

# PHOTODYNAMIC THERAPY WITH A NEW PHOTSENSITIZER PHOTODITHAZINE - A DERIVATIVE OF CHLORIN E6

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## Abstract

Efficacy of PDT with new photosensitizer chlorin e6 derivative Photodithazine (Photochlorin) has been tested. Out of 72 patients complete tumor resorption was achieved in 44 cases, partial - in 28, including 15 patients treated for palliation.

Rapid elimination of photodithazine from the organism solves the problem of skin phototoxicity. This property of photodithazine together with its high tumor to normal ratio makes it a promising photosensitizer for PDT, taking into consideration the availability of inexpensive portable diode lasers with proper wavelength.

**Keywords:** photodynamic therapy, Photodithazine, Photochlorin, phototoxicity, diode lasers.

## Introduction

Photodynamic therapy (PDT) a new treatment modality for malignant tumors, premalignant lesions and some non-tumoral diseases. In the State Research Center for Laser Medicine clinical testing of PDT was started in 1992<sup>1</sup>. Wide experience of photosensitizers' application has been stored. A certain number PDT schemes for a variety of tumor locations had been developed and tested<sup>2</sup>. However, long-term skin phototoxicity, caused by hematoporphyrin derivative and sulphonated aluminum phthalocyanine, remains a serious drawback of this technique<sup>3,4,5</sup>.

In past few years several new photosensitizers with short period of phototoxicity have been synthesized. One of them – Photodithazine (Photochlorin) – is a new drug of a chlorin e6 group. It is a well water-soluble glucamine derivative of chlorin e6. Photodithazine is produced by original technology devised in the Institute of Biomedical Chemistry of Russian Academy of Medical Sciences under the guidance of professor G.V.Ponomariov<sup>6,7</sup>. Photodithazine has absorption maximum at 662 nm. It possesses high photodynamic activity, high coefficient of contrast (tumor to normal ratio = 10:1), rapid clearance (in 1 day after injection 6% of administered dose remains in the organism, in 2 days after injection - 2%). New diode lasers with wavelength 662 nm are optional sources of light for PDT with this preparation. Pilot study of tolerance and efficacy of PDT with Photodithazine has been performed.

## 1. Materials and methods

Tolerance of PDT with Photodithazine was assessed in 72 patients with malignant tumors of skin, oral cavity, larynx, lung, esophagus, stomach, bladder and vulva. Male to female ratio was 42:30 within age range from 35 to 88 years. Photodithazine was used intravenously as a photosensitizer in dosage 0,3 - 1,5 mg/kg. Out of 72 patients single-course PDT was performed in 54 cases, 2 PDT courses were performed in 11 cases; 7 patients underwent 3 - 5 PDT courses. Total of 104 PDT courses were performed in 72 patients: 101 with intravenous photodithazine administration and 3 with topical administration (table 1).

**Table 1.**

### Number of PDT courses with Photodithazine

	Number of patients	Number of PDT courses
1 course	54	54

2 courses	11	22
3-5 courses	7	28
TOTAL	72	104

Laser irradiation was performed with solid state laser: "Poljus-2" with output power 2 W,  $\lambda=670$  nm (produced by NPO "Poljus", Russia); and diode lasers: "Milon" with output power 2,5 W,  $\lambda=662$  nm (produced by "Milon & Sigm Plus" JSC, Russia) and «Ceralas» with output power 1,0 W,  $\lambda=662$  nm (produced by "CeramOptec" AG, Germany).

Preliminary testing of PDT efficacy with Photodithazine was performed according to 2 protocols:

1. PDT as a curative procedure for primary and recurrent basal-cell skin cancer in 41 patient (21 male, 20 female, age from 35 to 88 years). Primary tumors were in 20 cases, 21 patient has been treated for recurrent skin cancer after conventional treatment. The patients had total of 140 tumoral nodes. Types of tumor growth were superficial, ulcerated, infiltrating and mixed. Tumor thickness varied from 0,2 to 0,7 cm.

Photodithazine was used in dosage from 0,3 to 1,1 mg/kg. Superficial laser irradiation was performed 60 - 90 minutes after drug injection, power density was 0,2-1,0 W/cm<sup>2</sup>, energy density was 280-600 J/cm<sup>2</sup>. Duration of treatment procedure (from drug injection till the end of laser irradiation) did not exceed 3 hours.

2. Palliative PDT for recanalization of hollow organs was applied to 12 patients with squamous cell cancer of middle and lower part of the esophagus, gastric adenocarcinoma spreading to lower part of esophagus and squamous cell IV stage cancer of trachea and bronchi. The length of stenotic section of esophagus made up from 1,5 to 12 cm. Lung tumors were complicated by atelectasis and hypoventilation. In all of the patients radical surgical operation could not be performed due to metastases in lungs and/or liver and multiple non-resectable metastases in mediastinal lymphatic nodes. Earlier 4 of the patients with esophageal cancer underwent Nd:YAG laser recanalization, including 2, who took 10 and 12 procedures with partial short-term effect.

