RADIATION DOSIMETRY OF ^{204}Bi- AND ^{206}Bi-CITRATES

Rodney E. Bigler, Gerald A. Russ, and John S. Laughlin

Memorial Sloan-Kettering Cancer Center, New York, New York

The absorbed-radiation doses from ^{204}Bi- and ^{206}Bi-citrates to humans are calculated from available nuclear and biologic data in order to evaluate the relative radiation risk of these radionuclides. The calculations reveal that the radiation dose to the kidneys is reduced by a factor of 8 if ^{204}Bi replaces ^{206}Bi. This reduction suggests that ^{204}Bi should be investigated further as a possible soft-tissue scanning agent.

Malignant breast tumors have been observed to concentrate ^{206}Bi-citrate to a much greater extent than either benign breast lesions or normal breast tissue (*1*). Other reports have shown that bismuth salts are selectively retained in primary brain tumors and in implanted experimental tumors (*2–8*). Russ et al (*9*) have shown that conventional scanning equipment can be used to image this radionuclide. These findings suggest that ^{206}Bi-citrate may be useful as a soft-tissue tumor localizing agent; however, its use for this purpose appears to be limited by its high absorbed-radiation dose to the kidneys (*9*).

Recently, a method for the preparation of another bismuth isotope ^{204}Bi has been established (*10*). The much shorter half-life and similar decay mode of ^{204}Bi, compared to ^{206}Bi, suggest that ^{204}Bi may reduce this radiation dose limitation. The purpose of this report is to calculate the absorbed-radiation dose from ^{204}Bi- and ^{206}Bi-citrates in order to determine whether the above suggestion is correct and, if so, to show how significant a reduction is achieved.

RADIOPHARMACEUTICAL

Bismuth-206 is conveniently produced in 20-mCi amounts by irradiation of natural lead for 4 hr with 15-MeV protons. It is prepared as citrate by methods described previously (*9*). Bismuth-204 is prepared in approximately the same amounts by irradiating ^{206}Pb (99.8% isotopic enrichment) with protons of energy 30–32 MeV for 1.5–2 hr. Details of the technology involved in producing high-quality ^{204}Bi are described by Kinsley et al (*10*).

NUCLEAR DATA

Bismuth-204 has a half-life of 11.2 hr and decays by electron capture with a complex spectrum of 238 gamma emissions ranging from 79 keV to 3.06 MeV. Bismuth-206 has a half-life of 6.24 days and decays by electron capture with 68 gamma emissions ranging between 35 keV and 2.76 MeV. The radiation parameters for ^{204}Bi and ^{206}Bi are summarized in Tables 1 and 2, respectively. Complete compilations of the nuclear data used to prepare these summaries were prepared by Dillman for ^{204}Bi (*11*) and ^{206}Bi (*12*) by the methods established by the MIRD Committee (*13*).

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For reprints contact: R. E. Bigler, Biophysics Div., Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, N.Y. 10021.

TABLE 1. RADIATION PARAMETERS FOR ^{204}Bi (*11*)

Radiation*	Mean number per disintegration, n_i	Mean energy per particle, E_i (MeV)	Equilibrium dose constant, Δ_i (gm-rad/μCi-hr)
Gamma 1	0.7603	0.3747	0.6068
Gamma 2	0.1070	0.6707	0.1528
Gamma 3	0.9914	0.8991	1.8987
Gamma 4	0.1381	0.9117	0.2682
Gamma 5	0.1122	0.9119	0.2180
Gamma 6	0.1098	0.9182	0.2149
Gamma 7	0.5884	0.9839	1.2333
All other gamma photons			2.1149
X-rays			0.1615
Internal-conversion electrons			0.1475
Auger electrons			0.0288

* Gamma photons with equilibrium dose constants greater than 0.1 are listed individually.

TABLE 2. RADIATION PARAMETERS FOR ^{206}Bi (*12*)

Radiation*	Mean number per disintegration, n_i	Mean energy per particle, E_i (MeV)	Equilibrium dose constant, Δ_i (gm-rad/ μCi-hr)
Gamma 1	0.2296	0.3434	0.1679
Gamma 2	0.1520	0.4970	0.1609
Gamma 3	0.3954	0.5161	0.4347
Gamma 4	0.2927	0.5374	0.3351
Gamma 5	0.9896	0.8030	1.6926
Gamma 6	0.6662	0.8810	1.2502
Gamma 7	0.1536	0.8950	0.2928
Gamma 8	0.0728	1.0186	0.1580
Gamma 9	0.1386	1.0982	0.3243
Gamma 10	0.0503	1.5952	0.1710
Gamma 11	0.3206	1.7187	1.1739
All other gamma photons			0.5936
X-rays			0.1825
Internal-conversion electrons			0.2456
Auger electrons			0.0333

* Gamma photons with equilibrium dose constants greater than 0.1 are listed individually.

