ORIGINAL PAPER

THEORETICAL DOCKING STUDIES OF ANESTHETIC DRUGS INTERACTIONS USED IN EMERGENCY DEPARTMENTS

DANIELA CIOBANU[1], MIHAI BANICIOIU-COVEI[2], LUCIANA TEODORA ROTARU[3*], SILVIA NICA[4], ALINA PETRICA[5], MONICA PUTICIU[6]

Manuscript received: 27.02.2020; Accepted paper: 05.04.2020;
Published online: 30.06.2020

Abstract. *The use of an anesthetic cocktail is a common practice in the department of emergency and intensive care. This therapeutic practice must be carefully monitored and customized in patients with associated pathologies. Anesthesia should be administered with great caution in situations of metabolic acidosis. The present study aimed at the theoretical evaluation of the influence of metabolic acidosis on the combined administration of an opioid and a benzodiazepine anesthetic. The molecular docking technique was performed using the software Autodock4.2, which allows a simulation of the interaction of the protonated target in the range of ph 6.8-7.4 with the therapeutic ligand. The ligand / target interaction was visualized using Discovery Studio software, which creates 2D maps and shows the type of interaction between the two entities. From the obtained data it is observed that metabolic acidosis in the range 6.8-7.1 increases the strength of the ligand / target interaction, both in the case of the opioid / target and in the case of the benzodiazepine / target interactions. Taking into account the potentiated cumulative effect and the patient possible pathologies associated, it is necessary to adjust the doses of anesthetic in the case of metabolic acidosis, to avoid the occurrence of adverse reactions.*

Keywords: *benzodiazepines, anesthetic drugs, emergency departments, molecular docking, Autodock 4.2.*

1. INTRODUCTION

The use of sedative, hypnotic and anesthetic medications in emergency departments and mobile intensive care units is constant [1]. The pathological profiles of patients requiring different sequences of procedural analgesia going to general anesthesia are extremely varied, as well as their ages [2].

It is also important to consider that, in the pre-existing chronic conditions of the patients, many of the unknown, non-dialysis and untreated patients may involve not only the variability of the main effects, but also the adverse effects, the modification of the

[1] University of Medicine and Pharmacy, Faculty of Medicine, Internal Medicine Department, 200349 Craiova, Romania.
[2] University of Medicine and Pharmacy, Faculty of Medicine, Emergency Medicine & First Aid Department, 200349 Craiova, Romania.
[3] University of Medicine and Pharmacy, Faculty of Medicine, Department of Emergency's First Aid & Prehospital Care, 200349 Craiova, Romania.
**Corresponding author* e-mail: lucianarotaru@yahoo.com.
[4] University of Medicine and Pharmacy, Emergency Department, 050474 Bucharest, Romania.
[5] University of Medicine and Pharmacy, Emergency Department, 300041 Timisoara, Romania.
[6] Vasile Goldis Western University, Emergency Department, 310025 Arad, Romania.

pharmacodynamics and kinetics in the conditions of dishomeostasis, hypoxia, anemia, hypoproteinemia, hemodynamic impairment [3].

Last but not least, the associated renal orhepatic impairment impacts the degradation and elimination of drugs from the body, requiring drug's adaptation schemes and associations necessary for induction, maintenance and reversal of sedation and anesthesia [4].

For these reasons, the variety of classes and associations used in each of these situations must be large enough to provide solutions of the highest accuracy and safety for the patient, in the conditions of his own pathological context and at the same time appropriate to the requirements contained in the guidelines of good practice [5].

The special framework in which the medical action is carried out in the emergency medicine, the golden standards of time imposed, the fundamental principle, "run and play", the impossibility of obtaining information about the pre-existing conditions or the current medication from a critical patient, sometimes with unknown identity, without relatives to provide details, requires the use of prospective extensive theoretical and experimental studies to test drug compatibilities and variability of the effects of the main classes of anesthetics and hypnotics frequently used in emergencies.

It is extremely unlikely that retrospective observational studies will enroll a significant number of patients, with current pathological profiles and similar background, of comparable ages under the legal conditions for obtaining informed consent, a fundamental ethical requirement in these cases, so as to become. scientifically relevant [6].

