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# RADIOLABELED PORPHYRIN VERSUS GALLIUM-67 CITRATE FOR THE DETECTION OF HUMAN MELANOMA IN ATHYMIC MICE

Abbreviated Title: Radiolabeled Porphyrin for Melanoma Detection

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## ABSTRACT

We performed the biodistribution and imaging studies of $^{111}In$ and $^{67}Ga$ labeled tetra(4-N-methylpyridyl) porphine, (T4NMPYP), and compared it to that of $^{67}Ga$ citrate in athymic mice bearing a human melanoma xenograft. The biodistribution results of both $^{111}In$ and $^{67}Ga$ labeled T4NMPYP (3, 6, 24 and 48 hours) were similar but differed from that of $^{67}Ga$ citrate (48 hours). The optimum tumor uptake of both radiolabeled porphyrins was at 6 hours postinjection and was lower than the tumor uptake of $^{67}Ga$ citrate at 48 hours postinjection. Kidney was the only organ showing higher uptake of radiolabeled porphyrin compared to that of $^{67}Ga$ citrate. The imaging studies performed with $^{111}In$ T4NMPYP and $^{67}Ga$ citrate correspond to the biodistribution results. Osteomyelitis present in one mouse showed good localization of $^{111}In$ T4NMPYP.

The tumor localizing properties of $^{67}$Ga citrate were first discovered and utilized by Edwards and Hayes in 1969 (Edwards 1969). Since that time, gallium citrate has been used successfully for detection or staging of a number of malignancies, including lymphoma, hepatoma and melanoma. Nonetheless, $^{67}$Ga citrate is an imperfect tumor imaging agent. It demonstrates poor localization in a variety of common malignancies. Furthermore, the radionuclide demonstrates relatively high uptake in certain normal tissues including liver and bone. Such localization tends to obscure lesions in or about these organs. Furthermore, the slow clearance of $^{67}$Ga citrate from the blood leads to a relatively high overall body background. For these reasons, the search for better general and specific tumor detecting agents continues (Halpern 1985, Burragi 1985, von Lier 1984).

For over six decades, porphyrins have been known for their preferential accumulation in tumors (Thompson 1986). Hematoporphyrin has been the most extensively studied porphyrin. For diagnostic purposes, synthetic porphyrins which are able to penetrate tumor cell membrane have given positive indication of presence of tumorous growth (Zanelli 1981). Recently, Foster et al. published encouraging biodistribution and imaging results using the synthetic cationic porphyrin, $^{111}$In-tetra(4-N-methypyridyl) porphine, ($^{111}$In T4NMPYP), in Syrian Golden hamsters bearing the Fortner Malignant Melanoma I (MMI) (Foster 1985). In order to extend Foster and associates' findings, we have performed biodistribution and imaging studies on $^{111}$In T4NMPYP in athymic mice bearing a human melanoma xenograft. These results were compared to those obtained using $^{67}$Ga citrate. In addition, we have also labeled T4NMPYP with $^{67}$Ga and performed similar in vivo studies on this labeled compound in the same human melanoma-nude mouse model.

## MATERIALS AND METHODS

### Chemicals

The following chemicals were obtained from commercial sources: tetra (4-N methylpyridyl) porphine tetratosylate[1], indium tetra (4-N-methylpyridyl) porphine chloride[2], gallium tetra (4-N-methylpyridyl) porphine chloride[3], $^{111}$In-chloride[4] and $^{67}$Ga citrate[5].

### Radiolabeled Porphyrins

$^{111}$In labeled T4NMPYP was prepared according to the method of Vaum et al (Vaum 1982) with slight modification. An autoclave was used instead of a hot water bath for the labeling procedure. The reaction mixture was autoclaved at 120°C for 30 minutes. The radiochemical purity was 92.3%. The identity of the label compound was confirmed by instant thin layer chromatography (ITLC) (Gelman) using the non-radioactive indium T4NMPYP as the reference compound. The solvent systems used were:

1. $(CH_3)_2$ SO: $CH_3CH_2OH$: 0.5 N NaOH (1:1:1) Rf=0.43;
2. $(CH_3)_2$ SO: 0.5 N NaOH (1:3) Rf=0.87;
3. $(CH_3)_2CO$: 0.5 N NaOH (1:1) Rf=0.73.

