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ANALYSIS OF THE EFFECT OF LEVODOPA ON NITROGENOUS BASES USING QUANTUM METHOD

Oscar Sánchez-Parada[1], Manuel Aparicio-Razo[2,3], Emmanuel Vázquez-López[3], Juan Jesús García-Mar[3], Iliana Herrera-Cantú[3], Karina García-Aguilar[3,5], Erick Pedraza-Gress[3], Lillhian Arely Flores-González[3] and Manuel González-Pérez*[3,4]

[1]Escuela de Medicina Universidad Popular Autónoma del Estado de Puebla.

[2]Benemérita Universidad Autónoma de Puebla, Facultad de Ciencias de la Electrónica.

[3]Universidad Popular Autónoma del Estado de Puebla A.C. (UPAEP). Centro Interdisciplinario De Posgrados (CIP). Posgrado en Ciencias de la Ingeniería Biomédica.

[4]Sistema Nacional De Investigadores. Nivel 1.

[5]Instituto Tecnológico Superior de Coatzacoalcos, Academia de ingeniería Bioquímica.

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***Corresponding Author**
Dr. Manuel González-Pérez
Universidad Popular Autónoma del Estado de Puebla A.C. (UPAEP). Centro Interdisciplinario De Posgrados (CIP). Posgrado en Ciencias de la Ingeniería Biomédica.

ABSTRACT

L-3,4-Dihydroxyphenylalanine (DOPA) or Levodopa (Lev) has been used since the 1960s and has become one of the most widely used drugs in neurology. Lev is a metabolic precursor drug for dopamine. Its therapeutic and harmful effects result from its decarboxylation in dopamine through the enzyme decarboxylase. Said metabolic processes can produce genetic mutations, which are the result of the alteration of the nitrogenous bases or the loss of some of them, giving rise to a disturbance in the formation of proteins. The objective of the study is to determine, using the parametric semi-empirical quantum method 3 (SE-PM3), that Nitrogenous Bases (NB) have a higher affinity with Lev. Through Hyperchem Professional software, it is possible to perform molecular models and analysis of the Lev and NB. The result of the simulations shows that there is a loss of electrons from the NB Guanine, which can be correlated with the beginning of serious problems, forming a variety of complex molecules, resulting in the onset of genetic diseases.

KEYWORDS: Levodopa, Nitrogenous Bases, Quantum method, Hyperchem, SE-PM3.

INTRODUCTION

The Lev is a neutral amino acid long chain that is naturally present in some legumes.[1] The conversion of the Lev to dopamine is highly efficient. However, there are adverse effects due to the stimulation of the area postrema in the bulb.[2] After years of treatment with Lev, about 40% of patients develop motor complications manifested by the reduction in the duration of the effect (deterioration wear or end of dose) and the emergence of movements involuntary (dyskinesias).[3] This, along with in vitro studies showing neuronal death accelerated by the presence of the Lev, has raised the possibility that this compound is toxic for the remaining neurons in the treatment of Parkinson's disease.[4]

The Lev has several metabolic changes since one of their metabolic pathways is through catechol-O-methyltransferase (COMT), which makes the Lev 3-OMD6 by methylation. This step uses S-adenosyl methionine as a donor group methyl, then converted into S-adenosyl homocysteine and subsequently in homocysteine.[5] The use of the enzyme inhibitor dopadescarboxilaza (DDC) in conjunction with the Lev generates the preferential metabolic pathway is preferentially deflected by COMT, increasing levels of homocysteine.[6] They rise above normal levels in Parkinson's patients treated with Lev.[5,7] Studies in other populations of patients have shown that homocysteine is a factor of risk for vascular events and the emergence of cognitive impairment.[8] The role of homocysteine in the development of complications in Parkinson's disease is unknown.[6]

So far, it is known that up to 10% of cases of Parkinsonism are of genetic origin. These genetic alterations occur, from time to time and family.[9] From 10 to 25% of the cases appears a particular pattern of family heritage. In the remaining percentage, to not perform, no variation, or not to present any identifiable inheritance pattern, is called sporadic.

