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Pharmacokinetic parameter prediction from drug structure using artificial neural networks

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Abstract

Simple methods for determining the human pharmacokinetics of known and unknown drug-like compounds is a much sought-after goal in the pharmaceutical industry. The current study made use of artificial neural networks (ANNs) for the prediction of clearances, fraction bound to plasma proteins, and volume of distribution of a series of structurally diverse compounds. A number of theoretical descriptors were generated from the drug structures and both automated and manual pruning were used to derive optimal subsets of descriptors for quantitative structure-pharmacokinetic relationship models. Models were trained on one set of compounds and validated with another. Absolute predicted ability was evaluated using a further independent test set of compounds. Correlations for test compounds ranged from 0.855 to 0.992. Predicted values agreed closely with experimental values for total clearance, renal clearance, and volume of distribution, while predictions for protein binding were encouraging. The combination of descriptor generation, ANNs, and the speed and success of this technique compared with conventional methods shows strong potential for use in pharmaceutical product development.

Keywords: QSPkR; QSPR; Neural networks; ANN; Theoretical descriptors

1. Introduction

Recent advances in lead compound identification using high throughput and *in silico* techniques have allowed rapid identification of compounds exhibiting possible pharmacological effects at known drug receptor sites (Grass and Sinko, 2001). However, potential receptor affinity alone does not provide sufficient evidence to justify development of a particular chemical entity. Successful drug candidates must also possess other attributes to make them suitable for clinical application.

Ultimately, successful drugs must be administered to humans so properties such as human toxicity, bioavailability and other pharmacokinetic parameters become crucial. Screening for absorption, distribution, metabolism, and excretion (ADME) properties and toxicity is often performed in vitro or with various animal models which can be both time-consuming and expensive (Norris et al., 2000). Even then, results may not accurately reflect human pharmacokinetics, and it has been reported that the majority of drugs dropped from development was due to efficacy and/or pharmacokinetic difficulties (Grass and Sinko, 2001).

Prediction of human pharmacokinetic parameters is an area in need of progress to aid in pharmaceutical product development. Conventional quantitative structure–pharmacokinetic relationship (QSPkR) anal-

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yses in general employ methods relating experimentally-derived properties such as tissue:blood partition coefficients and octanol:buffer partition coefficients to predict drug pharmacokinetic parameters. Experimental generation of this information is time and resource intensive, and has proven difficult because of the complex physiological processes involved in drug ADME and the nonlinear relationships present amongst drug data (Fouchecourt et al., 2001).

Methods of generating descriptors solely from drug structure are gaining popularity because of their resource-saving potential and success in quantitative structure–activity and structure–property relationship (QSAR and QSPR) analyses. These descriptors range in complexity from simple one-dimensional atomic and functional group counts, to two-dimensional topological and charge indices, to complex three-dimensional descriptors which often rely on conformational aspects of a molecule. Both one- and two-dimensional topological indices have been used extensively to numerically relate molecular structure with activity and/or property (Ghafourian and Fooladi, 2001). These descriptors rely only on the molecular graph for their calculation. In contrast, three-dimensional descriptors require the absolute conformation of a molecule to be described, and information gained is specific to that conformation. They, too, have been successfully used to develop QSPRs (Feher et al., 2000).

Various methods for constructing QSAR/QSPR models have been used including multilinear regression (MLR), principal component analysis (PCA) and partial least-squares (PLS) regression. In addition, artificial neural networks (ANNs) have become popular due to their success where complex nonlinear relationships exist amongst data, as is often the case when dealing with drug data sets (Turner et al., 2003b). Moreover, the generalisation ability of ANNs makes them useful for construction of predictive models. Hence, due to their inherent nonlinearity and suitability for predictive applications, ANNs were the method of choice in the current study. For a review of ANN use in the pharmaceutical area see Agatonovic-Kustrin and Beresford (Agatonovic-Kustrin and Beresford, 2000).

