
Effects of Propylthiouracil on the Biodistribution of an Iodine-131-Labeled Anti-Myeloid Antibody in Normal Dogs: Dosimetry and Clinical Implications

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Despite the use of near maximal doses of chemoradiotherapy, tumor recurrence remains the most frequent cause of treatment failure following marrow transplantation for leukemia. We have previously demonstrated that it is possible to selectively deliver radiation to the marrow space. In that study an initial short half-life of the radionuclide was observed. In this study we attempted to prolong the retention of the radioiodine in marrow through the use of propylthiouracil (PTU). When administered to normal dogs, PTU pretreatment resulted in improved marrow localization of ¹³¹I-labeled DM-5. There was no appreciable loss of activity from the marrow during the 2–4 hr postinjection time interval; a finding in contrast to the control animals where marrow activity declined a mean $45 \pm 0.5\%$ over the same time period. Additionally, in contrast to controls, a rise in plasma trichloroacetic acid (TCA) nonprecipitable activity was not demonstrated in the PTU treated group during this 2–4 hr period. These results suggest that PTU's inhibition of deiodinases resulted in longer residence time of the radionuclide in its target tissue without adversely affecting distribution to non-target organs.

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For selected patients with hematologic malignancies, bone marrow transplantation offers the best chance for long-term disease-free survival (1,2). Most preparative regimens have combined high doses of various chemotherapeutic agents with external beam total body irradiation (TBI). Such regimens have been designed to deliver the maximum tolerated dose of chemoradiotherapy approaching the limit of non-hematopoietic

organ toxicity and are associated with a 10–15% fatality rate due to transplant-related complications (3). Despite the use of near maximal doses of chemoradiotherapy, tumor recurrence remains the most frequent cause of treatment failure. Disease recurrence can be expected in >50% of patients transplanted for acute lymphocytic leukemia (ALL), acute nonlymphocytic leukemia (ANL), malignant lymphoma in relapse, or chronic myelogenous leukemia (CML) in blast crisis, and in >25% of patients treated for these diseases while in remission.

The use of monoclonal antibodies (MAbs) as carriers for radioisotopes should allow a more directed delivery of radiotherapy than is achievable with external beam TBI. Their selective binding to target cells make them potentially useful to preferentially deliver therapy to tumor while sparing normal non-target organ toxicity. In many studies the radionuclide used has been iodine-131 (¹³¹I). Iodine-131 has medium-energy beta emissions ($E = 0.183$ MeV), a proven therapeutic cytotoxic effect, sufficient gamma emission for imaging and is relatively inexpensive and commercially readily available. The chemistry associated with the radioiodination of MAbs has been well described (4–6). Oxidizing agents like chloramine-T and tetrachlorodiphenylglycouril (IODO-GEN) result in the iodination of the phenyl ring of tyrosine residues adjacent to the hydroxyl group which, in most cases, can be performed without appreciably altering the biologic activity of the radiolabeled antibody (7,8).

For radioimmunoconjugate therapy to be effective, in addition to its selectivity, the radionuclide must be retained long enough for maximal target localization. One major drawback with the application of ¹³¹I for immunoconjugate radiotherapy in some tumor-antibody systems is the significant loss of the radiolabel through metabolism of the antibody and dehalogena-

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tion in target tissues. The loss of radioiodine is associated with an increase in free iodine excretion with reabsorption in the gastrointestinal tract and thyroid tissue; ultimately the free iodine is eliminated in the urine.

We have previously reported on the biodistribution of an ^{131}I -labeled anti-myeloid antibody (DM.5) in normal dogs (9). That study demonstrated the ability to target marrow with a high degree of selectivity and specificity achieving marrow: blood ratios at 48 hr of 20:1 (22.9 ± 7.5). The marrow clearance curve for the immunoconjugate revealed a biphasic elimination with a short half-life of 4.75 hr for the early phase, after which clearance of the radionuclide from the marrow proceeded at a slower rate ($t_{1/2} = 22$ hr). Associated with the decline in marrow activity was an appreciable rise in plasma free iodine as trichloroacetic acid (TCA) non-precipitable radioactivity, presumably reflecting enzymatic deiodination of the radioimmunoconjugate and release of non-protein bound iodine into plasma.

