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Molecular Orbital Index-Activity Relationship between Atrial Antiarrhythmic Activity and Disopyramide Derivatives

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A model has been proposed to explain and determine biological response to antiarrhythmic compounds. A series of compounds was administered to mongrel dogs and tested for their ability to correct the induced arrhythmias. This drug response is shown to be a function of lipophilicity, IR-absorption and electrostatic interaction. Frontier electron density is shown as a good parameter in the comparison of electrostatic interaction between different molecules and is significantly correlated with biological activity. This parameter is shown as a possible explanation for the observation that compounds with a high value of lipophilicity and low value of electrostatic factor may show good ventricular antiarrhythmic activity but fail to show atrial antiarrhythmic activity.

The study on charge density around N of the tertiary amine of disopyramide analogs which was previously noted[2] is reported here. Previously, analogs which have structural variation at the neighborhood of the carbonyl group were investigated. The interaction between the carbonyl group and the receptor involves the adsorption process which stimulates the biological system and finally induces the ventricular antiarrhythmic activity. It is noted here that there are differences in the pharmacology of atrial and ventricular antiarrhythmic activities. In many cases, active compounds in ventricular antiarrhythmic activity are inactive in atrial antiarrhythmic activity and *vice versa*.

Experimental

Biology——Mongrel dogs of either sex were anesthetized with sodium pentobarbital 30 mg/kg intravenously. Artificial respiration was maintained by a mechanical respirator through an endotracheal tube. The heart was exposed by a surgical thoracotomy between the 4th and 5th ribs and subsequent pericardectomy. Bipolar recording electrodes were sewn onto the right atrium and the atrial electrogram and ECG Lead II were recorded by means of a Grass oscillographic recorder. Control records were taken and then the atrial wall near the intercaval bridge was crushed by means of a hemostat and the right atrium was stimulated at 5—10 volts, 15—30 Hz with 0.5 ms square wave pulses for 5—10 seconds. When the stimulus was removed, half of the dogs exhibited an atrial flutter of 300—400 beats/minute. In control experiments, all flutters which persisted 20 minutes were found to continue idefinitely. Dogs with persistent atrial flutter were administered test compounds at a rate of 1 mg/kg/minute through a cannula in the femoral vein. The infusion was continued until normal sinus rhythm occurred or a total dose of 12 mg/kg was administered. Each compound was tested in two dogs which had not previously received a test compound. The numbers of animals tested per compound were small due to the difficulty in producing this type of arrhythmia. The procedure used was a modification of that reported by Winbury, *et al.*[3]

Mathematics

Consider the following equation:

$$\frac{d(\text{biological response})}{dt} = ACp^{a1}(\text{step 1}) \times p^{a2}(\text{step 2}) \times \cdots p^{an}(\text{step } n) \qquad (1)$$

where p (step i) represents the probability of accomplishing step i, where $i=1,2,\ldots.n$, C is the drug concentration, and A is the proportionality constant, which has the same unit as d

1) Location: *Chicago, Illinois 60680.*
2) T.K. Lin, Y.W Chien, R.R Dean, J.E. Dutt, H.W. Sause, C.H, Yen, and P.K. Yonan, *J. Med. Chen*, **17**, 751 (1974).
3) M.M. Winbury, M.L. Hemmer, and D.W. Calhoun, *Acta Physiol. Pharm. Neerl.*, **5**, 468 (1957).

(biological response)/Cdt. Eq. 1 is a general expression in which step i implies any step of actions such as dissolution, absorption, penetration, adsorption, electronic interaction, metabolism, and excretion, en route from oral administration to the sites of drug action which exerts biological response.

In previous treatments[2] only two mechanisms were considered. Here the treatment considers three mechanisms. In the first mechanism, a drug molecule penetrates the membrane from outside the cell to reach and interact with the receptor by the action of lipophilicity, and in the second mechanism, a binding between the receptor and the drug molecule involves an adsorption process. The third mechanism involves the electrostatic interaction between the drug molecule and the receptor.

