Argonne-Utah Studies of ^{224}Ra Endosteal Surface Dosimetry*

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Running Title: ^{224}Ra Endosteal Dosimetry

SUMMARY

The activities of ^{212}Pb relative to ^{224}Ra and of ^{222}Rn relative to ^{226}Ra were measured in bone surface deposits 24 h after radium injection into beagles. The fractional retention of ^{220}Rn atoms was measured *in vitro* with hydrated and dehydrated bone samples to determine the effect of water content on the escape of radon from bone surfaces. The experimental data suggest that substantial ^{224}Ra daughter product disequilibrium exists in bone surface deposits. Estimates for the lower and upper limits on the fractional retention of ^{220}Rn *in vivo* are 0.05 and 0.25, respectively. The average bone surface activity of ^{212}Pb relative to ^{224}Ra ranged from 0.34 to 0.71 for four dogs, with the majority of the values toward the low end of the range. Only a

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small portion of the deposited ^{212}Pb came from lead in the injection solution despite near equilibrium between ^{224}Ra and its daughters at the time of injection. The retention data indicate that the endosteal tissue dose rate in the dogs at one day was actually one-third to about one-half that which would be calculated assuming equilibrium of ^{224}Ra daughter products in bone surface deposits.

INTRODUCTION

The German patients injected with ^{224}Ra to alleviate the pain of certain diseases of the skeleton [5,10] provide one of the best sources of information on the risk of cancer in humans from internal emitter exposure. Doses to bone have been calculated with the assumption that ^{224}Ra daughter products are completely retained [11], but three retention studies conclude or imply the opposite [2,3,4]. We have focused on this question with an experiment designed to examine the state of equilibrium between ^{224}Ra and two of its daughters, ^{220}Rn and ^{212}Pb, at the endosteal surfaces of dog bone.

MATERIALS AND METHODS

Six beagles, 19 to 25 months of age, were selected from the University of Utah colony. Four were injected with ^{224}Ra nearly in equilibrium with its daughter products; one was injected with ^{226}Ra separated from its daughters; and the sixth was injected with ^{212}Pb. All were sacrificed 24 h after injection. Information on sex, weight, injection level, and age is given in Table 1. The dog identification numbers are slightly modified from those found in the tabular data on experimental dogs listed annually in the University of Utah progress report under the heading "Test Animals" [7].

Long bones were defleshed, the mid-diaphyses excised and cut longitudinally, and the marrow was removed, usually with a pressurized stream of n-butyl alcohol. Samples were transported to Argonne by airplane, and the endosteal surface activity was measured in vacuum by alpha spectrometry in a way similar to that previously described [9] but without collimation. In some cases, marrow removal was delayed until the samples arrived at Argonne.

Alpha spectra similar to those shown in Fig. 1 were obtained from all samples measured in vacuum except in cases of equipment failure. The spectrum peaks correspond to alpha particle emission from bone surface deposits and the

tails to emission from volume deposits. In some cases, the spectra of individual radionuclides were separated from the total by stripping techniques. In all cases, the heights of peak maxima above the substructure from higher energy alphas were measured. To obtain experimental data on the retention of ^{220}Rn, ^{212}Bi and ^{212}Po for the dogs injected with ^{224}Ra and ^{214}Po for the dog injected with ^{226}Ra, we derived ratios of daughter product to parent activity from integrals of the peaks in stripped spectra or from the peak heights.

Bone sample surface areas measured from photographs taken from the vantage point of the detector were used to normalize peak counting rates for the intercomparison of bone surface uptake in different dogs. The areas obtained were systematic underestimates, probably by about 5 to 15%, of the true three-dimensional surface areas. Although these underestimates affected the normalized counting rate, the error was not large enough to invalidate the comparison. The values obtained, however, were especially useful for interpretation of the data from the dog injected with ^{212}Pb.

RADON RETENTION

(a) ^{220}Rn Retention in Vacuum

Fractional retention is presented in Table 2. Since the half-life of ^{220}Rn is only 55 s, the data do not reflect the retention in vivo but can be used to establish an upper limit for it.

When hydrated bone samples containing ^{226}Ra are placed in vacuum, they dry rapidly and ^{222}Rn retention increases abruptly. The classic buildup of radioactivity in Fig. 2, observed by alpha spectrometry of the cortical endosteal surface of a bone piece from the University of Utah collection is consistent with a near instantaneous increase in ^{222}Rn retention coincident with the start of measurement in vacuum. Although not demonstrated here, rehydration of the vacuum-dried bone by exposure to an atmosphere saturated with water vapor reduces the ^{222}Rn retention substantially.