Iodinated tyrosine residues in the immunoglobulin are similar in structure to thyroid hormone suggesting they may be substrates for the enzymatic systems responsible for thyroidal hormonal metabolism (Fig. 1). As much as 80% of the active thyroid hormone, triiodothyronine (T₃), is generated in peripheral tissues by monodeiodination of tetraiodothyronine (T₄); (a reductive enzymatic process resulting in the hydrolytic removal of iodine atoms from either a phenolic or tyrosine ring). In an attempt to reduce dehalogenation, Zalberg et al. (10) used the anti-thyroid drug, propylthiouracil, (PTU) in mice treated with ^{131}I -labeled MAb (250–30.6) directed at a secretory component of malignant gastrointestinal epithelium in human tumor xenografts. That study showed a threefold increase in total body retention of radioactivity in the PTU-treated mice over untreated controls. Because iodinated tyrosine residues on radiolabeled MAbs are similar in structure to

thyroid hormone, we investigated the use of PTU in an attempt to similarly inhibit or reduce peripheral deiodination of an ^{131}I -labeled anti-myeloid antibody. This report examines and compares the biodistribution over time of ^{131}I -labeled DM.5 in normal dogs with and without PTU pretreatment.

MATERIALS AND METHODS

Dogs

Beagles, 7–15 mo old, weighing 7–12 kg, and raised at the Fred Hutchinson Cancer Research Center or purchased from commercial kennels were dewormed, vaccinated against distemper, leptospirosis, hepatitis and parvovirus and were observed for at least 2 mo before study.

Monoclonal Antibodies

MoAb 6.4 is an IgG_{2b} murine MAb directed at the Thy 1.1 antigen in mice that does not cross react with canine cells and was used as a negative, non-binding control antibody in this study. Monoclonal DM-5, is an I₂G₁ which recognizes 35–50% of normal canine marrow cells and greater than 95% of circulating neutrophils. DM-5 does not recognize peripheral blood monocytes or lymphocytes. Immunoperoxidase staining of a variety of dog tissues demonstrate DM-5 to be essentially myeloid specific. DM-5 appears to recognize three glycosylation variants of 15 kD polypeptide core with the glycoprotein variants migrating at 19, 21, and 23 (kD) (Sandemaier unpublished observations). Antibodies were purified from ascites by adsorption and pH stepwise elution from a staph protein A-Sepharose column (Sigma Chemical Co., St. Louis, MO). Antibody concentration was determined by a Coomassie blue binding assay standardized with bovine gamma globulin (Bio Rad Laboratories, Richmond, CA).

Iodination and Characterization

Iodination was performed in 20-ml glass scintillation vials coated with 100 μg Iodogen (Pierce Chemical Co., Rockford, IL). Antibody was diluted in phosphate buffered saline (PBS) to a volume of 1 ml in the iodogen-coated vial, and 1 mCi of radioiodine (^{125}I or ^{131}I -labeled Na; specific activity 17 Ci/mg I and 18.5 Ci/mg I, respectively (ICN Biomedicals Inc., Irvine,