ANNs represent learning tools which are distinctly different from standard statistical methods, and as such are not necessarily bound by the same constraints that linear methods are. One important parameter in MLR studies is the relationship between the number of experimental data points and optimisable parameters. A requirement for MLR models is that the ratio of the former to the latter should be greater than a certain threshold. The required ratio for ANN models is not so straightforward, however, since the optimum value depends upon the nature of the data set itself (So and Richards, 1992). It has been found that ρ, defined as the ratio of the number of patterns (compounds) to the number of connections can vary greatly without compromising the results of an ANN model (Turner et al., 2003a).

The aim of the current study was to use theoretically derived descriptors as inputs for ANN models to predict the pharmacokinetic parameters of structurally diverse compounds.

2. Materials and methods

2.1. Experimental data

The ANN technique develops data-driven models, such that known information about drugs from empirical methods does not influence the system. Human pharmacokinetic data for the current study (Table 1) was taken from the literature after careful screening. Absolute values gained from intravenous administration were accepted over apparent values based on the bioavailable fraction of a drug.

The data set of 62 compounds was divided randomly into a working data set for model construction and a testing set to evaluate the predictive performance of each model. The working set was further divided into a training subset of 50 compounds and a validation subset of six compounds used to monitor network performance during training. Final predictive ability was determined using the six independent compounds in the testing set. Subsets were all examined statistically to ensure that validation and testing data did not lie outside the limits of the training set (Loukas, 2001). Separate models were generated for each pharmacokinetic parameter. Parameters investigated were systemic and renal clearances (CL and CL_R, respectively), volume of distribution at steady state (V_{ss}), and fraction bound to plasma proteins (f_b).

