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Theoretical modeling of oral absorption of barbiturates

Taravat Ghafourian*, Mohammad Barzegar-Jalali

School of Pharmacy, Tabriz Medical Sciences University, Tabriz 51664, Iran

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Abstract

The structural characteristics governing gastric absorption of barbiturates were studied using QSAR methodology. The results showed that the gastric absorption rate constant could be modeled using the theoretical parameters, accessible surface area, atomic charges and electrostatic potentials. Using molecular connectivity indexes was also satisfactory in modeling the absorption.

Keywords: Absorption; QSAR; Barbiturate; Gastric; Oral absorption

1. Introduction

An important prerequisite for a drug to be active is that it is able to reach its site of action. Therefore, there is a need for rapid and efficient computational method in order to predict the permeation properties prior to experimental determinations of permeability or actual synthesis of the designed compounds. The preferred and most widely used route of drug administration is the oral route, and the most common mechanism of absorption from the gastrointestinal tract is passive diffusion through the intestinal epithelial cells. In vitro cell culture system (Caco-2 cell) has been used as a model to predict oral drug absorption. In a study of the relationship between gastrointestinal (GI) absorption in humans and Caco-2 cell permeability, it was concluded that the Caco-2 cell permeability could not be used to precisely predict human GI absorption [1].

The aim of the present study was to investigate the structural characteristics governing oral absorption of drugs. To this end, we started with some barbituric acid analogs for which the absorption coefficients were available [2]. The theoretical parameters used in this study are readily available and can indicate the precise structural requirements for the absorption.

2. Experimental

Gastric absorption rate constants of barbiturates in rat (k_a) were taken from the literature [2]. The Structures of the compounds were optimized using the COSMIC force field and semiempirical MNDO method prior to the calculation of structural descriptors. Structural parameters were mainly calculated using semiempirical (MNDO method in MOPAC 7.0) and various molecular mechanical softwares and also MOLCONN-Z software. The parameters consisted of dipole moment, atomic charges, energies of the frontier orbitals, accessible surface area, molecular electrostatic potentials, principle moments of inertia, molecular connectivity indexes, molecular shape indexes and also electrotopological state indexes. In addition, energy of vaporization, molar volume, and solubility parameter were calculated by the group contribution method of Fedors [3]. Octanol–water partition coefficients were calculated by the CLOGP program, version 4.72 of Daylight Chemical Information Systems Inc. [4].

The structural descriptors were correlated against k_a and $\log k_a$ using the stepwise regression analysis in MINITAB statistical software. The resulting equations were controlled for any colinearity of the parameters and the correlations with highly intercorrelated independent variables were discarded.

* Corresponding author
E-mail address: ghafourt@tbzmed.ac.ir (T. Ghafourian).

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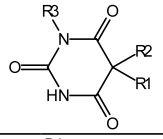
Table 1
Structures of the barbiturates



Barbiturate Number	Name	R1	R2	R3
1	Barbital	$-C_2H_5$	$-C_2H_5$	H
2	Ethallobarbital	$-CH_2CH=CH_2$	$-C_2H_5$	H
3	Heptobarbital	$-C_6H_5$	-CH3	H
4	Allobarbital	$-CH_2CH=CH_2$	$-CH_2CH=CH_2$	H
5	Aprobarbital	$-CH_2CH=CH_2$	$-CH(CH_3)CH_3$	H
6	Secbutobarbital	$-CH(CH_3)CH_3$	$-C_2H_5$	H
7	Phenobarbital	$-C_6H_5$	$-C_2H_5$	H
8	Butobarbital	$-CH_2CH_2CH_2CH_3$	$-C_2H_5$	H
9	Cyclobarbital	1-Cyclohexen-1-yl	$-C_2H_5$	H
10	Talbutal	$-CH_2CH=CH_2$	$-CH(CH_3)CH_2CH_3$	H
11	Idobutal	$-CH_2CH=CH_2$	$-CH_2CH_2CH_2CH_3$	H
12	Pentobarbital	$-CH(CH_3)CH_2CH_2CH_3$	$-C_2H_5$	H
13	Amobarbital	$-CH_2CH_2CH(CH_3)CH_3$	$-C_2H_5$	H
14	Secobarbital	$-CH_2CH_2CH(CH_3)CH_3$	$-CH_2CH=CH_2$	H
15	Hexobarbital	1-Cyclohexen-1-yl	$-CH_3$	$-CH_3$
16	Mephobarbital	$-C_6H_5$	$-C_2H_5$	$-CH_3$

3. Results and discussion

The transport may be modeled as a partitioning between an aqueous and a lipidic (usually octanol) phase. Wagner [2] proposed a theoretical model based on the octanol/water partition coefficients, P_{oct}, with an excellent accuracy, $r = 0.985$ for 13 compounds (Eq. (1)).

$$k_a = k_{um} P_{oct}^n / (Z + P_{oct}^n) \quad (1)$$

In this equation k_{um}, Z and n are constants calculated by an iterative procedure. Unfortunately, the model and the goodness-of-fit are strictly dependent on the group of compounds being studied and addition of a few structures deteriorates the relationship. For example, fitting the k_a and P_{oct} values of the 16 barbiturates listed in Table 1 reduces the regression coefficient to $r = 0.763$.