Since only three mechanisms are considered at this time, eq. 1 can be specifically represented by the following equation:

$$\frac{d(\text{response})}{dt} = ACp^{a1}(\text{lipophilicity})p^{a2}(\text{adsorption})p^{a3}(\text{electrostatic interaction}) \qquad (2)$$

For brevity, the detailed derivations of p(lipophilicity) and p(adsorption) are omitted. (See eq 18 of part II[4] and eq 20 of part I[5] for the mathematical derivations).

$$p(\text{lipophilicity}) = V \exp\left[-Ma^2b^2(\pi-\Pi_0)^2/6k^2T^2\right] \qquad (3)$$

where V and b are the proportionality constants. A drug molecule has to make M steps (the length of each step is a) in Brownian motion from the extracellular phase to reach the specific receptor site. Π is Hansch's parameter of the lipophilicity of the drug and Π_0 is the optimal value of lipophilicity. k is the Boltzman constant and T is the absolute temperature of the membrane which can be regarded as constant.

$$p(\text{adsorption}) = B \exp\left(-hcv/2kT\right) \qquad (4)$$

Where B is a proportionality constant, h is the Planck constant, c is the speed of light, and v is the wave number of the stretching vibrational mode of the carbonyl group. Eq 3 is derived for the first mechanism and eq. 4 for the second mechanism. We shall formulate the third mechanism p(electrostatic interaction) in the following paragraph.

If the topological shape of the drug molecule provides a certain defined distance between the adsorption site 1 (carbonyl site) and the electrostatic site 2 (*tert*-nitrogen), then the electrostatic interaction between the drug molecule and the receptor site will occur. A deviation from the optimal distance will weaken this electrostatic interaction. This concept is within the framework of Kier's model.[6-9] Since the site 2 is not involved in adsorption process but rather in electrostatic interaction, the site partition function q_2 for site 2 can be expressed as:

$$q_2 = q_t q_r q_v q_e q_n = aq_e \qquad (5)$$

where q_t is translational, q_r is rotational, q_v is vibrational, q_n is nuclear and q_e is electronic. Except for q_n, $q_t q_r q_v$ is close to 1 in comparison with q_e, hence, the contribution of ln $(q_t q_r q_v)$ is negligible. q_n is constant because the active atom of the drug molecule is in ground nuclear state. Therefore, $q_2 = aq_e$, where a is constant.

In the search for useful parameters the total charge density and the frontier electron density on the tertiary nitrogen are computed. It is seen that only the frontier electron

4) T.K. Lin, *J. Med. Chem.*, **17**, 749 (1974).
5) T.K. Lin, *J. Med. Chem.*, **17**, 151 (1974).
6) L.B. Kier, "Molecular Orbital Studies in Chemical Pharmacology," Springer-Verlag, New York, N.Y., 1970, pp. 82—104.
7) L.B. Kier, *J. Med. Chem.*, **11**, 915 (1968).
8) L.B. Kier, *J. Pharm. Sci.*, **57**, 1188 (1968).
9) L.B. Kier, *J. Pharm. Sci.*, **59**, 112 (1970).

density is significantly correlated with the biological activity. The frontier electron density in this case is the lone pair electron density on the nitrogen. Based on the empirical method, it is suggested that the electrostatic interaction is the kind of interaction between the lone pair electrons on tertiary nitrogen of the drug molecule and the charge center of the receptor because the lone pair electrons occupy the highest occupied molecular orbital.

The electrostatic interaction is calculated as an electron-charge coulombic interaction between the frontier electron density of N atom on the drug molecule with the charge center on the receptor site. The frontier electron density used (for ground state) was calculated using the MINDO/2 computer program.[10] Now, q_e of eq. 5 is expressed as:

$$q_e = \exp(-f_N \cdot Q_r / R_{N-r} kT) \tag{6}$$

where f_N is the frontier electron density of the nitrogen atom, Q_r is the average charge density of the receptor site 2 which is taken as constant. R_{N-r} is the distance between the lone pair of N atom and the receptor site 2. R_{N-r} is considered constant in this case. Substituting eq. 6 into eq. 5 we have:

$$q_2 = a \exp(-f_N Q_r / R_{N-r} kT) \tag{7}$$

and

$$p(\text{electrostatic interaction}) = q_2 = a \exp(-f_N Q_r / R_{N-r} kT) \tag{8}$$