Radiochromatograms were recorded on a Berthold TLC scanner.

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1. Sigma Chemical Company, St. Louis, MO
2. Prophyrin Product, Inc., Logan, UT
3. Mid-Century Chemicals, Posen, IL
4. Amersham Corporation, Arlington Heights, IL
5. duPont NEN Medical Products, North Billerica, MA

The method of preparation of $^{67}$Ga T4NMPYP was essentially the same as that for $^{111}$In T4NMPYP except $^{67}$Ga citrate was used instead of $^{111}$In chloride, and the $^{67}$Ga citrate was not dried before autoclaving with T4NMPYP. The radiochemical purity was 94.7%. The identity of the labeled compound was also confirmed chromatographically using the following solvent systems:

1. $CH_3OH$: 0.5 N NaOH (3:1) Rf=0.78;
2. $(CH_3)_2SO$: 0.5 N NaOH (1:3) Rf=0.80;
3. $CH_3OH$: $(CH_3)_2SO$: 0.5 N NaOH (1:1:1) Rf=0.90.

Human Melanoma Xenografts

Female athymic BALB/c mice (NIH) were used as the host animals. Human malignant melanoma was derived from the melanoma cells obtained with patient's consent and established and maintained in tissue culture in our Oncology Laboratory. Mice were 3 to 7 weeks of age and weighing approximately 15 grams when the human malignant melanoma was implanted subcutaneously by trocar (13 G) and allowed to grow for 5 to 8 weeks prior to the injection of radiolabeled compound. The tumor size ranged from 0.04-1.34 g (in total of 60 mice). The serial passage of the tumor through three generations of BALB/c nude mice was performed prior to the experiment.

Biodistribution Studies

Three groups of mice bearing a human melanoma were injected via tail vein with 185 KBq of one of the following radiochemicals per mouse: $^{111}$In T4NMPYP (24 mice), $^{67}$Ga T4NMPYP (24 mice), or $^{67}$Ga citrate (12 mice). Mice receiving radiolabeled T4NMPYP were sacrificed at 3, 6, 24 and 48 hours postinjection. These studies were conducted in such a way as to have a total of 6 animals for each time interval. Although a total of 12 animals were

injected with $^{67}$Ga citrate, they were actually studied in groups of 6 in conjunction with a cohort of animals injected with either $^{111}$In T4NMPYP or $^{67}$Ga T4NMPYP. Tables 1-4 represent comparisons of uptake of labeled T4NMPYP with the appropriate $^{67}$Ga citrate studies performed on the same cohort of animals.

Various tissues were excised, rinsed with saline, blotted dry and weighed. The radioactivity associated with different tissues was counted using a Beckman automatic gamma counter. Results are expressed as percent injected dose per gram of tissue (% ID/g) as well as tumor to tissue ratios.

Data Analysis

Statistical analysis of the results was performed using Student's t-test. Wilcoxon non-paired rank sum test was applied in cases where normal distribution could not be assumed.

Imaging Studies

Two groups of melanoma bearing mice (2 mice per group) were injected with approximately 14.8 MBq of $^{111}$In T4NMPYP or $^{67}$Ga citrate. A third group of two non-tumor bearing mice was injected with 14.8 MBq of $^{111}$In T4NMPYP. Images were obtained using a gamma camera equipped with a pinhole collimator at 3, 6, 24 and 48 hours postinjection.

