A new method for predicting conduction anesthesia

*E. V. Bartashevich, V. A. Potemkin, and A. V. Belik**

Department of Chemistry, Chelyabinsk State University,
129 ul. Br. Kashirinykh, 454136 Chelyabinsk, Russian Federation.
Fax: 007 (351 2) 42 0925. E-mail: belik@cgu.chel.su

A new method for predicting conduction anesthesia has been suggested. The method is based on calculation of the **P** matrix probabilities of interatomic contacts for each molecule of the compounds considered. The **P** matrix enables one to evaluate the main tendencies of atoms and atomic groups to interact in biochemical sorption on the nerve fiber surface. The minimum effective concentrations calculated for 25 compounds are in good agreement with the experimental data. The correlation coefficient between the experimental and calculated values is 0.98 when the standard deviation is 0.1 mmol L^{-1}.

Key words: conduction anesthesia, computer prediction; intermolecular interactions; molecular volume.

The search for relationships between the molecular structure and properties of compounds is the most important component of theoretical studies of various effects, including the biological activity. The relationships between several parameters of the molecular structure and various types of biological activity have been studied in recent years. The whole rich series of methods of regression and polynomial description, sample recognition, *etc.* is used to establish the "structure—biological activity" interrelation.[1—4] The determining contribution in this direction was made by the works of Academician N. S. Zefirov and his coworkers.[5—8]

The characteristic feature of the known mathematical methods for the processing of information based on fundamental statements of mathematical statistics is the fact that the resulting regularities are not assumed, as a rule, to be physically interpreted. This does not allow one to establish the mechanisms of the processes and decreases the prognostication value of the models obtained. Therefore, mathematical methods that allow some physical interpretation of the results obtained should be developed along with traditional approaches.

In this work, we attempted to develop a mathematical model based on certain physical concepts of the object under study. The conduction anesthesia activity, which has been described in detail in previous works,[9,10] is considered as the biological activity. The anesthesia action is known to be related to adsorption of the specimen molecules on the nerve fiber surface, due to which the propagation of the pulse caused by the surface depolarization is blocked. A certain concentration of the anesthetic in the intertissue liquid is required for complete blocking of the nerve impulse. This concentration is a quantitative criterion of the activity of the specimen and is named the minimum effective concentration (MEC). The study of conduction anesthesia makes it possible to analyze directly the pharmacokinetic stage (*i.e.*, interaction of the anesthetic molecules with the nerve fiber) without the difficult problems of transporting the specimen to the action site, because a solution of the anesthetic is applied directly onto the tissue. Therefore, the problem of modeling the "structure—property" relation can include the question on the direct correlation between the MEC value and the parameters of the compounds studied.

In several works, the activity of local anesthetics was related to their different physicochemical properties and parameters: basicity, lipophilicity, solubility, and molecular refraction.[10—12] In our opinion, the relation between the anesthetic action and sorption processes suggests that the necessary effect depends on the coverage of the membrane surface of the nerve cell, *i.e.*, on the average size of the territory blocked by one anesthetic molecule. When the value (thickness) of the sorption layer (as a monolayer) is assumed to be approximately constant, the established[10] inverse dependence between the MEC and molecular refraction becomes clear, since the latter correlates well with the molecular volume. In addition, according to classical concepts, the energy of dispersion interactions is closely related to the molecular refraction, molecular volume, and lipophilicity, which has been previously established.[12]

The molecular refraction can evidently be used as a characteristic of the sorption ability only when isotropism of the dispersion interaction field is assumed. This field determines the propensity of molecules for, *e.g.*, solvation, association, micelle formation, *etc.* In the first approximation to this problem, the molecule itself plays the main role in the formation of the intermolecular interaction field. The propensity of a specific molecule for interactions can be estimated taking into account its ability to form associates in the individual substance.

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The development of a model for prognostication of conduction anesthesia can be based on a quantitative expression of this ability in the form of an estimation of probabilities of atom-atom contacts.[13]

In this model, the intermolecular interaction field and the type of molecular environment in the individual substance can be estimated by a **P** matrix, which is conventionally called the matrix of probabilities of atomic contacts. It can be calculated, as shown previously,[14–16] from structural data for a single molecule. The calculation scheme is based on the representation of the molecule in the form of several overlapping atomic spheres (DENSON model),[17,18] whose radii depend functionally on intermolecular distances (valent and nonvalent) and temperature.

