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POTENTIAL USE OF ^{109}Pd-PORPHYRIN COMPLEXES FOR SELECTIVE LYMPHATIC ABLATION

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DISCLAIMER

INTRODUCTION

Various porphyrins and metalloporphyrins show marked affinity for lymphatic tissue (1,2,3). Since lymphatic tissue plays an important role in mediating the immune process responsible for homograft rejection (4), the possibility arose of using radioactive metalloporphyrins for selective lymphatic ablation for control of homograft rejection.

Certain criteria should be met for the successful use of internally administered radioactive compounds for control of homograft rejection. While procedures directed at total destruction of lymphoid tissue have been shown to obtund homograft rejection, the resulting generalized immunologic crippling has severely limited the usefulness of these methods (5,6). It would be desirable to selectively destroy lymphoid tissue immunologically committed to react to the antigens of the homograft and to spare immunologically uncommitted lymphoid tissue which would tolerate the homograft and reconstitute the immune apparatus. There is evidence indicating that thymocytes may be immunologically uncommitted. They do not respond to antigenic stimulation (7,8,9,10,11), and it takes a thymocyte about 6 weeks after its release from the thymus to gain full immunologic competence (12). Moreover, one of the best tests for immunologic competence, the graft versus host reaction, indicates that cells derived from the thymus are capable of inducing but a very weak graft versus host reaction and even this weak reaction may possibly be due to mature competent lymphocytes present in the medullary cords of the thymus rather than to thymocytes per se (13). Since lymph nodes and spleen contain a significant number of committed cells (14,15,16,17), we felt that a radioactive compound showing large concentrations in the

lymph nodes and spleen, and relatively lower concentrations in the thymus, would be of potential value in the control of homograft rejection. In addition to providing large doses of radiation to the lymph nodes and spleen the radioisotope must show relatively lower concentrations in such critical and radiosensitive organs as intestinal mucosa and bone marrow, and must release its energy locally as occurs with alpha, or beta, or low energy gamma emitting radionuclides, since highly energetic gammas deposit a significant amount of energy away from their site of localization.

In this report we demonstrate that the ^{109}Pd-hematoporphyrin and the ^{109}Pd-protoporphyrin complexes meet the above mentioned criteria and we feel that their trial for selective lymphatic ablation for control of homograft rejection is warranted.

MATERIALS AND METHODS

Hematoporphyrin free base was obtained from the K and K Laboratories (Plain View, N.J.). Protoporphyrin IX was obtained from Calbiochem (Los Angeles, Calif.). $^{109}PdCl_2$ was obtained from the Nuclear Science Corporation (Pittsburgh, Penn.). The ^{109}Pd-porphyrin complex was prepared according to the method of Theorell (18). The porphyrin (100 mg.) was refluxed in glacial acetic acid with 30 mg. of $^{109}PdCl_2$ for 10 minutes. Sodium acetate (250 mg.) was added to the solution and refluxing continued for 2 hours. Another 250 mg. of sodium acetate was then added, the solution diluted with water, and the precipitate recovered. Fifteen ml. of 0.05 N NaOH dissolved part of the precipitate. Further addition of NaOH did not cause further dissolution of the precipitate.

The radioactive yield of the ^{109}Pd-porphyrin was determined by

dividing the radioactivity present in the $^{109}PdCl_2$ into the radioactivity found in the alkali soluble ^{109}Pd-porphyrin solution. The radioactivity was determined by the use of the whole body counter and the 5% 0.088 MEV gamma ray emitted by ^{109m}Ag ($^{109}Pd \xrightarrow{5\%} {}^{109m}Ag$).

In the first series of experiments 6 dogs were injected intravenously with 5 mg. of ^{109}Pd-hematoporphyrin 10 minutes after the intravenous administration of a loading dose of 100 mg. of carrier hematoporphyrin free base.

In the second series of experiments 2 dogs were injected intravenously with 5 mg. of ^{109}Pd-protoporphyrin 10 minutes after the intravenous administration of a loading dose of 100 mg. of carrier Pd-protoporphyrin.

In the third series of experiments 4 dogs, whose ages ranged between 2 and 3 months, were injected intravenously with 5 mg. of ^{109}Pd-hematoporphyrin 10 minutes after the intravenous administration of a loading dose of 100 mg. of carrier hematoporphyrin free base.