Table 1
Drug data set

Compound	Use[a]	CL (ml/min/kg)	CL_R (ml/min/kg)	V_{ss} (l/kg)	f_b	Reference
Acebutolol	tra	11.0	4.21	1.33	0.26	Hinderling et al. (1984a)
Alprenolol	tra	6.47	0.26	1.07	0.76	Hinderling et al. (1984a)
Amitriptyline	tra	11.5	0.12	15.0	0.95	Schulz et al. (1985)
Amlodipine	tra	5.90	0.59	16.0	0.93	Meredith and Elliott (1992)
Amoxicillin	tra	2.60	2.24	0.21	0.18	Sjovall et al. (1986)
Ampicillin	tra	1.70	1.39	0.28	0.18	Ehrnebo et al. (1979)
Atenolol	tra	2.54	2.40	1.11	0.03	Hinderling et al. (1984a)
Betamethasone	tra	2.90	0.14	1.40	0.64	Petersen et al. (1983)
Bufuralol	tes	7.70	0.06	1.86	0.91	Hinderling et al. (1984a)
Bupivacaine	tra	7.10	0.14	0.90	0.95	Burm (1989)
Cefaclor	tra	6.10	3.17	0.36	0.25	Sides et al. (1988), Brumfitt and Hamilton-Miller (1999)
Cefadroxil	tra	2.90	2.70	0.24	0.20	Welling et al. (1985)
Cefprozil	tra	3.00	2.19	0.22	0.40	Wiseman and Benfield (1993)
Ceftizoxime	tra	1.10	1.02	0.36	0.28	Barriere and Flaherty (1984)
Cephalexin	tes	4.30	3.91	0.26	0.14	Spyker et al. (1978)
Cephalothin	val	6.70	3.48	0.26	0.71	Bergan (1987)
Cephapirin	tes	6.90	4.28	0.21	0.07	Bergan (1977)
Cephradine	tra	4.80	4.13	0.46	0.14	Schwinghammer et al. (1990)
Chlorothiazide	tra	4.50	4.14	0.20	0.95	Osman et al. (1982)
Cimetidine	tra	8.30	5.15	1.00	0.19	Schentag et al. (1981)
Cinoxacin	tra	2.50	1.81	0.33	0.63	Sisca et al. (1983)
Ciprofloxacin	tra	6.00	3.90	1.80	0.40	Sorgel et al. (1989)
Clindamycin	tra	5.00	0.65	1.10	0.94	Plaisance et al. (1989)
Dexamethasone	tes	3.70	0.10	0.82	0.68	Gustavson and Benet (1985)
Diltiazem	tra	12.0	0.24	3.10	0.78	Echizen and Eichelbaum (1986)
Diphenhydramine	tra	6.20	0.12	4.50	0.78	Blyden et al. (1986)
Domperidone	tra	8.33	0.08	5.50	0.92	Lauritsen et al. (1990a)
Doxycycline	tra	0.53	0.22	0.75	0.88	Saivin and Houin (1988)
Fentanyl	tra	13.0	1.04	4.00	0.84	Olkkola et al. (1995)
Flecainide	val	5.60	2.41	4.90	0.61	Funck-Brentano et al. (1994)
Granisetron	tes	11.0	1.76	3.00	0.65	Allen et al. (1994)
Imipramine	tra	13.3	0.13	18.1	0.78	Sallee and Pollock (1990)
Indomethacin	tra	1.40	0.21	0.29	0.90	Oberbauer et al. (1993)
Isradipine	tra	10.0	0.00	4.00	0.97	Fitton and Benfield (1990)
Ketoprofen	tra	1.20	1.19	0.15	0.99	Jamali and Brocks (1990)
Lomefloxacin	tra	3.30	2.15	2.30	0.10	Freeman et al. (1993)
Lorazepam	val	1.10	0.00	1.30	0.91	Greenblatt (1981)
Mepirzepine	tra	7.29	0.29	4.84	0.85	Timmer et al. (2000)
Methadone	tra	1.23	0.06	3.59	0.88	Inturrisi et al. (1987)
Methylprednisolone	tra	6.20	0.30	1.20	0.78	Lew et al. (1993)
Metoclopramide	tra	6.20	1.24	3.40	0.40	Lauritsen et al. (1990b)
Metoprolol	val	11.3	1.33	3.19	0.08	Hinderling et al. (1984a)
Midazolam	tra	6.60	3.70	1.10	0.95	Garzone and Kroboth (1989)
Nadolol	tra	2.89	2.19	1.90	0.28	Hinderling et al. (1984a)
Nafcillin	tra	7.50	2.03	0.35	0.89	Marshall et al. (1977)
Nitrendipine	tes	5.90	0.12	3.60	0.94	Soons and Breimer (1991)
Norfloxacin	tra	2.52	0.73	1.12	0.18	Sorgel et al. (1989)
Ofloxacin	tra	3.50	2.24	1.80	0.25	Lamp et al. (1992)
Ondansetron	tra	5.90	0.30	1.90	0.73	Roila and Del Favero (1995)
Oxacillin	tra	6.10	2.81	0.33	0.92	Dittert et al. (1969)
Phencyclidine	tra	5.43	0.47	6.20	0.65	Busto et al. (1989)
Pindolol	val	7.69	3.89	1.16	0.59	Hinderling et al. (1984a)

Table 1 (*Continued*)

Compound	Use[a]	CL (ml/min/kg)	CL_R (ml/min/kg)	V_{ss} (l/kg)	f_b	Reference
Pirenzepine	val	3.57	1.71	0.20	0.12	Lauritsen et al. (1990a)
Pravastatin	tra	3.50	1.65	0.46	0.46	Quion and Jones (1994)
Propranolol	tra	10.0	0.39	1.96	0.93	Hinderling et al. (1984a)
Pyrimethamine	tra	0.41	0.27	2.30	0.87	Weinstein et al. (1992)
Sufentanil	tra	12.7	0.76	1.74	0.93	Bovill et al. (1984)
Sulfinpyrazone	tra	0.96	0.37	0.29	0.99	Schlicht et al. (1985)
Terazosin	tra	1.10	0.13	0.80	0.92	Titmarsh and Monk (1987)
Timolol	tra	8.49	1.00	1.43	0.60	Hinderling et al. (1984b)
Tolamolol	tra	10.8	0.53	2.11	0.91	Hinderling et al. (1984a)
Tolmetin	tra	1.30	0.09	0.54	1.00	Hyneck et al. (1988)

[a] Tra: training, val: validation, tes: testing.