Using the theoretical parameters rather than the P_{oct} parameter has the main advantage of giving detailed information about the structural characteristics governing the oral absorption. Table 2 contains the biological and structural parameters that have been used in the following equations. The stepwise regression analyses using the structural parameters calculated by MOPAC and NEMESIS (Oxford molecular limited) resulted in the following equation:

$$\log k_a = 4.3 + 0.012\mathrm{ASA} - 32.8q^+ + 0.012\mathrm{ESP}^- \quad (2)$$

$n = 16$, $r = 0.975$, $s = 0.054$; where ASA is the accessible surface area calculated by the method of Connolly [5], q^+ is the highest atomic charge on the hydrogen bonding hydrogen atoms of a molecule, and ESP^- is the most negative electrostatic potential on the Connolly surface of the molecule. Eq. (2) shows that increasing the size of the molecules leads to a higher permeation rate. This is probably because of the better partitioning of the large barbiturate molecules to the lipid membrane due to the presence of larger alkyl substituents in larger molecules (Table 1). The parameter q^+ has been used as a hydrogen-bonding-donor ability parameter [6]. Esp^- can be considered as a hydrogen-bonding-acceptor ability parameter [7].

Using graph theoretical parameters led to the following equation:

$$\log k_a = 0.430\,{}^0\chi_p^v - 0.295\,{}^1\chi_p^v - 0.204\mu - 2.93 \quad (3)$$

$n = 16$, $r = 0.968$, $s = 0.063$; in which, ${}^0\chi_p^v$ and ${}^1\chi_p^v$ are the zero order and the first order valence-corrected molecular connectivity indexes and μ is the dipole moment calculated by a classical method [8]. The zero order connectivity indexes is a descriptor of the size, which has a positive effect on the oral absorption. This could also be due to the higher lipophilicity of the

Table 2
The parameters used in equations 1–4

Barbiturate number	$\log k_a$	ASA	q^+	ESP^-	${}^0\chi_p^v$	${}^1\chi_p^v$	μ	clog P_{oct}	κ_1
1	−1.25964	190.411	0.2235	−41.080	7.639	4.234	1.74	0.655	11.077
2	−1.15490	204.549	0.2221	−40.797	7.923	4.343	1.62	0.700	12.071
3	−1.07058	210.377	0.2242	−41.293	8.612	4.773	1.92	0.836	12.457
4	−1.04576	216.645	0.2233	−41.209	8.208	4.453	1.76	0.745	13.067
5	−0.97881	216.162	0.2227	−40.816	8.794	4.726	1.62	1.099	13.067
6	−0.88941	218.080	0.2214	−41.081	9.216	5.154	1.79	1.054	13.067
7	−0.88273	221.102	0.2212	−41.303	9.319	5.334	1.89	1.365	13.432
8	−0.86012	223.455	0.2239	−41.174	9.053	5.234	1.78	1.713	13.067
9	−0.85387	236.174	0.2244	−40.568	9.838	5.974	1.61	1.873	13.432
10	−0.77989	225.959	0.2225	−40.891	8.794	4.726	1.66	1.628	13.067
11	−0.75203	238.717	0.2249	−40.759	9.338	5.343	1.62	1.758	14.063
12	−0.69037	233.388	0.2218	−41.212	9.923	5.654	1.82	2.112	14.063
13	−0.70115	241.585	0.2235	−41.161	9.923	5.590	1.81	2.112	14.063
14	−0.58336	251.539	0.2228	−40.983	10.208	5.764	1.66	2.157	15.059
15	−0.55909	241.804	0.2211	−31.048	10.078	5.807	1.40	1.630	13.432
16	−0.45100	240.126	0.2210	−31.126	10.266	5.728	1.12	1.851	14.410

larger molecules possessing larger alkyl groups as the substituents. For instance, the correlation coefficient of the relationship between ${}^{0}\chi_{p}^{v}$ and clog$P$ is 0.88. The first order connectivity index has information about branching, which according to this equation, is favored for the absorption. The negative slope of the dipole moment indicates that the polarity negates the oral absorption of the compounds.

Forcing clog P_{oct} (calculated log P_{oct}) in the stepwise regression analysis resulted in Eq. (4). The equation shows that clog P_{oct} needs to be corrected in order to model the permeability. The correlation coefficient of the regression between log k_a and clog P_{oct} is 0.858. The parabolic model for clog P_{oct} was also examined which was not statistically significant.

$$\log k_a = -1.43 + 0.165\text{clog}\,P_{oct} + 0.026\text{ESP}^{-} + 0.104\kappa_1 \quad (4)$$

$n = 16$, $r = 0.985$, $s = 0.043$. In Eq. (4), κ_1 is the first-order molecular shape index calculated by MOLCONN-Z. The index normally indicates the degree of complexity, or more precisely, the cyclicity of a molecule. In the case of the barbiturates, the number of cycles is invariably one. Regression analyses between κ_1 and other structural parameters revealed that it is correlated with size parameters, log ASA, ASA, ${}^{0}\chi_{p}$ and ${}^{0}\chi_{p}{}^{v}$, therefore it can indicate the size of the molecule. The equation shows the opposing effect of the more negative ESP^{-} values on oral absorption. The lower ESP^{-} values is a result of the stronger electron donating substituents, which place more negative atomic charge on the oxygen atoms of the barbiturate structure.

In a QSPR study of human intestinal absorption, Wessel et al. developed a nonlinear neural network model concluding that a simple linear model could not fit the absorption data due to the diversity of the data set [9]. The results of this study indicates that modeling of oral absorption using multiple regression analysis is possible where the data set consists of the closely related compounds.

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