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QUANTITATIVE STRUCTURE – PHARMACOKINETICS RELATIONSHIP FOR THE STEADY STATE VOLUME OF DISTRIBUTION OF BASIC AND NEUTRAL DRUGS

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ABSTRACT

Objective: The success of new drug candidates is critically dependent on its pharmacokinetic (PK) behavior. Therefore the early prediction of PK parameters of new drug candidates became a vital step of drug development process. The study presents a new quantitative structure – pharmacokinetics relationship (QSPkR) for prediction of V_{ss} for neutral and basic drugs. **Methods:** The dataset consisted of 407 drugs, separated into training set (n = 339) and external test set (n = 68). Chemical structures were encoded by 130 theoretical descriptors. Genetic algorithm and step wise multiple linear regression were applied for model generation. The models were evaluated by internal and external validation. **Results:** Significant, predictive and interpretable QSPkR model was developed with explained variance r^2 = 0.547, cross-validated correlation coefficients $q^2_{LOO\text{-}CV}$ = 0.505 and $q^2_{LGO\text{-}CV}$=0.519, external test set predictive coefficient r^2_{pred} = 0.556 and geometric mean fold error of prediction GMFEP = 1.89. The model was able to predict the V_{ss} for 69% of the drugs in the external test set within the 2-fold error of experimental values. **Conclusions:** The model reveals the main molecular features governing V_{ss}. Lipophilicity, basicity and the presence of aromatic rings contribute positively to V_{ss}, while polarity, molecular size and hydrogen bonding ability disfavor V_{ss}. The model shows fairly good predictivity for moderate and high-V_{ss} drugs (with V_{ss} in the range 0.7 – 10 L/kg) and poor performance for extremely high-V_{ss} drugs which follow unique distribution patterns.

KEYWORDS: QSPkR, steady state volume of distribution, ADME prediction.

INTRODUCTION

The volume of distribution (V_d) is important pharmacokinetic (PK) parameter relating the amount of the drug in the body and its plasma concentration. V_d rarely matches any anatomic space and varies between a few liters (for drugs confined mainly in plasma) and several thousand liters (e. g. hydroxychloroquine with V_{ss} of 700 L/kg).[1] Several types of V_d have been defined depending on the route of administration and the time of plasma concentration measurment.[2] The most accurate and useful measure for drug distribution is the steady state volume of distribution following *iv* multiple administration (V_{ss}), measured at the time when the rate of administration equals the rate of elimination. V_{ss} is determined by the binding capacities of blood, organs and tissues and could be influenced by permeation and dissociation rates.[3]

V_{ss} is a key determinant of both maintaining and loading dose in multiple drug regimen.[4] Together with drug clearance, it determines drug half-life. Drugs with high V_{ss} may require higher doses to maintain desired therapeutic concentration and may have a long residence in the body.

It has been long realized that one of the main reasons for the failure of promising drug candidates is the lack of in vivo activity, most frequently due to improper PK behavior.[5] Therefore the early optimization of the key PK parameters became an essential step in drug development process. Various approaches have been proposed for the prediction of V_{ss} in human, based on in vivo data from preclinical species (allometric scaling and extrapolation to human), in vitro experiments – alone or combined with in vivo or theoretical parameters, and entirely in silico methods. The current state of the methodology has been thoroughly reviewed.[6][7][8][9][10][11][12][13] One of the most convenient and throughputs tools for early prediction of PK parameters is quantitative structure – pharmacokinetics relationship (QSPkR) modeling. It can be based solely on easily computed molecular descriptors, allows predictions to be made even on virtual structures and enables screening of large databases of potential drug candidates with high efficiency with respect to time, labor and cost. In addition, QSPkR models may give valuable information about the main structural features governing any PK parameter and enables the design of molecules with acceptable, if not ideal, PK behavior.

