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Analysis Relationships Between Pharmacokinetic Parameters *in silico/in vivo* of Selected Antiviral Drugs Based on Structural Analysis*

Analiza zależności parametrów farmakokinetycznych *in silico/in vivo* wybranych leków przeciwwirusowych na podstawie analizy budowy cząsteczki

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Abstract

Background. Pharmacokinetic calculations *in silico* are the main e-ADME verification tool. Besides forecasting a drug's pharmacokinetic parameters, one aim for this kind of analysis is the retrospective evaluation of a drug's pharmacokinetics *in vivo*.
Objectives. The aim of the analysis was to calculate the physiochemical parameters of selected drugs used in the treatment or prevention of influenza and compare them with selected *in vivo* pharmacokinetic data.
Material and Methods. Selected topological, constitutional, geometric, and electrostatic parameters of amantadine, rimantadine, carboxyoseltamivir, oseltamivir, and zanamivir were calculated. The parameters were correlated with data illustrating the pharmacokinetics of these drugs *in vivo* to determine *in silico/in vivo* (ADME/e-ADME) correlations.
Results. Significant differences in LogP values between adamantadane derivatives and oseltamivir and zanamivir were found. Amantadine's and rimantadine's PSA values were low and satisfied the conditions of the rule of five, which clearly forecasts high bioavailability. All the analyzed drugs had completely different aPSA to PSA ratios, which means that *in vivo* SASA, and thus the possibility of disposition in the body, has a high to low sequence of rimantadine > amantadine > oseltamivir and very low for zanamivir, which is reflected in the formulation of the drug.
Conclusions. The lipophilicities (LogP and LogD) of both the rimantadine and amantadine molecules are reflected by the half-lives of the drugs. The decidedly lipophilic character of both molecules combined with very low tPSA and PSA values results in relatively high values of distribution *in vivo*. In carboxyoseltamivir and zanamivir, the *in vivo* distribution volumes are small and the half-lives of the drugs are short. The reasons for this include the hydrophilicity and the large polar surface area of their molecules. The significant hydrophilicity of both drugs is also a reason for their large total clearance *in vivo* (**Adv Clin Exp Med 2008, 17, 3, 285–292**).

Key words: CLogP, PSA, rimantadine, bioavailability, pharmacokinetics.

Streszczenie

Wprowadzenie. Analiza farmakokinetyczna w płaszczyźnie *in silico* jest jednym z najważniejszych narzędzi weryfikacji potencjalnej charakterystyki DMPK (*drug metabolism and pharmacokinetics*) leku. Jednym z kierunków wykorzystania narzędzi obliczeniowych SAR (*structure activity relationship*) jest retrospektywna analiza porównawcza parametrów farmakokinetycznych uzyskanych w doświadczeniach *in vivo* z wynikami analizy *in silico*.
Cel pracy. Obliczenie parametrów fizjochemicznych wybranych leków stosowanych w leczeniu lub profilaktyce grypy w odniesieniu do poznanych wartości parametrów farmakokinetycznych tych leków uzyskanych *in vivo*.

* Part of the results was presented on congress of Polish Association of Pharmacology in Katowice, Poland (25–28 September, 2007, Abstract Vol. 1 S.08.P-53, 289).

