Free Rad. Res. Comms., Vol. 7, No. 3–6, pp. 139–142
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PREPARATION AND PHOTOSENSITIZING PROPERTIES OF HEMATOPORPHYRIN ETHERS

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Hematoporphyrin ethers having acyl or aryl substituents in the 2 and 4 positions of the porphyrin ring have been synthesized, starting from protoporphyrin HBr adduct, and tested for photosensitizing efficiency on cells *in vitro* and transplanted tumors in mice. In general, they resemble the tumorlocalizing fraction of hematoporphyrin derivative (Hpd). Cellular uptake and retention runs parallel with the degree of their non-polarity and *in vitro* sensitizing efficiencies are up to ten times that of Hpd or Photofrin II (P II). They have high quantum yields for inactivation of cells and also relatively low *in vivo* skin/tumor concentration ratios.

KEY WORDS: Hematoporphyrin ethers, cancer, photodynamic therapy.

INTRODUCTION

The material known as Hematoporphyrin derivative (Hpd) and its purified version (Photofrin II) are empirically produced porphyrin preparations which are being tested clinically for use as sensitizers in the photodynamic treatment of cancer.

Hpd is a complex mixture of porphyrins of which only a small fraction is clinically active and the chemical composition of this active fraction is still uncertain although it is thought to consist mainly of dihematoporphyrin ethers and/or esters.[1,2] It is only these which are taken up and retained by tumor cells.[3] This led us to prepare synthetically a series of individual diethers of hematoporphyrin having known chemical constitution and to evaluate their photodynamic efficiency experimentally and clinically.

MATERIALS AND METHODS

A generalized synthetic procedure has been evolved starting from the HBr adduct of protoporphyrin and reacting this with a selected acyl or aryl alcohol.[4,5]

RESULTS

In this way hematoporphyrin diethers have been prepared with methyl, ethyl, propyl and *iso*propyl, normal, *iso*- and *tertiary*-butyl, amyl, hexyl, cyclohexyl or phenyl residues in the 2 and 4 positions of the porphyrin ring, Figure 1.

Their degree of non-polarity increases regularly with the size of the substituent moiety, as does also their cellular uptake and photosensitizing efficiency, Figure 2.

The least polar of the diethers tested on cultured tumor cells have much higher

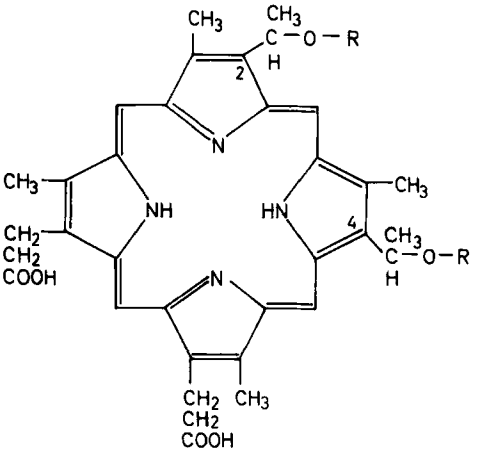

FIGURE 1 Chemical structure of hematoporphyrin-diethers. R represents the particular acyl or aryl substituting group.

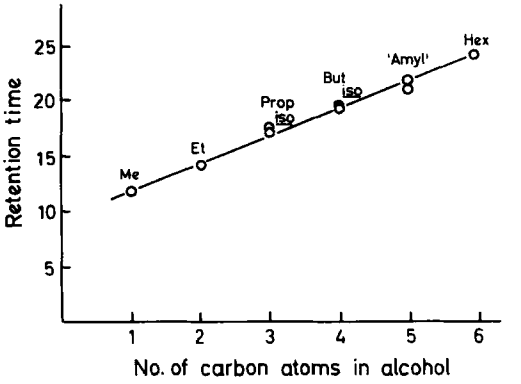

FIGURE 2 Increase of non-polarity (HPLC retention time) with size of substituent moiety.

sensitizing efficiencies, by factors up to 10 times, than those of Hpd and Photofrin II, Table 1. They have high quantum yields for cell inactivation, Table 2.

Tested on tumor-bearing mice by measuring growth times of the tumors as compared with those of untreated controls, they again showed increasing efficiency with decreasing polarity; hematoporphyrin-diamyl ether was as efficient as Photofrin II and markedly more efficient than Hpd.[6]

DISCUSSION

Hematoporphyrin derivative and its partially purified form, photofrin II, currently used for photodynamic cancer therapy, are products of ill-defined composition and of which only a fraction is biologically active. The use of chemically synthesized

TABLE 1

Sensitizing effects of different porphyrin products (12.5 μg/ml) on tumor cells

Porphyrin	Relative sensitizing efficiency	Reduction in sensitizing efficiency on washing (%)
Hpd	1.0	10 ± 5
Photofrin II	1.0 ± 0.2	10 ± 5
Hp dimethyl ether	1.2 ± 0.2	>90
Hp diethyl ether	2.4 ± 0.3	70 ± 10
Hp dipropyl ether	5.1 ± 0.4	40 ± 10
Hp dibutyl ether	7.8 ± 0.4	
Hp di-iso-butyl ether	11.3 ± 0.5	20 ± 5
Protoporphyrin	< 1.0	

TABLE 2

	Relative quantum yields	
	Cell inactivation	Fluorescence
Photofrin II	1.0	1.0
Hp-dihexyl ether	1.8	2.1
Hp-dicyclohexyl ether	1.8	1.9
Hp-diphenyl ether	2.1	2.0

materials such as the hematoporphyrin diethers offers considerable advantage over these and their photosensitizing efficiency is also superior. Moreover, another favourable feature which they exhibit is that they have relatively low *in vivo* ratios of skin to tumor concentration.[7]

The hematoporphyrin diethers are thus attractive candidates for photodynamic therapy of cancer.

Acknowledgement

This work was supported by the Association for International Cancer Research and by the Norwegian Cancer Society (Landsforeningen mot Kreft).

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Accepted by Prof. T.F. Slater