BRAIN. Broad Research in Artificial Intelligence and Neuroscience,
ISSN 2067-3957, Volume 1, October 2010,
Special Issue on Advances in Applied Sciences,
Eds Barna Iantovics, Marius Măruşteri, Rodica-M. Ion, Roumen Kountchev

MATHEMATICAL MODEL FOR TSPP DRUG-DELIVERY IN NANOMEDICINE

Rodica Mariana Ion, Adriana Filip,
Simona Clichici, Adriana Muresan

Abstract. Helping improve humanity is one of the promises of nanotechnology and nanomedicine. This paper will highlight some of the research findings in the nanomedicine area by creating a pharmacokinetic model of 5,10,15,20-tetra-(4-sulfonatophenyl)porphyrin (TSPP) used as sensitizer in photodynamic therapy.

Keywords: *nanomedicine, photodynamic therapy, TSPP, mathematical model, laser*

2000 Mathematics Subject Classifcation: 05C65, 62H30

1. Introduction

Photodynamic therapy (PDT) is a promising method for treating malignant tumors combining the action of a special dye - photosensitizer (PS), oxygen, and radiation on biological tissues. Treatment consists of several sequential stages: injection of the PS (intravenous or local), leaving it for up to $24h$, and irradiation for 15-20 min. In general, any coherent or incoherent light source with a proper spectrum can be used for therapy. The most widely used devices are continuous nonionizing lasers with a power density of up to 250 W/cm^2. The wavelength is, as a rule, within the limits of the "therapeutic window" of 600-1200 nm. In this case, the light penetrates deeper into the tissue compared to the remaining part of the visible spectrum. PDT is based on the photodynamic action (PA) affecting living structures, which was discovered at the end of the 19th to the beginning of the 20th centuries. At the molecular level destruction of cancer cells by PDT occurs through the formation of singlet oxygen (reaction of the second kind) - a very active oxidizer.

This paper will highlight some of the research findings in the nanomedicine area and a pharmacokinetic model of TSPP used as sensitizer in photodynamic therapy.

2. Materials and methods

5,10,15,20-tetra-(4-sulfonatophenyl)porphyrin (TSPP), Figure 1, was synthesized and purified in the laboratory after the literature methods [2]. It was solubilized in water at 10^{-4} M concentration. All the stock solutions were stored at 4^oC in the dark and used in the 14 days interval.

3. Results and discussion

3.1 PDT protocol

50 male Wistar rats, weighting 200±20g were used for this study. They were anesthetized (90 mg kg^{-1} ketamine, 10 mg kg^{-1} xylazine, i.p) and grafted on the shaved right thigh with small fragments of Walker tumor. Ten rats with Walker carcinosarcoma represented the control group; the others underwent PDT with TSPP. Once the tumor reached 1 cm^3 it was treated with PDT.

3.2. TSPP concentration in tumor homogenate

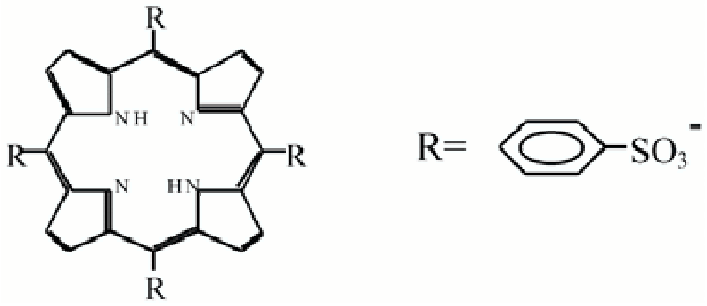


Figure 1: The chemical structure of TSPP

The tumor was homogenised with a solution containing 80 percent sucrose 0,25 M and 20 percent NaOH 0,1 N. In the supernatant obtained after centrifugation TSPP was determined fluorimetrically using a Perkin-Elmer spectrofluorimeter (excitation 412 nm and emission 643nm), using a calibrating curve.

3.3. A Pharmacokinetic Model of TSPP

TSPP is intravenously injected at 2 mg/kg over a period of five minutes, and it attains a high saturation level from 24 to 36 hours

$$\frac{dC_1}{dt} = \frac{k_0}{v} - kC_1 \tag{1}$$

after injection. The 12 hour period between the 24 th and 36th hour is called the treatment window, and at some time within this period a physician focuses a 630nm light on the targeted area. Different tissues absorb and expel substances from the blood at different rates, and hence the concentration of TSPP varies from tissue to tissue. Results show that maximum tumor TSPP concentration levels were achieved at approximately 24 hours after administration. We model C_1 with the following first order, linear differential equation:

$$C_1 = \frac{k_0}{v_k}[1 - e^{kt}] \tag{2}$$

Where:

- C_1 is the plasma concentration during injection;
- k is the rate of elimination;

- $k0$ is the rate of infusion;
- V is the volume of distribution.