In the fourth series of experiments 4 rabbits were injected with 1 mg. of ^{109}Pd-hematoporphyrin 10 minutes after the intravenous administration of 25 mg. of a carrier dose of hematoporphyrin free base.

The administration of a loading dose of carrier porphyrin or metalloporphyrin prior to the administration of the ^{109}Pd-porphyrin complex was prompted by studies which indicated that the porphyrin free base and its corresponding metalloporphyrin compete for the same plasma binding sites and that when these sites are saturated the excess metalloporphyrin is concentrated to a greater extent by lymph nodes (19).

In all experiments plasma samples were obtained every 15 to 60

minutes for the first 5 to 6 hours of the study and also at 12 and 24 hours. The plasma radioactivity was determined utilizing a scintillation counter.

At the end of 24 hours of the initiation of the experiment the dogs and rabbits were killed with intravenous barbiturates, their tissues weighed, and water added to bring each tissue sample to a total weight of 2 g. The tissues were then digested with NaOH and the radioactivity determined using the scintillation counter. Since in dogs the mesenteric lymph nodes consist of two large nodal masses, the right and left mesenteric nodes, three sections were obtained from each of these two nodes and the radioactivity in each of the sections determined.

RESULTS

Table 1 shows the yield obtained when hematoporphyrin is made to react with $PdCl_2$. About 30% of the theoretically expected weight of Pd-hematoporphyrin was recovered in the final injectable alkali solution (Table 1 above the double line). From 20 to 30% of the radioactivity originally present in the $^{109}PdCl_2$ was recovered in the final injectable alkali solution (Table 1 below the double line). An increase on the molar ratio of hematoporphyrin relative to $PdCl_2$ did not result in an increase in the radioactive yield of ^{109}Pd-hematoporphyrin (Table 1 below the double line). Pd-protoporphyrin yields were similar to Pd-hematoporphyrin yields (20).

Figure 1 shows the pattern of disappearance of radioactivity from the plasma of six dogs injected intravenously with ^{109}Pd-hematoporphyrin. The abscissa represents time after the intravenous administration of radioactivity and the ordinate the percent of

administered radioactivity remaining in the plasma. During the first 5 to 6 hours the disappearance of radioactivity from the plasma followed a single exponential clearance function with an average t 1/2 of 4 hours and 31 minutes (range 3 hours and 24 minutes to 5 hours and 24 minutes). Six hours after the administration of ^{109}Pd-hematoporphyrin there is a change in the slope of the curve with the emergence of a second exponential component (average t 1/2 of about 50 hours). About 95% of the administered ^{109}Pd-hematoporphyrin is cleared from the plasma with an average t 1/2 of about 4 1/2 hours and 5% with an average t 1/2 of about 50 hours.

Table 2 shows the tissue distribution of radioactivity in the six dogs 24 hours after the injection of ^{109}Pd-hematoporphyrin. The concentration of radioactivity in tissues is expressed as the fraction of the administered dose x 10^{-6} per gram of wet weight. The average concentration of radioactivity in mesenteric lymph nodes was 4.7 times greater than bone marrow and 17.6 times greater than duodenal mucosa (range 6.9 and 25.9 times greater than bone marrow and duodenal mucosa respectively to 2.0 and 5.6 times greater than bone marrow and duodenal mucosa respectively)*. The average concentration of ^{109}Pd-hematoporphyrin in non-mesenteric lymph nodes (popliteal, femoral and cervical) was 2.3 times greater than bone marrow and 8.7 times greater than duodenal mucosa (range 3.2 and 12.2 times greater than bone marrow and duodenal mucosa respectively to 2.0 and 6 times greater than bone marrow and duodenal mucosa respectively)*. In the same animal the concentration of ^{109}Pd-hematoporphyrin in the various lymph nodes varied markedly. Even sections

*Very few lymph nodes showed much lower ratios and were not included in this evaluation.