Materiał i metody. Wykonano obliczenia wybranych parametrów topologicznych, konstytucjonalnych, geometrycznych i elektrostatycznych amantadyny, rymantadyny, karboksyoseltamiwiru, oseltamiwiru i zanamiwiru. Uzyskane wartości odniesiono do znanych parametrów farmakokinetycznych wybranych leków porównując wartości w środowiskach *in silico*/*in vivo* (ADME/e-ADME) (*absorption, distribution, metabolism, elimination*).
Wyniki. Uzyskane wyniki ilustrują duże zróżnicowanie analizowanych leków pod względem ich lipofilności wyrażonej jako LogP. Amantadyna i rymantadyna charakteryzują się małą wartością PSA (*polar surface area*), co predysponuje je do łatwego transportu biernego przez błony biologiczne. Wszystkie analizowane związki charakteryzuje duże zróżnicowanie stosunku aPSA (*apolar surface area*) do PSA, co ma odniesienie do dostępności biologicznej leków *in vivo* odpowiednio najwyższej dla rymantadyny > amantadyny > oseltamiwiru, oraz bardzo niewielkiej dla zanamiwiru, co w tym wypadku znalazło odniesienie w zastosowanej dla tej cząsteczki postaci leku.
Wnioski. Zarówno w przypadku amantadyny, jak i rymantadyny wyższe wartości LogP mają odniesienie do dłuższych okresów półtrwania leku *in vivo*. Zdecydowanie lipofilny charakter obu cząsteczek w połączeniu z małą wartością PSA umożliwia łatwą dystrybucję leku *in vivo*. W przypadku oseltamiwiru i zanamiwiru zarówno objętość dystrybucji, jak i okres półtrwania w fazie eliminacji uzyskują małe wartości. Przyczyną tego stanu są większa hydrofilność obu cząsteczek oraz większe wartości PSA. Skutkuje to również wyższym od lipofilnych cząsteczek klirensem *in vivo* (**Adv Clin Exp Med 2008, 17, 3, 285–292**).

Słowa kluczowe: CLogP, PSA, rymantadyna, biodostępność, farmakokinetyka.

At least several hundred different drug features are currently taken into account in SAR (structure-activity relationship) and similar analyses. Besides forecasting a drug's pharmacokinetic parameters, one aim of this kind of analysis is the retrospective evaluation of the drug's pharmacokinetics *in vivo*. One of the known and frequently calculated SAR parameters is the octanol-water partition coefficient (LogP) and the polar surface area (PSA). The octanol-water partition coefficient is a parameter that, to some extent, defines drug molecules' ability to pass through biological membranes. The merely partial possibility to define the parameter precisely is a result of the complex character of the drug's distribution in lipophilic tissues. Lipophilicity results from the hydrophilicity and polarity of a molecule. Hydrophilicity can be defined as the capacity to dissolve in water, but polarity is a much more complex parameter. Polarity is most frequently presented as the resultant ensue[*?] of the interaction of a substance (drug) with three kinds of solvents: ethanol (a strongly polar proton donor), dioxane (a weakly polar proton donor), and nitromethane (a strongly polar proton acceptor).

Lipophilicity is one of the most important physiochemical parameters influencing bioavailability and the apparent volume of drug distribution. It is, however, a parameter that provides information of a very complex character. At present this index is calculated according to algorithms and relationships determined on the basis of experimental data for many thousand compounds and with the use of appropriate software [1]. The most frequently applied algorithms allow calculating LogKOW (U.S. Environmental Protection Agency), MiLogP [2–4], CLogP [5], LogP Broto [6], and many others. High LogP values (strongly and extremely lipophilic drugs) are not always connected with high bioavailability. The reason for this is the binding of extremely lipophilic drugs in membrane substructures with a high affinity for this kind of drug. This, in turn, hinders transfer in hydrophilic spaces and further distribution of the drug in the body [7]. In extreme cases the drug may not even be subject to absorption, as in the case for paraffin oil. High lipophilicity, i.e. LogP5 (the rule of five), is usually linked with augmented affinity for the P-gp protein, higher affinity for CYP enzymes, and higher variability in the pharmacokinetic parameters of the drug, including an intensified "first passage" effect. Very highly lipophilic compounds are usually also weakly polar; hence, the mean resistance time of this kind of molecule and its half-life ($t_{1/2}$) are usually longer. Elimination of this kind of compound via the renal pathway with urine requires the previous participation of the proper enzymatic systems which transform the molecule into a more polar form. Strongly lipophilic drugs usually bind to proteins to a large extent and have large apparent distribution volumes, which is usually positively correlated with their effectiveness.