A good number of QSPkR for prediction of V_{ss} using various statistical techniques have been proposed and they have been critically reviewed recently.[14] There is an agreement, that

lipophilicity (expressed as logP or logD) affects positively V_{ss}. However there are many examples for drugs with comparable lipophilicity parameter's values and 4-5 fold differences in the Vss values. Most of the models contain descriptors discriminating between acidic and basic drugs implying that acidic drugs should have low V_{ss} and basic drugs – high V_{ss}.

It is well known, that the drugs follow different distribution patterns depending on their ionization state. Bases have high affinity to phospholipid membranes due to interactions between cationic center and acidic head groups. They bind mostly to alpha-1 acid glycoprotein (AGP) and frequently to human serum albumin (HSA) and can be accumulated by ion trapping into lysosomes.[15] About 65% of V_{ss} of bases (on average) was supposed to be due to storage in fat tissue.[3] Therefore, bases have the highest values of V_{ss}. In contrast, acidic drugs are negatively charged at physiological pH 7.4 and frequently have low trans-membrane permeability. Majority of them are highly bound to HSA. As all drug binding proteins are presented extravascularly, acids may have higher V_{ss} than plasma or blood volume. However, on average, V_{ss} of acids is lower than that of bases. Neutral drugs have moderate trans-membrane permeability and binding affinity to both HSA and AGP, depending on their lipophilicity.[15] This is in accordance with the experimental values for V_{ss} in the recently published Obach's database summarizing data for the key PK parameters of 669 drugs following iv administration.[1] The V_{ss} for acids (n = 132) varies between 0.04 and 15 L/kg (mean 0.54, median 0.22); for neutral drugs (n = 145) – between 0.16 and 25 L/kg (mean 1.94, median 1.00) and for bases (n = 262) – between 0.073 and 140 L/kg (mean 5.90, median 2.45).

It seems reasonable to construct separate QSPkR models with respect to the ionization state. Such models may identify the main structural features governing distribution and V_{ss} of drugs of various types and may provide better predictive performance. The only reports on separate QSPkR modeling of V_{ss} clearly demonstrated that V_{ss} of bases and acids depends on different molecular features.[16][17] The separate models have shown lower predictability as compared with the models for the whole dataset which may be due to the limited size of the datasets, inconsistent separation of the classes and unspecified measure of V_d as an end-point variable. Recently we reported a robust, predictive and interpretable QSPkRs for V_{ss} of 132 acidic drugs.[18] The present study is focused on QSPkR for V_{ss} of basic and neutral drugs.

MATERIALS AND METHODS

Datasets

The dataset consisted of 407 drugs (262 basic and 145 neutral), extracted from Obach's database.[1] A drug was considered as neutral, if the fraction ionized as an acid (f_A) or as a base (f_B) at pH 7.4 didn't exceed 3%. Drugs with $f_B > 3\%$ were classified as bases provided that f_B was considerably higher than f_A. The fractions ionized at pH 7.4 were calculated as previously described.[18]

The mol-files of the drugs were derived from several public databases – Drug Bank, Chemical Book, or ChEBI.[19][20][21] The end-point variable V_{ss} was logarithmically transformed in order to achieve close to normal distribution.

For model validation purposes the dataset was separated into training and external test set on the basis of the end-point variable values. To this end the molecules were arranged in an ascending order with respect to their V_{ss} values and one of every six drugs was allocated to different subset. The first subset (n = 68) was left aside as an external test set and the other five (n = 339) were used as a training set for QSPkR model development. On the other hand, for leave-group-out cross-validation (LGO-CV), each subset in the training set was excluded once, a model was built on a training set composed of the other four subsets, and was tested on the compounds in the excluded subset.