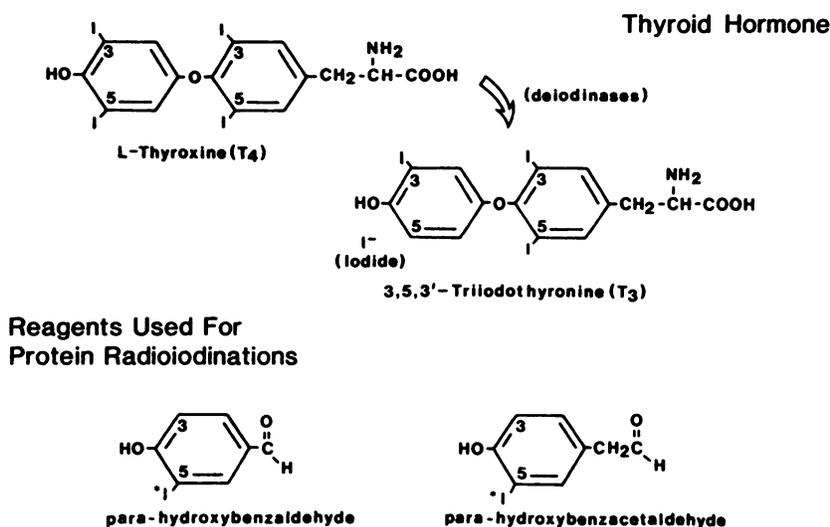


FIGURE 1

Structural similarities between reagents used for protein radiiodinations and thyroid hormone (L-thyroxine).

CA) were added. The vial was incubated at room temperature with intermittent agitation for 10 min. Unbound iodine was removed by passage over a Sephadex PD-10, G-25 column (Pharmacia Fine Chemicals, Piscataway, NJ).

After each labeling, protein concentration was determined using the Biorad protein assay standardized with bovine gamma globulin. Immunoreactivity (% labeled antibody able to bind antigen) and avidity were determined as previously described (11). Briefly, for determination of immunoreactivity a constant amount of labeled antibody (40 ng) was incubated with varying numbers ($1 \times 10^7 - 1 \times 10^4$ cells) of normal canine marrow cells in the wells of a microtiter plate (total volume 0.2 ml) for 1 hr at 37°C. After washing, bound activity was counted and immunoreactivity was determined by extrapolation of a Lineweaver-Burke plot of the data to infinite antigen excess. Avidity was determined from Scatchard plots of the binding of labeled antibody to viable normal canine marrow cells. Known quantities of antibody were diluted in tissue culture media (RPMI 1640, 2% bovine serum albumin, and 0.02% sodium azide) and incubated with 2×10^5 cells in microtiter plates in a total volume of 0.2 ml for 1 hr at 37°C. The cells were washed three times and bound radioactivity was counted.

Antibody Localization

The double isotope labeling method of Pressman was used along with opposing view external gamma camera imaging (12). All dogs received Lugol's solution, starting 5 days before study, diluted 1:20, at 2 cc/day for non-PTU treated dogs and 0.5 cc/day for dogs pretreated with PTU. All dogs were pretreated with 1 mg unlabeled DM.5/kg 2 hr before infusion of the labeled antibody mixture as previously described (9). In that study pretreatment with "cold" unlabeled DM.5 resulted in the elimination of the majority of circulating myeloid cells; as a result, hepatic uptake was significantly reduced and marrow localization increased over that observed in non-pretreated animals. On the first day of study, a mixture of 1 mg ^{131}I -labeled relevant antibody/kg (DM-5) and 1 mg ^{125}I -labeled irrelevant antibody/kg (MoAb 6.4) was infused over 15 sec with the dog anesthetized and placed under a gamma camera. Dynamic images were obtained at 30 sec/frame over the first 2 hr after infusion. Static scans were performed at 2 and 48 hr. Regions of interest over liver, lung, marrow and heart (blood pool) were created and time activity curves normalized to counts per pixel were generated. Blood samples were obtained at 1, 5, 10, 30, 60, 90, and 120 min postinfusion and then at 4, 24, and 48 hr. Bone marrow biopsies using a Jamshidi needle were performed at 2, 4, 24, and 48 hr as well. At 48 hr, representative animals were euthanized with phenobarbital. Lung, liver, spleen, and kidney were removed intact and weighed and core (<1 gm) samples of these and various other tissues were removed, rinsed of excess surface blood, blotted dry and weighed. Content of the ^{131}I and ^{125}I in tissue and blood samples were measured in a multiple-channel gamma counter (Auto-Gamma spectrometer, Model 5330, Packard Instruments, Downers Grove, IL). Data were corrected for decay of ^{131}I and ^{125}I and adjusted for downscatter. A weighed standard of injectate was counted simultaneously and results were expressed as percent of injected dose per gram of tissue.