Histopathologic Studies

One of the mice showed focal uptake of radioactivity, at the region of the left orbit, in addition to the tumor site (Fig. 3). To determine whether this represented metastasis, the mouse was necropsied for examination of tissues by light microscopy using standard hematoxylin and eosin stains. Additional immunohistochemical studies were done using a modified Avidin-Biotin immunohistochemical method. Melanoma specific murine monoclonal antibody

(HMB-45) was a gift from Dr. Allen Gown of the University of Washington, Seattle. Biotinylated goat anti-mouse secondary antibody was obtained commercially.[6] Diamino benzidine (peroxidized) was used as the chromogen substrate.

## RESULTS

### Biodistribution Studies

The biodistribution patterns of both $^{111}$In and $^{67}$Ga labeled T4NMPYP were similar, but differed from that of $^{67}$Ga citrate (Tables 1 and 2). In general, tissue uptake of the radiolabeled porphyrins were lower than that of $^{67}$Ga citrate in all of the tissues studied except the kidneys.

Both $^{111}$In T4NMPYP and $^{67}$Ga T4NMPYP were rapidly taken up by the tumor. Maximum absolute tumor uptake of both labeled porphyrins occurred 6 hours postinjection, although tumor uptake of $^{111}$In T4NMPYP was consistently higher than that of $^{67}$Ga T4NMPYP at all time points studied.

Absolute tumor uptake of the labeled porphyrins was substantially lower than that of $^{67}$Ga citrate. On the other hand, the blood level of radiolabeled porphyrin dropped dramatically over a period of 48 hours, resulting in tumor-to-blood ratios which were substantially higher than that of $^{67}$Ga citrate (Tables 3 and 4).

### Imaging Studies

The results of imaging studies using $^{111}$In T4NMPYP showed good correlation with the biodistribution results. The tumor was best visualized at 6 hours postinjection (Fig. 1). For comparison purposes, the optimal $^{67}$Ga citrate tumor image at 48 hour postinjection is shown in Fig. 2.

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6. Vector Labs, Burlingame, CA

One of the mice, which carried a small tumor (approximately 20 mg) at the right lateral chest wall, showed an intense focal uptake of activity at the left orbit when imaged with $^{111}$In T4NMPYP (Fig. 3). A follow-up bone scan using $^{99m}$Tc MDP also revealed focal uptake of activity at the same orbit (image not shown), although the uptake of $^{99m}$Tc MDP appeared less intense than the uptake of $^{111}$In T4NMPYP. The tumor in this mouse was not clearly defined due to its proximity to the liver which showed high uptake of radioactivity.

Histopathologic Studies

A 0.6 x 0.4 x 0.45 cm subcutaneous tumor nodule was examined by light microscopy which showed an undifferentiated malignant tumor nodule with 30-40% tumor necrosis. The tumor cells were epithelial in character, having prominent nucleoli and variable cytoplasm. Cytoplasmic melanoma-associated antigen was present by Avidin-Biotin immunohistochemical reactivity using melanoma specific monoclonal antibody (HMB-45). Sections of the bony calvaria nearest the left cerebral hemisphere (inferior and lateral skull) showed acute osteomyelitis as reflected by diffuse infiltrates of polymorphonuclear leukocytes and macrophages filling the intratrabecular zones. There was no reactivity with melanoma-specific monoclonal antibody, HMB-45, with the dermal melanoma of the animal serving as positive control. Thus the region of scan positively was due to acute osteomyelitis and not melanoma.

## DISCUSSION

Localization of porphyrin in tumor was first recorded in 1924 by Policard who observed intense red fluorescence of tumors exposed to ultraviolet light (Policard 1984). The finding was subsequently confirmed by various

investigators (Wang 1981, Figge 1948). In 1948, Figge extended the work to include metalloporphyrins and demonstrated that incorporation of metal into porphyrins did not destroy their tumor-seeking property (Figge 1948).

The possibility of using radiolabeled porphyrins for tumor therapy and diagnosis began in 1962 with the work of Winkelman (Winkelman 1963). Numerous porphyrin analogs have since been labeled with various radiometals and the resulting labeled porphyrins studied for their tumor localizing property (Wang 1981, Rousseau 1985, 1983). While some of the labeled porphyrins showed tumor-to-blood ratios more favorable than those obtained using $^{67}$Ga citrate, virtually all the compounds studied showed high uptake in the liver and the kidneys. Foster et al, however, demonstrated localization of $^{111}$In T4NMPYP in a hamster melanoma while uptake of the compound in the liver and the kidneys was rather low (Foster 1985).