2.2. Descriptors

Presentation of data containing adequately useful information to ANNs is the basis for construction of effective predictive models. Descriptors were generated solely from the drug structure and aimed to numerically encode meaningful features of each molecule. A wide range of one- and two-dimensional descriptors were generated (Table 2) representing hydrophobic, steric and electronic properties to encode drug features from an atomic to holistic level. Three-dimensional descriptors were not used since the current study sought to avoid dependence on molecular conformation.

Calculated log *P* (clogP) values were determined using the PrologP 5.1 module in Pallas (CompuDrug International, 1997). In-house computer routines were written in Visual Basic (Microsoft, 1998) to generate

Table 2
List of molecular descriptors generated

Descriptor type	Symbol	Reference
Atom and functional group counts[a]	010H, 112C, 113C, 120C, 121C, 122C, 130C, 131C, 140C, 210N, 212N, 220N, 221N, 230N, 310O, 311O, 320O, 611S, 620S, 630S, 640S, 710Cl, 810Br, C, N, O, S, Hal	Kier and Hall (1999)
Connectivity index differences[b]	${}^0\Delta^v$, ${}^1\Delta^v$, ${}^2\Delta^v$, ${}^3\Delta^v$, ${}^3\Delta_c^v$, ${}^4\Delta^v$, ${}^4\Delta_c^v$, ${}^4\Delta_{pc}^v$	Galvez et al. (1994)
Connectivity index quotients[b]	${}^0\xi^v$, ${}^1\xi^v$, ${}^2\xi^v$, ${}^3\xi^v$, ${}^3\xi_c^v$, ${}^4\xi^v$, ${}^4\xi_c^v$, ${}^4\xi_{pc}^v$	Galvez et al. (1994)
Charge indices[c]	*G*1, *G*2, *G*3, *G*4, *G*5, $G1^v$, $G2^v$, $G3^v$, $G4^v$, $G5^v$, *J*1, *J*2, *J*3, *J*4, *J*5, $J1^v$, $J2^v$, $J3^v$, $J4^v$, $J5^v$	Galvez et al. (1995))
Vertex counts[d]	n, L, V3, V4	Galvez et al. (1995)
Ramifications[e]	Pr1, Pr2, Pr3	Galvez et al. (1995)
Wiener number[f]	W	Galvez et al. (1995)
Molecular weight and derivatives[g]	MW, ISRMW, ICRMW	Jacobs (1967), Herman and Veng-Pedersen (1994)
clogP and cross-products[h]	At5, CDR, At5x, CDRx, clogPx	Rekker and De Kort (1979), Viswanadhan et al. (1989)
Random	Ran	Maddalena and Johnston (1995)

[a] Chemical constitution of molecule.
[b] Linear combinations of connectivity indices derived from molecular graph.
[c] Derived from molecular graph: describe charge distribution.
[d] Counts of non-hydrogen atoms.
[e] Atom adjacency counts.
[f] Sum of topological distances in molecular graph.
[g] Diffusional characteristics.
[h] Log *P* calculated from molecular structure.

all other descriptors from the molecular graph. An additional random descriptor (Maddalena and Johnston, 1995) was also included as a quality control measure to monitor ANN performance.

2.3. ANN modeling

The ANN program used was Statistica Neural Networks (StatSoft Inc., 2000). All networks were of the three-layered feed-forward back-propagation (multilayer perceptron) type, containing a bias neuron in each layer and a single neuron in the output layer. A sigmoidal transfer function was employed in all neurons and weight adjustment was performed according to the generalised delta rule (Bourquin et al., 1997). Connection weights were initialised with random values.

Models were constructed using the training set of compounds. The validation subset was then used to provide an indication of model performance. All generated descriptors were included in the initial model. Redundant descriptors were then pruned and the system was re-trained. Once optimum models were achieved true predictive ability was assessed using the testing subset of compounds.

Both manual and automated methods were employed for descriptor selection. Sensitivity analysis of inputs was used to identify significance of individual molecular descriptors and to select descriptors that were considered the most important. Descriptors with sensitivities lower than one were deemed to be detrimental to the model. The higher the sensitivity above one the greater its influence on the model. Hence, those with lower sensitivities were able to be sequentially removed. The ANN program also utilized regularization and search algorithms for automated descriptor selection.