from the same mesenteric lymph nodes were found to vary. At present we have no explanation for the high uptake of porphyrins and metalloporphyrins by lymph nodes nor for the wide variations in the concentration of metalloporphyrins in the lymph nodes of the same animal. The concentration of ^{109}Pd-hematoporphyrin in the spleen was considerably below that achieved by the lymph nodes. At autopsy the spleen of these dogs was markedly enlarged probably due to the vascular pooling subsequent to barbiturate administration (21). Thus the low concentration of ^{109}Pd-hematoporphyrin in the spleen of dogs may be due to the dilutional effect of vascular pooling. Since in rabbits vascular pooling in the spleen does not occur following barbiturate administration, we studied the tissue distribution of radioactivity in 4 rabbits killed with barbiturates, 24 hours after the intravenous administration of ^{109}Pd-hematoporphyrin. As can be seen from Table 3, the concentration of ^{109}Pd-hematoporphyrin in the spleen of rabbits is comparable to that found in lymph nodes. Otherwise the pattern of tissue radioactivity is essentially similar to that observed in dogs with one difference: in rabbits the concentration of ^{109}Pd-hematoporphyrin in the bone marrow is considerably greater than that observed in dogs. Whether this high uptake of ^{109}Pd-hematoporphyrin in the bone marrow of dogs is related to the acidophilic character of the neutrophils and its precursors or to other factors is conjectural at this point (22).

Figure 2 shows the pattern of disappearance of radioactivity in 2 dogs injected intravenously with ^{109}Pd-protoporphyrin. For the first 5 hours of the study, the disappearance of radioactivity from the plasma followed a single exponential function with an average

t 1/2 of 3 hours and 28 minutes.

Table 4 shows the tissue distribution of radioactivity in the two mature dogs injected intravenously with ^{109}Pd-protoporphyrin. The pattern of tissue distribution of radioactivity is very similar to that observed following the administration of ^{109}Pd-hematoporphyrin.

Table 5 shows the tissue distribution of radioactivity in the three dogs, aged 2-3 months, injected intravenously with ^{109}Pd-hematoporphyrin. In these animals the concentration of radioactivity in the thymus is low both in absolute and relative terms.

DISCUSSION

With a few exceptions, even when the ratio of concentration of ^{109}Pd-porphyrin in lymph nodes relative to bone marrow, intestinal mucosa and thymus is at its lowest it is still possible to achieve in the dog a differential in exposure dose whereby the vast majority of lymph nodes are exposed to doses of 1000 rads and above, the bone marrow to doses below 500 rads, the intestinal mucosa to doses below 180 rads, and the thymus to doses below 30 rads. Since exposure of lymphoid tissue to doses of 1000 rads appears to be sufficient to abrogate the immune response (23,24), while in mammals doses of 500 rads to bone marrow and 140 rads to intestinal mucosa may not be lethal if proper symptomatic therapy is instituted (25,26,27), it is expected that at these dose levels the animal would tolerate a homograft and would not succumb to the ill effects of acute radiation. Moreover, if thymocytes are immunologically uncommitted cells and if cellular traffic from the thymus to the circulation and eventually lymph nodes does occur as is reported (28), and if thymocytes are not

end cells, then it is conceivable that these thymocytes will repopulate the lymphatic system with cells capable of tolerating the homograft and of reconstituting a functional immune apparatus.

As mentioned earlier, the low concentration of ^{109}Pd-hematoporphyrin in the spleen may be simply due to vascular pooling in this organ subsequent to barbiturate administration. The studies in rabbits favour this hypothesis. However, even if this were not the case, splenectomy would be an alternate way of ridding the body of committed cells found in this organ.

One of the obvious shortcomings of this method is the relatively high radiation dose delivered to the liver and renal cortices, (2300 and 600 rads respectively). While at these dose levels these organs are not acutely affected, there is evidence, especially in the case of the kidneys, that vascular changes would ultimately result in deranged function (29).

In spite of its shortcomings we believe that a trial of ^{109}Pd-hematoporphyrin or ^{109}Pd-protoporphyrin is justified and we are presently engaged in such an investigation. We have chosen to use the ^{109}Pd-protoporphyrin rather than the metallohematoporphyrin because we have observed bleeding abnormalities following the administration of large quantities of the latter compound, but not with the former. We have also chosen to give repeated doses of milk of magnesia to the experimental animals receiving such large radioactive doses of ^{109}Pd-protoporphyrin, since the large amounts of ^{109}Pd-protoporphyrin which accumulate in the lumen of the lower ileum and colon (probably due to the biliary excretion of the metalloporphyrin) were not observed following ingestion of cathartic doses of milk of magnesia (30).

