as independent variables, higher correlations were established.

Eq. 1:

$$\text{Renal el.}_{\text{pred}}(\%) = 7.995(\pm 2.718)\text{Clog}P - 0.175(\pm 0.082)\text{Mw} + 105.907(\pm 30.889)$$

where n = 8; $R^2 = 0.658$; S.D. = 8.666; F = 4.801;

Eq. 2:

$$\text{Renal el.}_{\text{pred}}(\%) = 8.108(\pm 2.930)\text{Clog}P - 0.136(\pm 0.072)\text{Vol} + 84.467(\pm 23.902)$$

where n = 8; $R^2 = 0.619$; S.D. = 9.142; F = 4.062.

The better correlation, obtained using MLR analysis applying Clog*P* and Mw as independent variables (Eq. 1) is presented in Fig. 1. The established correlation can be considered as good, as has been proposed previously by Asuero et al. (2006), with acceptable P values, due to the limited number of compounds.

The correlation that was found between CCB renal elimination data and their *in silico* molecular descriptors, the lipophilicity parameter (Clog*P)* and the constitutional parameter (molecular weight (Mw)), confirmed descriptor calculation as the high-throughput screening technique (HTS) for evaluation of elimination of the selected compounds.

DISCUSSION

In this research nine CCBs (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil and diltiazem) were studied in order to evaluate the correlation between their renal and fecal elimination data 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 elimination data of the selected CCBs. Several CCB molecular descriptors were calculated using three different software packages. All calculated descriptors, electronic descriptor – PSA, constitutional parameter – Mw, geometric descriptor – Vol, lipophilicity descriptors – Clog*P* values, as well as aqueous solubility data – logS, play an important role in drug absorption, distribution, metabolism and route of elimination.

The molecules with high lipophilicity show a higher degree of absorption, better penetration into tissues and distribution compared to less lipophilic molecules with similar properties. Drug absorption as well as duration of action or efficiency and elimination is highly affected by its lipophilicity, solubility, molecular size and other molecular properties (Lipinski, 2000; Ghose el al. 1999). The weakly lipophilic drugs are mostly eliminated by urine, while the highly lipophilic ones usually exhibit a high degree of fecal elimination.

According to the available literature, CCB pharmacokinetics, pharmacodynamics and efficacy were investigated by a number of authors (Pozo and Baeyens, 1986; Sepehr-Ara et al., 2011; Ian Whyte et al., 2012; Mayama, 2014). Also, various authors suggested several assays that could be employed in studies of the elimination of different drugs (Hellstern et al., 1990; Kullak-Ublick and Becker, 2003; Verho et al., 1995; Martin et al., 2003). However, most of these methods have certain limitations and a new approach for a fast, reliable and cost-effective evaluation of the CCB route of elimination should be developed. Since the route and degree of elimination of drugs may affect their duration of action and activity, the application

of computed molecular descriptors in the prediction of drug elimination are of great importance, especially for the newly synthesized drugs.

In the present study, the correlations between calculated CCB molecular descriptors and their elimination data obtained from relevant literature were examined. In the first step of the investigation the correlations between CCBs elimination data obtained from relevant literature and the calculated descriptors were investigated using simple linear regression. Fecal elimination data and CCBs molecular descriptors – Vol, Mw and log*S*, showed very low correlations (R^2<0.10), while only the electronic descriptor (polar surface area, PSA) and lipophilicity descriptor (Clog*P*) provided correlation with coefficients (R^2) of around 0.25. In the next stage of the study, the relationship between CCB renal as well as fecal elimination data and two different CCB molecular descriptors were investigated using multiple linear regression. Clog*P* was chosen as the first independent variable since it showed the best correlations with CCB elimination data (renal as well as fecal), while values of Mw, Vol and log*S* were chosen as possible second independent variables. Values of electronic descriptor (PSA) couldn't be used as the second independent variable, since in correlation with Clog*P*, R^2 was 0.39. The relationship between CCB fecal elimination data and lipophilicity with application of log*S* as the second independent variable provided very poor correlation (R^2 < 0.25). Correlations between CCB fecal elimination data and lipophilicity with the application of molecular weight or volume data as additional independent variables provided the same coefficients (R^2 = 0.39), while correlations with R^2 = 0.37 were established for renal elimination data. However, among all investigated CCBs, only for nimodipine was renal elimination appointed as the major route of elimination, without absolute values of fecal elimination data. Therefore, the investigated relationships were recalculated after excluding nimodipine and significantly higher correlations were found. The best correlation was established between renal elimination data collected from relevant literature and those predicted applying the computed Clog*P* and Mw (R^2 = 0.66).

CONCLUSION

The correlation between nine CCB elimination data and five different molecular descriptors were investigated. The applicability of calculated molecular descriptors, especially the lipophilicity descriptor, Clog*P* and molecular weight (Mw) in CCB elimination evaluation was established. The proposed methodology confirmed that lipophilicity, together with other molecular properties, is essential for drug elimination and could assist in the *in vitro* approach to assessing CCB elimination.

Acknowledgments: This work was partly supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia as a part of Project TR34031.

Authors' contribution: Jasna Trbojević Stanković, Jadranka Odović and Biljana Stojimirović were responsible for the study conception and design and the drafting of the manuscript. Jasna Trbojević-Stanković, Dejan Nešić and Ratomir Antić collected the literature. Jasna Trbojević-Stanković, Jadranka Odović and Biljana Stojimirović made critical revisions to the paper. Dejan Nešić and Ratomir Antić provided statistical expertise.

Conflict of interest disclosure: The contents of the manuscript have not been published previously, or submitted elsewhere for consideration, nor are they in press. All of the authors have seen and approved the manuscript. There is no conflict of interest, including any financial, personal or other relationships with other people or organizations.