Substituting eq. 3, 4, and 8 into 2, and setting $d(\text{response})/dt$=constant because the laboratory observation of biological response in this case is a constant response, we have:

$$\frac{d(\text{response})}{dt} = AC\{V \exp[-Ma^2b^2(\Pi - \Pi_0)^2/6k^2T^2]\}^{a1} \{B \exp(-hc\nu/2kT)\}^{a2} \{a \exp(-f_N Q_r / R_{N-r} kT)\}^{a3} = \text{constant} \tag{9}$$

Taking logarithms on both sides, setting constant, and rearranging, we obtain:

$$\ln \frac{1}{c} = k_1 + k_2\Pi - k_3\nu - k_4 f_N - k_5\Pi^2 \tag{10}$$

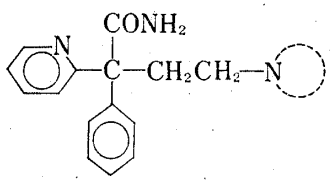
One notices that Q_r, the charge density on the receptor site 2, is taken as positive charge. If $k_2 \gg k_5$, the Π^2 term can be omitted, and eq. 10 can be written as:

$$\ln(1/c) = k_1 + k_2\Pi - k_3\nu - k_4 f_N \tag{11}$$

Eq. 11 is the final equation representing the three mechanisms (rate determining steps for the interaction among drug molecule, membrane, and receptor).

Results and Discussion

The compounds used in this study are listed in Table I, and their chemical structure is given by the following general formula:

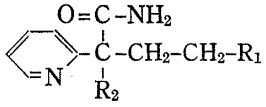


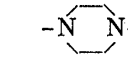
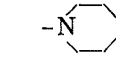
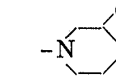
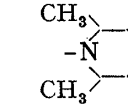
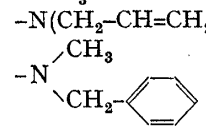
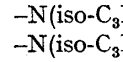
Because we are interested only in the electron density of the lone pair electrons on the tertiary nitrogen, whose wave function belongs to a highly localized molecular orbital, therefore, the fragment H–N⟨ ⟩ is used to undergo the molecular orbital calculations. Use of either

10) QCPE 217, Indiana University.

CH_3 or H as substituent on the nitrogen atom is justified because we are not interested in the absolute values of the electron density, but rather in the relative values. The use of either CH_3 or H as substituent can fulfill our objective. Therefore, we choose H as the substituent for computational purposes.

TABLE I. Data for Observed and Calculated Atiral Anitarrhythmic Potency



Comp. No.	SC No.	R_1	R_2	M.W. (gm)[a]	MED[b] (mg/kg)	Observed[c] $\ln p$	Π[d]	$\nu_{C=O}$ (cm^{-1})[e]	f_N[f]	Calculated[g] $\ln p$
1	07031	$-N(iso\text{-}C_3H_7)_2$	C_6H_5	339.5	3.0	1.39	−0.18	1678	−0.6380	1.28
2	12857	$-N(iso\text{-}C_3H_7)_2$	3,4-$(OMe)_2C_6H_3$	399.5	7.5	0.63	−0.84	1681	−0.6380	0.87
3	12875	$-N(iso\text{-}C_3H_7)_2$	3-$CH_3C_6H_4$	353.5	2.5	1.61	0.12	1678	−0.6380	1.37
4	13173		C_6H_5	338.4	12.0	0.00	0.50	1681	−0.2054	0.00
5	13212		C_6H_5	337.5	3.0	1.38	0.56	1681	−0.7136	1.54
6	13259		C_6H_5	337.5	1.5	2.07	0.57	1681	−0.7047	1.52
7	13260		C_6H_5	353.5	10.0	0.22	1.23	1684	−0.2248	0.10
8	13486	$-N(CH_2\text{–}CH{=}CH_2)_2$	C_6H_5	335.4	6.0	0.68	0.88	1684	−0.5898	1.08
9	13489		C_6H_5	359.4	5.0	0.93	1.12	1689	−0.6036	0.86
10	13068	$-N(iso\text{-}C_3H_7)_2$	4-cl-C_6H_4	373.9	5.0	0.97	0.73	1683	−0.6380	1.24
11	13234	$-N(iso\text{-}C_3H_7)_2$	4-F-C_6H_4	357.5	7.0	0.59	0.21	1689	−0.6380	0.68
12	13052		C_6H_5	323.4	3.25	1.26	−0.06	1681	−0.7251	1.38
13	13251	$-N(CH_3)_2$	C_6H_5	479.5	10.0	0.53	−0.55	1695	−0.7406	0.35