While the lower ileum and colon are reported to be relatively radio-resistant (31), we feel that it is advisable not to expose any part of the gastro-intestinal tract to large doses of radiation.

SUMMARY

Following the intravenous administration of ^{109}Pd-hematoporphyrin or ^{109}Pd-protoporphyrin in dogs it is possible to obtain a differential in radiation exposure, whereby lymph nodes are exposed to doses of about 1000 rads and above, the bone marrow to doses of 500 rads, the intestinal mucosa to doses of 140 rads and the thymus to doses of 30 rads.

It is suggested that such a differential in the exposure dose may result in tolerance to a homograft and at the same time in the reconstitution of a functional immune apparatus. Possible delayed effects due to vascular injury with subsequent functional derangement, especially in liver and kidneys, is an obvious shortcoming in the use of radioactive metalloporphyrins for control of homograft rejection.

Figure 1 shows the pattern of disappearance of radioactivity from the plasma of six dogs injected intravenously with ^{109}Pd-hematoporphyrin.

Figure 2 shows the pattern of disappearance of radioactivity in two dogs injected intravenously with ^{109}Pd-protoporphyrin.

Table 1 shows the yield obtained when hematoporphyrin is made to react with $PdCl_2$.

Table 2 shows the tissue distribution of radioactivity in six dogs two hours after the injection of ^{109}Pd-hematoporphyrin.

Table 3 shows the tissue distribution of radioactivity in four rabbits, killed with barbiturates, 24 hours after the intravenous administration of ^{109}Pd-hematoporphyrin.

Table 4 shows the tissue distribution of radioactivity in two dogs injected intravenously with ^{109}Pd-protoporphyrin.

Table 5 shows the tissue distribution of radioactivity in three dogs, aged 2-3 months, injected intravenously with ^{109}Pd-hematoporphyrin.

TABLE 1. Pd-HEMATOPORPHYRIN YIELDS

Weight of $PdCl_2$	Weight of Hematoporphyrin	Weight of product of reaction of $PdCl_2$ with hematoporphyrin (soluble in NaOH)	Ratio of moles of hematoporphyrin to moles of $PdCl_2$	Yield
186 mg	589 mg	202 mg	1 : 1	29.2%

cpm present in $^{109}PdCl_2$	cpm present in product of reaction of $^{109}PdCl_2$ with hematoporphyrin (soluble in NaOH)	Ratio of moles of hematoporphyrin to moles of $^{109}PdCl_2$	Yield
1559000	313800	1.2 : 1	20.1%
648000	197150	1.2 : 1	30.6%
407153	96209	3.7 : 1	23.6%
1184420	248000	24 : 1	21.0%

TABLE 2. FRACTION OF ADMINISTERED ^{109}Pd-HEMATOPORPHYRIN x 10^{-6} PER GRAM WET WEIGHT

Tissue	Dog # 1	2	3	4	5	6	Average for all dogs	
Liver	2260	2400	2140	2600	2500	2210	2350	
Renal cortex	560	660	480	650	650	650	608	
Femoral bone marrow	480	530	480	470	560	250*	504	
Adrenal	450	480	410	390	420	350	417	
Spleen	250	400	610	200	500	400	393	
Duodenal Mucosa	110	150	150	120	170	110	135	
Lung	51	52	43	48	53	43	48	
Renal Medulla	42	38	51	53	51	46	47	
Pancreas	14	22	19	19	16	19	18	
Muscle	8	10	10	12	8	8	9	
Right popliteal lymph node	1080	1230	1150	1340	1130	1070	1121	
Left popliteal lymph node	1160	1270	1320	1240	860	810	1153	
Right femoral lymph node	1350	1050	890	910	1300	1020	1086	1182
Left femoral lymph node	1040	1220	1640	1210	1060	1110	1213	
Left cervical lymph node	1320	1470	1060	1650	1430	1110	1340	
Right mesenteric lymph node								
Section #1	1800	3290	1820	3320	2260	3040		
Section #2	1490	2190	1620	1980	2020	3070		
Section #3	2000	1750	2130	760	3500	2100		
Left mesenteric lymph node							2385	
Section #1	1210	1800	2150	2150	3150	2400		
Section #2	2000	2700	1600	3000	1460	2260		
Section #3	2240	2150	1140	1470	1490	960		

*Very fatty marrow; value obtained not included in calculating average concentration of radioactivity in bone marrow.