Because these drugs are electrolytes, lipophilicity depends on the degree of dissociation and it is possible to calculate LogD based on the dissociation constant pK. LogD is similar to LogP but takes into consideration changes in lipophilicity depending on the degree of dissociation in a buffer, for example with pH 7.4, i.e. close to that of blood plasma. Strongly hydrophilic drugs (LogP > –4) are those that usually achieve small distribution volumes, bind weakly to proteins (and thus have a weak affinity to the CYP enzyme family), are most frequently eliminated via the renal pathway, and have a short elimination half-life.

Polar surface area (PSA) is a physicochemical parameter linked closely to bioavailability [8]. At present, an equally large cognitive role is attributed to this parameter as to that of LogP. This

applies especially to the analysis of e-ADME of a drug for forecasting the level of bioavailability and its later disposition in the body. This has been confirmed based on SAR analyses of most of the currently known drugs indexed in the World Drug Index. The vast majority of drugs possessing a PSA value <140 A^2 show high bioavailability, reaching 90% or more. For the majority of drugs, high PSA values (PSA >250 A^2) are connected with significantly decreased bioavailability as well as distribution possibilities and the ability to penetrate consecutive membrane systems *in vivo*. The topological polar surface area tPSA is a derivative of PSA and its analysis is performed mainly based on analysis of the substituents of a compound. Analysis of the ratio of apolar surface area (aPSA) to polar surface area (PSA) makes it possible to determine the surface area of a drug accessible to a solvent (SASA). Thus the comparison of the aPSA/PSA ratio makes it possible to perform a comparative analysis of several compounds with various molecular volumes, spherical shapes, folding, geometry, and molecular weights. Significant differences in PSA and the aPSA to PSA ratio indicate not only differences in drugs' bioavailability, but also differences in affinity and the quality of drug transfer to various spaces of the biophase.

It was decided to verify the prognostic significance of the above considerations in practice. The aim of the analysis was to calculate the physicochemical parameters of selected drugs used in the treatment and prevention of influenza. These parameters were compared with data illustrating the pharmacokinetics of those drugs *in vivo* in order to determine *in silico*/*in vivo* (ADME/e-ADME) correlations.

Material and Methods

Calculations of selected topological, constitutional, geometric, and electrostatic parameters of amantadine, rimantadine, carboxyoseltamivir, oseltamivir, and zanamivir were performed. The selection of carboxyoseltamivir was justified by the fact that the compound is an active metabolite. The preliminary SAR analysis of amantadine, rimantadine, oseltamivir, and zanamivir required the transformation of the stoichiometric formulas of the above compounds into a SMILES code (Simplified Molecular Input Line Entry System). The program ACD Chem/Sketch v. 5.12/22 Mar 2002 (www.acdlabs.com) was used for this purpose. The SMILES code was applied to calculate LogP values in two variants (LogKOW, CLogP) and tPSA (Tab. 1). LogKOW was calculated with the Epiwin v. 3.10 software provided by the U.S. Environmental Protection Agency (www.epa.gov.com). CLogP was calculated with the ALOGPS 2.1 program. The other calculations were performed using the Java applet Molinspiration (www.molinspiration.com) and the preADMET software (Research Institute of Bioinformatics & Molecular Design, Korea; http://preadmet.bmdrc.org/pradmet/index.php). Calculations of PSA and aPSA (r=1.4 A) were performed with the Vega Open GL Standard software ed., release 1.5.0.92 (www.ddl.unimit.it/vega/index_noanim.htm) [9, 10]. The analysis of the significance of the results obtained for groups of parameters (permeability and aPSA/PSA) was performed with Student's *t* test. Differences with $P < 0.05$ were considered statistically significant.

Results

The lipophilicity sequence of the analyzed compounds from highest to lowest was shown to be rimantadine > amantadine > carboxyoseltamivir > zanamivir (Tab. 2). The same is true for the LogD value. Increased lipophilicity (both for LogP and LogD) fully corresponded to long mean half-life (Fig. 1). The values show significant differences in LogP between adamantadane derivatives and oseltamivir and zanamivir.