People with Parkinson's disease may present a 30% probability of carrying either a mutation in the GBA (Glucosidase Beta Acid) or in LRRK2 (Leucine-rich repeat kinase 2), This depends on the ethnic group; Therefore these susceptibility genes should be considered as important risk factors.[10,11] The mechanism of mutation is the result of alterations of the NB, sequence these encode genome and define the nature of proteins.[12]

The objective of the study is to determine, using the quantum three parametric semi-empirical method (it-PM3), NB to have a greater affinity for the Lev. Hyperchem is a program for molecular modeling graphic interface, which allows researchers to carry out chemical

simulations that facilitate multiple data entry. Through the program, it is possible to analyze the transfer of Electro (ETC) of every interaction coefficient. ETC is the parameter that identifies the probability of a union between various compounds.[13,14]

MATERIALS AND MÉTHODS

SE-PM3 is a molecular modeling program used by scientists to analyze the quantum composition of molecules and to obtain HOMO-LUMO, BG, EP, ETC and other properties. These data are used to form the table where the interaction of Lev and NB. Hyperchem Professional Software performed Molecular Modeling and Analysis of Levodopa and NB (Hyperchem, Hypercube, Multi On for Windows, Series 12-800- 1501800080. Multi On, South 1236-301 Tlacoquemecatl Insurgentes Col. Del Valle, Benito Juarez, DF, Mexico C.P. 03200).

Table 1: Parameters used for quantum computing molecular orbitals-smoke anLUMO.[14,15]

Parameter	Value	Parameter	Value
Total charge	0	Polarizability	Not
Spin Multiplicity	1	Geometry Optimization algorithm	Polak-Ribiere (Conjugate Gradient)
Spin Pairing	RHF	Termination condition RMS gradient of	0.1 Kcal/Amol
State Lowest Convergent Limit	0.01	Termination condition or	1000 maximum cycles
Interaction Limit	50	Termination condition or	In vacuo
Accelerate Convergence	Yes	Screen refresh period	1 cycle

Table 2: Parameters that are used to display the map of the electrostatic potential of molecules.[14,15]

Parameter	Value	Parameter	Value
Molecular Property	Property Electrostatic Potential	Contour Grid increment	0.05
Representation	3D Mapped Isosurface	Mapped Function Options	Default
Isosurface Grid: Grid Mesh Size	Coarse	Transparency level	A criteria
Isosurface Grid: Grid Layout	Default	Isosurface Rendering: Total charge density contour value	0.015
Contour Grid: Starting Value	Default	Rendering Wire Mesh	

RESULTS AND CONCLUSION

Table 3 shows the comparison between the NB with its own ETC´s, stressing that Guanine has a value less than everyone else. It means that Guanine has a high possibility of being altered by Lev.

Table 3. NB Pure.									
No.	**Give**	**Accept**	**HOMO**	**LUMO**	**BG**	**E-**	**E+**	**EP**	**ETC**
1	Uracil 1	Uracil 1	-9.71	-0.511	9.2	-0.126	0.171	0.297	30.975
2	Thymine	Thymine	-9.441	-0.475	8.966	-0.123	0.169	0.292	30.707
3	Adenine	Adenine	-8.654	-0.213	8.441	-0.14	0.156	0.296	28.518
4	Uracil 2	Uracil 2	-9.91	-0.415	9.495	-0.147	0.202	0.349	27.208
5	Cytosine	Cytosine	-9.142	-0.344	8.799	-0.174	0.161	0.335	26.265
6	**Guanine**	**Guanine**	**-8.537**	**-0.206**	**8.331**	**-0.15**	**0.172**	**0.322**	**25.872**

Figure 1 shows the interaction between the Lev and the Guanine, where in figure 1 see that the Lev has a high probability of being an oxidative agent, while Guanine plays an anti-oxidant or reducing paper.

