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Drug, dosage, activity, studies of antimalarials by physical methods - II

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Abstract:
Studies pertaining to drug-DNA interactions in treating a disease efficiently have taken an important place in recent times. Murthy and colleagues were active in correlating the drug activity, with physical parameters like refractivity, susceptibility, molecular electron ionization cross-section and the dosage. The molecular polarizability, diamagnetic susceptibility and molecular electron ionization cross section Q have been evaluated. An analysis of Q in the light of the data available on plasma protein binding, bio availability, Log P and half-Life show semblance of regular dependence of Q on them and hence an effort is made to bring this dependence into a regular mathematical relationship. The dosage of each drug is calculated. A critical look at the results arrived on Q and dosages reveal that a highly active drug with large Q need to be monitored in very small quantities and any minute increase in dosage is resulting in unwanted toxic effects and vice versa. The algebraic formulae enable one to calculate the dosages theoretically from the value of Q and other parameters and the calculated dosage through the formulae agreed favorably well with suggested dosages. For example, in primaquine phosphate, the calculated dosage is 30 mg per day against the suggested practical dosage of 26.3 mg per day. A similar observation is made in mepacrine with theoretical dosage of 60 mg per day as against the suggested practical dosage of 100 mg per day. In short, the molecular structure followed by refraction and susceptibility measurements and Q will throw light on dosage, toxicity of a drug. Thus the present investigations pave way for a new direction of approach for study of drug activity without recourse to techniques involving highly expensive instrumentation and highly theoretical approaches involving quantum mechanical methods.

Keywords: drug; dosage; activity; antimalarials

Background:
The constant pursuit in pharmacology and pharmaco chemistry is to study how efficiently a drug acts to treat a particular disease. Usually many physico-chemical and quantum mechanical methods as well as physical techniques like IR, Raman etc., have been used to study drug-DNA interactions. The drug-DNA interaction studies have acquired a lot of importance in recent days owing to dreadful diseases like AIDS, cancer and Alzheimer's. Murthy and colleagues **[1-11]** were active in correlating the drug activity with physical parameters like electron ionization cross-section and λ_m.

The present work is an extension of the same made to antimalarials, starting from evaluation of polarizabilities α_M, susceptibilities χ_M and molecular electron ionisation cross-section **[15]** Q to the drug activity and dosage through an algebraic expression 11, utilising the data of medicinal parameters the dosages thus obtained are correlated with experimental values. The required parameters are taken from references 5-14.

Methodology:
Many physico-chemical as well as quantum mechanical techniques are in vogue in studying drug-DNA interactions. An attempt is made by Murthy and his colleagues since 1995 to correlate the molecular electron ionization cross-section with the dosage of the medicine and the toxic effects. The physical parameters like electronic polarizability, diamagnetic susceptibilities and molecular electron ionization cross-section are utilized in evaluating the dosage of a drug. The above parameters are obtained through quantum mechanical approach of Lippincott, bond polarizability and bond refractivity of Le Fevre **[1]** and also by the molecular dynamic method.

The molecular dynamic method is considered to be highly sensitive to conformational changes and so is taken as standard. The very fact of studying these physical properties of medically important compounds is to show the usefulness of these methods in correlating molecular electron ionization cross-section with dosage and using the data of protein binding PB, bio availability BA, half life HL and Log P in calculating the dosage and toxic effect of drug through an algebraic formula described in equation 11.

The mean polarizability of these drugs have been experimentally studied using refractivity as a technique and confirmed by

theoretical approaches of Lippincott and Stutman **[13, 14]** additivity of bond refractions and molecular force field studies.

The details of these approaches are given in the earlier papers of Murthy. **[1-6]** The formulae for polarizabilities, susceptibilities and electron ionization cross-sections are given in equations 1 to 10 (see supplementary material). The parameters used in equations 1 to 10 are explained in references 1, 2 to 4, 9 and 10. Their values are also taken from references 1, 2 to 4, 9 and 10. The required data on bond distances are taken from Landolt and Bornstein Tabullen. The data on vibrational frequencies necessary to calculate the bond polarizabilities and molecular polarizabilities are taken from the data of frequencies of the bonds of nearest chemical environment from CRC hand book. The data on 'A' the reduced electro negativity C_R and α_M the atomic polarizability are taken from the work of Lippincott. **[13, 14]** Molecular polarizability α_M, diamagnetic susceptibility χ_M for these antimalarial drugs have been calculated by Rao and Murthy's method using equation 9, along with electron ionisation cross-section are presented in Table 1 (supplementary material). All the above values are evaluated from the molecular dynamic method.