Table 1. SMILES codes applied for the calculations

Tabela 1. Kody SMILES zaadoptowane do analizy

Substance (Substancja)	SMILES notation (Zapis SMILES)
Rimantadine	CC(C12CC3CC(C1)CC(C3)C2)N
Amantadine	C1C2CC3CC1CC(C2)(C3)N
Carboxy Oseltamivir	NC1C\C(=C/C(OC(CC)CC)C1NC(C)=O)C(O)=O
Zanamivir	CC(=O)NC1C(C=C(OC1C(C(CO)O)O)C(=O)O)N=C(N)N
Oseltamivir	CCC(CC)OC1C=C(CC(C1NC(=O)C)N)C(=O)OCC

SMILES – simplified molecular input line entry system.

Table 2. LogP and LogD values of the analyzed drugs

Tabela 2. Wartości LogP oraz LogD analizowanych leków

Lipophilicity (Lipofilność)	Rimantadine	Amantadine	Carboxy oseltamivir	Zanamivir	Oseltamivir
XLogP	3.58	2.31	0.27	–3.01	1.01
LogKOWIN	3.34	2.44	0.18	–4.58	0.95
CLogP	3.96	1.99	–1.24	–5.57	2.13
MiLogP	2.46	2.65	–0.14	–3.64	0.85
Mean	3.33	2.35	–0.23	–4.20	1.24
$LogD_{(7.4)}$	0.82	0.176	–1.73	–6.53	–0.073

ClogP – octanol-water partition coefficient (calculated by the ALOGPS 2.1 program).
$LogD_{(7.4)}$ – octanol-water distribution coefficient for the physiological pH of blood plasma.
LogKOW – octanol-water partition coefficient (calculated by the Epi Suite program).
LogP – octanol-water partition coefficient.
MiLogP – Moriguchi octanol-water partition coefficient (based on the Moriguchi algorithm).
XlogP – database octanol-water partition coefficient.

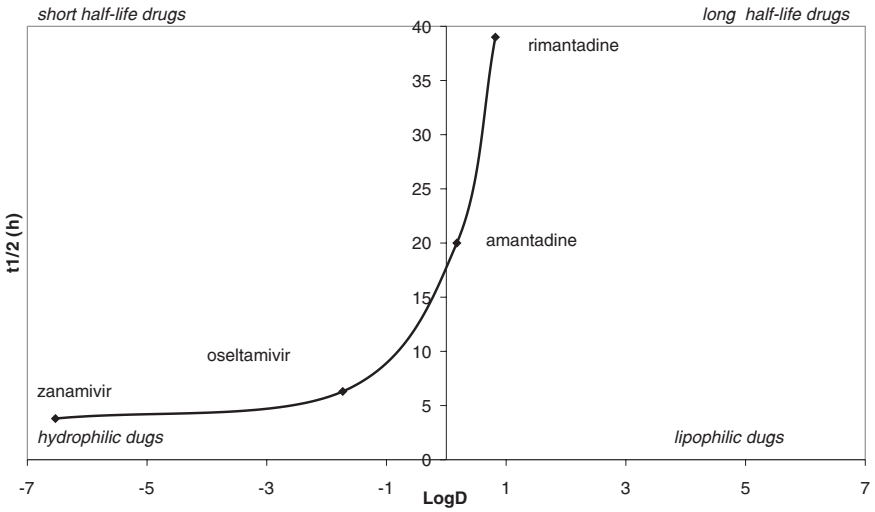

Fig. 1. Relationship between lipophilicity and the half-life of the analysed drugs

Ryc. 1. Zależność między lipofilnością a okresem półtrwania analizowanych leków

Rimantadine is the drug with the highest LogP value in the whole analyzed group. However, the calculated value does not suggest extreme lipophilicity of the drug. In the analyzed group, only rimantadine has lipophilicity of a value consistent with the currently preferred range of the rule of five and the rule of three. The lipophilicity analysis performed using several different algorithms makes it possible to classify rimantadine and amantadine as weakly lipophilic drugs. Oseltamivir and zanamivir have LogP values characteristic for both weakly (oseltamivir) and strongly (zanamivir) hydrophilic drugs [1].

