QSAR APPROACH TO ESTIMATION OF THE DISTRIBUTION OF XENOBIOTICS AND THE TARGET ORGAN IN THE BODY

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SUMMARY

QSAR analysis is one of the methods of predicting toxicity and it is also used in theoretical studies. This study is devoted to transport and distribution processes in the body.

The use of QSAR analysis for predicting tissue-gas and tissue-tissue partition coefficients (biosolubility and tissue selectivity) was demonstrated. The estimation is carried out by a series of correlation equations for individual tissues /1/ using oil-gas and water-gas partition coefficients.

Biosolubilities are used mostly in physiologically-based simulation models for predicting the distribution of xenobiotics among body tissues and liquids. Tissue selectivities can be used for estimating a target site of a xenobiotic which is not necessarily a critical site.

Estimates obtained for some halogenated hydrocarbons were compared with estimates calculated using Paterson's and Mackay's /2/ data and with experimentally obtained biosolubilities. The estimates generated by the QSAR approach differed from the experimental values by not more than 50%, which represents a reasonable performance.

KEY WORDS

quantitative structure - activity relationships (QSAR), distribution of xenobiotics, tissue - tissue partition coefficients, biosolubilities

INTRODUCTION

The biological fate of xenobiotics involves biotransformation and transport processes. Transport processes depend on the route of administration and the dose or both. These factors may affect the site of action, the intensity and sometimes even the nature of biotransformation. The distribution of xenobiotics may be influenced by interactions with other xenobiotics in the system.

Toxicokinetic models have been proved to be useful in predicting concentration-time courses of xenobiotics in blood or body tissues and the distribution of xenobiotics in the body. These models depend on a knowledge of the blood-gas and the tissue-blood partition coefficients. There have been attempts to develop methods to predict these coefficients /1-3/. A model combining physiologically-based simulation kinetics and QSAR (quantitative structure - activity relationships) analysis /1,4/ has been shown to be helpful in estimating the distribution of volatile xenobiotics among body tissues and liquids, their kinetics and also saturation and desaturation curves in the tissues /1,5/.

We have made an attempt to estimate the partitioning characteristics of xenobiotics among biological tissues, knowing only physicochemical properties or the chemical structure of the xenobiotic under study. We have attempted to predict a target site for the xenobiotic. QSAR analysis was used for these purposes.

Tissue-gas partition coefficients, P(tg), are directly related to the property called biosolubility /1/. Biosolubility is that property of a xenobiotic which is responsible for the distribution of the xenobiotic and its kinetics. Biosolubility is the maximum concentration of a chemical that can be reached in body tissues or liquids at a given exposure concentration and body temperature.

Factor analysis of P(tg) of various series of xenobiotics has revealed /1,4/ that two factors describe all P(tg)s of a series of xenobiotics and tissues. Partition coefficients between oil and gas, P(og), and between water and gas, P(wg), are the most promising properties simulating these factors /3,4,6/:

$$\log P_x(t_y g) = k_1 \log P_x(og) + k_2 \log P_x(wg) + k_3 \qquad [1]$$

where x denotes a xenobiotic, y the respective tissue, k_1, k_2 and k_3 the regression coefficients and a constant obtained by the regression analysis of the data. Equation 1 has been found to be the best model among the ones tested /7/. The two-parameter equation

involving only P(og) and P(wg) /6/ has less general applicability. This is the reason why the oil-water partition coefficient possesses a lower predictive power when used for a similar set of xenobiotics.

The selectivity concept /8/ can help to estimate a target site using biosolubilities instead of the biological activities suggested previously /8/ or reaction rate constants of organic reactions in the original application. Selectivity S_x can then be written as:

$$S_x = \log P_x(t1g) - \log P_x(t2g) = \log P_x(t1/t2) \qquad [2]$$

where t1 and t2 are the concentrations of a xenobiotic x in two different body tissues or liquids under steady-state conditions. The formal tissue-tissue partition coefficients calculated using Eq. 2, $P_x(t1/t2)$, indicate the probable degree of a transfer of the xenobiotic into tissue 1, t1, or tissue 2, t2.