3. Results and discussion

3.1. Data analysis and training

The distribution of values for the pharmacokinetic parameters of the subsets were examined and all were shown to have homogeneous variances (Table 3). This enabled ANOVA to be performed to compare means. The ANOVA significance values were sufficiently high to accept that there were no significant differences between the subsets for all pharmacokinetic parameters examined (Table 3).

Table 3
Statistical analysis of data sets

Pharmacokinetic parameter	Levene[a]	ANOVA[b]
CL	0.086	0.966
CL_R	0.143	0.483
V_{ss}	0.668	0.863
f_b	0.764	0.554

[a] Levene's homogeneity of variance.
[b] Analysis of variance.

3.2. Training and validation

All 85 descriptors generated were used to train the ANN, after which pruning was implemented. Groups of descriptors were removed at a time resulting in models with generally decreasing error from initial to final models (Table 4). Magnitude of the root mean squared (RMS) error varied between individual pharmacokinetic parameters indicating the difference in modeling capability of the ANN for each parameter. Models for CL had the highest RMS error whereas those for f_b had the lowest. Such a difference pointed to the greater complexity involved in xenobiotic metabolism and excretion compared with the more simple processes involved in protein binding. Even so, the RMS error is a measure of training performance and although errors for CL were higher than for f_b, this was not necessarily an indication of the absolute predictive performance of the ANN models.

Large numbers of input variables cause overfitting of data resulting in models with a poor ability to generalise. This was the case with initial models since all descriptors were included. As expected, initial validation correlations began relatively low and then increased as redundant descriptors were removed (Fig. 1). After a number of runs the validation correlation actually decreased. It was possible that the group of descriptors removed in a single training run may have contained some useful information. However, many of the descriptors were correlated amongst themselves (Basak et al., 2000) so that removal would not have entirely eliminated their information content from the system.

Table 4
ANN models over the course of pruning

Parameter	Architecture[a]	RMS error[b]	Pruning details[c]
CL	85-*30*-1	2.14	Subset selection
	59-*21*-1	1.80	Sensitivity < 1.05
	38-*20*-1	2.04	Subset selection
	26-*16*-1	1.92	Subset selection
	12-*13*-1	1.51	Sensitivity < 1.15
	7-*13*-1	1.84	N/A
CL_R	85-*21*-1	0.78	Subset selection
	56-*21*-1	0.88	Subset selection
	36-*12*-1	0.54	Sensitivity < 1.05
	13-*13*-1	0.55	Subset selection
	4-*4*-1	0.59	N/A
V_{ss}	85-*15*-1	1.06	Subset selection
	66-*11*-1	0.75	Sensitivity < 1.03
	39-*8*-1	0.69	Subset selection
	15-*8*-1	0.59	Sensitivity < 1.05
	12-*14*-1	0.44	Subset selection
	4-*13*-1	0.50	N/A
f_b	85-*30*-1	0.24	Sensitivity < 1.02
	46-*24*-1	0.26	Sensitivity < 1.03
	25-*20*-1	0.23	Subset selection
	12-*6*-1	0.21	Sensitivity < 1.17
	8-*20*-1	0.21	Subset selection
	5-*2*-1	0.18	N/A

[a] Inputs-*hiddens*-outputs.
[b] Root mean squared error.
[c] Subset selection was automated whereas sensitivity-based pruning was manual.

