^{19}F MR Quantitation of Fluorine Labeled Photosensitizers in Tumors and Normal Tissue

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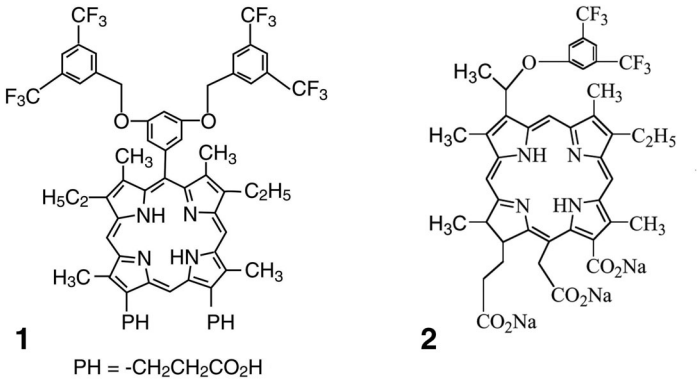
Introduction

Photodynamic therapy (PDT) is a cancer treatment modality that combines light sensitive drug and lasers [1]. PDT is most beneficial when laser light is delivered at a time when the photosensitizer is greater in the tumor than the surrounding normal tissue. Monitoring the photosensitizer (PS) in the tumor and in normal tissue is helpful in the development of new photosensitizers. The assessment of the PS in the skin and underlying muscle has the potential to provide information about the cutaneous toxicity. Syntheses of photosensitizers labeled with an NMR observable nucleus, such as Fluorine-19, offer the advantage of noninvasive assessment of the photosensitizer concentration in a living subject [2]. In this work we present the construction of pharmacokinetic profiles of two new photosensitizers in the tumor and muscle and their utility in PDT studies. The structures of the two photosensitizers are shown in Figure 1. The details of the synthesis and subsequent confirmation of the structures have been recently published [3]. Here we report the in vivo results obtained using new fluorine labeled photosensitizers that were monitored in tumor bearing mice.

Figure 1



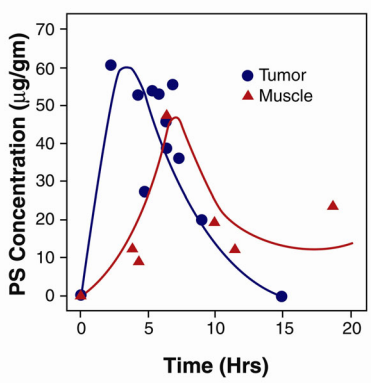
Methods

Tumor model: The Radiation induced fibrosarcoma (RIF) cells were maintained according to the protocol of Twentyman et al [4]. Tumors were grown on mouse foot dorsum by inoculating $2x10^5$ fresh cells. A total of 12 animals were studied here.

Laser and Delivery system: An argon ion (Spectra physics model 2017) pumped dye laser (Spectra Physics, 375B) was used. PDT measurements were performed at 630 nm for sensitizer **1** and at 650 nm for sensitizer **2**. Laser irradiation was done for 30 minutes at a power of 150 mW cm^{-2} leading to a total light dose of 270 J cm^{-2}. Fractionated laser irradiation was also employed in some studies.

In vivo MR and PDT studies: In vivo MR and PDT measurements were performed under mild anesthesia maintained by 1% isoflurane mixed with Nitrous oxide and Oxygen in 70:30 ratio. The photosensitizer was administered IP (~100µM). ^{19}F MR spectra were collected on a Bruker 7T instrument using a home built surface coil. The ^{19}F MR spectral parameters included an RF pulse of 16µs, a spectral width of 20 KHz, 8K data points, and a 2s repetition time for a total accumulation time of 30 minutes. The magnetic field homogeneity was optimized for each tumor by shimming on the water proton signal. The in vivo ^{19}F signal was compared with the signal from a phantom of known concentration to quantify the photosensitizer in the tumor. These values were used to construct the profiles for the tumor and the muscle. Figure 2 shows the data for compound **1**. The data for compound could be obtained on the muscle but not on foot tumors indicating compound **2** is less sensitive to detection in the tumor due to less number of fluorines in the molecule and small size of the tumors studied. Alternatively the accumulation of the PS in the tumor may be significantly low compared to that in the muscle.

Figure 2



Results

The mean values of relaxation times for compound **1** in the solution were 924±38 ms for T_1 and 150±2 ms for T_2. Similarly for compound **2** the mean values were 250and 25 ms respectively. These values were used in the optimization of tumor ^{19}F spectra. The signals from the labeled sensitizers were found to be broad with mean line widths at 404±176 and 481±150 Hz for **1** and **2** respectively. The Pharmacokinetic profile of PS **1** in tumor model was constructed using three tumors (Figure 2). Based on this profile, PDT was performed at 2, 4 or 24 hrs post drug administration. The PDT studies performed at 2 and 4 hours led to tumor regression while that done at 24 hrs did not show any tumor regression. These data are in accordance with the pharmacokinetics of compound **1** shown in Figure 2. While using compound **2**, laser irradiation was done at 24 hrs post drug administration and there was significant tumor regression following PDT.

Conclusions

MR studies can provide quantitative data on photosensitizer in tumor and a rational basis for PDT initiation. PDT studies designed using the pharmacokinetic data showed significant tumor regression.

References

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Acknowledgement

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