The chemical identity of ^{220}Rn and ^{222}Rn guarantees that the same qualitative behavior occurs for fractional ^{220}Rn retention during dehydration under vacuum, but the change is so abrupt and the ^{220}Rn half-life so short that the change cannot be observed with the normal counting intervals of 4000 s or more.

It, therefore, seems certain that ^{220}Rn retention at bone surfaces in the fluid saturated state that exists *in vivo* would be no greater than the values given in Table 1; despite its short half-life, ^{220}Rn generated by bone surface deposits of ^{224}Ra *in vivo* is not in equilibrium with ^{224}Ra.

(b) ^{222}Rn Retention at Bone Surfaces *In Vivo*

The ratio of ^{222}Rn to ^{226}Ra activities, based on observations of surface-deposited ^{214}Po and ^{226}Ra in seven bone samples from dog T115R5, is shown in Table 3. Because the half-life of ^{222}Rn is 3.83 days and measurement began within 9 h of sacrifice, the data strongly reflect the retention *in vivo* during the 24 h between injection and death. By lengthy analyses, the data can be shown to be consistent with a constant fractional retention of the ^{222}Rn atoms produced *in vivo* between 0.05 and 0.10 during the survival period. Due to the chemical identity of the two isotopes, it is not likely that ^{220}Rn retention would be less than ^{222}Rn retention. Therefore, the ^{222}Rn data set a lower limit to the fractional retention of ^{220}Rn *in vivo*.

(c) Effect of Water

During the course of these studies, it became clear that surface water content was a major controlling factor in determining surface retention of ^{220}Rn. This factor was demonstrated indirectly by studies of ^{222}Rn retention, such as shown in Fig. 2, and directly, by observations of dramatic decreases in ^{220}Rn retention when surface moisture was added to vacuum-dehydrated samples from dog T31Q5. The results of one series of experiments in which samples were placed at room temperature in a chamber containing 100% relative humidity are reported in Table 4. The samples were in the chamber long enough to establish radioactive equilibrium between ^{212}Pb and retained ^{220}Rn. This equilibrium allowed measurement of ^{220}Rn retention in the water-vapor-saturated atmosphere to be based on observation of ^{212}Pb daughters by alpha spectrometry in vacuum. Fractional retention during storage in the vapor-saturated atmosphere was only one-fifth that observed in vacuum following storage (0.19 vs. 0.95). Other samples under similar conditions of storage gave average fractional retentions in the range 0.20-0.30.

The moisture level of bone bathed in body fluid is higher than that in a vapor-saturated atmosphere as judged by differences between bone sample

weights after water soaking and exposure to vapor. Therefore, the fractional retention *in vivo* should be at least as low as in the vapor chamber and might be lower if an additional reduction accompanies additional water. The upper limit to fractional ^{220}Rn retention *in vivo* therefore appears to be about 0.25.

(d) Rate of Diffusion

The surface deposit of radium in dog bone is almost certainly less than 3-μm thick [8]. The time required for a diffusing radon gas atom to travel this distance by random walk is 0.2 s, assuming a diffusion coefficient of 2.2×10^{-7} cm^2/s [1], identical to that for photographic emulsion, which, like bone, is a composite of inorganic crystals and organic matrix. This time is less than 1/250 of the half-life of ^{220}Rn. By this argument, nearly all ^{220}Rn atoms not trapped in bone crystals [6] should escape the surface deposit and the difference in retentions between ^{220}Rn and ^{222}Rn should be negligible.

When fresh bone samples are measured in vacuum for many half-lives, the fractional retentions of ^{220}Rn and ^{222}Rn approach asymptotic values, which differ substantially from one another -- about 0.30 for ^{222}Rn and about 0.75 for ^{220}Rn -- contrary to the above prediction. The conditions of measurement, the surface deposit thicknesses [8] and the mechanisms of retention and transport are essentially identical for both isotopes. The only difference is in the half-lives. Therefore, at the low moisture content in vacuum, the actual rate of diffusion is apparently much slower than implied by the diffusion coefficient previously assumed. Though perhaps coincidental, the ratio of fractional retentions after prolonged measurement in vacuum ($0.75/0.30 = 2.5$) is about the same as the ratio of the fractional retention of ^{220}Rn in water vapor saturated bone to the fractional retention of ^{222}Rn *in vivo* ($\cong 0.25/0.1 = 2.5$). This similarity in values may mean that diffusion is also slow in fully hydrated bone, though such a conclusion would be speculative since vapor-saturated bone is not fully hydrated.