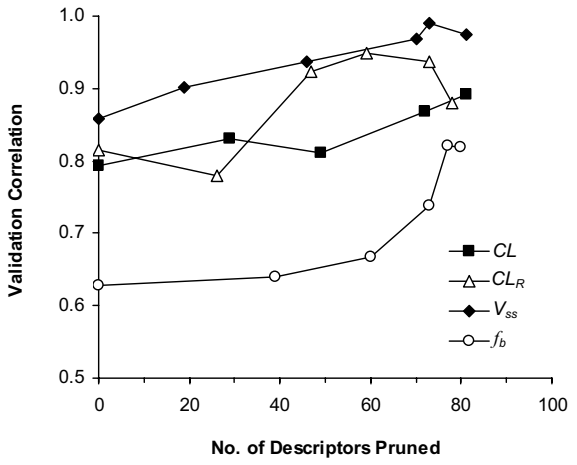

Fig. 1. Validation correlation over the course of pruning for CL, CL_R, V_{ss}, and f_b.

Table 5
Optimum ANN models

Parameter	Testing correlation	Descriptors	ρ[a]
CL	0.855	122C, 221N, 320O, $^0\Delta^v$, $^0\xi^v$, CDR, At5x	0.4
CL_R	0.992	220N, 221N, $J1^v$, At5,	2.0
V_{ss}	0.956	320O, $^4\xi^v_{pc}$, At5x, CDRx	0.6
f_b	0.863	230N, 320O, Hal, Pr1, At5	3.3

[a] Ratio of the number of compounds to the number of ANN connections.

3.3. Optimum models

Each pharmacokinetic parameter studied was described by different optimum models. The ratio, ρ, has previously been suggested to lie within the range $1.8 > \rho > 2.2$ for optimal results (Andrea and Kalayeh, 1991), however, a more current and correct view is that ρ is implementation dependent (So and Richards, 1992). The values of ρ in the optimum models lay within the range 0.4–3.3 (Table 5). A number of other studies have also presented successful ANN models with similar values of ρ: 0.2–0.7 for mode of action of anti-cancer drugs (Weinstein et al., 1992), 3.4 for DHFR inhibition of triazines (Andrea and Kalayeh, 1991), and 7.5 for mutagenicity of aromatic amines (Villemin et al., 1993). Other work performed specifically to determine the effect of ρ during selective pruning in ANN studies has found that useful models may be developed for a broad range of ρ values (Turner et al., 2003a). Hence, the combination of the pruning technique and the nature of the data set enabled the development of sound ANN models in the current study. This was further evidenced by the high validation correlations and predictive ability of the models developed which would not be the case if the models were unsound.

With respect to the optimum models developed, it was found necessary to vary numbers of neurons in the hidden layer of the ANN to best model the individual pharmacokinetic parameters (Table 4). The second finding was that optimum models contained distinct combinations of descriptors. The third finding was that, except for CL_R and V_{ss}, optimum models contained a different final number of descriptors.

The number of descriptors and hidden neurons required to predict a given pharmacokinetic parameter

may reflect the relative complexity of that particular parameter. Clearance is a measure of drug elimination from the body and occurs due to many physiological processes. As long as linear elimination processes are involved total body clearance can be expressed as the sum of renal and nonrenal clearances. In comparison, CL_R is relatively simple, generally involving the processes of glomerular filtration, reabsorption, and tubular secretion, whereas CL is more complex since most drugs undergo a wide variety of metabolic reactions primarily in the liver. This was reflected by the relative complexity of the optimum ANN model for each clearance parameter: seven hidden neurons and 13 descriptors were required for CL and only four hidden neurons and four descriptors for CL_R. Good predictive performance was achieved for these pharmacokinetic parameters with high testing correlations being recorded for both (Table 5).

Predicted values were compared with experimental values (Fig. 2) in order of ascending values of each pharmacokinetic parameter. Error bars represented the error associated with each data point either from the literature (observed experimental values) or within the ANN models (predicted values). Most prediction data points for CL_R and V_{ss} showed strong agreement with experimental values. In addition, clear segregation of high and low values was seen for these pharmacokinetic parameters. Error at each predicted point for CL, CL_R, and V_{ss} was very low demonstrating good precision.