Biodistribution curves for organs of interest (liver, lung, marrow and heart blood pool) were determined by scaling the

gamma camera derived time activity curves by the radioiodine concentration per gram of tissue measured directly from necropsy samples. Data were analyzed using a paired Students' T-test (Statview II®, Abacus). A total of 3 dogs were studied in each group.

Trichloroacetic Acid Precipitation

After small aliquots of whole blood were weighed and activity counted, corresponding blood samples were centrifuged at 1200 rpm for 10 min (IEC Centra-7, International Equipment Co.) and plasma removed 20 μl of plasma (.02 gm) at each time point was similarly counted. For determination of cell free, non-protein bound activity, 20 μl of plasma was mixed with 230 μl RPMI 1640, 2% bovine serum albumin and 250 μl of 20% TCA, agitated and cooled on ice for 15 min. These samples were then centrifuged and the supernatant removed, counted and recorded as %/gm TCA soluble activity.

Radiation Dosimetric Estimates

Absorbed organ doses were estimated using methods recommended by the Medical Internal Radiation Dose Committee (MIRD) (13,14,15). Utilizing a MIRD infant human "phantom" geometric model containing organs with anatomic composition and density approximating man, energy deposited by penetrating photon cross-organ and same-organ irradiation and by the short-range, locally absorbed beta radiation spectrum was considered. Residence times for ^{131}I in imaged and biopsied source organs were determined for calculating the cumulative doses to organs of interest (lung, liver and marrow). Long-term retention was estimated by fitting exponential functions to the organ retention data at known time points. The dogs' mean organ masses, obtained at autopsy, were used for internal dose calculations and compared to a standardized reference MIRD infant model.

PTU Pretreatment

Three dogs received PTU at a dose of 21 mg/kg/day orally in three divided doses starting 2 hr prior to the infusion of the ^{131}I -labeled DM.5/ ^{125}I -6.4 mixture. PTU was continued for three days (day 0, +1, +2). Because of the competitive interaction between PTU and iodine the dose of supersaturated potassium iodine (Lugol's) was reduced from 2 cc in the control group to 0.5 cc in the PTU group.

RESULTS

Antibody Immunoreactivity

Scatchard analysis of DM-5 binding to normal canine marrow cells is shown in Figure 2. Based on the molecular weight of the antibody (160 kD) and the number of cells in the incubation (2×10^5) for DM-5, the association constant was 4.9×10^8 (molar⁻¹) and the number of molecules bound per cell was 1.45×10^6 .

Biodistribution

Mean blood levels of the radionuclide associated with DM.5, with and without PTU pretreatment and the irrelevant control Ab (n = 3 animals in each group) are shown in Figure 3. The early fall in the concentration of DM-5 represents antigen specific binding since this fall was not observed with the irrelevant antibody 6.4.

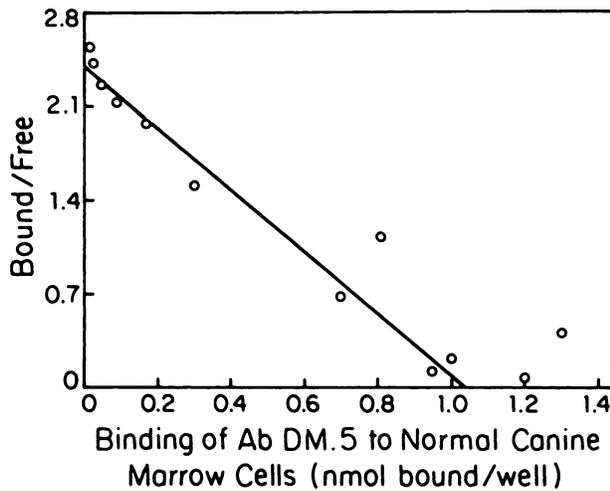


FIGURE 2
Scatchard plot of the binding (nanomoles bound/well) of anti-body DM.5 to normal canine marrow cells ($n = 3$).

After the initial rapid fall, the slope of the curve of DM-5 both with and without PTU remained steeper than that of the control antibody suggesting that antibody-antigen binding continued after the early phase. There was no significant difference in mean blood levels of DM.5 with or without PTU treatment.