TABLE 3. FRACTION OF ADMINISTERED ^{109}Pd-HEMATOPORPHYRIN x 10^{-6} PER GRAM WET WEIGHT

Tissue	Rabbits 1	2	3	4	Average for all rabbits
Liver	3650	3420	3490	3180	3435
Femoral bone marrow	3150	2740	3740	3520	3287
Spleen	2460	2830	3290	2940	2880
Mesenteric lymph node	2220	2160	2990	2780	2537
Popliteal lymph node	1700	760	1440	1930	1457
Renal cortex	1040	1080	910	1210	1060
Muscle	26	22	31	34	28
Pancreas	78	72	74	61	71

TABLE 4. FRACTION OF ADMINISTERED ^{109}Pd-PROTOPORPHYRIN x 10^{-6} PER GRAM WET WEIGHT

Tissue	Dog 7	Dog 8	Average for the 2 dogs
Liver	2210	2600	2405
Renal cortex	600	600	600
Femoral bone marrow	370	410	390
Spleen	320	160	240
Duodenal mucosa	115	140	128
Muscle	13	11	12
Right popliteal lymph node	1310	1410	1360
Left popliteal lymph node	1670	1050	1360
Right cervical lymph node	1420	1030	1225
Right mesenteric lymph node			
Section #1	1460	3300	
Section #2	2730	2180	
Section #3	2320	820	
Left Mesenteric lymph node			1905
Section #1	2700	1660	
Section #2	2790	1580	
Section #3	1020	300	

TABLE 5. FRACTION OF ADMINISTERED ^{109}Pd-HEMATOPORPHYRIN x 10^{-6} PER GRAM WET WEIGHT

Tissue	Average of 4 dogs (#9,10,11,12)	Ratio of average concentration in tissue to average concentration in muscle
Liver	2100	190
Lymph node mesenteric	1920	174
Lymph node popliteal	1240	113
Lymph node femoral	1130	102
Lymph node cervical	1040	94.5
Kidney	590	54
Femoral bone marrow	446	40.5
Spleen	297	27
Duodenal mucosa	118	11
Thymus	29	2.6
Muscle	11	1

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Appendix

Following the intravenous administration of ^{109}Pd-hematoporphyrin, the radiation dose delivered to the various tissues can be calculated as follows:

Let

$N_i(t)$ = the fraction of administered radioactivity present per gram of tissue "i" at any time (t)

k_i = the fraction of blood radioactivity entering 1 gram of tissue "i" per unit time

kp = the physical decay constant of the radioactive substance

f(t) = the radioactivity in the blood at any time (t).

Then

$$\frac{dNi}{dt} = ki\ f(t) - kpN_i \qquad (A)$$

Assuming $N_{io} = 0$, then

$$N_i(t) = ki\ e^{-kpt} \int_0^t e^{kpt}\ f(t)\ dt \qquad (B)$$

The solution for $f(t) = (Ae^{-r_1 t} + Be^{-r_2 t})\ e^{-kpt}$ (C)*

Therefore

$$N_{i(t)} = k_i\ e^{-kpt}\left[\frac{A}{r_1}\ (1-e^{-r_1 t}) + \frac{B}{r_2}\ (1-e^{-r_2 t})\right]$$

For a given value of t = T we can calculate k_i:

$$k_i = \frac{N_{i(T)}\ e^{kpT}}{\left[\frac{A}{r_1}\ (1-e^{-r_1 T}) + \frac{B}{r_2}\ (1-e^{-r_2 T})\right]}$$

*In all dogs injected with ^{109}Pd-hematoporphyrin, subsequent to a loading dose of 100 mg of hematoporphyrin free base, the disappearance of radioactivity from the plasma could be described by two exponential components. These components were evaluated subsequent to correction for physical decay.

where

A = fraction of administered radioactivity cleared from the plasma at a rate r_1 and