Quantitative predictions for V_{ss} were quite accurate and the majority of values were close to or within the experimental error associated with the observed values. Similar results were seen for CL_R although there was somewhat more deviation from observed values. In relative terms the predictive errors for dexamethasone and nitrendipine were high but the absolute differences between predicted and observed values were low due to their small renal clearance values. This model was able to distinctly separate compounds

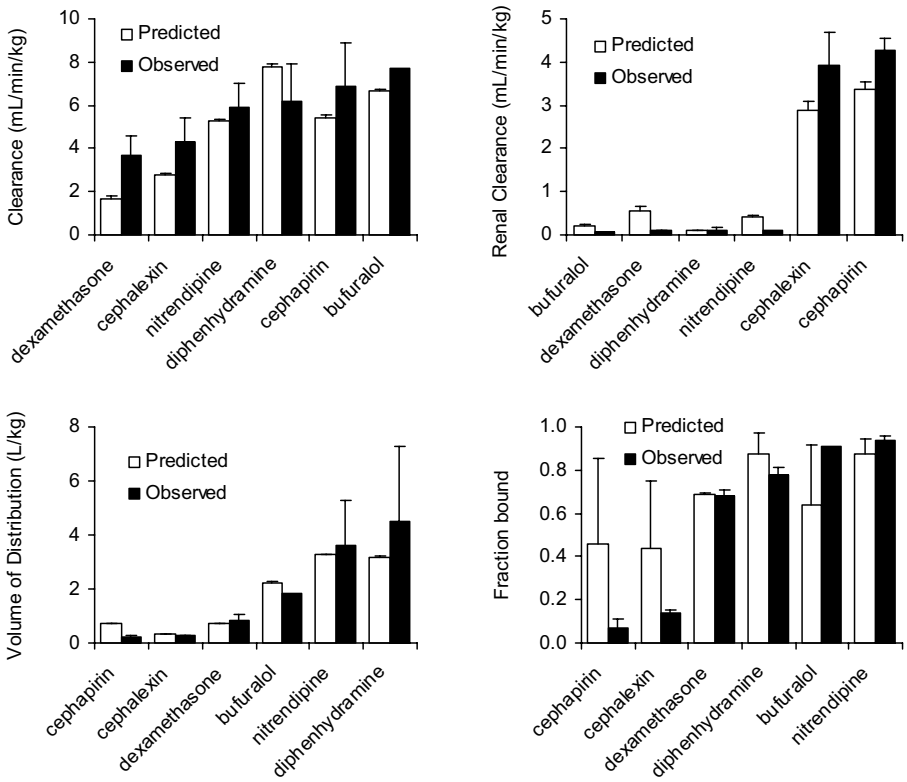

Fig. 2. Predicted vs. observed experimental values for optimum ANN models.

with high and low renal clearances. Observed systemic clearance values were more evenly distributed. Again, quantitative predictions were close to or within the error range of observed clearances. Predicted clearance for dexamethasone was half the observed value. Nevertheless, this was the smallest predicted value for the testing set and dexamethasone had the lowest observed experimental clearance. Similar results were seen for cephalexin clearance. It is the predictive ability of a model that makes it useful, rather than training ability. Therefore, models for CL, CL_R, and V_{ss} demonstrated excellent performance based on predictions for the independent testing compounds.

Predicted values for f_b displayed higher RMS errors than for the other pharmacokinetic parameters. This was particularly the case for compounds with low protein binding. Predictions for compounds with high protein binding were more accurate and had smaller associated error. Accurate estimation of f_b is most important clinically when f_b is high. In contrast, low f_b is much less significant clinically. Hence, the optimum model showed a smaller RMS where it was most important. Protein binding is a relatively simple pharmacokinetic parameter involving weak non-covalent bonds being formed between the two species. Nevertheless, the optimum model for f_b contained more descriptors than those for CL_R and V_{ss} indicating a more subtle relationship than first thought. Protein binding is influenced by the three-dimensional conformation of a molecule which determines the accessibility of functional groups for interaction with the protein. The lack of three-dimensional descriptors in the current study may have led to the higher error seen for some predictions. Although this model suffered somewhat in quantitatively predicting low f_b, nevertheless, compounds with high protein binding were predicted well and the model was able to qualitatively differentiate between compounds with high and low protein binding values.