Molecular descriptors and variable selection

Chemical structures of the compounds were encoded by 130 molecular descriptors calculated by ACD/logD version 9.08 (Advanced Chemistry Development Inc., Ontario, Canada) and MDL QSAR version 2.2 (MDL Information Systems Inc, San Leandro, CA). Several types of descriptors were computed: physicochemical (logP, $logD_{7.4}$, PSA, dipole moment, polarizability), constitutional (number of atoms and groups of given type, rings, circles, hydrogen bond donors and acceptors, etc.); geometrical (volume, surface, ovality), electrotopological state and connectivity indices, etc. The most significant descriptors were selected in a three step procedure: 1. manual rejection of descriptors with non-zero values for less than 10 molecules; 2. filtering through genetic algorithm (GA); 3. Stepwise linear regression (SWR) with Fisher criteria F-to-enter 4.00 and F-to-remove 3.99. Both GA and SWR were implemented in the MDL QSAR package.

Development of QSPkR models for V_{ss}

Several QSPkR models were generated on the training test of 339 molecules using different combination of descriptors. Drugs, which $logV_{ss}$ values were predicted with high residuals, not obeying normal distribution, were considered as outliers and removed before building of the final model. Several statistical metrics were used for assessment of the best fit: explained variance (r^2), root mean squared error (RMSE), Fisher criteria F, etc.[14]

Validation of generated QSPkR model

Predictive ability of the developed QSPkR model for VD_{ss} was evaluated by internal validation on the training set – leave-one-out cross-validation (LOO-CV) and LGO-CV, as well as on the external test set not involved in any step of model development. The following statistical metrics were calculated: cross-validated coefficients ($q^2_{LOO\text{-}CV}$ and $q^2_{LGO\text{-}CV}$), prediction coefficient for the external test set (r^2_{pred}), mean fold error of prediction (MFEP), geometric mean fold error of prediction (GMFEP), RMSE.[14] QSPkR models were considered as predictive if they fulfilled the recently accepted criteria for $q^2_{LOO\text{-}CV} > 0.5$ and $r^2_{pred} > 0.5$.[22]

RESULTS

The dataset used in the present study consisted of 407 basic and neutral drugs with V_{ss} values spanning in four orders of magnitude: from 0.073L/kg (netilmicin) to 140 L/kg (chloroquine) with mean value of 4.49 ± 6.53 and median 1.7. Respectively, $logV_{ss}$ varied between -1.137 and 2.146 (range 3.283), with mean 0.280 and median 0.230. The structures covered a broad chemical space. Molecular weight ranged between 76 and 1431 mol/L (mean 367 ± 223 mol/L) and logP varied between -5.72 and 8.89 (mean 1.99 ± 2.22). For basic drugs the fraction ionized as a base at pH 7.4 varied between 0.037 and 1.00 with 58% almost completely ionized ($f_B > 95\%$). According to the V_{ss} value, drugs can be classified in four groups:

- Low $V_{ss} \leq 0.7$L/kg – 82 drugs (13.7% of the basic, 31.7% of the neutral).
- Moderate V_{ss} (0.7 – 2L/kg) – 149 drugs (31.3% of the basic, 46.2% of the neutral).
- High V_{ss} (2 – 10L/kg) – 132 drugs (39.7% of the basic, 20% of the neutral).
- Very high $V_{ss} >$ 10L/kg – 44 drugs (15.3% of the basic, 2% of the neutral).

QSPkR model for V_{ss} of neutral and basic drugs

Numerous significant models were generated on the training set of 339 molecules using different combinations of descriptors. The best one in terms of statistics is given below:

$$\log VD_{ss} = 0.079(\pm 0.011) * \log P + 0.321(\pm 0.046) * f_B - 0.055(\pm 0.013) * SssO\_acnt +$$
$$+ 27.53(\pm 5.87) * xvch10 - 0.043(\pm 0.010) * SHBint10\_Acnt - 0.017(\pm 0.006) * Dipole +$$
$$+ 0.041(\pm 0.009) * SaasC\_acnt - 0.0731(\pm 0.015) * SssssC + 0.066(\pm 0.020) * G_{min} +$$
$$+ 0.040(\pm 0.016) * SHBint4\_Acnt - 7.64(\pm 0.97) * xvch9 - 0.061$$
$$n = 320 \qquad r^2 = 0.547 \qquad RMSE = 0.334 \qquad F = 33.83$$

Nineteen drugs were identified as outliers and were removed before development of the final model.