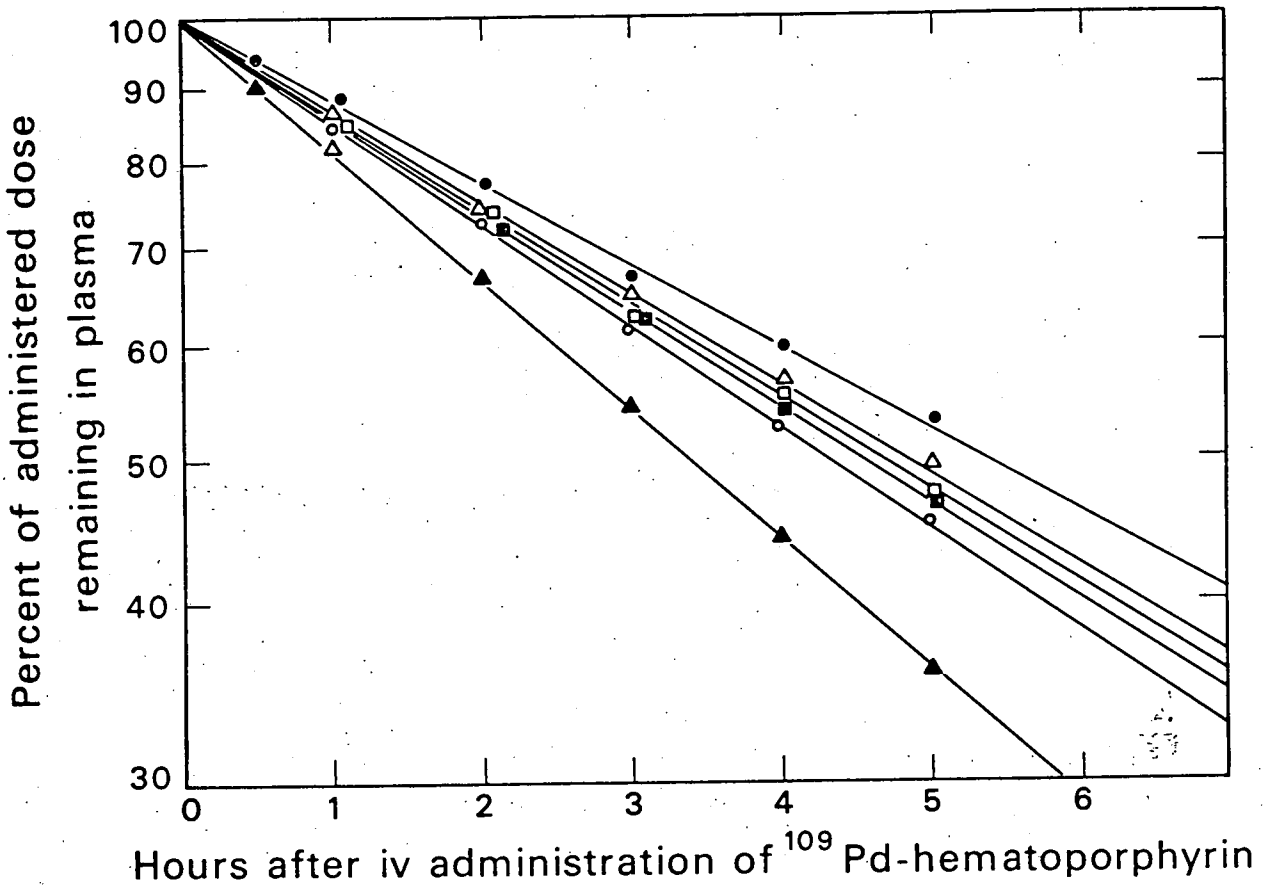
B = fraction of administered radioactivity cleared from the plasma at a rate r_2.