It is well known that there is no rigorous theory to explain molecular electron ionization cross-section. **[15]** There are several semi empirical results to explain the experimental observations of the electron ionization cross-section. Beran and Kevan observed proportionality between molecular polarizability and susceptibility on one hand, susceptibility and electron ionization cross-section on the other hand. When both these formulae are put together the dependence of Q on α_M or χ_M becomes expressive. The unsaturated characters of these bonds are expected to affect the values. So Rao and Murthy modified the equation of Beran and Kevan to equation 10.

The molecular electron ionization cross-section of these antimalarial drugs has been calculated using equation 10 of Rao. **[7]** In equation 10, γ is saturation factor and σ is Pauling covalency factor. The values of Q obtained from χ_M of equation 10 are compiled in Table 1 (supplementary material). The dosages and toxic effects of these antimalarial drugs have been compiled in Table 2 (supplementary material). The data on the dosages and toxic effects have taken from reference 16. The data on PB, BA, HL and Log P for these systems is taken from drug bank of Wikipedia. **[16]** These data are used along with Q to arrive at a more analytical approach through an algebraic expression described in equation 11.

The drug-DNA interaction is mainly based on the electronic transfer and electronic polarizability affected during interaction. Similarly the process of electron transfer is associated with relevant magnetization effects like susceptibility variations. It is thus understandable to think of electronic polarization and diamagnetic susceptibility variations taking place in a particular drug molecule during drug-DNA interaction. Thus a detailed study of molecular polarizability and diamagnetic susceptibility of these systems are taken up in the present investigation.

Primaquine phosphate or malrid is subjected to magnetic field and its diamagnetic susceptibility is tested on Vibrating sample Magnetometer at IIT Madras, India. The diamagnetic susceptibility reported is 60.325 micro CGS units where as the calculated value is 63.6275 micro CGS units. These studies follow electron ionization cross-section Q at molecular level and hence the justification of evaluating molecular electron ionization cross-section.

Discussion:

The mean molecular polarizabilities reported by different methods are in good agreement with the theoretical values there by lending strong support to the strong theoretical basis. However the molecular dynamic method seems to be more sensitive to conformational changes and hence is taken as standard. In a similar manner the diamagnetic susceptibilities that are determined from molecular polarizabilities obtained by different methods show fairly good agreement. The molecular electron ionization cross-sections obtained from susceptibilities also show similar good agreement.

The values of PB, BA, log p and HL taken from reference 16 when used along with Q in the algebraic expression 11 has resulted in a constant value of K. This supports the contention of the authors of the usefulness of relationship of Q with all other parameters successfully in giving information on dosages etc., In fact, the dosage calculation from given PB, BA, log p, HL and K for these systems have taken up as a test of utility of the method.

A close look at the Table 2 (supplementary material) on electron ionization cross-section and dosage reveal the following. The lower the value of Q higher is the activity of the compound. This is shown by lower values of Q in mefloquine with Q = 12.2401 x 10 power 16 square cm. The lower value of Q reveals the readiness of the molecule to interact with the DNA and operate curatively. It also reveals that more of the effective area is available for interaction. However the higher activity is to be taken care of in monitoring dosages. It is monitored in a dosage of 1250.0 mg per day as a single dose. Any increase of this drug is going to cause undesirable electron activity and also cause severe depression, anxiety, insomnia, vestibular disorders and CNS problems.

Quinine, having a Q value of 13.4404 x 10 power 16 square cm is also very active, but less than that of mefloquine. So it is monitored in higher dose of 1875.0 mg per day, for seven days. But any increase in specified dosage of quinine is leading to skin allergy, deafness and mental depression.

Thus, in short, it can be inferred that a drug with lower Q is highly active and is need to be monitored in smaller dosages whereas a drug of higher Q is not going to give any prominent toxic effects even if its dosage is slightly more. Thus it is inferred that a structure of drug followed by a measurement of fundamental parameters like refractivity, susceptibility and electron ionization cross section along with the data on PB, BA, log p and HL are helpful in estimating the dosages and toxicity.