QSPkR model validation

The cross-validation on the training set resulted in $q^2_{LOO\text{-}CV} = 0.505$ and $q^2_{LGO\text{-}CV} = 0.519 \pm 0.045$.

The QSPkR model showed very good predictivity on the external test set of 68 molecules, not involved in any step of model development as proved by the statistical metrics: $r^2_{pred} = 0.556$, GMFEP 1.83, RMSE 0.338, accuracy at 2-fold error level = 69%, accuracy at 3-fold error level = 80%. Three drugs were suggested as outliers from the model. The plot of $logVD_{ss,obs}$ vs. $logVD_{ss,pred}$ is shown in Fig. 1.

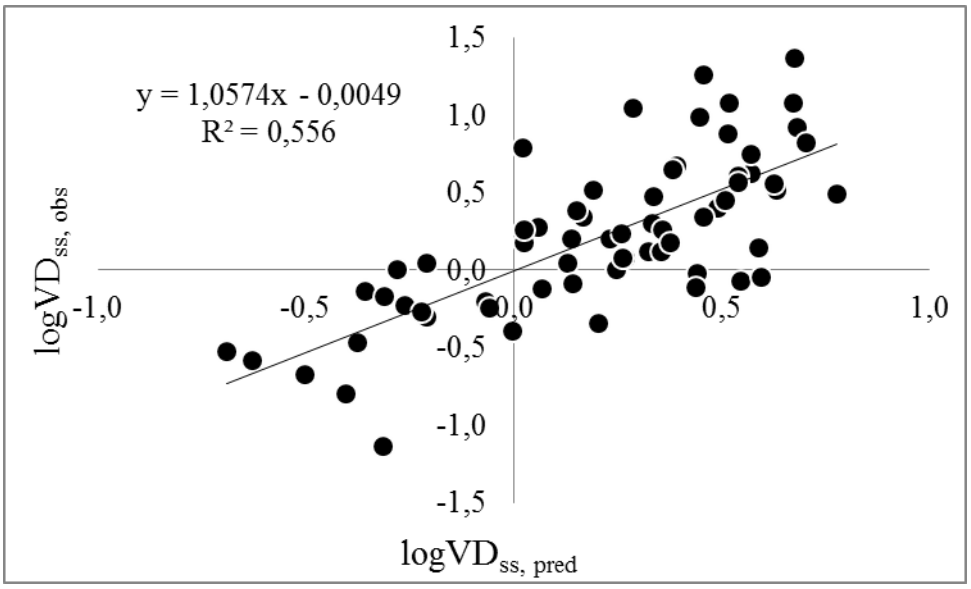

Figure 1: Observed vs. predicted by the QSPkR model values of $logV_{ss}$ for the external test set.

DISCUSSION

A number of QSPkRs for logVD_{ss} of basic and neutral drugs were developed on a training set of 339 molecules covering wide chemical and therapeutic space. A total of 130 descriptors of the chemical structure were calculated. GA, SWR and MLR were used for variable selection and model development. The best fit model was assessed by internal (LOO-CV and LGO-CV) and external validation. The model is significant, robust and predictive with r^2 = 0.547, $q^2_{LOO\text{-}CV}$ = 0.505, $q^2_{LGO\text{-}CV}$ = 0.519±0.045 and external r^2_{pred} = 0.556, GMFEP = 1.83 and RMSE = 0.338. Statistical metrics meet the accepted criteria for good performing QSPkR models.[22][23][24] It was able to predict 69% of the drugs in the external test set within the 2-fold error and 80% - within the 3-fold error of experimental values.