Similar to the results obtained by Foster et al, we observed the absolute tumor uptake of $^{111}$In T4NMPYP to be rather low (Table 5), nonetheless in both tumor models the tumor-to-blood ratios were more favorable than that of $^{67}$Ga citrate. In contrast to the hamster melanoma model used by Foster, liver and kidney uptake of $^{111}$In T4NMPYP in the human melanoma-nude mouse model were rather high. The relatively high liver and kidney uptake in the human melanoma model is in agreement with the results reported by Wang et al (Wang 1981), who studied the $^{57}$Co T4NMPYP in rats with transitional cell carcinoma. While it is difficult to predict how the human liver and kidneys would handle $^{111}$In T4NMPYP, it is safe to say that any human studies using $^{111}$In T4NMPYP must pay particular attention to potential uptake in liver and kidney.

Wang et al studied the structure-localization properties of numerous

metalloporphyrin derivatives and noted that metals that chelate strongly to porphyrins have little effect on the ultimate biodistribution of the metalloporphyrins. The results of our study show that substitution of $^{111}In$ with $^{67}Ga$ results in a decrease in tissue uptake of the labeled porphyrin although the overall distribution pattern of both $^{111}In$ T4NMPYP and $^{67}Ga$ T4NMPYP are similar.

To conclude, the results of our study show uptake of $^{111}In$ T4NMPYP in human melanoma. While the tumor-to-blood ratio for $^{111}In$ T4NMPYP at 6 H is high, the absolute tumor uptake is low comparing to $^{67}Ga$ citrate at 48 H. In contrast to uptake in the hamster melanoma model previously reported by Foster et al (Foster 1985), high uptake of $^{111}In$ T4NMPYP in the liver and kidneys was observed. These results cast doubt on the potential application of $^{111}In$ T4NMPYP for detection of human melanoma. The incidental observation of $^{111}In$ T4NMPYP uptake at a site of acute osteomyelitis warrants further investigation.

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Table 1: Biodistribution of $^{111}$In T4NMPYP and $^{67}$Ga citrate in human melanoma bearing athymic mice expressed as mean percent injected dose per gram of tissue ± s.d. (6 animals per group)

| | $^{111}$In T4NMPYP | | | | $^{67}$Ga citrate |
|---|---|---|---|---|---|
| | 3 H | 6 H | 24 H | 48 H | 48 H |
| Blood | 0.27±0.06 | 0.28±0.11 | 0.06±0.01 | 0.04±0.00 | 0.79±0.12 |
| Tumor | 6.83±1.33 | 9.12±3.76 | 4.98±0.56 | 3.80±0.81 | 21.20±2.97 |
| Heart | 0.43±0.00 | 0.53±0.18 | 0.28±0.09 | 0.58±0.24*,+ | 0.90±0.08 |
| Lung | 1.91±0.36* | 1.93±0.65* | 0.68±0.10 | 0.82±0.34 | 2.04±0.40 |
| Liver | 3.86±0.54 | 6.28±1.83* | 4.23±0.63 | 12.42±1.56 | 7.68±0.76 |
| Spleen | 2.54±0.57 | 3.68±1.04* | 2.54±0.50 | 7.25±2.11 | 3.48±0.61 |
| Kidney | 41.87±6.90+ | 51.38±6.74+ | 34.81±6.21+ | 32.27±2.71+ | 7.88±1.36 |
| Intestine | 1.05±0.21 | 1.58±0.49 | 0.72±0.11 | 1.42±0.17 | 3.56±0.77 |
| Muscle | 0.30±0.12* | 0.34±0.13* | 0.14±0.04 | 0.23±0.07 | 0.37±0.10 |
| Bone | 3.35±0.89 | 3.14±0.88 | 1.02±0.25 | 1.35±0.26 | 7.34±1.70 |
| Skin | 1.84±0.36 | 2.11±0.54* | 1.17±0.17 | 2.15±0.36* | 2.80±0.74 |

* Data are not significantly different from the ones obtained with Ga-67 citrate.

