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Evaluation of chlorin p6 for photodynamic treatment of squamous cell carcinoma in the hamster cheek pouch model

Alok Dube *, Sulbha Sharma, Pradeep Kumar Gupta

Biomedical Applications Section, Centre for Advanced Technology, Rajendra Nagar, PO CAT, Indore, MP 452 013, India

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Summary We studied pharmacokinetics and tumor response to photodynamic therapy (PDT) using chlorin p6 (CP6) in hamster cheek pouch model. CP6 was administered either intraperitoneally (IP) at a dose of 1.5 mg/kg body weight or applied topically at 1.0 mg/kg body weight and its accumulation in tumor, normal mucosa, and abdominal skin was measured by optical fiber-based fluorescence spectroscopy. Photodynamic therapy was performed by superficial illumination of tumor with 660 nm (±25 nm) light at a fluence rate of 100 J/cm^2 and tumor response to PDT was analyzed by histological examination. CP6 accumulation was higher in tumors as compared to adjoining tissue and normal mucosa at 4–6 h after its IP administration. For relatively large tumors (size >8 mm) topical application was observed to be more effective than IP. The level of CP6 in tumor, surrounding tissue, normal mucosa and skin was seen to decrease rapidly within 24 h after its administration and was undetectable at longer time (>72 h) intervals. PDT of small tumors at 4 h after IP injection of CP6 resulted in complete tumor necrosis. Whereas, PDT of large tumors receiving CP6 topically caused necrosis in 300–800 μm superficial region of the tumor. In one animal kept for follow up in each treatment group, it was observed that small tumors disappeared completely leaving scar tissue, while large tumor had significant reduction in tumor size. The use of CP6 for PDT of oral cancer is suggested.
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Introduction

Oral cancer is one of the 10 most frequently occurring cancers worldwide and its incidence in India ranges from 50% to 70% among all cancer patients

* Corresponding author. Tel.: +91 731 2488487; fax: +91 731 2488430.
E-mail address: okdube@cat.ernet.in (A. Dube).

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compared to 2—3% in the UK and USA.[1] Oral cancer is treated by surgery, radiation and chemotherapy or a combination of these methods. These modalities however result in adverse systemic and cytotoxic effects and development of resistance to therapy. Recently, treatment of cancer by photodynamic therapy (PDT) has gained considerable interest.[2] PDT relies on selective accumulation of a photosensitive drug (photosensitizer) in tumor tissue, which on illumination with light of appropriate wavelength generates reactive oxygen species destroying the tumor tissue. The major advantage of PDT over the available therapies is high selectivity of tumor destruction and minimum damage to normal tissues. PDT using porfimer sodium (hematoporphyrin derivatives) as a photosensitizer has been approved in more than 40 countries for treatment of various types of cancer.[2] The use of PDT for treatment of head and neck cancer is however limited to some clinical trials wherein photosensitizers such as porfimer sodium, aminolevulinic acid and temophrin (*meta*-tetrahydroxyphenylchlorin) have been used, but so far, only temophrin is approved for this indication in some European countries.[2] Both porfimer sodium and temophrin however give rise to prolonged skin photosensitivity and the time delay between drug administration and light treatment is typically 96 h during which the patient must be protected from light.[2]

We have shown earlier that chlorin p6 (CP6), a chlorophyll-*a* derivative exerts a strong phototoxic effect on human cancer cells of breast and colon adenocarcinoma in vitro.[3] The absorption of CP6 in the wavelength region (600—800 nm) of therapeutic interest is high and because of presence of carboxylic groups in the molecule it is soluble in aqueous environment allowing easy drug delivery. Further, our previous studies show that CP6 exists as anion at physiological pH but protonation of carboxylic groups at low pH (<6.0) leads to increase in its hydrophobicity, a property that is believed to be one of the determinants of tumor selectivity.[4] In this paper, we have examined accumulation of CP6 in hamster cheek pouch tumors and subsequent PDT following its systemic or topical application. We show that the clearance of CP6 from body is relatively fast and PDT performed at 4—6 h after its application results in tumor necrosis.

Materials and methods

Animal model

Male Syrian Golden hamsters (*Mesocricetus auratus*, retired breeders 150—200 g) were used for experiments. The hamsters were housed in plastic cages under controlled environmental conditions with a 12 h light/dark cycle, and had free access to both water and standard food. A 0.5% solution of 7,12-dimethyl-benz(*a*)anthracene (DMBA, Sigma) in mineral oil was applied topically in left cheek pouch mucosa three times a week for 14 weeks to induce tumors.[5]

Photosensitizer treatment

CP6 was synthesized as described in Ref. 6. The photosensitizer was dissolved in phosphate buffered saline (PBS) pH 7.4. The photosensitizer was administered either systemically through a intraperitoneal injection at dose of 1.5 mg/kg body weight or applied topically by putting 200 μl solution of CP6 (1.0 mg/kg body weight) in the right cheek pouch. The animals were kept in diffuse light throughout the experiments to avoid any unwanted phototoxicity.

Fluorescence measurements

Photosensitizer accumulation in tumor, surrounding tissue, normal cheek pouch and skin of abdomen was monitored by spectrofluorometer (fluorolog-2, Spex, USA) equipped with a fiber optic probe. The spectrophotometer was set at ~400 nm excitation and fluorescence emission was monitored from 550 to 750 nm. The animals were kept under ketaminium hydrochloride anesthesia both during fluorescence measurements and photodynamic treatment.

Photodynamic treatment

At 4—5 h after CP6 administration, the buccal cheek pouch of the animal was everted and the tumors were exposed to light of 662 nm (±25 nm) from a light source Lumacare LC122-A (Ci-Tec, USA) using a fiber optic probe (diameter 1 cm). The power at the fiber optic tip was measured with a power meter (Ophir). The fluence was measured to be 0.19 W/cm^2 and delivered at a fluence rate of ~100 J/cm^2.

Histological examination

The animals were sacrificed by excessive ether inhalation; tissues were excised and placed in 10% formalin for routine histological preparation. The tissues sections were stained with hematoxylin and eosin (HE) and examined under a microscope (Axiovert 135, Zeiss, Germany). The images were

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