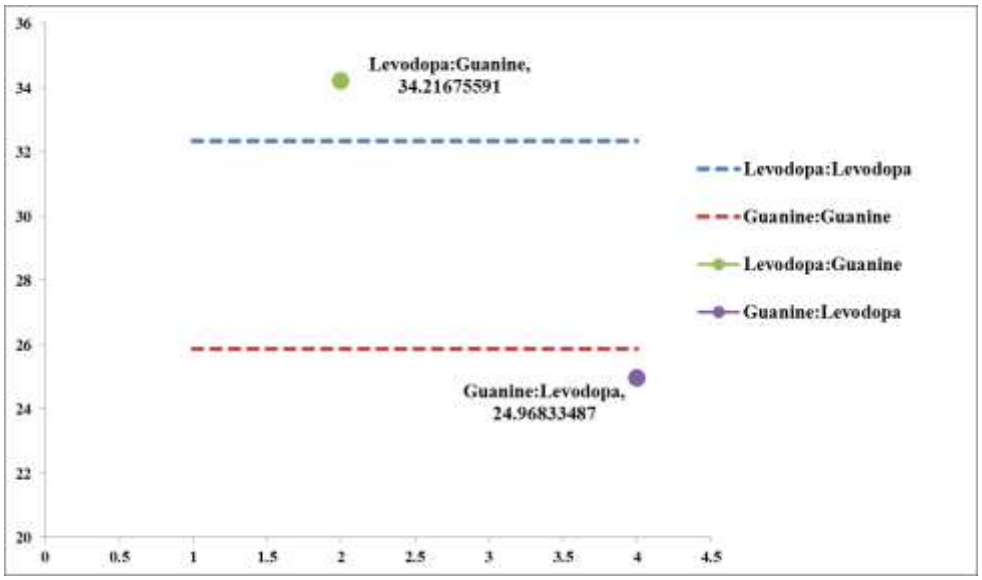

Figure 1. Lev and Guanine quantum well.

In table 4, we can observe the NB cross bands, highlighting that the interactions between the groups "Adenine-Uracil 2", "Cytosine-Uracil 2" and "Guanine-Uracil 2" present ability to interact with the Lev.

Figure 2 Shows the interaction of Guanine-Uracil 2 with the Lev in the area of the probability of average but with a 24.9683 ETC.

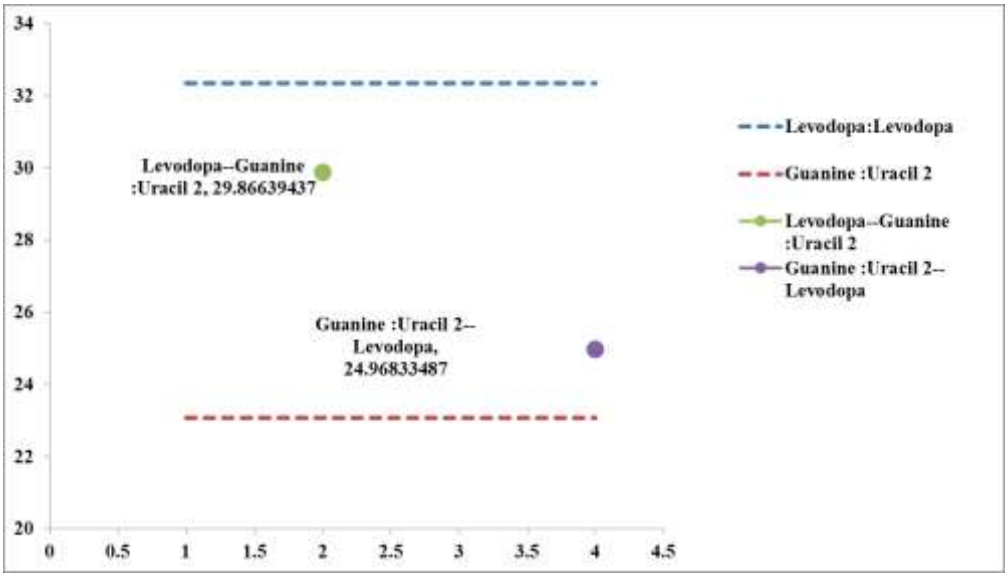

Figure 2. Guanine and Uracil 2 quantum well.

Table 4. Cross bands of the NB.