Descriptors in the QSPkR model have clear physical sense and give insight into the main structural features governing VD_{ss} of basic and neutral drugs. According to QSPkR, logP, f_B, SaasC_acnt, xvch10, G_{min} and SHBint10_acnt contribute positively to VD_{ss}. Lipophilicity, expressed with logP, appears to be the most important determinant of V_{ss}, accounting for 27% of the explained variance. 44% of low-V_{ss} drugs have negative logP values, while for 35% of high-V_{ss} drugs and 86% of very high-V_{ss} drugs logP > 3. This is reasonable as lipophilicity is a prerequisite for passive diffusion through cell membranes and interactions in various tissues, especially the fat tissue. Another positive factor for V_{ss} is basicity, expressed as f_B. The presence of a strong basic center enables ion-pairs interactions with the charged acidic head-groups of membrane phospholipids, the binding to phosphatidylserine in the cell membranes in several tissues and ion trapping in lysosomes.[3][15] As already shown, basic drugs have higher values of V_{ss} compared with neutral drugs. The percentage of drugs with $f_B \geq 0.9$ increases from 34% (low-V_{ss} group) to 72% (very high-V_{ss} group). Descriptor SaasC_acnt represents the number of substituted aromatic C-atoms in the molecule. Molecules with high number of aasC atoms usually contain at least two aromatic rings. The 10^{th} order valence connectivity index (xvch10) encodes information about the presence and electronic state of a 10-member ring system – usually represented by two fused aromatic rings. The presence of aromatic rings is a condition for occurrences of specific interactions at binding sites of tissue proteins such as CH-π and π-π stacking, Van der Waals interactions, and hydrophobic interactions. G_{min} represents the lowest E-state value in the molecule and corresponds to the most electrophile atom. This descriptor has low, negative values for C-atoms, connected with large number of strong electronegative atoms (-CF_3, -$C(SO_2NH_2)$, etc.). High positive values of G_{min} are observed for terminal C-atoms, connected with N-

atoms, which are relatively strong basic centers. The highest values for G_{min} were observed for amitriptyline, imipramine, desipramine, etc., which are relatively strong bases with pK_a > 9. Hence, positive value of G_{min} also implies high basicity, favorable for extensive distribution. According to the model, SHBint4_Acnt (accounting for the number of HB acceptor – HB donor couples with 4-atom skeletal bond between donor and acceptor), affects positively V_{ss}, however, used individually, the effect is negative. Hence, the effect of this descriptor on VD_{ss} is not perfectly clear.

Descriptors Dipole, SssO_acnt, xvch9, SHBint10_acnt and SssssC affect negatively V_{ss}. Dipole represents the dipole moment of the molecule. It is a measure of unequal distribution of the electron density and has higher values for large molecules with M > 1000 g/mol, extended molecules with a strong electrophile located peripherally, or fused structures like steroids. Polarity should not be confused with hydrophilicity as there are many drugs with both high Dipole and high logP value. The negative effect of polarity may be due to steric hindrances by crossing cell membranes and/or reduced ability for hydrophobic interactions with tissue constituents. Descriptor SssO_acnt represents the number of ether O-atoms in the molecule, which are potential hydrogen bond (HB) acceptors. HB ability affects negatively lipophilicity which may restrict trans-membrane transport. Similarly, the negative effect of SHBint10_Acnt (encoding the number of HB acceptor – HB donor couples with 10-atom skeletal bond between donor and acceptor) could be explained with a high HB ability of the molecule. Descriptor xvch9 (9^{th} order valence connectivity index) encodes information about the presence and electronic state of a 9-member ring system – represented by fused six- and five-member rings. This descriptor has low values for aromatic heterocyclic rings (containing at least two of N-atoms) and high values for non-aromatic rings. Hence, the presence of aliphatic fused rings disfavors V_{ss}. SssssC encodes the sum of E-state values for quaternary C atoms. The value of SssssC depends on the number of ssssC atoms and the nature of the substituents. It varies from high negative values (for C-atom, connected with 2-3 electronegative atoms or groups like F-, OH,), etc., to positive values (for C-atom, connected only to aliphatic C-atoms). The negative contribution of SssssC to $logV_{ss}$ confirms the unfavorable impact of the presence of aliphatic C-atoms to drug V_{ss}. Analysis of the dataset allowed defining a threshold for each descriptor as a condition for high value of V_{ss} (Table 2).