Figure 4 shows the activity, expressed as percent of the injected dose per gram of tissue, of ^{131}I -labeled DM.5 in various organs of interest with and without PTU pretreatment. PTU did not appear to increase localization of DM.5 in non-target organs. There was little appreciable decrease in marrow activity between 2-4 hr after infusion in the PTU group when compared to the non-PTU treated animals (all values are mean, $n = 3$ animals in each group). Although marrow localization at 2 hr was not significantly different between the two groups ($0.32 \pm .02$ vs $0.29 \pm .03$) more radioactivity was present, however, at 4, 24 and 48 hr in the PTU-

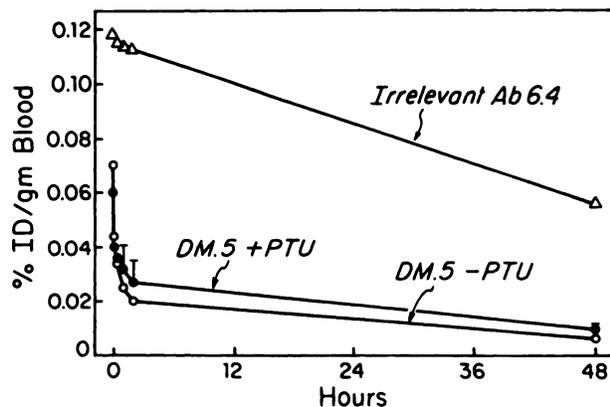


FIGURE 3
Mean blood levels of ^{131}I -labeled DM.5 (relevant) with and without PTU and ^{125}I -labeled 6.4 (irrelevant) antibodies following the injection of 1 mg/kg into normal dogs. (Bars indicate standard error).

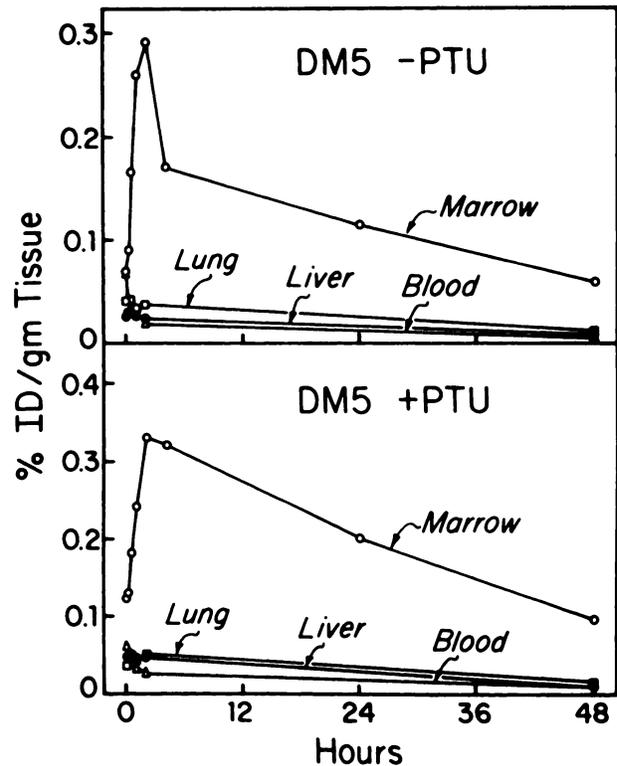


FIGURE 4
Mean activity curves for organs of interest (liver, lung, marrow, and blood) with and without PTU pretreatments, generated by establishing a correlation between counts per pixel obtained by external imaging and the actual radionuclide concentration per gram of tissue measured directly in a well counter. All values are mean ($n = 3$ in each group) and expressed as %ID/g of tissue.

treated group when compared to the control animals ($p = 0.04$).