No.	Give	Accept	HOMO	LUMO	BG	E-	E+	EP	ETC
1	Uracil 1	Adenine	-9.71	-0.213	9.497	-0.126	0.156	0.282	33.679
2	Timine	Adenine	-9.441	-0.213	9.228	-0.123	0.156	0.279	33.076
3	Uracil 1	Cytosine	-9.71	-0.344	9.367	-0.126	0.161	0.287	32.637
4	Timine	Cytosine	-9.441	-0.344	9.098	-0.123	0.161	0.284	32.033
5	Uracil 2	Adenine	-9.91	-0.213	9.697	-0.147	0.156	0.303	32.004
6	Uracil 1	Guanine	-9.71	-0.206	9.504	-0.126	0.172	0.298	31.894
7	Uracil 1	Timine	-9.71	-0.475	9.236	-0.126	0.169	0.295	31.307
8	Timine	Guanine	-9.441	-0.206	9.235	-0.123	0.172	0.295	31.305
9	Uracil 2	Cytosine	-9.91	-0.344	9.567	-0.147	0.161	0.308	31.061
10	Uracil 1	Uracil 1	-9.71	-0.511	9.2	-0.126	0.171	0.297	30.975
11	Timine	Timine	-9.441	-0.475	8.966	-0.123	0.169	0.292	30.707
12	Uracil 2	Guanine	-9.91	-0.206	9.704	-0.147	0.172	0.319	30.42
13	Timine	Uracil 1	-9.441	-0.511	8.93	-0.123	0.171	0.294	30.375
14	Uracil 2	Timine	-9.91	-0.475	9.435	-0.147	0.169	0.316	29.859
15	Uracil 2	Uracil 1	-9.91	-0.511	9.399	-0.147	0.171	0.318	29.558
16	Adenine	Adenine	-8.654	-0.213	8.441	-0.14	0.156	0.296	28.518
17	Uracil 1	Uracil 2	-9.71	-0.415	9.296	-0.126	0.202	0.328	28.34
18	Timine	Uracil 2	-9.441	-0.415	9.026	-0.123	0.202	0.325	27.773
19	Adenine	Cytosine	-8.654	-0.344	8.311	-0.14	0.161	0.301	27.61
20	Uracil 2	Uracil 2	-9.91	-0.415	9.495	-0.147	0.202	0.349	27.208
21	Guanine	Adenine	-8.537	-0.213	8.324	-0.15	0.156	0.306	27.202
22	Adenine	Guanine	-8.654	-0.206	8.448	-0.14	0.172	0.312	27.078
23	Cytosine	Adenine	-9.142	-0.213	8.929	-0.174	0.156	0.33	27.058
24	Adenine	Timine	-8.654	-0.475	8.18	-0.14	0.169	0.309	26.471
25	Guanine	Cytosine	-8.537	-0.344	8.193	-0.15	0.161	0.311	26.345
26	Cytosine	Cytosine	-9.142	-0.344	8.799	-0.174	0.161	0.335	26.265
27	Adenine	Uracil 1	-8.654	-0.511	8.144	-0.14	0.171	0.311	26.185
28	Guanine	Guanine	-8.537	-0.206	8.331	-0.15	0.172	0.322	25.872

29	Cytosine	Guanine	-9.142	-0.206	8.936	-0.174	0.172	0.346	25.827
30	Guanine	Timine	-8.537	-0.475	8.062	-0.15	0.169	0.319	25.273
31	Cytosine	Timine	-9.142	-0.475	8.668	-0.174	0.169	0.343	25.27
32	Cytosine	Uracil 1	-9.142	-0.511	8.632	-0.174	0.171	0.345	25.019
33	Guanine	Uracil 1	-8.537	-0.511	8.026	-0.15	0.171	0.321	25.003
34	**Adenine**	**Uracil 2**	**-8.654**	**-0.415**	**8.24**	**-0.14**	**0.202**	**0.342**	**24.092**
35	**Cytosine**	**Uracil 2**	**-9.142**	**-0.415**	**8.728**	**-0.174**	**0.202**	**0.376**	**23.212**
36	**Guanine**	**Uracil 2**	**-8.537**	**-0.415**	**8.122**	**-0.15**	**0.202**	**0.352**	**23.074**

Figure 3 Shows the interaction of the Cytosine-Uracil 2 Lev in the area of the probability of average but with a 24.9838 ETC.