Table 1: Percentage of drugs belonging to different V_{ss} classes meeting the criteria for high V_{ss}.

Class V_{ss}	Positive criteria							Negative criteria				
	logP≥3	f_B≥0.9	aasC>3	xvch10	G_{min}>0	ssssC<0	SHBint4	ssO≥2	Dip>5	xvch9	SHBint10	logP<0
low	13%	34%	32%	26%	7%	28%	44%	43%	47%	29%	28%	44%
mod	27%	25%	29%	25%	21%	19%	40%	19%	42%	30%	15%	15%
high	35%	48%	37%	31%	24%	37%	32%	25%	30%	28%	13%	5%
very high	86%	72%	72%	56%	53%	28%	42%	28%	22%	17%	25%	0%

The QSPkR model shows different predictive accuracy for the drugs with different V_{ss} values:

- Low V_{ss}: GMFEP 2.19, Accuracy 52.4%; five outliers.
- Moderate V_{ss}: GMFEP 1.65, Accuracy 75.6%; one outlier.
- High V_{ss}: GMFEP 1.63, Accuracy 72.9%; five outliers
- Very high V_{ss}: GMFEP 2.80, Accuracy 22.2%; eleven outliers.

Predictive ability is fairly good for drugs with moderate and high V_{ss} (in the range 0.7 – 10 L/kg), allowing prediction of V_{ss} of more than 70% of the drugs within the 2-fold error of experimental values. In contrast, the model shows poor performance for very high-V_{ss} drugs identifying 25% of them as outliers. These drugs have extremely large V_{ss} values (13 – 140 L/kg) which implies considerable tissue accumulation and unique distribution patterns not captured by the model. The low predicted V_{ss} of triamterene (V_{ss} 13 L/kg, predicted 0.64 L/kg) is mainly due to its low lipophilicity (logP 0.18). In addition, the drug is extensively bound in tissues in the central compartment and cleared by hepatic metabolism and biliary excretion.[25][26] The extremely high V_{ss} of azithromycine (V_{ss} 33 L/kg, predicted 2.14 L/kg) and pentamidyne (V_{ss} 53 L/kg, predicted 4.52 L/kg) and topixantrone (V_{ss} 57 L/kg, predicted 4.51 l/kg) is most probably due to the presence of a two strong basic centers in the molecule.[15] Besides, extensive uptake and slow release from tissues have been suggested for the long drug half-life of azithrimycine.[27] Pentamidine is a substrate of the organic cation transporters facilitating extensive distribution in kidneys, liver and bile.[28] Topixantrone displays a prominent affinity for DNA.[29] Chloroquine is the drug with the largest V_{ss} in the dataset (V_{ss} 140 L/kg, predicted 9.5 L/kg). It distributes widely in numerous tissues and accumulates in skin and eye with a slow release from the pigmented tissues.[30i][31] Ion trapping was suggested as the main reason for chloroquine tissue accumulation.[32] The main assumption by QSPkR modeling is passive diffusion across cell membranes and rapid distribution from tissues which is not always fulfilled in reality. The unique distribution

patterns of the extremely high-V_{ss} drugs are the main reason for their under-prediction by developed QSPkR model.

CONCLUSIONS

Significant, predictive and interpretable QSPkR for V_{ss} of basic and neutral drugs is developed on a dataset of 407 drugs. The model allows prediction of 69% of the drugs in an external test set within the two-fold error of the experimental values. It reveals the main molecular features governing V_{ss}. Lipophilicity, basicity and the presence of aromatic rings to contribute positively to V_{ss}, while polarity, molecular size and hydrogen bonding ability disfavor V_{ss}. The model shows fairly good predictivity for moderate and high-V_{ss} drugs (with V_{ss} in the range 0.7 – 10 L/kg) and poor performance for extremely high-V_{ss} drugs which are largely accumulated in tissues due to unique distribution patterns.

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