This specific limitation for emergency work further reinforces the idea that clinical studies in emergency departments are not, at least at this time the magic solution of management optimization regarding analgesia in emergency structures [7].

As a wide range of clinical situations requires refining research into the safety and efficacy of using emergency anesthetic medication, further study models should be sought that lead to specifying behaviors of anesthetic drug associations in a multitude of clinical situations. Finally, they lead, regardless of the initiation mechanism, to certain categories of acid-base, hematological or electrolytic modifications [8]. If they cause the expected effects to change, then the benefit of knowing these types of interactions can help the emergency physician decide on dose adjustments, appropriate changes in re-administration intervals, use of antidotes, or even opting for drugs with higher stability in these situations and with variability. minimum efficiency and effectiveness in the given pathological context [9]. Patient safety is improved, the risks of overdoses are minimized, the expectation of certain events increases, and teams are aware of the monitoring and intervention on adverse or residual effects [10].

2. MATERIALS AND METHODS

The proposed study is a comparison of the sedation effect of anesthesia performed by diazepam, as the main benzodiazepine widely used in emergency situations such as hypnotic or anxiolytic, associated with different synthetic opioids, respectively fentanyl / sulfentanyl / remifentanyl, in metabolic acidosis

2.1. MATERIALS

Molecular modeling. All structures was optimized using Gaussian 09 software (Gauss View 16 interface) using the DFT / b3LYP / 6-31 G, 2dp method. Molecular quantum calculations of molecular geometries were performed using the MOPAC 2016 program. The output data contains physico-chemical information about selected molecules [11].

2.2. METHODS

In the present study we will follow the diazepam binding behavior associated with the 3 types of fentanyl in a row, under the conditions of the pH drop from 7.4 to 6.8. As a result, we will be able to assess the changes in stability and action under these conditions and we will also be able to draw conclusions regarding the antagonizing effects of any overdose (reversal of effects by flumazemil, respectively naloxone).

The principle of using AUTODOCK 4.2. Theoretical calculation of pharmacological activity

The target proteins were downloaded from the Protein Data Bank database (miu-opioid receptor (ID:5C1M) and benzodiazepinic receptor (ID: 6DW0)) and optimized with the ModRefiner software. For the molecular docking method of protein targets we added all the hydrogen atoms and select Gasteiger charge. In the grid stage we established the grid box of 126X126X126, at a distance of 1 angstrom from the center of the proteic structure. In the docking stage we will use Lamarckian Genetic Algorithm (LGA) with a total of 30 runs. LGA ensures acceleration of the search for most favorable docking orientations [12].

The images of the complex ligands / target will be viewed using PyMol software (Schrodinger) and Biovia Discovery Studio (Cambridge) [13].

3. RESULTS AND DISCUSSION

Total energy (kcal/mol) of the molecule is an important parameter, a more negative value representing a more stable molecule [14-18]. The difference in energy between HOMO and LUMO levels ($\Delta E = E_{LUMO} - E_{HOMO}$) is an important chemical molecular descriptor which explains the stability of the molecule, a low value indicating that the molecule is highly reactive. Another important parameter of the molecular quantum chemical calculations is the electric dipole moment, reflecting partial separation of electric charge in the molecule. The molecular descriptor is also a predictor of the chemical reactivity of the molecules, being a measure of the polarity of the molecular system [19,20].

The most stable drug molecule, taking into account the total energy of the molecule, is remifentanil (-105954.76 kcal / mol). This descriptor correlates very well with the high binding energy of the ligand / target interaction, remifentanil, binding most strongly to the opioid receptor. The most polar molecule is sufentanyl, having the dipole moment of 4.654 debye, which has a strong interaction with the protein target. The most reactive molecule (ΔE) is fentanyl and sufentanyl, the quantum-molecular descriptors correlating very well with the ligand / target binding energy (Tables 1-2, Fig. 1).

Table 1. Molecular properties of ligands.