The Wienner and Balaban indexes make it possible to classify a chemical compound as similar to currently known drugs (drugability). Besides these indexes, calculations were also performed for MDCK membrane permeability, Caco-2, HIA (human intestinal absorption), and solvation energy, using the preADME neuron network (Tab. 3). The Wienner index for all the analyzed molecules had values typical of currently known drugs. In the case of the Balaban index, the prodrug (oseltamivir), its active form, and zanamivir exceeded the optimal value of the parameter [11, 12]. The relationship between the PermMDCK value and the distribution volume of rimantadine, amantadine, and carboxyoseltamivir was defined based on calculations (Fig. 2). A high value of molecule transfer through membrane systems usually results in an increase in drug distribution volume. The solvation energies of all the analyzed molecules were negative. This points to an easy disruption of the crystalline structures of these substances and the solvation of all discussed drugs. The parameter indirectly modulates both the absorption, distribution, and redistribution of the drugs in the body.

Amantadine's and rimantadine's PSA values were low and satisfy the conditions of the rule of five, which unanimously forecasts high bioavailability (Tab. 6, Fig. 5) [13–15]. The only exception is zanamivir, for which the value significantly exceeds 140 A^2. The value for carboxyoseltamivir is also close to the limit of the optimal value suggested by Lipinski. In both compounds, the high PSA values and hydrophilic character determine a shorter half-

Table 3. Values of selected topological descriptors and analysis of permeability of membrane systems for the analyzed drugs

Tabela 3. Wartości wybranych parametrów topologicznych oraz wartości przepuszczalności przez układy błonowe

Indexes (Wskaźniki)	Drug (Lek)				
	rimantadine	amantadine	carboxy oseltamivir	zanamivir	oseltamivir
Wienner index	204	124	801	1114	1060
Balaban index	1.91	1.94	2.99	3.34	3.02
Perm Caco-2 (cm/s) × 10^6	2172	21.32	12.97	19.16	14.12
Perm MDCK (cm/s) × 10^6	170.89	68.78	1.82	0.75	5.03
HIA (%)	100	100	72.61	4.064	87.16
Free energy of solvation (KJ/M)	–5.38	–6.82	–19.75	–32.29	–15.26

Caco-2 – colon carcinoma cancer cells.
MDCK – Martin Darby canine kidney cancer cells.
Perm – permeability.
HIA – Human Intestinal Absorption.

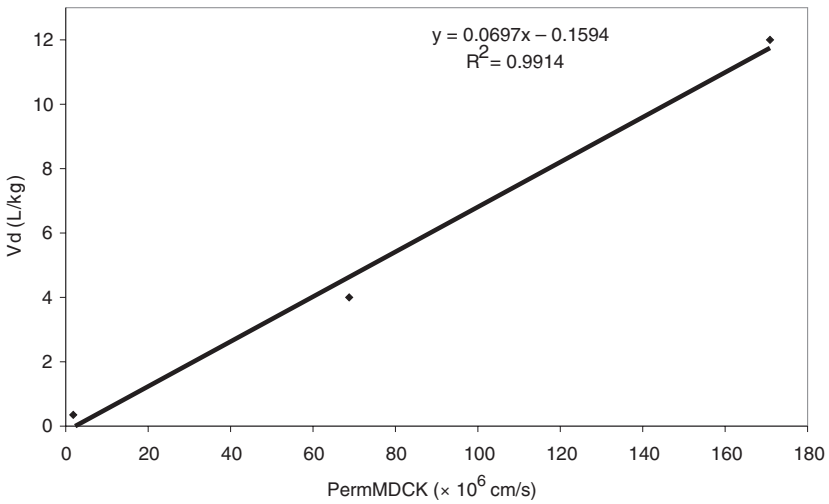

Fig. 2. Relationship between PermMDCK *in silico* and the distribution volume value *in vivo* (from left to right: of carboxyoseltamivir, amantadine and rimantadine)