BIOLOGIC DATA

Since no human retention data are currently available in suitable form for radiation dose calculations, previously reported data on rats were used (*9*). These total-body and organ retention data were termed *relative retentions* and defined as

$$\frac{\mu\text{Ci found per gram of specimen}}{\mu\text{Ci administered per gram of body weight}} \times 100\%.$$

Data expressed in this form allow a meaningful comparison to be made between metabolic patterns in different species and should be termed *percent relative concentrations*, abbreviated %RC (*14*). The kidney has been identified as the major organ of accumulation of bismuth. Its relative concentration is approximately two orders of magnitude higher than that for the spleen, ovaries, whole bone, and liver, and three orders of magnitude higher than that of blood. Brain and muscle accumulate very little activity. The relative concentration data measured at various times after radiobismuth administration were fitted by the least-squares method to an expression made up of a sum of exponential terms. The parameters derived using this fitting procedure are contained in Ref. *9*. These expressions can be converted into a form suitable for human radiation dose estimates with the equation

$$F(t) = \frac{m}{m_{tb}} (RC), \tag{1}$$

where F is the fraction of administered activity at time t (hr), and m and m_{tb} are the human organ and total-body masses, respectively.

ABSORBED-DOSE ESTIMATES

The calculation of absorbed dose is based upon the basic schema proposed by Loevinger and Berman in MIRD Pamphlet No. 1 (*15*) with additional refinements by Cloutier et al (*16*). The basic relationship is

$$\overline{D}_{(v \leftarrow r)} = \frac{\tilde{A}_r}{m_v} \sum_i \Delta_i \phi_{i\,(v \leftarrow r)} \text{ (rad)}, \tag{2}$$

where $\overline{D}$ is the mean absorbed dose (rad) for complete decay and elimination of radiobismuth, $\tilde{A}_r$ is the cumulated activity (μCi-hr) in the source region r, m_v is the mass (gm) of the target volume v, Δ_i is the equilibrium dose constant (gm-rad/μCi-hr), and ϕ_i is the absorbed fraction.

The activity A(t) is obtained using the relation

$$A(t) = A_0 e^{-\lambda t} F(t)$$
$$= A_0 e^{-\lambda t} \sum_i f_i e^{-\lambda_i t} \; (\mu\text{Ci}), \tag{3}$$

where A_0 is the administered activity (μCi), λ is the physical decay constant (hr^{-1}), F(t) was defined in Equation 1, and f_i are the fractions of activity with the biologic parameters λ_i (hr^{-1}). The cumulated activity $\tilde{A}$ in each organ is obtained by integrating A(t) over time from zero to infinity:

TABLE 3. BIOLOGIC PARAMETERS DESCRIBING THE DISTRIBUTION FOR RADIOBISMUTH FROM A SINGLE INTRAVENOUS ADMINISTRATION OF Bi-CITRATE

	Fraction of administered activity per organ			Biologic disappearance constants (hr^{-1})		
Tissue	f_1	f_2	f_3	λ_1	λ_2	λ_3
Kidneys	0.1695	0.0649	—	0.0390	*	—
Ovaries	1.01×10^{-4}	1.69×10^{-5}	—	0.1655	*	—
Total body	0.4400	0.2569	0.30	0.0522	0.00566	†

* Biologic disappearance consistent with no elimination.
† Biologic disappearance very rapid, therefore contributing a negligible amount to the cumulated activity.

TABLE 4. ABSORBED FRACTIONS USED FOR ^{204}Bi DOSIMETRY CALCULATIONS

Radiation	$\phi_{tb \leftarrow tb}$	$\phi_{k \leftarrow tb}$	$\phi_{k \leftarrow k}$	$\phi_{ov \leftarrow tb}$*	$\phi_{ov \leftarrow k}$†	$\phi_{ov \leftarrow ov}$
Gamma 1	0.336	0.00143	0.083	0.000061	0.000035	0.020
Gamma 2	0.332	0.00154	0.078	0.000058	0.000034	0.020
Gamma 3	0.325	0.00160	0.068	0.000057	0.000031	0.020
Gamma 4	0.325	0.00160	0.068	0.000057	0.000031	0.020
Gamma 5	0.325	0.00160	0.068	0.000057	0.000031	0.020
Gamma 6	0.325	0.00160	0.068	0.000057	0.000031	0.020
Gamma 7	0.322	0.00160	0.065	0.000056	0.000030	0.020
EFFECTIVE ABSORBED ENERGIES $\Sigma\Delta\phi$						
All gamma photons	2.062	0.01184	0.4502	0.0003776	0.0002067	0.1176
X-rays	0.073	0.00034	0.0211	0.0000131	0.0000043	0.0037

* $m_{ov}/m_{tb} = 8.8/70{,}000$.
† $m_{ov}/m_k = 8.8/288$.
Note. ov, Ovaries; k, kidneys; tb, total body.