As per the suggestions in recent literature, the correlation of electron ionization cross-section with other parameters like protein binding, bio availability, Log P and half life was taken note of and the dependence of Q on these antimalarial drugs are investigated. From the investigations made, a semi algebraic expression 11, relating Q with dosage, protein binding etc., could be formulated. An evaluation of the dosage from this algebraic expression is made and the results are encouraging.

Conclusion:

The dosages thus obtained through the above expression 11 agreed in many systems of medicinal compounds and with order of magnitude in other cases. As an example in the case of quinine the calculated dosage value is 1125.78 mg per day as against the experimental dosage value of 1875.0 mg per day. Also in the case of primaquine phosphate the calculated dosage value is 30.0 mg per day as against the experimental value of 26.3 mg per day. The same observations are made in the case of mepacrine and atovaquone. The formula is applied to other systems like anti-depressants, anti-histamines, anti-inflammatory and antibiotics. In almost all the cases the calculated dosage values fairly agreed with the experimental values. The above formula can be used with fairly reliably to calculate dosages and toxic effects of medically important systems. The importance of the present investigation involving electron ionization cross-section and other medicinal parameters lies in the fact of predicting the dosages from the available information on physical parameters like refractivity, susceptibility and chemical structure.

Thus the present method opens a new line of approach to the study of drug-DNA interactions besides quantum mechanical approaches and other physico-chemical methods that are available today. In fact a close look at the molecular structure, its refractivities and allied properties show that they alone are sufficient to give an insight into the medical activity of the drug without recourse to the highly expensive physico-chemical methods and highly cumbersome quantum mechanical approaches. The advantage of the present method over quantum mechanical method lies in the simplicity of the approach without requiring much of computational time and speed.

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References:

[01] V. R. Murthy, *et al., Asian J Phy.,* 5:393 (1996)
[02] V. R. Murthy, *et al., Asian J. Sci. Tech. Devel.,* 14:51 (1997)
[03] V. R. Murthy, *Ind. J. Biochemand Biophys.,* 16:32 (1979)
[04] V. R. Murthy, *et al., Ind. J. Phy.,* 65B:565 (1991)
[05] V. R. Murthy, *et al., Ind. J. Biochem and Biophys.,* 16:42 (1979)
[06] V. R. Murthy, *et al., Ind. J. Biochem and Biophys.,* 17:160 (1980)
[07] B. P. Rao, *et al., Actaciencia Indica,* 5:118 (1979)
[08] B. P. Rao, *et al., Ind. Chem. J.,* 13:17 (1979)
[09] D. V. Subbiah, *et al., J. Mol.struct.,* 87:105 (1982)
[10] D. V. Subbiah, *et al., J. Phys. Chem.,* 87:1730 (1983)
[11] T. V. S. A. Murthy, *et al., Actaciencia Indica,* 29P:231 (2003)
[12] R. J. W. LeFevre, *Adv. In Phys. Org. Chem.,* 3:1 (1966)
[13] E. R. Lippincott, *et al., J. Phy. Chem.,* 68:2926 (1964)
[14] E. R. Lippincott, *et al., J.Phy.Chem.,* 70:78 (1966)
[15] J. A. Beran and L. Kevan, *J. Phys. Chem.,* 73:3866 (1969)
[16] http://www.Wikipedia.com
[17] R. S. Miller, *et al., J. Trop. Med. Hyg.,* 74:401 (2006) [PMID:16525097]
[18] A. Ishih, *et al., South East Asian J. Trop. Med. Public Health,* 37:13(2006) [PMID:16771206]

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Supplementary material

List of equations used in this article are given below.