The numerical values of these radii are close to the van der Waals radii; however, they can be obtained from consideration of one molecule. It is enough to specify the average geometric parameters of the molecule or to optimize its structure in terms of molecular mechanics or quantum chemistry. Then atomic radii are calculated for the obtained geometry of the molecule.[13–18] The known values of the radii make it possible to calculate the molecular volume. Afterwards an ellipsoid, whose volume is equal to the previously calculated molecular volume, is circumscribed around the molecule.

Then possible intermolecular distances to potential neighbors (only their numerical values) are modeled for each of the atoms of the molecule. Let us designate the distance from the A atom of the considered molecule to the J atom of the hypothetical adjacent molecule of the same type as R_{AJ}. Let us consider that this distance is equal to the sum of the distances from the A atom to the molecular surface and from the J atom (of the same molecule) to its surface, which is specified in the form of an ellipsoid. The elements of the **P** matrix can be specified as follows:[13]

$$\mathbf{P}_{AJ} = \frac{N_{AJ} S_A \exp(-E_{AJ}/kT)}{\{1 + \sum_I \exp(-E_{AI}/kT)\}},$$

where N_{AJ} is the number of atoms of adjacent molecules that can contact with the A atom of the molecule considered (can be calculated by standard procedures[19]); S_A is the ratio of the surface area of the free surface of the A atom sphere to its overall surface area; the free surface is the part of the surface that is not in the volumes of atomic spheres of adjacent atoms; k is Boltzmann's constant; and T is the absolute temperature. The summation over I is performed for all atoms in the molecule. The analytical expression for E_{AJ} and E_{AI} was chosen similarly to the atom-atom approximation in the following form:

$$E_{AJ} = -2V_{AJ}(D_{AJ}/R_{AJ})^6 + V_{AJ}(D_{AJ}/R_{AJ})^{12} + Q_A Q_J/(4\pi\varepsilon_0 R_{AJ}),$$

where D_{AJ} is the sum of the atomic radii of the A and J atoms calculated in terms of the DENSON model; Q_A and Q_J are the charges on the A and J atoms, which can be calculated by one of the approximate methods (see, *e.g.*, Refs. 20 and 21). The other quantities take their normal values.

Calculating all elements of the square **P** matrix, we can determine its eigenvalues and eigenvectors. The sum of the positive eigenvalues of the **P** matrix can be a descriptor for the quantitative estimation of possible intermolecular interactions, because it correlates with experimentally established degrees of association of several molecules.[13] Analysis of the eigenvectors for each of the eigenvalues of the **P** matrix makes it possible to judge the character of the interactions assumed, because the components of the vectors reflect the participation of the corresponding atoms in the formation of the molecular associate. This conclusion can be drawn from the consideration of maximum absolute values of the vector coordinates. Therefore, each of the eigenvalues of the **P** matrix reflects a certain type of intermolecular interactions.

It can be assumed that the sorption of an anesthetic on a nerve fiber results in the type of intermolecular contacts that is most probable for this molecule (otherwise, the anesthetic would predominantly remain in the intertissue liquid). Thus, special attention should be given to the interaction determined by the maximum eigenvalue of the **P** matrix. The preliminary results for compounds of the ethaphon series showed that this eigenvalue results in the interaction of lipophilic groups of molecules. This agrees well with the known experimental data[11] indicating that the sorption of ethaphons is determined by the interaction of aryl and alkyl fragments with the nerve fiber.

Therefore, the maximum eigenvalue of the **P** matrix (λ_{max}) can act as the basic parameter, which reflects the ability of a molecule to be sorbed on the nerve fiber. All other positive eigenvalues of the **P** matrix correspond to all other types of contacts of the molecule and make it possible to determine the fraction of molecules sorbed by the surface

$$K = \lambda_{max}/\Sigma\lambda_i,$$

here the summation is performed over positive eigenvalues of the **P** matrix.