Drugs	Total energy [kcal/mol]	Dipole moment [Debye]	Homo	Lumo	$\Delta E = E_{LUMO} - E_{HOMO}$
Fentanyl	-84324.49	3.92	-8.775188	-0.0830981	8.6920899
Remifentanyl	-105954.76	3.716	-9.20612	-0.2445978	8.9615222
Sufentanyl	-96082.58	4.654	-8.750517	-0.3347542	8.4157628
Diazepam	-69868.17969	3.356	-9.197231	-0.7343836	8.4628474

Table 2. Energy of ligand-target binding (kcal/mol).

pH	Fentanyl /Target	Remifentanyl/ Target	Sufentanyl /Target	Diazepam /Target
7.4	-6.45	-3.96	-4.19	-6.12
7.3	-4.81	-4.04	-4.53	-5.60
7.2	-5.77	-3.82	-4.17	-5.81
7.1	-5.49	-3.61	-3.78	-5.78
7.0	-4.87	-4.05	-4.19	-5.39
6.9	-5.64	-3.52	-4.56	-5.69
6.8	-4.62	-3.81	-3.99	-5.99

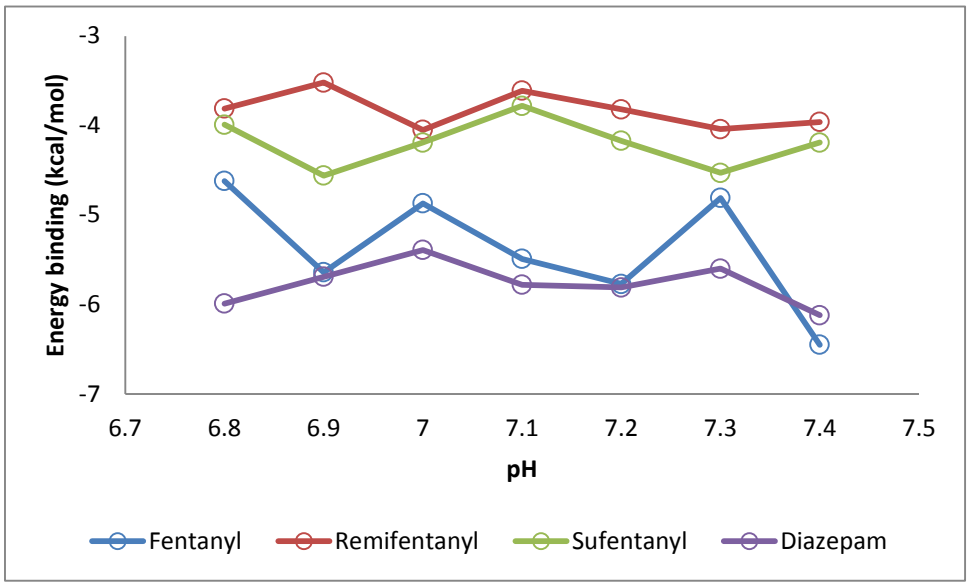

Figure 1. Graphical representation of the ligand / target binding energy variation, depending on blood pH.

Autodock is an automatic procedure for predicting the interaction between two or more molecules. It aims to achieve the global minimum of the interaction energy between two substances, exploring all degrees of freedom of the system. Autodock combines two methods to achieve this goal: fast energy scanning and efficient space evaluation. The conformations are then evaluated using semi-empirical force fields. The force field includes six pairs of evaluations and an estimation of the conformational entropy after the dock:

$$\Delta G = (V_{bound}^{L-L} - V_{unbound}^{L-L}) + (V_{bound}^{T-T} - V_{unbound}^{T-T}) + (V_{bound}^{T-L} - V_{unbound}^{T-L} + \Delta S_{conf})$$

where L refers to the ligand and T to the target structure (protein, other molecule with which the ligand interacts, etc.) in a molecular docking calculation. Each pair of energy terms includes evaluation of dispersion / repulsion, hydrogen bonds, electrostatic interaction and desolvation:

$$V = W_{vdw} \sum_{i,j} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{16}} \right) + W_{hbond} \sum_{i,j} \left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}} \right) + W_{elec} \sum_{i,j} \frac{q_i q_j}{[\![\epsilon(r)]\!]_{ij} r_{ij}} + W_{sol} \sum_{i,j} (S_i V_j - S_j V_i)\, e^{\left(-\frac{r_{ij}^2}{2\sigma^2}\right)}$$

The free binding energy that we will estimate is calculated as ΔG ~ binding ~ = ΔH - TΔS, where ΔH represents the enthalpy and TΔS the entropic contribution (only the negative value of ΔG is energetically favorable and the process is spontaneous.