From this and preceding sections, we conclude that fractional ^{220}Rn retention at bone surfaces *in vivo* is 1 to 2.5 times that for ^{222}Rn and lies somewhere in the range of about 0.05 to 0.25.

^{212}Pb RETENTION

The retention of ^{212}Pb is determined from the combined alpha activities of its daughters, ^{212}Bi and ^{212}Po, with the aid of the Bateman equations. The calculation depends on the ^{220}Rn retention during the time between death and first measurement, a period of 8.7 to 11.1 h for the ^{224}Ra-injected dogs. During most of this time, the samples were sealed in plastic bags. The fractional ^{220}Rn retention for bagged samples was estimated to be 0.27 from observations on bone from dog T31Q5 prepared, packaged, and shipped under the same conditions as most other samples.

The retention of ^{212}Pb *in vivo*, expressed as the ratio of ^{212}Pb activity to ^{224}Ra activity at death, is presented in Table 5. The values for dog T28Q5 are substantially higher than the values for the other dogs. We do not believe that this is an artifact but have no explanation for it other than biological variability.

Lead activity on bone surfaces in the ^{224}Ra-injected dogs comes from two sources: the decay of ^{224}Ra and its daughters and the uptake of ^{212}Pb contained in the injected solution. The relative amounts of ^{212}Pb activity at death normalized to the projected bone surface area and to the injected activity of ^{212}Pb are given in Table 6 for three ^{224}Ra-injected dogs and for the ^{212}Pb-injected dog. The ^{212}Pb-injected dog is much lower than any of the ^{224}Ra-injected dogs with the clear implication that, 24 h after injection, little bone surface ^{212}Pb comes from the injection solution. Therefore, injected ^{212}Pb has little influence on the endosteal dose rate one day after injection.

ENERGY RELEASE

The fractional reduction in the endosteal dose rate from surface deposits caused by the disequilibrium of ^{224}Ra daughter products at bone surfaces can be estimated by comparing the average alpha particle energy released per ^{224}Ra disintegration under the different retention assumptions. Values are given in Table 7 for the four ^{224}Ra-injected dogs assuming ^{212}Bi and ^{212}Po are in equilibrium with ^{212}Pb and fractional ^{220}Rn retentions of 0.05 and 0.25. For comparison, the average energy released is 27.6 MeV under the assumption of decay series equilibrium and is 26.5 MeV under the assumption of complete retention with no deposition of injected daughters. Therefore, the actual

endosteal dose rate at 24 h is one-third to about one-half of the equilibrium dose rate, depending on the dog.

APPLICABILITY TO HUMAN DOSIMETRY

Because ^{220}Rn is chemically inert, species differences in retention are not likely to arise from differences in body chemistry. Thicknesses of radionuclide deposits on bone surfaces are the same in humans and dogs [8]. Therefore, the distance which a ^{220}Rn atom must travel to escape from the deposit is the same in both species. Differences in retention could arise from differences in the rate of diffusion. It should be possible to judge whether this occurs by studies of ^{220}Rn retention following bone surface deposition in vitro.

Lead-212 is a chemically reactive metal and there is no reason to believe that ^{212}Pb retention would be the same in humans and dogs. The retention in humans might be estimated by extrapolation of ^{212}Pb retention from the species in which it has been measured.

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FIGURE LEGENDS

Figure 1 Alpha particle spectra emitted from the endosteal surfaces of mid-diaphysis bone samples from the right (T28Q5-K6-A) and left (T28Q5-K7-B) tibiae of dog T28Q5. Starting at the left, the peaks correspond to ^{224}Ra, ^{212}Bi, ^{220}Rn, ^{216}Po, and ^{212}Po.

Figure 2 Buildup of ^{214}Po activity in a bone sample from the right tibia of a dog injected with ^{226}Ra, as a function of time in vacuum. Prior to evacuation, the sample was in radioactive equilibrium. The ordinate is proportional to the ratio of ^{222}Rn and ^{226}Ra activities. The curve fit to the data is based on the decay constant of ^{222}Rn, 0.181 day^{-1}. Data were collected by alpha spectrometry of the endosteal surface.

Table 1. Data on experimental animals.

Dog No.	Sex	Age, days	Weight, kg	Nuclide	Activity Injected, μCi
T28Q5	M	577	10.9	^{224}Ra	91.8
T29Q5	M	593	13.0	^{224}Ra	95.3
T30Q5	M	606	12.1	^{224}Ra	119
T31Q5	F	775	10.5	^{224}Ra	111
T115R5	M	572	11.4	^{226}Ra	99.6
T21L5	F	605	7.2	^{212}Pb	106

Table 2. Fractional retention of ^{220}Rn in vacuum during the initial 400 s of observation.