Half-life

When the elimination kinetics of marrow activity was analyzed on a semi-logarithmic scale of %ID/gm vs time a single elimination half-life was observed for the PTU treated animals ($t_{1/2} = 24.6 \pm 0.6$ hr) (Fig. 5). The three non-PTU treated dogs all exhibited a biphasic elimination with an early $t_{1/2} = 2.6 \pm 0.18$ hr followed by a slower clearance with a $t_{1/2} = 26.2 \pm 0.4$ hr.

Effect of PTU on Plasma TCA Soluble Radioactivity

Plasma TCA soluble (non-protein bound) radioactivity increased significantly during the 2-4 hr postinfusion period in the control animals (Fig. 6). PTU pretreated animals showed no appreciable rise in plasma TCA soluble Radioactivity during the same time period.

Estimated Radiation Dosimetry with and without PTU Pretreatment

Based on the mean organ weights obtained at autopsy in PTU and non-PTU treated animals, ($n = 3$, total body weight 10.3 kg, lung 71 g, liver 326 g, marrow 214 g) the estimated radiation dose (cGy/mCi ^{131}I injected) delivered was determined (Table I). PTU did not ad-

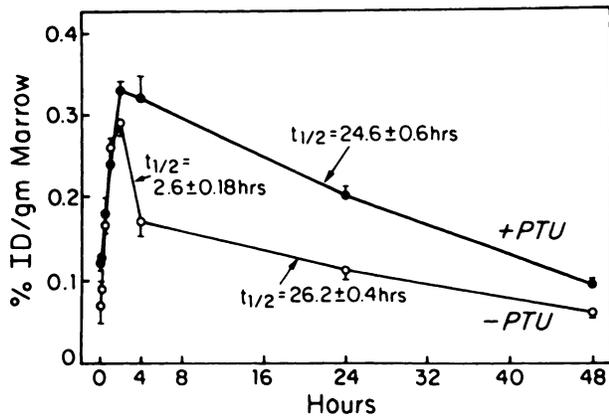


FIGURE 5

Marrow clearance curves with and without PTU pretreatment. A single elimination half-life ($t_{1/2} = 24.6 \pm 0.6$ hr) is observed in the PTU-treated dogs while the nontreated group exhibited a biphasic elimination with an early phase ($t_{1/2} = 2.6 \pm 0.18$ hr) followed by a slower clearance ($t_{1/2} = 26.6 \pm 0.4$). Values are mean \pm s.d. ($n = 3$) and expressed as %ID/g marrow.

versely affect radiation delivery to non-target organs but markedly increased the total dose delivered to marrow per mCi of ^{131}I injected by 35% over the untreated group. Therefore in the non-PTU pretreated animals, a given dose of 1800 cGy to red marrow would deliver 350 cGy to liver and 393 cGy to lung. Pretreatment with PTU would allow the same dose (1800 cGy) to marrow but would decrease the dose delivered to liver and lung by 30% (242 cGy) and 25% (296 cGy) respectively.

DISCUSSION

We previously demonstrated the ability to selectively target marrow with a high degree of specificity utilizing

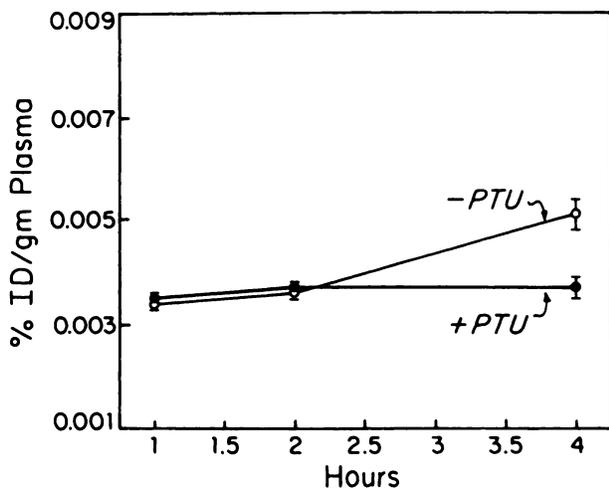


FIGURE 6

Plasma TCA soluble radioactivity expressed as %ID/g of plasma. Unlike the control group, PTU pretreated dogs showed no rise in TCA soluble radioactivity during the 2–4 hr time interval. Values are mean ($n = 3$ in each group).