Ryc. 2. Zależność między PermMDCK *in silico* a objętością dystrybucji warunkach *in vivo* (od lewej: karboksyoseltamiwir, amantadyna, rymantadyna)

life *in vivo*, higher total clearance, and a smaller volume of drug distribution in the body. All the analyzed drugs had completely different aPSA to PSA ratios, which means that *in vivo* SASA, and thus the possibility of disposition in the body, is highest for rimantadine, followed by amantadine and oseltamivir, and very small for zanamivir, which is reflected in the formulation of the drug (Tab. 4).

Complex comparison of the PermMDCK and PermCaco-2 values and of the aPSA/PSA ratio illustrates the distribution possibilities and the possibility of transfer through membrane barriers in the body (Fig. 3). From the point of view of e-ADME analysis, the values obtained for rimantadine are closest to the optimal values. Processes deciding the fate of a drug in the body results from numerous factors regarding the structure of a drug. Combining information regarding LogD and aPSA/PSA ratios made it possible to define a linear relationship between these parameters and the mean *in vivo* half-life of the analyzed drugs (Tab. 7, Fig. 4).

Discussion

The lipophilicity (LogP and LogD values) of both rimantadine and amantadine molecules was reflected in their half-lives (Fig. 1). The decidedly lipophilic character of both molecules combined with very low tPSA and PSA values results in relatively high values of distribution *in vivo*. Their higher lipophilicity does not exclude their easy transition into solution from the crystalline form. This is indicated by the negative value of the solvation energy. All the analyzed molecules have negative solvation energy (Tab. 3). The analysis of PermMDCK, PermCAco-2, and HIA *in silico* indicates the possibility of high disposition of rimantadine and amantadine molecules. This is confirmed by both the long half-lives of these compounds and the large distribution volumes [16]. Both rimantadine and amantadine meet the requirements of Lipinski's rule of five. In the case of carboxyoseltamivir and zanamivir, their *in vivo*

Table 4. Polar surface area (PSA) and apolar surface area (aPSA) values in the analyzed drugs

Tabela 4. Wartości polarnego pola powierzchni oraz apolarnego pola powierzchni w analizowanej grupie leków

Polar surface area (Polarne pole powierzchni)	Drug (Lek)				
	rimantadine	amantadine	carboxy oseltamivir	zanamivir	oseltamivir
tPSA (A^2)	26.02	26.02	101.65	200.73	90.66
PSA (A^2)	46.50	54.40	188.10	291.60	123.80
aPSA (A^2)	324.60	276.70	316.40	230.70	455.10
aPSA/PSA	6.98	5.09	1.68	0.79	3.68
aPSA/tPSA	12.48	10.63	3.11	1.15	5.02

PSA – polar surface area.
tPSA – topological polar surface area.
aPSA – apolar surface area.

Table 5. Values of selected structural parameters of the analyzed molecules

Tabela 5. Wartości wybranych parametrów strukturalnych analizowanych cząsteczek

Topological and structural indexes (Wskaźniki topologiczne i strukturalne)	Drug (Lek)				
	rimantadine	amantadine	carboxy oseltamivir	zanamivir	oseltamivir
HBD	1	1	4	7	2
HBA	1	1	6	10	5
MW	179.3	151.25	284.36	332.3	312.4
MV	192.58	159.196	275.27	283.97	309.59

HBD – hydrogen bond donors.
HBA – hydrogen bond acceptors.
MW – molecular weight.
MV – molecular volume.