Thus, the K value plays the role of the distribution constant between the intertissue liquid and nerve fiber surface. In this case, the number of sorbed M molecules on the nerve fiber surface should be proportional to the KC product, where C is the concentration of the anesthetic in the intertissue liquid. When some surface G of the nerve fiber must be isolated for complete blocking of the nerve impulse, L molecules in the surface layer are required: $L = G/G_m$, where G_m is the projection of the surface area of the molecule on the nerve fiber surface.

Then it is evident that the necessary concentration of the anesthetic in the solution (MEC by definition) can be determined from the equation $KC = G/G_m$. When

Table 1. Minimum effective concentrations (MEC) in conduction anesthesia

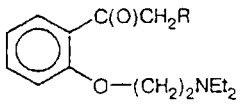
Compound	R	MEC/mmol L^{-1}	
		Experiment[9–11]	Calculation
o-(β-*N*,*N*-Diethylamino-ethoxy)-β-phenyl-propiophenone chlorohydrate	*p*-$EtC_6H_4CH_2$	2.66	2.61
	p-$Pr^iC_6H_4CH_2$	2.39	2.55
	p-*n*-$PrC_6H_4CH_2$	2.39	2.55
	p-$Bu^iC_6H_4CH_2$	2.38	2.47
	p-$PhCH_2C_6H_4CH_2$	2.21	2.16
	p-$PhC_6H_4CH_2$	2.29	2.34
	m-$BrC_6H_4CH_2$	2.26	2.27
	m-$FC_6H_4CH_2$	2.67	2.62
	m-$ClC_6H_4CH_2$	2.50	2.41
	m-$MeC_6H_4CH_2$	2.67	2.65
	o-$BrC_6H_4CH_2$	2.26	2.50
	o-$FC_6H_4CH_2$	2.36	2.61
	o-$ClC_6H_4CH_2$	2.51	2.50
	o-$MeC_6H_4CH_2$	2.67	2.62
	p-$BrC_6H_4CH_2$	2.26	2.30
	p-$FC_6H_4CH_2$	2.62	2.63
	p-$ClC_6H_4CH_2$	2.51	2.50
	p-$MeC_6H_4CH_2$	2.67	2.66
	$PhCH_2$	2.76	2.74
	$PhCH_2CH_2$	2.67	2.61
	$PhCH_2CH_2CH_2$	2.77	2.60
	o-$OMeC_6H_4CH_2$	2.66	2.46
	m-$OMeC_6H_4CH_2$	2.66	2.61
	p-$OMeC_6H_4CH_2$	2.66	2.56
	α-$C_{10}H_7CH_2$	2.40	2.46
Trimecaine		3.50	3.58
Novocaine		4.50	4.40

the thickness of the sorbed monolayer (h) is assumed constant within the series, the surface of the molecule can be replaced by its volume V_m, since $G_m = V_m/h$. Then we obtain $C = (hG)/(V_mK)$. Taking into account that C = MEC and the previously determined correlation for K, the resulting expression for MEC can be written in the form

$$MEC = hG \cdot \Sigma\lambda_i/(V_m\lambda_{max}) = const\Sigma\lambda_i/(V_m\lambda_{max}).$$

Results and Discussion

Compounds of the ethaphon class (*o*-(β-*N*,*N*-diethylaminoethoxy)-β-phenylpropiophenone chlorohydrate[9,11] (**1**)) and Novocaine and Trimecaine, widely used in medicine, were used to test the described model for calculating MEC.



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When the MEC and $1/V_m$ values are reduced to the single unit system (mmol L^{-1}), the previously obtained formula can be transformed into a form that is more convenient in calculations:

$$MEC = \Sigma\lambda_i/(V_m\lambda_{max}) + 0.517.$$

The results of calculations for the compounds considered and the experimental values of MEC are presented in Table 1. The correlation coefficient of the experimental and calculated MEC values was 0.98 with standard deviation $\sigma_{n-2} = 0.10$. It can be mentioned for comparison that agreement between the theory and experiment was previously obtained[10] with a linear correlation coefficient of 0.85.

It follows from the analysis of the components of the eigenvector of the **P** matrix corresponding to the λ_{max} eigenvalue that lipophilic groups of molecules participate in the sorption of anesthetics of the ethaphon series. A somewhat different mechanism is observed in the case of Novocaine, where the carbonyl oxygen atom plays a considerable role.

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