In this paper the QSAR approach is used for the estimation of biosolubilities, tissue-tissue partition coefficients, and for predicting target organs, which may or may not be the critical site where action of the xenobiotic takes place.

MATERIALS AND METHODS

Tissue-gas partition coefficients or biosolubilities, P(tg), were calculated using Eq. 1 with the coefficients k_1, k_2 and the constant k_3 found for a series of 25 hydrophobic compounds with blood and seven tissues /1/ and summarized in Table 1. The P(tg)s are defined as published /5,9/. Tissues were represented by their fine homogenates. The oil-gas and water-gas partition coefficients were taken from published tables /8,10/, unless they were determined by a direct gas chromatographic method using an oil-saturated column /11/ (Table 1).

The tissue-tissue partition coefficients of four chlorinated derivatives, selectivities S, were calculated using Eq. 2 and the biosolubilities P(tg), evaluated as described above.

Standard factor and linear correlation analyses of the data were used.

TABLE 1

Parameters used in the calculations of tissue-gas partition coefficients $P_x(tg)$

Regression equation 1[a]				
Tissue (t_y)	Abbreviation	k_1	k_2	k_3
Blood	BL	0.180	0.889	0.054
Brain	BR	0.471	0.630	-0.305
Lung	LU	0.373	0.416	-0.216
Kidneys	KI	0.466	0.379	-0.332
Liver	LI	0.746	0.178	-0.767
Fat	FA	0.782	0.201	0.432

Compound	log P(og)[b]	log P(wg)[b]
Dichloromethane	2.182	0.857
Chloroform	2.602	0.574
Trichloroethylene	2.913	0.176
Tetrachloromethane	2.558	-0.602

[a] Coefficients, their statistical enumeration and evaluation from references /1,7/.

[b] Experimental values from references /5,10/. Notation: o - oil, w - water, g - gas.

RESULTS AND DISCUSSION

The tissue-tissue partition coefficients, selectivities, defined by Eq. 2, for pairs of biological tissues and of blood are shown in Table 2 for tetrachloromethane and dichloromethane. These tissue selectivities reflect the tissue-tissue partition coefficients. Although they do not always have a physical representation (e.g., brain - liver), their values can be interpreted in the sense of probabilities. As long as the P(t1/t2) for a xenobiotic is lower than 1 (log lower than zero), its concentration will probably be higher in tissue 2 than in tissue 1. The probability may be related to the value: the higher the value of P(t1/t2), the higher the concentration in tissue 1 under steady-state conditions. Thus, a target site for accumulation of a xenobiotic can be estimated. This site is not necessarily the site responsible for a toxic action.

TABLE 2

A matrix of tissue selectivities[a] of dichloromethane and tetrachloromethane[b] for blood, brain, liver, kidney, lung, muscle and fat

t1 \ t2	BL	BR	LI	KI	LU	MU	FA
BL	1	0.89	1.58	1.74	1.78	1.32	0.088
		0.29	0.09	0.22	0.31	0.19	0.005
BR	1.12	1	1.78	1.78	2.04	1.48	0.090
	3.45		0.31	0.78	1.07	0.66	0.016
LI	0.63	0.63	1	1.00	1.15	0.83	0.050
	11.1	3.23		2.51	3.55	2.14	0.052
KI	0.57	0.56	1.00	1	1.15	0.98	0.050
	4.55	1.28	0.40		1.38	0.76	0.021
LU	0.56	0.49	0.87	0.87	1	0.74	0.040
	3.23	0.93	0.28	0.72		0.62	0.048
MU	0.76	0.86	1.20	1.02	1.35	1	0.060
	5.26	1.52	0.47	1.32	1.62		0.039
FA	13	11	20	20	23	17	1
	200	63	19	48	21	27	

[a] The selectivities S as defined by equation 2 were calculated using the tissue-gas partition coefficients P(tg) calculated by equation 1. The parameters of equation 1 are given in Table 1.