TABLE 1
Estimated Radiation Dose

Organ	+PTU group	-PTU group
Liver	7.1 cGy/mCi	6.63 cGy/mCi
Lungs	8.67 cGy/mCi	7.44 cGy/mCi
Marrow	52.6 cGy/mCi	34.0 cGy/mCi
* Liver	242 cGy	350 cGy
* Lungs	296 cGy	393 cGy
* Marrow	1800 cGy	1800 cGy

* A dose sufficient to deliver 1,800 cGy to red marrow in both groups would result in the following differences in non-target organ radiation. Pretreatment with PTU resulted in 30% less dose to liver and 25% less to lung.

an ^{131}I -labeled anti-myeloid antibody, DM.5, a finding which supports the use of this technique to deliver radiation to marrow-based diseases during a marrow transplant regimen. In that study, the in vivo biodistribution of radiolabeled DM.5 demonstrated rapid localization within the marrow space with peak activity occurring at 2 hr postinfusion. However, 50% of the maximal activity was cleared from the marrow within 4 hr of infusion accompanied by a sharp rise in plasma TCA soluble radioactivity. We reasoned that rapid internalization, digestion and dehalogenation of the antibody might be, at least in part, responsible for the initial rapid decline in marrow activity. Since iodinated proteins, including MAbs, may bear some resemblance to native thyroid hormone, they may be subject to similar enzymatic pathways responsible for the degradation of T4 to T3 (i.e., monodeiodination). PTU, a derivative of 2-thiouracil, inhibits 5' deiodinases in a competitive fashion. Therefore this agent was administered to dogs prior to receiving ^{131}I -radiolabeled DM.5 in an attempt to reduce deiodination of the radiolabeled antibody and possibly result in more stable retention of the immunoconjugate in the target tissue.

PTU pretreatment appeared to have the desired effect resulting in improved marrow localization of ^{131}I -labeled DM.5 with a greater percent of the injected dose present at 2 hr and with no appreciable loss of activity during the 2–4 hr time period, a finding in contrast to the control group where marrow activity declined a mean $45 \pm 0.5\%$ over this same time interval. Additionally, a rise in plasma TCA soluble radioactivity was not demonstrated in the PTU treated group within the same 2–4 hr time period.

These results suggest that inhibition of deiodinases resulted in longer residence time of the radionuclide in its target tissue. Additionally PTU did not adversely affect biodistribution to other critical non-target organs when compared to the control animals. Dosimetric estimates extrapolated from these trace biodistribution

studies support an improvement in dosimetry for the PTU treated group allowing 35% more radiation delivered to marrow per mCi ^{131}I injected. Arguably PTU may inhibit other enzyme systems involved in protein degradation in addition to deiodinases which may have contributed to the observed elimination kinetics between the two groups. The finding of stable marrow: blood ratios between the 2–4 hr time period along with the absence of a rise in plasma TCA soluble activity would favor the inhibition of deiodinases.

The effect of PTU seen here was likely dependent on the particular antibody-target antigen system studied. For instance, there are other systems in which bound antibody is not internalized, and in theory an effect of PTU would be less likely. Even if internalized, differences in the mechanisms by which radiolabeled MAbs against different antigens are metabolized might have a significant influence on the retention of the radionuclide in target tissue. Further contrasting results might be expected if other labeling methods resistant to dehalogenation were used (16).

Nevertheless, in this study the ability of PTU to favorably alter the elimination kinetics of an ^{131}I -labeled anti-myeloid antibody resulting in longer residence time in the target organ and more favorable dosimetry was demonstrated. Whether or not PTU will have a positive effect on actual ablative studies is currently being examined. Potentially problematic is the fact that PTU has been reported to act as an anti-oxidant. Theoretically, this attribute may allow the "escape" of cells from the lethal effects of irradiation. Alternate labeling methods resistant to dehalogenation as well as the use of other radionuclides with more favorable radiochemistry are therefore also being investigated in this model.

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Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council

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