PHOTODYNAMIC THERAPY OF MALIGNANCIES USING HEMATOPORPHYRIN AND ITS DERIVATIVES : PHARMACOKINETICS AND THERAPEUTIC RESPONSE

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ABSTRACT

The aim of this study is to investigate the use of the simpler porphyrin, Hematoporphyrin (Hp) as a possible photosensitizer for the treatment of malignancies using the alternative Immediate photodynamic therapy (PDT) procedure. In Immediate PDT, photoradiation was administered 5 mins after the administration of drugs as opposed to the conventional delayed (24-48 hrs) treatment procedure. The serum and tissues pharmacokinetics of Hp with comparison to its derivatives, HpD and their therapeutic efficacies have been investigated. A five compartmental model was developed to quantify the analysis of serum and tissue distribution of the drugs with liver as the main store. The pharmacokinetics showed that Hp has a 4 times smaller half-life in serum than HpD. The oligomeric component of HpD has an excretion rate of about 90 times slower from the liver than the monomeric component of Hp from the serum and tissues. The murine tumour response indicated that Hp needed a 3.5 times more drug-light dose product for a similar therapeutic effect with comparison to HpD. Nevertheless one could still minimise skin photosensitivity because of its rapid excretion. A study on the histomorphological changes in both the drugs indicated comparable tumour cell, surrounding normal tissue and vasculature necrosis. A comparison of the skin reaction and the duration of skin photosensitivity were also investigated. The results showed that Hp exhibited negligible skin photosensitivity compared to HpD. In order to develop a local Hp-Immediate PDT protocol for clinical trials in the near future, the conventional delayed PDT procedure with HpD was employed on three patients for the necessity of groundwork. The basis of this includes the preparation and characterization of HpD and the development of two alternative halogen light sources. Studies carried out using the halogen light sources

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showed that they were reliable, cost-effective and their manoeuvrability in the clinical environment made them suitable as an alternative to the laser for the surface irradiation of tumours. The clinical results showed significant responses in palliation control on advanced external lesions.

ABSTRAK

Keberkesanan Hematoporphyrin (Hp) sebagai bahan fotopemeka yang berpotensi untuk merawat barah dengan menggunakan prosedur *terapi fotodinamik (PDT) serta-merta* telah dikaji. *PDT serta-merta* melibatkan penyinaran cahaya dilakukan 5 minit selepas suntikan bahan fotopemeka, manakala prosedur lama melibatkan penyinaran cahaya dilakukan 24-48 jam selepas suntikan bahan. Perbandingan telah dilakukan di antara famakokinetik serum dan tisu-tisu Hematoporphyrin (Hp) dengan terbitannya iaitu HpD. Kecekapan terapeutik Hp dan HpD juga dikaji. Model lima ruangan telah dibina untuk menganalisa data serum dan tisu-tisu secara kuantitatif. Famakokinetik menunjukkan Hp mempunyai separuh hayat dalam serum 4 kali kurang daripada HpD. Komponen oligomerik HpD mempunyai kadar kumuhan dari hati sebanyak 90 kali kurang daripada komponen monomerik Hp. Hp memerlukan 3.5 kali lebih produk dos bahan-cahaya untuk menghasilkan tindakbalas yang menyerupai HpD pada barah tikus. Walaubagaimanapun, kesan fotosensitif Hp tetap dapat diminimakan disebabkan oleh kumuhan segeranya dari serum dan tisu-tisu. Histomorfologi menunjukkan nekrosis sel-sel barah, tisu-tisu normal berdekatan dengan sel-sel barah dan salur darah adalah sama apabila kedua-dua bahan digunakan. Perbandingan reaksi kulit dan tempoh fotosensitif kulit juga telah dilakukan. Hp menghasilkan fotosensitif kulit yang amat minima berbanding dengan HpD. Untuk mancapai matlamat percubaan klinikal pada masa depan dengan menggunakan prosedur *Hp PDT serta-merta*, prosedur lama telah digunakan terdahulu pada tiga pesakit sebagai asas kajian. Persediaan dan pencirian HpD bersama-sama pembinaan dua sumber cahaya halogen alternatif telah dilakukan. Kajian menunjukkan bahawa kedua-dua sumber cahaya ini adalah mudah dialih di kawasan klinik dan pengendalian melibatkan kos rendah. Oleh

itu, lampu-lampu halogen ini menghasilkan satu alternatif kepada sistem laser sebagai punca penyinaran pada permukaan sel-sel barah. Percubaan klinikal menunjukkan tindakbalas pengawalan pemulihan yang baik pada sel-sel barah tahap serius.