Where C_A is the plasma concentration after infusion.

So, assuming that the infusion ends at time $\gamma = 0.083\ h^{-1}$, or 5 minutes, we have that $dC_A/dt = -kC_A$, from which we conclude that

$$C_A = C_1(\gamma)c^{kt} = k_0[1 - e^{kt}]e^{-k(t-\gamma)} \tag{3}$$

The infusion rate k_0 is based on the fact that the drug is injected at 2mg/kg over a period of 5 minutes. Under such conditions, we have that

0.4 mg/mouse of TSPP are delivered in 5 minutes, and thus k_0 is 4.8 mg/h. The rate of elimination, k, is calculated by solving:

$$t_{\frac{1}{2}} = \frac{ln(2)}{k} \tag{4}$$

where the half-life for TSPP is $t_{1/2}$= 336 hours. Hence, k = 0.00206 h^{-1}.

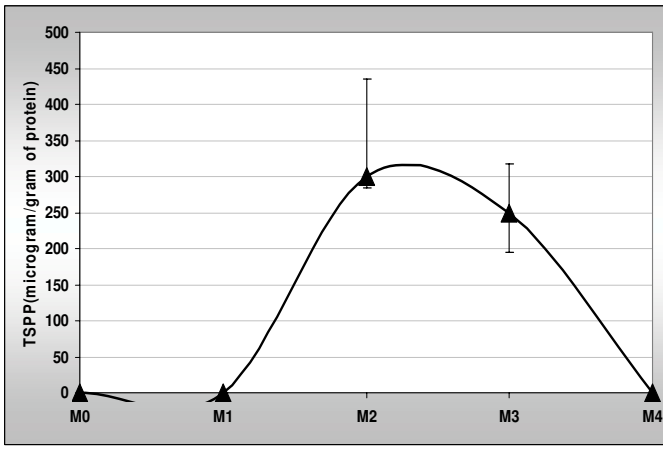
TSPP nanosystem has found the correct diseased cell of interest. Then it must pass the cell membrane and acts as apoptotic body for cell destruction[4,5]. Since the nanosystem is only about one millionth the volume of a human cell, for it to have therapeutic efficacy with its contained package, it must deliver that drug to the appropriate site within the living cell. All of these problems remain major obstacles to successful drug delivery with a minimum of deleterious side effects to the patient[6].

4. Conclusions

This paper will highlight some of the research findings in the nanomedicine area by creating a mathematical model for pharmacokinetic activity of TSPP used as sensitizer in photodynamic therapy. Results show that maximum tumor TSPP concentration levels were achieved at approximately 24 hours after administration.

References

[1] R.M.Ion, R. C. Fierascu, and I. Dumitriu, Photonic metallic nanostructures in photodynamic therapy, Advanced Topics in Optoelectronics, Microelectronics, and Nanotechnologies IV, Proceedings of the SPIE, 7297, pp. 72970H-729723 (2009).



M_0=controls
M_1=5 hours
M_2=24 hours
M_3=48 hours
M_4=arbitrary point over 48 hours.
Points represent absolute median TSPP concentration levels.

Figure 2: Dynamic curve of TSPP tissue concentration within the tumor

[2] RM Ion, New trends in photodynamic therapy-review, in "Aspects of Photodynamic medicine" Biomedicine Engineering Acta, 3/2008, pp.123-159, H.Podbielska, A.Sieron, W.Strek, (Eds.), Wroclaw, Poland, 2008;

[3] R.M.Ion, L. Maresca, D. Migoni, F.P. Fanizzi, Porphyrin - Cis-Platin drug system for HeLa cells photodynamic, International Journal On Advances in Life Sciences, 1(1), 2009, pp.36-45.

[4] K. K. Jain, Nanomedicine: Application of nanobiotechnology in medical practice. Medical Principles and Practice, 7(2): 2008. p. 89-101.

[5] S. B. Brown, E. A. Brown and I. Walker, The present and future role of photodynamic therapy in cancer treatment. Lancet Oncology, 5(8): 2004. p.497-508.

[6] M.M.Seale, D. Zemlyanov, C.L.Cooper, E.Haglund, T.W.Prow, L.M.Reece, J.F.Leary, Multifunctional nanoparticles for drug/gene delivery in nanomedicine Nanoscale Imaging, Spectroscopy, Sensing, and Actuation for Biomedical Applications IV. Edited by Cartwright, Alexander N.; Nicolau, Dan V.. Proceedings of the SPIE, Volume 6447, pp. 64470E (2007).

Rodica Mariana Ion
National Research and Development Institute of Chemistry and Petrochemistry - ICECHIM Bucharest, Romania
Valahia University, Targoviste, Romania
e-mail:*rodica_ion2000@yahoo.co.uk*

Adriana Filip, Simona Clichici, Adriana Muresan
Physiology Department
University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca Romania