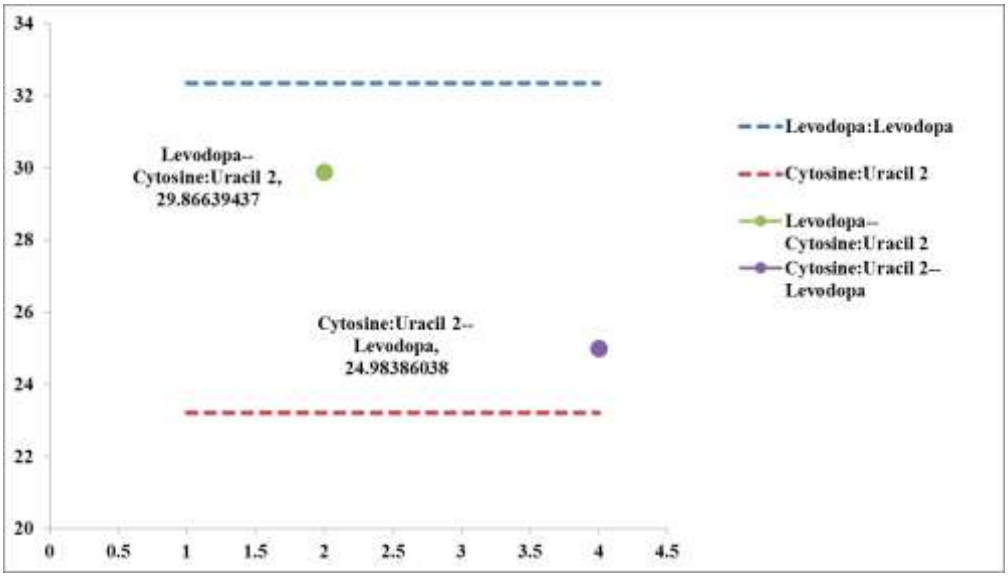

Figure 3. Cytosine and Uracil 2 quantum well.

Figure 4 Shows the interaction of Adenine-Uracil 2 with the Lev in the area of the probability of average but with a 26.0564 ETC.

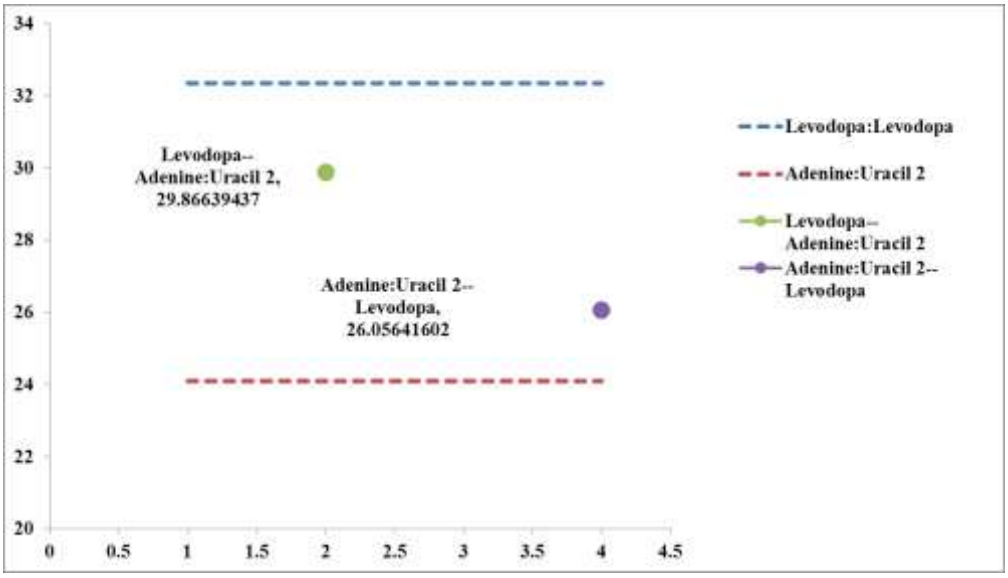

Figure 4. Adenine and Uracil 2 quantum well.

After show quantum wells of the bases with the Lev and the bands cross with the Lev, we can highlight that Guanine presents a more significant interaction with the drug, compared with crossbands.

CONCLUSIONS

The loss of an electron from the Guanine base can be the beginning of serious problems, since oxidation is causing an interaction with water, forming a variety of complex molecules. The most common are 8-oxo Guanine, which does not match Adenine (its regular partner) and Cytosine. Therefore, if the cell divides while carrying "8-oxo Guanine", the resulting daughter cells have a 50/50 chance of splitting with an Adenine where the Cytosine should be, thereby producing a mutation. This type of variation can end up in cancer, a genetic disease or cell death.

The study of the quantum deposits between substances and chemical compounds created by the human body gives us the possibility of studying and analyzing the interactions between them. In the particular case of the oxidation of Guanine by the Lev (Figure 1) we can conclude that said oxidation can be correlated with the side effects of said drug leading to future investigations.

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