a) molecular weight in grams
b) minimum effective dose in mg/kg (average of two dogs)
c) p is calculated by eq. 13.
d) Π=log (partition coefficient). See ref. 10)
e) $\nu_{C=O}$ is the wave number of the carbonyl group.
f) f_N is the frontier electron density on the nitrogen of group R_1.
g) calculated from eq. 12

The calculated frontier electron density can represent fairly well the electron density of the lone pair electrons on the nitrogen atom, since the lone pair electrons occupy the highest occupied molecular orbital. The experimental values of the relative lipophilicity Π[11,12] and the wave number of the carbonyl group $\nu_{C=O}$ along with the calculated frontier electron density f_N of the nitrogen atom are shown in Table I. The multiple linear regression was performed on these data to obtain the coefficient of eq. 11. The resultant equation is:

$$\ln p = 109.991(\pm 0.182) + 0.319(\pm 0.343)\Pi - 0.0659(\pm 0.039)\nu_{C=O} - 2.991(\pm 1.239)f_N \quad (12)$$
$$n=13,\ r=0.90,\ s=0.29$$

where values in parentheses are 95% confidence limits and the potency p is defined as:

11) Y.W. Chien, H.J. Lambert, and A. Karim, *J. Pharm. Sci.*, **63**, 1877 (1974).
12) Y.W. Chien, H.J. Lambert, and T.K. Lin, *J. Pharm. Sci.*, **64**, 961 (1975).

$$p = \frac{12/\text{M.W. of compd. 1}}{\text{MED/M.W.}} \qquad (13)$$

where MED, the minimum effective dose, M.W., the molecular weight, along with the calculated and the observed ln p are listed in Table I. The coefficient of $\nu_{C=O}$ is very small. This is because the wave number of carbonyl group is very large. However, this coefficient is statistically significant though it has a relatively constant contribution. The $\nu_{C=O}$ term contributes to the adsorption mechanism. The correlation with two of the parameters is given as follows:

$$\ln p = 105.863(\pm 0.208) - 0.0632(\pm 0.045)\nu_{C=O} - 2.462(\pm 1.256)f_N \qquad (14)$$

$$n=13,\ r=0.85,\ s=0.34$$

The parameters in eq 14 are selected by eliminating the statistically not significant parameter, Π, of eq. 12. The computed t values for parameters Π, $\nu_{C=O}$, and f_N are 2.10, −3.79, and −5.46 respectively for eq. 12.

In previous note,[3] it was found that the lipophilicity Π is significantly correlated with the ventricular antiarrhythmia. In the present work, however, it is found that Π is not significantly correlated with the atrial antiarrhythmia. This may explain the fact that some active compounds in ventricular antiarrhythmic activity are inactive in atrial antiarrhythmic activity. Those compounds with very high value of Π and low value of electronic factor may show good ventricular antiarrhythmic activity, however, they fail to show atrial antiarrhythmic activity, because the former needs high value of Π to increase its activity and the later does not require the lipophilicity to enhance its activity. Those compounds with low value of Π and very high value of electronic factor may show good atrial antiarrhythmic activity and fail to show ventricular antiarrhythmic activity.

Finally, it is worthwhile to point out that in their *frontier electron theory*[13] Fukui, *et al.*[14] do permit comparison of this parameter between different compounds. We have shown that the frontier electron density is a good parameter for correlating the biological activity.

Acknowledgement We are greatly indebted to Dr. Richard Dean, Department of Biological Research, Searle Laboratories, for his technical assistance and consultation in the biological experiment.

13) K. Fukui, T. Yonezawa, and H. Shingu, *J. Chem. Phys.*, **20**, 722 (1952).
14) K. Fukui, T. Yonezawa, and C. Nagata, *J. Chem. Phys.*, **27**, 1247 (1957).