A major advantage of the current technique is that generation of descriptors requires knowledge only of the chemical structure of the drug, thus making preliminary physicochemical studies unnecessary. Other published QSPkRs utilised methods based on experimental determination of physicochemical data for use as model inputs (Hinderling et al., 1984a; Gobburu and Shelver, 1995). These included reversed phase high-performance liquid chromatography for calculation of apparent octanol/buffer partition coefficient, the shake flask method for pK_a and apparent octanol/buffer partition coefficient calculation, and experimentally-determined f_b as a model input. Using only descriptors generated from drug structure the current study achieved accurate quantitative predictions for independent testing compounds for CL, CL_R and V_{ss} and good qualitative results for prediction of f_b.

Optimum models were constructed based on 50 compounds representing a broad range of structural motifs. It is necessary to evaluate a model on a subset of structures due to the vast number of possible drug-like structures available. For example, targeted or focussed chemical libraries do not represent the entire chemical space available but may still contain considerably large numbers of structures with a common characteristic such as susceptibility to metabolism by a particular cytochrome P450 isozyme. Should the chemical structures in such a library lie within the bounds of the models developed in the current study then fast and reliable prediction of their pharmacokinetic parameters could be achieved. Those exhibiting poor predicted pharmacokinetics could be eliminated early during drug development to avoid the considerable expense of late failure. The models presented have demonstrated that prediction of various pharmacokinetic parameters for unknown compounds is possible based on simple descriptors derived from chemical structure. The potential also exists to extend the models presented in the current study to include larger numbers of chemical structures and substructures.

3.4. Descriptor analysis

A number of descriptors remaining in optimum models described features of drugs generally known to relate to their physicochemical properties. All optimum models included clogP descriptors which are closely related to lipophilicity (Table 5). Lipophilicity has been used to describe the dissociation constant K_D between a drug-protein complex for a homologous series (Seydel and Schaper, 1981) and so clogP descriptors were expected in final models for f_b. Furthermore, only unbound drug is able to undergo glomerular filtration so clogP was expected to indirectly influence CL_R prediction.

Connectivity indices up to the fourth order are known to encode various molecular properties includ-

ing molecular density, branching and aromatic ring substitutions (Kier and Hall, 1986) and have recently been correlated with f_b (Murcia-Soler et al., 2001). Linear recombination of connectivity indices provide more useful information for prediction (Galvez et al., 1994) so it was reasonable to expect their inclusion in optimum models for V_{ss} and CL. Connectivity indices derive information from the hydrogen-depleted molecular graph where all vertices are considered equal. Charge indices rely on the valence state of graph vertices so encode information about the heterogeneity of a molecule. Different atoms can contribute in different ways to the properties exhibited by a molecule. For example, an aromatic ring composed of carbon atoms provides a hydrophobic region which can promote π-stacking and alignment with other aromatic rings. This is in contrast to the positioning of an oxygen atom between two carbon atoms forming an ether group. Such an arrangement exhibits two lone-pairs of electrons on the oxygen which can then partially polarise the atom. This may then permit interaction with polar sites of other small molecules or proteins and thus affect whole-molecule behaviour.

Similar polarisation and lone-pair interactions are exhibited by various halogen, nitrogen and oxygen groups on a molecule. The influences of these groups can combine positively or negatively based on their proximity to each other across a molecule. Adjacency counts could provide such a link between individual and combined influences of functional groups. Since all optimum models contained both charge indices and functional groups counts, this indicated the significance of structural considerations at an atomic level in determining the pharmacokinetic behaviour of a compound.

4. Conclusions

The current study has shown that useful information can be derived from the chemical structure of a drug to generate descriptors encoding various properties of that drug. Using the theoretically calculated descriptors for a set of structurally diverse compounds, validated ANN models were successfully able to predict pharmacokinetic parameters for independent testing compounds. Different numbers of descriptors were required to model individual pharmacokinetic parameters and this reflected their relative complexity. Furthermore, certain descriptors and combinations of descriptors were shown to be important for different pharmacokinetic parameters. Time and cost savings gained from using this *in silico* method makes it a relevant and applicable tool in pharmaceutical product development.

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