Using the average values for A, B, r_1 and r_2 obtained from the data measured in this study (A = 0.95, B = 0.05, r_1 = 0.0072 days^{-1}, and r_2 = 0.00055 days $^{-1}$) and using the fraction of the administered radioactivity found in a gram of a given tissue when the animal is sacrificed at time T, a value ki can be calculated from E. One can then calculate the equilibrium dose in a given tissue from ^{109}Pd β^- emission by the following formula:

$$\text{Dose} = 51.2\ \bar{E}\ I \int_0^\infty N_1(t)\ dt \qquad (32)$$

where I = administered radioactivity in μCi

and $\bar{E}$ = average energy of ^{109}Pd in MEV


Percent of administered dose
remaining in plasma
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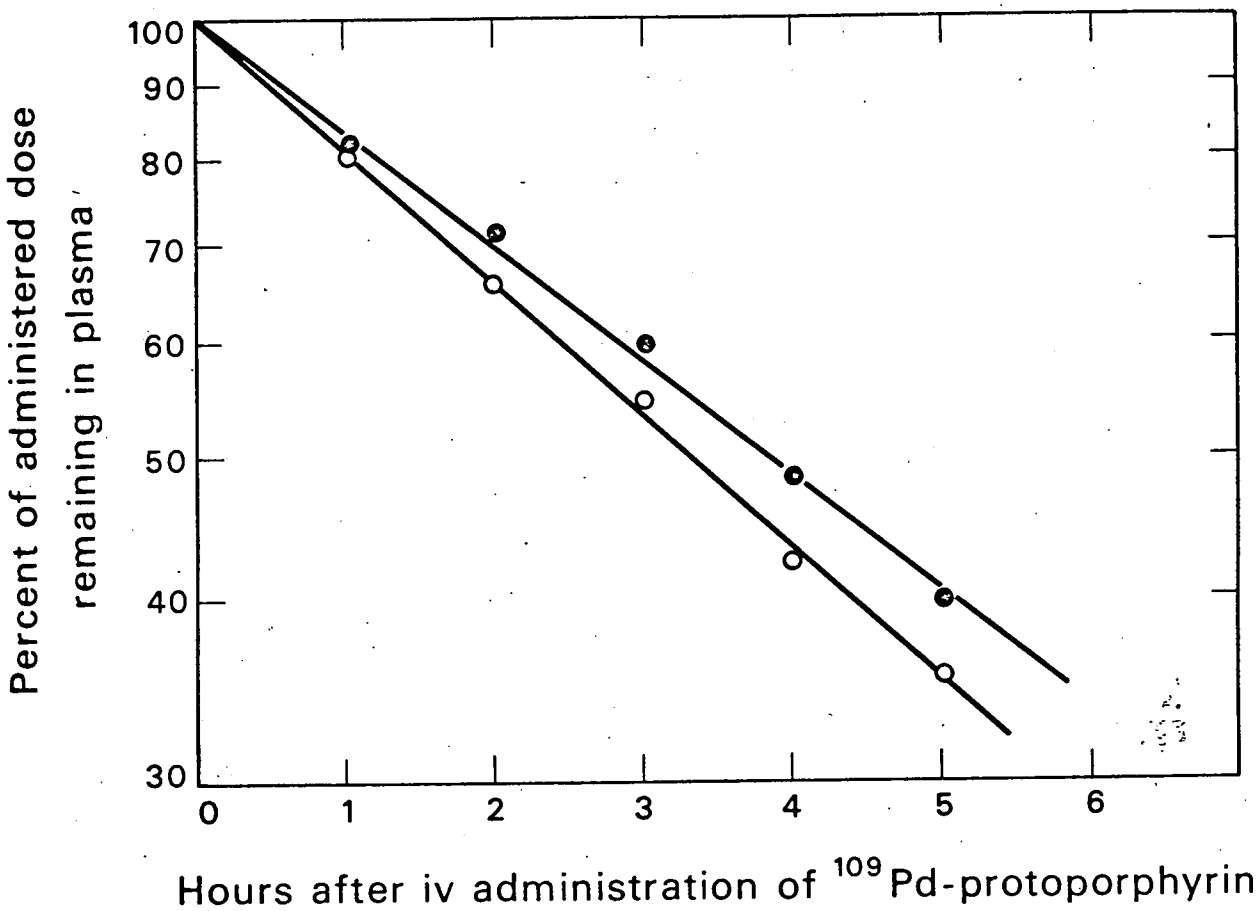
Hours after iv administration of ^{109}Pd-hematoporphyrin

DBL 705 5730


Percent of administered dose remaining in plasma
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Hours after iv administration of ^{109}Pd-protoporphyrin

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