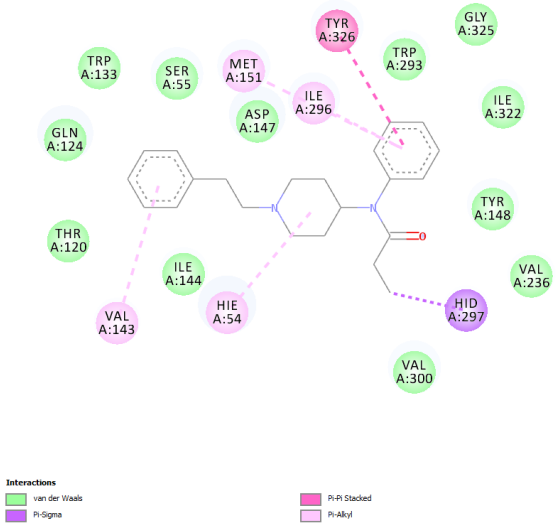

Figure 2. 2D map interaction between fentanyl and miu-opioid receptor.

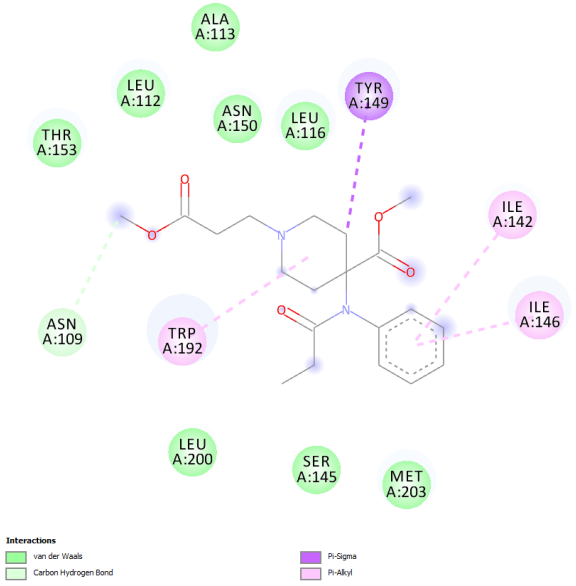

Figure 3. 2D map interaction between remifentanyl and miu-opioid receptor.

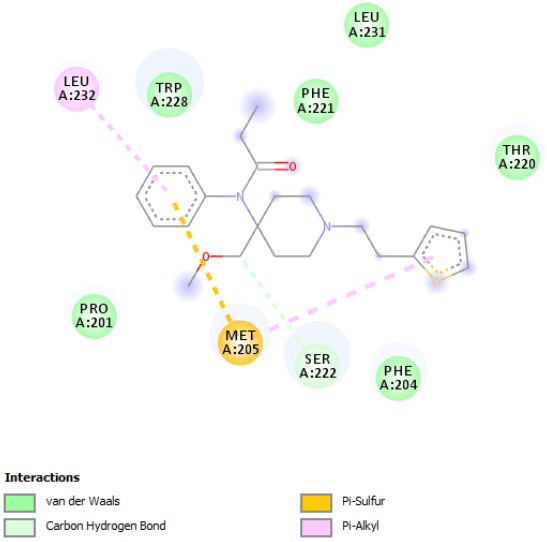

Figure 4. 2D map interaction between sufentanyl and miu-opioid receptor.

High binding energy means higher stability, so we can see that acidosis promotes stabilization of the opioid receptor binding, almost equal to that of the benzodiazepine receptor, so both principles of diazanalgesia. This is most pronounced in the field of significant and very severe acidosis (6.8-7.1), so the pH range in which we usually direct the patient's management towards the correction of acidosis. The most pronounced situation occurs in the case of fentanyl, where acidosis favors its therapeutic effect.