[b] The values for dichloromethane are in the first line, for tetrachloromethane in the second line.

Abbreviations for tissues as in Table 1.

This estimation is valid when a biological system is in a steady state, i.e., there is equilibrium among its tissues – compartments in the open biological system. However, steady state is generally not reached. Nevertheless, even under non-equilibrium conditions, the tissue-gas partition coefficients (biosolubilities) still govern the fate of xenobiotics.

Saturation and desaturation of organs can be followed with the aid of physiologically-based kinetics simulation models /1,5/. The tissue-tissue partition coefficients (tissue selectivities) may serve not only to indicate the probable degree of distribution of a xenobiotic among body tissues and body liquids, but the values can be compared for a series of xenobiotics for one tissue to study the relation between chemical structure and affinity for particular tissues (e.g., brain) (Table 3).

TABLE 3

An example of blood-tissue partition coefficients calculated for a series of arbitrarily chosen xenobiotics using equations 1 and 2[a]

Compound	Tissue		
	BR	LI	KI
Ethylene	1.12	1.00	0.65
Dichloromethane	0.89	1.58	1.74
Cyclopropane	0.74	0.52	0.52
Halothane	0.45	0.26	0.46
2,2,2-Trifluoroethyl vinyl ether	0.44	0.17	0.29
Tetrachloroethane	0.37	0.41	1.02
Trichloroethylene	0.36	0.20	0.44
Tetrachloromethane	0.29	0.087	0.22

[a] The parameters of equation 1 are summarized in Table 1. The values of log P(og) and log P(wg) are taken from references /5 and 10/.

When the blood-brain partition coefficient of a xenobiotic is lower than 1, the xenobiotic is probably readily transferred from blood to brain – the lower the value, the more readily. If the blood-kidney partition coefficient is lower than 1, the xenobiotic might have a tendency to be eliminated in the urine. A brain-kidney partition coefficient of higher than 1 might mean, however, that the xenobiotic would accumulate in the brain rather than be eliminated in the urine.

Paterson and Mackay /2/ have developed another equation for estimating the tissue-gas partition coefficients of xenobiotics. It involves physicochemical properties, such as solubilities in water and in octanol, octanol-water or gas-water partition coefficients to estimate a tissue solubility and saturated vapor pressure to calculate their "air solubility". A comparison of their estimates of P(tg) and P(t1/t2) with those obtained by the QSAR approach and with experimentally obtained values is made in Tables 4 and 5.

The QSAR estimated tissue-tissue partition coefficients [tissue selectivities, P(t1/t2)] of four selected chemicals (Table 4) vary from those calculated from the experimental values by not more than 50% and even this value is an exception. The values calculated using the Paterson-Mackay data /2/ (Table 3) are, on average,

TABLE 4

A comparison of tissue selectivities P(t1/t2) calculated by the QSAR method (this paper) (A)[a], by the approach of Paterson and Mackay /2/ (B) and using experimental biosolubilities (C)[b] in man

Compound	Approach	P (blood-tissue) Tissues				
		BR	LU	KI	LI	FA
Dichloromethane	A	0.89	1.78	1.74	1.58	0.088
	B	1.62	1.67	1.67	1.35	0.114
	C	1.33	1.38	1.38	1.11	0.094
Chloroform	A	0.56	1.09	0.86	0.57	0.028
	B	0.51	1.47	0.94	0.61	0.037
	C	0.48	1.38	0.88	0.57	0.034
Trichloroethylene	A	0.36	0.62	0.44	0.20	0.010
	B	0.45	0.68	0.63	0.33	0.017
	C	0.42	0.66	0.74	0.32	0.015
Tetrachloromethane	A	0.29	0.31	0.22	0.09	0.005
	B	-	-	-	-	-
	C	-	-	-	-	-

[a] Parameters of equation 1, see Table 1; biosolubilities, see Table 5.
[b] Experimental data from reference /5/, Vol. 1, Tables 2 and 3, pp. 16-23.

closer. Table 5 demonstrates the biosolubilities of the same chemicals (no experimental data nor data in the Paterson and Mackay paper were found for tetrachloromethane).