REFERENCES

Asuero, A.G., Sayago, A. and *A.G. Gonzalez* (2006). The correlation coefficient: An overview. *Crit. Rev. Anal. Chem.* **36,** 41-59.

Beale, J.M. and *J.H. Block* (eds) Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 12th ed. Wolters Kluwer, Lippincott Williams and Wolters, Philadelphia, 2011.

Christiaans, J.A.M., Windhorst, A.D., Groenenberg, P.M., van der Goot, H. and *H. Timmerman* (1993). Synthesis and *in vitro* pharmacology of new 1,4-dihydropyridines. 1.

2-(ω-Aminoalkylthiomethyl)-1,4-dihydropyridines as potent calcium channel blockers. *Eur. J. Med. Chem.* **28** (11), 859-867.

Di, L. and *E.H. Kernsy* (2003). Profiling drug-like properties in discovery research. *Curr. Opin. Chem. Biol.* **7,** 402-408.

Ghose, A.K., Viswanadhan, V.N. and *J.J. Wendoloski* (1999). A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. *J Combin. Chem.* **1,** 55-68.

Hartmann, T. and *J. Schmitt* (2004). Lipophilicity – beyond octanol/water: a short comparison of modern technologies. *Drug Discov. Today Techn.* **1**(4), 431-439.

Hellstern, A., Hildebrand, M., Humpel, M., Hellenbrecht, D., Saller, R. and *C. Madetzki* (1990). Minimal biliary excretion and enterohepatic recirculation of lormetazepam in man as investigated by a new nasobiliary drainage technique. *Int. J Clin. Pharmacol. Ther. Toxicol.* **28**(6), 256-261.

Ian Whyte, I., Buckley, N. and *A. Dawson* (2012). Calcium channel blockers. *Medicine*, **40**(3), 112-114.

Kalavagunta, P.K., Bagul, P.K., Jallapally, A., Kantevari, S., Banerjee, S.K. and *N. Ravirala* (2014). Design and green synthesis of 2-(diarylalkyl)aminobenzothiazole derivatives and their dual activities as angiotensin converting enzyme inhibitors and calcium channel blockers. *Eur. J. Med.Chem.* **83**,344-354.

Kullak-Ublick, G.A. and *M.B. Becker* (2003). Regulation of drug and bile salt transporters in liver and intestine. *Drug Metab. Rev.* **35**(4), 305-317.

Lemke, T.L. and *D.A. Williams* (eds), The Foye's Principles of Medicinal Chemistry, 6th ed. Wolters Kluwer, Lippincott Williams & Wilkins, Philadelphia, 2008.

Lipinski, C.A. (2000). Drug-like properties and the causes of poor solubility and poor permeability. *J Pharmacol. Toxicol. Met.* **44**, 235-249.

Martin, P.D., Warwick, M.J., Dane, A.L., Hill, S.J., Giles, P.B., Phillips, P.J. and *E. Lenz* (2003). Metabolism, excretion, and pharmacokinetics of rosuvastatin in healthy adult male volunteers. *Clin Ther.* **25**(11), 2822-2835.

Mayama, C. (2014) Calcium channels and their blockers in intraocular pressure and glaucoma. *Eur. J. Pharmacol.* **739**, 96-105.

Moffat, A.C., Osselton, M.D. and *B. Widdop* (eds), Clarke's Analysis of Drugs and Poisons 4th ed., Pharmaceutical Press, London, (2011).

Pozo, E.D. and *J.M. Baeyens* (1986). Effects of calcium channel blockers on neuromuscular blockade induced by aminoglycoside antibiotics. *Eur. J. Pharmacol.* **128**(1-2), 49-54.

Remko, M., Swart, M. and *F. Matthias Bickelhaupt* (2006) Theoretical study of structure, pKa, lipophilicity, solubility, absorption and polar surface area of some centrally acting antihypertensives. *Bioorg. Med. Chem.* **14,** 1715-1728.

Remko M. (2007). Acidity, lipophilicity, solubility, absorption, and polar surface area of some ACE inhibitors. *Chem. Pap.* **61**(2), 133-141.

Sepehr-Ara, L., Seyed Ahmad Mohajeri, S.A. and *M. Mahmoudian* (2011). Effect of the two new calcium channel blockers mebudipine and dibudipine on vascular flow of isolated kidney of normal and diabetic rats. *Pathophysiology* **18**(3), 175-184.

Stella, V.J., Borchardt, R.T., Hageman, M.J., Oliyai, R., Maag, H. and *J.W. Tilley* (eds), Biotechnology: Pharmaceutical Aspects, Prodrugs: Challenges and Rewards, 18th Springer Science, Business Media, New York, 2007.

Sweetman S.C. (ed) Martindale: The Complete Drug Reference, 36th ed. Pharmaceutical Press, London, 2009.

Tetko IV. Virtual Computational Chemistry Laboratory. Available from URL: www.vcclab.org

Verho, M., Luck, C., Stelter, W.J., Rangoonwala, B. and *N. Bender* (1995). Pharmacokinetics, metabolism and biliary and urinary excretion of oral ramipril in man. *Curr. Med. Res. Opin.* **13**(5), 264-273 .

Zhao, Y.H., Le, J., Abraham, M.H., Hersey, A., Eddershaw, P.J., Luscombe, C.N., Boutina, D., Beck, G., Sherbone, B., Cooper, I. and *J.A. Platts* (2001). Evaluation of human intestinal absorption data and subsequent derivation of a quantitative structure-activity relationship (QSAR) with the Abraham descriptors. *J. Pharm. Sci.* **90**, 749-784.