+ Wilcoxon non-paired rank sum test

Table 2: Biodistribution of $^{67}$Ga T4NMPYP and $^{67}$Ga citrate in human melanoma bearing athymic mice expressed as mean percent injected dose per gram of tissue ± s.d. (6 animals per group)

| | $^{67}$Ga T4NMPYP | | | | $^{67}$Ga citrate |
|---|---|---|---|---|---|
| | 3 H | 6 H | 24 H | 48 H | 48 H |
| Blood | 0.23±0.07 | 0.15±0.06 | 0.04±0.01 | 0.01±0.00 | 0.78±0.33 |
| Tumor | 3.74±0.92 | 4.48±1.51 | 2.19±0.60 | 2.01±0.61 | 23.87±3.91 |
| Heart | 0.33±0.09 | 0.32±0.04 | 0.26±0.03 | 0.30±0.17$^{+}$ | 0.97±0.27 |
| Lung | 1.15±0.48 | 1.16±0.23 | 0.62±0.14 | 0.46±0.09 | 2.14±0.75 |
| Liver | 5.09±1.02 | 6.11±0.90* | 6.90±0.79$^{+}$ | 5.77±0.91 | 9.19±3.27 |
| Spleen | 2.31±0.61 | 3.09±0.54* | 2.95±0.34* | 2.65±0.57 | 4.28±1.39 |
| Kidney | 25.21±3.90$^{+}$ | 34.31±8.07$^{+}$ | 31.28±3.26$^{+}$ | 22.77+4.29$^{+}$ | 9.31±3.56 |
| Intestine | 0.64±0.13 | 0.68±0.15 | 0.62±0.09 | 0.57±0.07 | 4.05±0.92 |
| Muscle | 0.30±0.16* | 0.38±0.26* | 0.40±0.56*,$^{+}$ | 0.12±0.02 | 0.43±0.06 |
| Bone | 3.26±0.94 | 2.85±0.51 | 1.41±0.29 | 0.77±0.17 | 10.79±2.15 |
| Skin | 1.66±0.34 | 1.40±0.20$^{+}$ | 1.23±0.20 | 1.12±0.29 | 2.75±0.49 |

* Data are not significantly different from the ones obtained with Ga-67 citrate.

$^{+}$ Wilcoxon non-paired rank sum test.

Table 3: Mean tumor-to-tissue ratios for $^{111}$In T4NMPYP and $^{67}$Ga citrate in human melanoma bearing athymic mice

| | $^{111}$In T4NMPYP | | | | $^{67}$Ga citrate |
|---|---|---|---|---|---|
| | 3 H | 6 H | 24 H | 48 H | 48 H |
| Blood | 25.54±3.83 | 33.30±7.63 | 87.23±11.92 | 100.67±30.28 | 27.58± 6.78 |
| Heart | 16.06±1.58 | 17.09±3.12 | 18.70±4.20 | 7.05± 2.33 | 23.85± 5.01 |
| Lung | 3.75±0.91 | 4.99±2.05 | 4.99±2.05 | 7.42± 0.81 | 10.56± 1.80 |
| Liver | 1.78±0.30 | 1.46±0.45 | 1.19±0.19 | 0.31± 0.07 | 2.78± 0.50 |
| Spleen | 2.75±0.55 | 2.45±0.61 | 2.00±0.28 | 0.55± 0.18 | 6.25± 1.44 |
| Kidney | 0.16±0.02 | 0.17±0.05 | 0.15±0.03 | 0.12± 0.03 | 2.73± 0.47 |
| Intestine | 6.64±1.24 | 5.76±1.51 | 7.03±1.25 | 2.68± 0.49 | 6.10± 1.09 |
| Muscle | 26.10±9.86 | 26.66±4.39 | 36.71±8.12 | 17.39± 5.50 | 61.45±17.41 |
| Bone | 2.13±0.60 | 2.85±0.65 | 5.00±0.69 | 2.88± 0.78 | 2.95± 0.46 |
| Skin | 3.80±0.79 | 4.29±1.10 | 4.34±1.11 | 1.79± 0.42 | 8.06± 2.54 |