The estimation by the QSAR analysis is fairly good, being either higher or lower than the experimental values. Those taken from the Paterson and Mackay paper are identical with the experimental data. Their tissue solubilities or pseudo-solubilities are calculated directly from the experimental tissue-gas partition coefficients. Thus, we obtain the original data when dividing by the air solubility. Our QSAR approach makes it possible to estimate the tissue-gas partition coefficients for xenobiotics even in the absence of experimental data. Therefore, it is possible to estimate the tissue selectivities, e.g., for tetrachloromethane (Table 2), where no experimental data are available.

TABLE 5

A comparison of biosolubilities P(tg) calculated by the QSAR method (this paper) (A)[a], by the approach of Paterson and Mackay (B)[b] and obtained experimentally (C)[c].

Compound	Approach	P (tissue-gas) Tissue					
		BL	BR	LU	KI	LI	FA
Dichloromethane	A	16.2	18.3	9.0	10.2	10.3	204
	B	9.7	6.0	5.8	5.8	7.2	85
	C	8(4) 6.0-9.7	6	5.8	5.8	7.2	85
Chloroform	A	10.8	19.2	9.9	12.6	18.9	382
	B	10.3	20.0	7.0	11.0	17.0	280
	C	9.6(5) 8-11	20(2) 16-24	7	11	17	280
Trichloroethylene	A	5.4	15.1	8.8	12.4	27.4	556
	B	9.5	21	14	15	29	569
	C	9.3(5) 9-9.9	21	14	15	29	598(2) 569-624

[a] Calculated by equation 1 of this paper, using the parameters in Table 1.

[b] Calculated as a ratio between calculated tissue solubilities or pseudosolubilities and air solubility from physicochemical properties (Ref. /2/, Tables 1 and 3).

[c] When a mean of several experimental observations is given, the number of observations is given in parentheses, and below their variation (reference /5/, Vol. I, Tables 2 and 3, pp. 16-23).

CONCLUSIONS

A predictive method for estimating distribution of xenobiotics among body tissues and for predicting target organs for xenobiotics is suggested. The QSAR approach makes it possible to predict values of tissue-gas partition coefficients (biosolubilities) and of tissue-tissue partition coefficients (tissue selectivities) of as yet untested xenobiotics. For these calculations, it is necessary to know the oil-gas and water-gas partition coefficients and a system of

correlation equations, the coefficients of which are shown as an example in Table 1 for a series of selected hydrophobic compounds. Hydrophilic compounds possess a different set of coefficients /4/. Separation of xenobiotics into different homogeneous series will probably lead to various sets of the correlation equations.

It is necessary to take into account the following limitations of the described predictive approaches using partition properties of xenobiotics:

- Exposure to some volatile xenobiotics may cause changes in tissue composition in experiments performed *in vitro*, inducing changes in the partition coefficients. The changes in isolated tissues or their homogenates may be different from those occurring *in vivo* /12/.
- The distribution of a xenobiotic in the body can be altered by the presence of other chemicals /13/. This may be caused by changes in metabolic rates as discussed previously /13/. However, it may also be caused by changes in the membrane or tissue composition mentioned above.
- The distribution is a function of parameters of the biological system under study. This is a flexible and open system and its history affects properties such as metabolic rate or capacity, induction, stimulation, inhibition of metabolic enzymes or carriers, immune responses, etc.
- Various models and analyses are time-dependent, as QSAR modeling shows. Time courses of saturation and desaturation curves of a series of xenobiotics ought, nevertheless, to be analyzed from the viewpoint of the chemical structure of the xenobiotics and the structure of the biological systems.

Modeling is in many cases the only available technique to obtain information about the fate of some xenobiotics in the body. It can help decision-makers as well as in planning experiments. It can save experimental animals. Most importantly, however, it contributes to new knowledge about mechanisms and theories of actions of xenobiotics.

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