Table 6. Values of the derivative LogD × PSA and *in vivo* bioavailability

Tabela 6. Wartości pochodnej $LogD_{(7.4)}$ × PSA w odniesieniu do dostępności biologicznej *in vivo*

Pharmacokinetic and structural indexes (Wskaźniki farmakokinetyczne i strukturalne)	Drug (Lek)			
	rimantadine	amantadine	carboxy oseltamivir	zanamivir
F(%)	100	95	80	11
$LogD_{(7.4)}$ × PSA	38.13	9.57	–325.41	–1904.15

F – absolute bioavailability.
PSA – polar surface area.
$LogD_{(7.4)}$ – octanol-water distribution coefficient for the physiological pH of blood plasma.

Table 7. Relationship between the derivative (aPSA/PSA) × LogD and *in vivo* half-life $t_{1/2}$ of the analyzed drugs

Tabela 7. Zależność między pochodną ([aPSA/PSA] × LogD) oraz okresem półtrwania $t_{1/2}$ uzyskanym w warunkach *in vivo* analizowanych leków

Pharmacokinetic and structural indexes (Wskaźniki farmakokinetyczne i strukturalne)	Drug (Lek)			
	rimantadine	amantadine	carboxy oseltamivir	zanamivir
aPSA/PSA × $LogD_{(7.4)}$	10.23	1.87	–5.38	–7.51
$t_{1/2}$ *in vivo* (h)	39	20	6.3	3.8

$LogD_{(7.4)}$ – octanol-water distribution coefficient according to the physiological pH of blood plasma.
PSA – polar surface area.
aPSA – apolar surface area.
$t_{1/2}$ – elimination half-life.

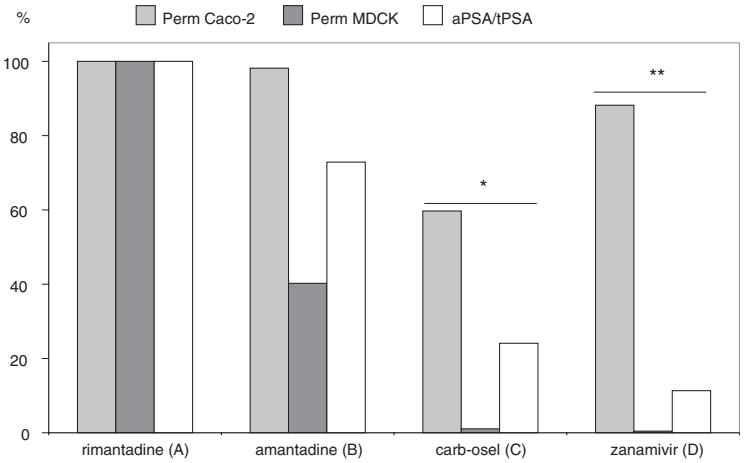

Fig. 3. Values of PermMDCK and Perm Caco-2 *in silico*, and aPSA/tPSA expressed as a percentage ratio, in relation to the highest value of a given parameter obtained in the analysed group of drugs. Statistically significant differences: * – $p < 0.05$ (A:C); ** – $p < 0.05$ (A:D)

Ryc. 3. Wartości PermMDCK, Perm Caco-2 *in silico*, oraz aPSA/tPSA wyrażone jako procent największej wartości uzyskanej dla danego parametru w grupie analizowanych związków. Różnice statystycznie istotne: * – $p < 0,05$ (A:C); ** – $p < 0,05$ (A:D)