Dog No.	No. Samples	$^{220}Rn/^{224}Ra$	
		Average	Range
T28Q5	7	0.58	0.41-0.72
T29Q5	8	0.76	0.65-0.91
T30Q5	8	0.58	0.41-0.70
T31Q5	8	0.64	0.55-0.69

Table 3. Ratio of ^{222}Rn to ^{226}Ra surface activities during the first 20000 s of measurement.

Sample No.	$^{222}Rn/^{226}Ra$
1	0.030
2	0.027
4	0.035
5	0.030
6	0.026
7	0.027
8	0.029
Average	0.029
Standard deviation	0.003

Table 4. Fractional ^{220}Rn retention for bone samples stored in a water-vapor-saturated atmosphere and in vacuum after storage.

Sample No.	Vapor	Vacuum
1	0.15	0.88
2	0.12	1
3	0.10	0.93
4	0.23	1
5	0.22	0.88
6	0.26	0.94
7	0.21	0.96
8	0.21	1
Average	0.19	0.95
Standard deviation	0.06	0.05

Table 5. Ratio of ^{212}Pb to ^{224}Ra surface activities at death.

Dog No.	$^{212}Pb/^{224}Ra$	
	Average	Range
T28Q5	0.71	0.41-1.3
T29Q5	0.34	0.26-0.40
T30Q5	0.40	0.31-0.48
T31Q5	0.36	0.28-0.43

Table 6. Concentrations of ^{212}Pb activity on bone surfaces at death normalized to the activity of ^{212}Pb in the injection solution.

Dog No.	Relative value, cm^{-2}
T28Q5	1.1 ± 0.3
T29Q5	0.5 ± 0.1
T30Q5	0.6 ± 0.1
T21L5	0.1 ± 0.07

Table 7. Average alpha energy (MeV) released per ^{224}Ra disintegration under different ^{220}Rn retention assumptions.

Dog No.	$^{220}Rn/^{224}Ra$ = 0.05	0.25
T28Q5	11.8	14.5
T29Q5	8.9	11.5
T30Q5	9.2	11.8
T31Q5	9.1	11.7

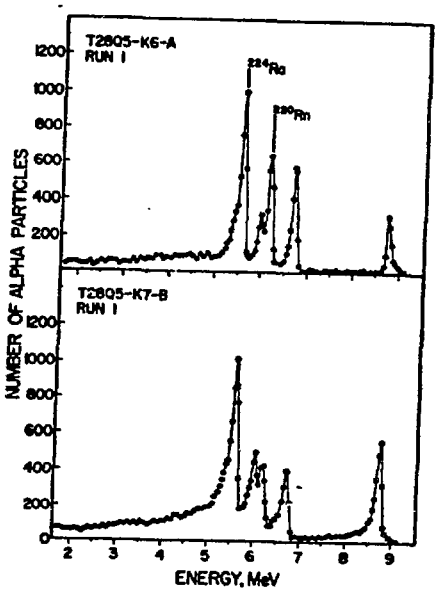
T28Q5-K6-A
RUN I
224Ra
220Rn
T28Q5-K7-B
RUN I
NUMBER OF ALPHA PARTICLES
ENERGY, MeV

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Figure 1

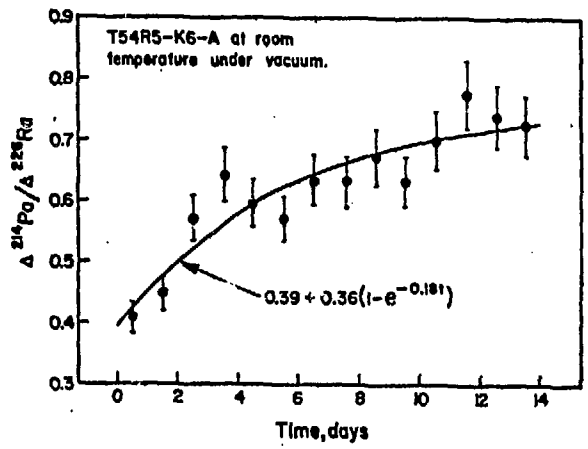
T54R5-K6-A at room temperature under vacuum.
$\Delta^{214}Po/\Delta^{226}Ra$
$0.39 + 0.36(1-e^{-0.18t})$
Time, days
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0
2
4
6
8
10
12
14

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Figure 2