TABLE 5. ABSORBED FRACTIONS USED FOR ^{206}Bi DOSIMETRY CALCULATIONS

Radiation	$\phi_{tb \leftarrow tb}$	$\phi_{k \leftarrow tb}$	$\phi_{k \leftarrow k}$	$\phi_{ov \leftarrow tb}$*	$\phi_{ov \leftarrow k}$†	$\phi_{ov \leftarrow ov}$
Gamma 1	0.337	0.00153	0.082	0.000119	0.000033	0.020
Gamma 2	0.335	0.00143	0.083	0.000100	0.000036	0.020
Gamma 3	0.335	0.00142	0.083	0.000098	0.000036	0.020
Gamma 4	0.335	0.00142	0.083	0.000096	0.000036	0.020
Gamma 5	0.328	0.00155	0.070	0.000076	0.000032	0.020
Gamma 6	0.325	0.00158	0.068	0.000073	0.000031	0.020
Gamma 7	0.325	0.00159	0.066	0.000073	0.000031	0.020
Gamma 8	0.320	0.00161	0.066	0.000070	0.000031	0.020
Gamma 9	0.317	0.00161	0.064	0.000068	0.000031	0.020
Gamma 10	0.298	0.00152	0.060	0.000064	0.000032	0.017
Gamma 11	0.295	0.00152	0.060	0.000064	0.000031	0.016
EFFECTIVE ABSORBED ENERGIES $\Sigma\Delta\phi$						
All gamma photons	2.166	0.00992	0.4684	0.0002743	0.0002176	0.1290
X-rays	0.078	0.00037	0.0241	0.0000148	0.0000048	0.0042

* $m_{ov}/m_{tb} = 8.8/70{,}000$.
† $m_{ov}/m_k = 8.8/288$.
Note. ov, Ovaries; k, kidneys; tb, total body.

$$\tilde{A} = A_0 \sum_i \frac{f_i}{\lambda_i + \lambda} \ (\mu\text{Ci-hr}). \qquad (4)$$

The values of f_i and λ_i used in these calculations are listed in Table 3.

Absorbed fractions for each source–target combination required for the major gamma photons of ^{204}Bi and ^{206}Bi are listed, respectively, in Tables 4 and 5. Tables 4 and 5 also include the effective absorbed energies for all gamma photons and x-rays. These absorbed fractions were determined by graphical interpolation of the values tabulated in the MIRD pamphlets (*17*). The reciprocity equations (*15*) were assumed to be valid for the absorbed fractions for the ovaries versus kidneys and ovaries versus the total body. The factors used to exchange target and source are indicated at the bottom of Tables 4 and 5. Absorbed fractions for internal conversion electrons and Auger electrons [considered to be nonpenetrating (np)] were set equal to unity.

The radiation dose to the total body was calculated from Equation 2 by setting the radiation source

TABLE 6. SUMMARY OF ESTIMATED ABSORBED DOSES FROM A SINGLE INTRAVENOUS ADMINISTRATION OF Bi-CITRATE

Tissue	Absorbed dose (mrad/μCi injected) ^{204}Bi	^{206}Bi	Ratio ^{206}Bi/^{204}Bi
Kidney	6.3	48.3	8
Ovaries	0.117	0.696	6
Total body	0.258	1.18	5

region (r) and the target volume (v) equal to the total body (tb). The radiation dose to the kidneys and ovaries was calculated from the general dose equation (*16*):

$$\bar{D}_v = \frac{\tilde{A}_v}{m_v} \sum \Delta_{np}\phi_{np} + \sum_{r=a}^{v} \frac{\tilde{A}_r}{m_v} \sum \Delta\phi_{(v \leftarrow r)} + \frac{\tilde{A}_{rem}}{m_v} \sum \Delta\phi_{(v \leftarrow rem)} \quad (5)$$

where

$$\tilde{A}_{rem} = \tilde{A}_{tb} - \sum_{r=a}^{v} \tilde{A}_r,$$

$$m_{rem} = m_{tb} - \sum_{r=a}^{v} m_r,$$

and

$$\phi_{(v \leftarrow rem)} = \frac{m_{tb}}{m_{rem}} \left[\phi_{(v \leftarrow tb)} - \sum_{r=a}^{v} \frac{m_r}{m_{tb}} \phi_{(v \leftarrow r)} \right].$$

The first term of Equation 5 is the nonpenetrating radiation dose to the target organ. The second term is the sum of the penetrating radiation doses to the target organ from activity contained within itself ($r = v$ in the summation) and from certain organs that contribute greatly to the radiation dose to the target organ. The third term includes the penetrating radiation dose to the target organ from the remaining (rem) activity within the total body, i.e., activity not included within the summation in the second term. The calculation of absorbed-radiation dose to the kidneys included only the kidneys in the sum over r in the above expressions. The calculation for the ovaries included a sum over the ovaries and the kidneys.

Table 6 gives results of the absorbed-dose calculations for ^{204}Bi and ^{206}Bi. The generally more rapid metabolism of small animals could possibly cause these values to underestimate the radiation dose to humans.

DISCUSSION

These calculations show that a substantial reduction in absorbed-radiation dose can be obtained if ^{204}Bi is substituted for ^{206}Bi administration to humans. If this radionuclide proves to be selectively taken up in human soft-tissue tumors, this reduction would likely justify the added production costs of ^{204}Bi, arising from the use of a high-energy cyclotron and enriched target material. The similar decay mode of ^{204}Bi, compared to ^{206}Bi, suggests that it will be possible to image it as readily as ^{206}Bi.

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