Table 4: Mean tumor-to-tissue ratios for $^{67}$Ga T4NMPYP and $^{67}$Ga citrate in human melanoma bearing athymic mice

| | $^{67}$Ga T4NMPYP | | | | $^{67}$Ga citrate |
|---|---|---|---|---|---|
| | 3 H | 6 H | 24 H | 48 H | 48 H |
| Blood | 16.69±3.96 | 32.97±15.65 | 49.64±4.92 | 168.59±71.80 | 34.41±11.85 |
| Heart | 11.61±2.61 | 14.26± 5.01 | 8.59±2.47 | 7.99± 3.71 | 25.58± 5.22 |
| Lung | 3.50±1.03 | 3.98± 1.48 | 3.60±1.04 | 4.44± 1.24 | 11.77± 2.69 |
| Liver | 0.73±0.13 | 0.73± 0.19 | 0.32±0.08 | 0.36± 0.15 | 2.81± 0.92 |
| Spleen | 1.64±0.26 | 1.46± 0.48 | 0.74±0.16 | 0.80± 0.35 | 5.98± 1.80 |
| Kidney | 0.15±0.03 | 0.13± 0.03 | 0.07±0.02 | 0.09± 0.04 | 2.71± 0.56 |
| Intestine | 5.87±1.20 | 6.68± 1.89 | 3.56±0.83 | 3.72± 1.71 | 6.04± 1.12 |
| Muscle | 15.22±8.80 | 16.06±10.18 | 10.04±4.51 | 17.21± 6.74 | 56.97±10.84 |
| Bone | 1.17±0.31 | 1.58± 0.51 | 1.61±0.53 | 2.74± 1.07 | 2.29± 0.61 |
| Skin | 2.25±0.31 | 3.24± 1.11 | 1.80±0.43 | 1.89± 0.70 | 8.88± 2.00 |

Table 5: Comparison of tissue uptake of $^{111}$In T4NMPYP in hamster melanoma* and human-nude mouse melanoma models (expressed as mean ± s.d. of percent injected dose per gram)

| | 6 H | | 24 H | | 48 H | |
|---|---|---|---|---|---|---|
| Tissue | Human/ Nude Mouse | Hamster* | Human/ Nude Mouse | Hamster* | Human/ Nude Mouse | Hamster* |
| Tumor | 9.12±3.76 | 3.35±1.25 | 4.98±0.56 | 1.50±0.82 | 3.80±0.81 | 1.72±0.83 |
| Blood | 0.28±0.11 | 0.08±0.01 | 0.06±0.01 | 0.02±0.01 | 0.04±0.00 | 0.02±0.02 |
| Liver | 6.28±1.83 | 0.72±0.09 | 4.23±0.63 | 1.34±0.48 | 12.42±1.56 | 1.52±0.48 |
| Kidney | 51.38±6.74 | 2.80±0.22 | 34.81±6.21 | 3.10±1.29 | 32.27±2.71 | 3.14-0.94 |

*Data from Foster et al. (11)

## LEGENDS TO FIGURES

Figure 1 — Scintigram of nude mouse bearing human melanoma (arrow) at 6 hours postinjection of In-111-T4NMPYP.

Figure 2 — Scintigram of nude mouse bearing human melanoma xenograft (arrow) at 48 hours postinjection of Ga-67 citrate.

Figure 3 — Scintigram of nude mouse bearing human melanoma at right lateral chest wall at 24 hours postinjection of In-111-T4NMPYP. The tumor (T) is not clearly defined. The uptake at the left orbit was found to be osteomyelitis (Os).