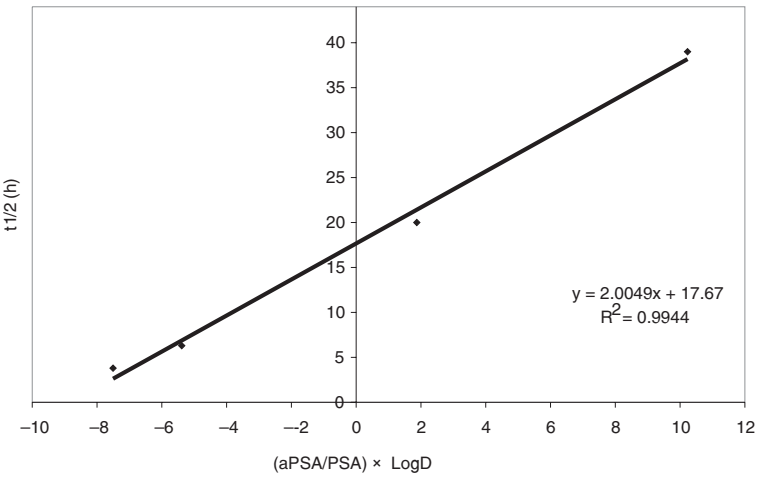

Fig. 4. Relationship between the derivative ([aPSA/PSA] × LogD) and the *in vivo* half-life $t_{1/2}$ of the analysed drugs

Ryc. 4. Zależność między pochodną ([aPSA/PSA] × LogD) oraz okresem półtrwania *in vivo* $t_{1/2}$ analizowanych leków

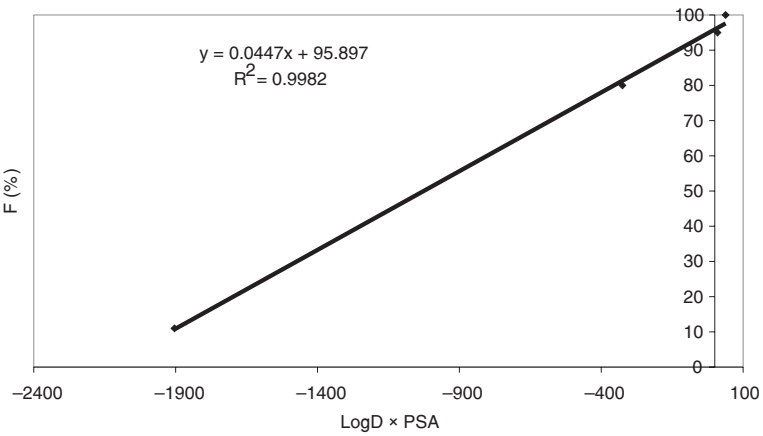

Fig. 5. Relationship between the derivative LogD × PSA and bioavailability of the analysed compounds in *in vivo* settings

Ryc. 5. Zależność między pochodną LogD × PSA oraz absolutną dostępnością biologiczną *in vivo* analizowanych leków

volumes of distribution are small and the half-lives of both drugs are short [17]. The reasons for this include the hydrophilicity and the large polar surface areas of their molecules. The significant hydrophilicity of both drugs is also a reason for the large total clearance *in vivo*. In the case of carboxyoseltamivir, the clearance is 2.5 times higher than the human glomerular filtration rate and is ca. 315 ml/min (GFR 125 ml/min for a human with a body surface area BSA of 1.73 m^2). This indicates that drug elimination is also carried out by the tubular secretion path. Both carboxyoseltamivir and zanamivir also have higher ramification index (R), molecular volume (MV), and molecular weight (MW) than rimantadine and amantadine (Tab. 5). In combination with the higher value of hydrogen bond donors and hydrogen bond acceptors, this results in a very low

bioavailability of the drug following oral administration of zanamivir. As a result, for zanamivir the only possibility is local administration (inhalation). The bioavailability of rimantadine following oral administration is approximately 100%, which is very high compared with that of zanamivir and oseltamivir [18]. A high value of bioavailability was also shown for amantadine [17]. For all the analyzed compounds the bioavailability values corresponded to their polar surface areas and also to their free energies of solvation (FenSolv). The pharmacokinetic parameters of the antiviral drugs cited in literature confirm the results of the analysis of their physical and physiochemical properties based on theoretical assumptions. Drawing conclusions regarding the clinical efficacy of individual drugs on this basis would require further studies, but the effort seems justified.

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