Average dose of Photodithazine was 0,8 mg/kg. In endoscopic PDT of inner organ energy density varied from 75 to 275 J/cm<sup>2</sup>. In 9 of 12 cases PDT for recanalization was performed repeatedly with interval of 7-14 days for "step by step recanalization" of the hollow organs. Maximal duration of treatment procedure (from drug injection till the end of laser irradiation) was 3 hours, maximal duration of endoscopy did not exceed 60 minutes.

## 2. Results And Discussion

Among 72 patients treated with Photodithazine-based PDT complete tumor resorption was achieved in 44 cases, partial - in 28 (table 2), including 15 patients treated for palliation (12 for recanalization of esophagus, cardia, trachea and bronchi and 3 for advanced tumors of oro- and nasopharynx). There was no significant difference in the results of solid-state and diode lasers application.

**Table 2.**

### Results of clinical PDT with Photodithazine

Tumor location	Number of patients	Result of PDT	
		CR	PR
Skin cancer	41	34	7
Skin melanoma	2	1	1
Cancer of oral mucosa, tongue, lip	6	3	3
Larynx cancer	5	4	1

Lung cancer	3	0	3*
Cancer of esophagus	8	0	8*
Cancer of stomach	2	1	1*
Other	5	1	4
Total	72 (100%)	44 (61%)	28 (39%)

CR - complete tumor resorption, PR - partial tumor resorption  
\* - palliative PDT for recanalization

Skin phototoxicity of Photodithazine was assessed in all cases. After injection of Photodithazine all patients were prescribed to remain in low-illumination rooms for 3 days. Three of the patients were volunteered to participate in a simple phototoxicity test: they exposed their hands to direct sunlight as soon as 24 and 48 hours after drug injection (the doses of Photodithazine: 0,6, 0,8 and 1,0 mg/kg of body weight). There were no signs of high skin photosensitivity in these patients, such as hyperemia or edema. However, the patients were not allowed to come outdoors to direct sunlight earlier than 3 days after the procedure. There were no complications, caused by skin phototoxicity.

Pilot study of photodithazine-based PDT efficacy in 41 patients with primary and recurrent cancer of the skin showed 100 % therapeutic efficacy with 83% rate of complete tumor resorption. Photodithazine proved to be effective photosensitizer for ulcerated and infiltrating tumors, as well as for superficial skin cancer, providing adequate necrosis. Minimal effective dose for superficial cancer was 0,3 mg/kg at energy density 400 J/cm<sup>2</sup>. In infiltrating tumors (4 - 6 mm of thickness) complete resorption was achieved at 0,7 mg/kg and 400 J/cm<sup>2</sup>. However, future research is required to estimate treatment protocols for various morphological and clinical types of primary and recurrent skin cancer.

Among the patients, who received palliative PDT for recanalization of hollow organ therapeutic effect took place in all cases. Out of 9 patients with esophageal obstruction in 8 marked effect of recanalization was achieved with restoration of normal food passage. Three of them during the first month after PDT gained weight by 15-20%. The effect of recanalization lasted from 3 to 7 months. In 1 patient each of 5 PDT courses led only to short-term restoration of food passage (and passage of contrast mass in X-ray control); in this case gastrostomy has been performed.

In all patients with cancer of trachea and bronchi adequate recanalization was achieved with elimination of short wind and stridulous breathing from 3 – 4 day after PDT. Control bronchoscopy after first PDT course revealed partial (50%) restoration of bronchial aperture, after 2 and 3 PDT courses – complete restoration of aperture with X-ray proven elimination of lung hypoventilation and atelectasis and restoration of lung tissue transparency.

Complications were met in 20 of 101 PDT courses with intravenous Photodithazine administration: chills - in 18 cases; vertigo, weakness in 1 (in a 74-year old female patient); in 1 case herpes labialis appeared on the 3 day after PDT. In most cases chills were light, began in 20 - 75 minutes after drug injection and lasted from 5 to 30 minutes; only in 3 cases chills were accompanied with fever up to 38°C, nausea and vomiting. Topical application of photodithazine did not cause any complications.

### 3. Conclusion

Clinical application of Photodithazine-based PDT was well-tolerated by the patients, including those with accompanying diseases of age. Rapid uptake of Photodithazine by tumoral tissue made it possible to complete treatment procedure within 2 - 3 hours. PDT with intravenous administration of Photodithazine induced a very short period of skin phototoxicity - less than 3 days.

The use of PDT with Photodithazine in 72 patients with various malignant tumors led to 100% therapeutic effect, including complete tumor resorption in 61% of cases.

Photodithazine-based PDT of skin cancer showed 100% therapeutic efficacy with 83% rate or complete tumor resorption. PDT with Photodithazine was effective in tumoral obturation of hollow organs: recanalization was adequate, effect of recanalization lasted from 3 to 7 months.

New convenient and inexpensive diode therapeutic lasers with wavelength 662 nm were successfully used as sources of light for PDT with Photodithazine.

Thus, it can be stated that Photodithazine (Photochlorin) is a new effective photosensitizer for PDT of malignant tumors. Fast elimination of Photodithazine from the organism solves the problem of long-term skin phototoxicity, which is caused by the majority of photosensitizers used in clinical practice. However, future clinical research is required to develop PDT protocols for various types of cancer and non-tumoral diseases.

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