Molecular docking studies do not allow us to evaluate the binding in 3 (opioid-benzodiazepine-receptor), to see if it has the same dynamics of molecular energies. This means that one of the related consequences of the alkalinization could be to decrease the stability of the analgesic medication binding in these classes on the recipients. If the alkalization stopped at pH = 7.1, then it can obtain benefits on analgesia without further increasing the doses or shortening the intervals of administering analgesia under the conditions of maintaining the dissociation course of oxyhemoglobin in the sense of superior yielding of the officer to the tissues (optimal cellular metabolism) and reasonable control of the other undesirable effects of medium acidosis (e.g., hyperkalemia).

4. CONCLUSION

Caution is advised when associating painkillers, particularly in patients with associated pathologies, where the pharmacokinetics of a drug can be substantially altered. In the theoretical study it is observed that metabolic acidosis influences the binding and stability of opioid and benzodiazepine sedatives, increasing the energy related to the protein target.

Acknowledgements: *The authors received funding for this manuscript from the project entitled "The correlation of the theoretical studies of docking of the interactions of the medication used in the emergency departments, with their physico-chemical molecular descriptors", contract no. 467/28.08.2019/University of Medicine and Pharmacy Craiova.*

REFERENCES

[1] Angelini, G., Ketzler, J.T., Coursin, D.B., *Crit. Care Clin.*, **17**(4), 863, 2001.
[2] Tobias, J.D., Leder, M., *Saudi J. Anaesth.*, **5**(4), 395, 2011.
[3] Brockmöller, J., Köchling, J., Weber, W., Looby, M., Roots, I., Neumayer, H.H., *Br. J. Clin. Pharmacol.*, **34**(6), 499, 1992.
[4] Dinis-Oliveira, R.J., *Biomed Res. Int.*, **2018**, 6852857, 2018.
[5] Hughes, R.G. (Ed.), *Patient Safety and Quality: An Evidence-Based Handbook for Nurses*, Rockville, Agency for Healthcare Research and Quality, 89, 2008.
[6] Wertheimer, A., *J. Law Biosci*., **1(**2), 137, 2014.
[7] Smith, J.E., Rockett, M. et al., *BMJ*, **350**, h3147, 2015.
[8] Cohen, S.P., Bhatia, A. et al., *Reg. Anesth. Pain Med.*, **43**(5), 521, 2018.
[9] Buckley, N.A., Dawson, A.H. et al., *Br. J. Clin. Pharmacol.*, **81**(3), 402, 2016.
[10] https://www.who.int/patientsafety/information_centre/Summary_evidence_on_patient_safety.pdf
[11] Istratoaie, O., Rotaru, L.T. et al., *Rev. Chimie (Bucharest)*, **69**(2), 459, 2018.
[12] Rotaru, L.T., Varut, R.M. et al., *Pharm. Chem. J.*, **53**(10), 891, 2020.
[13] Florescu, C., Rotaru, L.T. et al., *Rev. Chimie (Bucharest)*, **69**(4), 837, 2018.
[14] Rotaru, L.T., Nedelea, P. et al., *Rev. Chimie (Bucharest)*, **70**(3), 814, 2019.
[15] Radulescu, C, et al, *Dyes and Pigments*, **76**(2), 366, 2008
[16] Hossu, A.M., Maria, M.F., Radulescu, C, Ilie, M., Magearu, V., *Romanian Biotechnological Letters*, **14**(5), 4615, 2009.
[17] Radulescu, C, Hossu, A.M., Ionita, I., *Dyes and Pigments*, **65**(2), 175, 2005.
[18] Radulescu C, Hossu A.M., Ionita I., *Dyes and Pigments*, **71**(2), 123, 2006.
[19] Varut, R.M., Rotaru, L.T., Varut, M.C., *Rev. Chimie (Bucharest)*, **68**(8), 1776, 2017.
[20] Florescu, C., Rotaru, L.T. et al., *J. Sci. Arts*, **1**(50), 163, 2020.