Equation		Number
$(b_L\text{-}b_T) = A[(X_bX_c)^{1/2}(aN/(k\text{-}b))^{2/3}]^{\delta}$	→	(1)
$(b_L+2b_T) = Cp^j (j)^{n\beta} \sigma_e^{1/2}$	→	(2)
$\alpha_M = \Sigma\ [(N_i/3)(b_L+2b_T)_i]$	→	(3)
$\Sigma\ \alpha_{\|\|P} = 4nA/a_0\ [(R2/4) + (1/\ (2CR2))]^2$	→	(4)
$\alpha_{\|\|\ n} = \Sigma_j\ f_j\ \alpha_j$	→	(5)
$\Sigma 2\alpha_{\perp} = n_{df}\ [(\Sigma_j\ X_j^{\ 2}\alpha_j\ )\ /\ (\Sigma_j\ X_j^{\ 2})]$	→	(6)
$\alpha_M\ = 1/3[\Sigma\ \alpha_{\|\|P}+\Sigma\ \alpha_{\|\|\ n}+\Sigma 2\alpha_{\perp}]$	→	(7)
$\alpha_M = [3/(4\pi N\gamma)]\ (R_{\infty})_i$	→	(8)
$-\chi_M = \gamma_m\sigma'\alpha_M$	→	(9)
$Q\ (\text{in}10^{-16}\ \text{cm}^2) = 0.278\gamma\chi_M$	→	(10)
$K = \left(\frac{Q^{1/4}}{(DL)^{1/2} * \log P} \right)^{\frac{(PB)(BA)}{3}}$	→	(11)

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S. No	Name	α_M	χ_M	Q
I	QUININE DERIVATIVES			
1	Mefloquine	3.8054	60.3965	12.2401
2	Quinine	4.4145	63.3191	13.4404
II	7 CHLORO 4 AMINOQUINOLINES			
3	Hydroxy chloroquine	4.3038	69.9817	14.1826
4	Amodiaquine	4.31376	72.4452	14.6819
5	Chloroquine	4.1992	101.0751	20.4834
III	8 AMINOQUINOLINES			
6	Primaquine phosphate	3.5331	63.6275	12.8949
IV	9 AMINOCRIDINES			
7	Mepacrine	5.1947	85.2166	17.2702
V(a)	BIGUANIDES			
8	Proguanil Hcl	2.9090	60.1668	12.1935
V(b)	DIAMINOPYRIMIDINES			
9	Pyrimethamine	2.7771	71.3448	14.4589
VI	NAPHTHOQUINONES			
10	Atovaquone	4.2213	95.1564	19.2846

Table 1: Molecular polarizabilities (α_M) (x 10 power 23) cubic cm, diamagnetic susceptibilities (χ_M) (x 10 power 6 CGS units), electron ionization cross-section (Q x 10 power 16 square cm)

S. no	Name	Q	PB	BA	Log P	m	K	K^{2m}	HL	L days	Dosage[16]	
I	QUININE DERIVATIVES (K_A = 0.9469415)										Cal (mg per day)	Exp (mg per day)
1	Mefloquine	12.2401	0.98	0.1	3.81	30.6	1.01634	0.0355	2 week	14	484.45	1250
2	Quinine	13.4404	0.95	0.88	2.53	3.58	0.87754	0.676	18 hrs	0.75	1125.78	1875 **[17]**
II	7 CHLORO 4 AMINOQUINOLINES (K_A = 2.3964)											
3	Hydroxy-Chloro quine	14.1826	-	-	-	-	-	-	-	-	-	400 for 7 days
4	Amodia - quine	14.6819	-	-	4.33	-	-	-	5.2	-	-	1200
5	Chloro -quine	20.4834	0.55	0.9	4.47	6.06	2.3964	39876.25086	1 - 2 months	30	14.6749	71.4285 **[18]**
III	8 AMINOQUINOLINES (K_A = 1.08581)											
6	Primaquine Phosphate	12.8949	0.5	0.25	2.14	24	1.08581	52.0311	3.7 - 4.2 hrs	0.31	30	26.3
IV	9 AMINOCRIDINES (K_A = 0.95817)											
7	Mepacrine	17.2702	0.8	0.5	5.388	7.5	0.95817	0.4472	5 - 14 days	5	60	100
V(a)	BIGUANIDES (K_A = 1.1033)											
8	Proguanil Hcl	12.1935	0.75	0.5	2.558	8	1.1033	5.33657	20 hrs	0.833	120	100
V(b)	DIAMINOPYRIMIDINES (K_A = 1.31159)											
9	Pyrimeth - amine	14.4589	0.87	0.9	2.607	3.83141	1.31159	7.99251	96 hrs	4	17	25
VI	NAPHTHOQUINONES (K_A = 0.89243)											
10	Atova-quone	19.2846	0.99	0.47	5.25	6.38	0.89243	0.23358	2.2 - 3.2 days	2.2	309.91	750 twice for 21 days

Table 2: Dosage. Q determined by molecular vibration method