RADIATION RESEARCH 70, 444–448 (1977)

CORRESPONDENCE

The Osteosarcomogenic Effectiveness of the Short-Lived ^{224}Ra Compared with That of the Long-Lived ^{226}Ra in Mice

WALTER A. MÜLLER AND ARNE LUZ

Institut für Biologie der Gesellschaft für Strahlen- und Umweltforschung mbH, in Association with EURATOM (Contr. 090-72-1 BIAD) D-8042 Neuherberg, Germany F.R.

MÜLLER, W. A., AND LUZ, A. The Osteosarcomogenic Effectiveness of the Short-Lived ^{224}Ra Compared with That of the Long-Lived ^{226}Ra in Mice. *Radiat. Res.* 70, 444–448 (1977).

^{224}Ra was applied with one single injection or with repeated injections (twice weekly over various time periods, up to 36 weeks). In general the bone tumor incidence increased with dose but with the restriction that the maximum instantaneous dose rate be not too high. The 1080-rad total skeletal dose thus resulted in a bone tumor incidence between 15 and 90% depending on the length of the injection spans. These results were compared with the effect of singly injected long-lived ^{226}Ra, using data by M. Finkel *et al.* (*1*). It was observed that the specific bone tumor production by ^{226}Ra, expressed as incidence per unit of total accumulated skeletal dose, was steadily diminished with an increase of the dose. As a consequence, we found that mice after a single injection of the long-lived ^{226}Ra within the tested dose range had in general a considerably lower bone tumor incidence than those mice having received comparable skeletal doses through repeated injections of the short-lived ^{224}Ra over a longer period.

^{224}Ra, because of its short half-life (3.6 days), is a convenient model substance for studying the effects of dose, dose rate, and internal irradiation period by using different modes of administration.

One microcurie per kilogram body weight of ^{224}Ra causes a total mean skeletal dose of 30 rad and an initial maximum dose rate of 12 rad/day averaged over the whole skeleton (*2*). In the framework of large experimental series (*3*) ^{224}Ra was injected intraperitoneally into 4-week-old female NMRI mice. Experiments involving a single injection with protracted application at the same dose level were performed for the following range of parameters:

Total mean skeletal doses: 30–3000 rad (1–100 μCi/kg).
Maximum skeletal dose rates: 6–600 rad/day.
Internal irradiation period (injection span) up to 36 weeks.

Some of the results of these experiments are summarized in Fig. 1; in addition the bone tumor incidence after single injections of ^{226}Ra has been plotted from the

ISSN 0033-7587

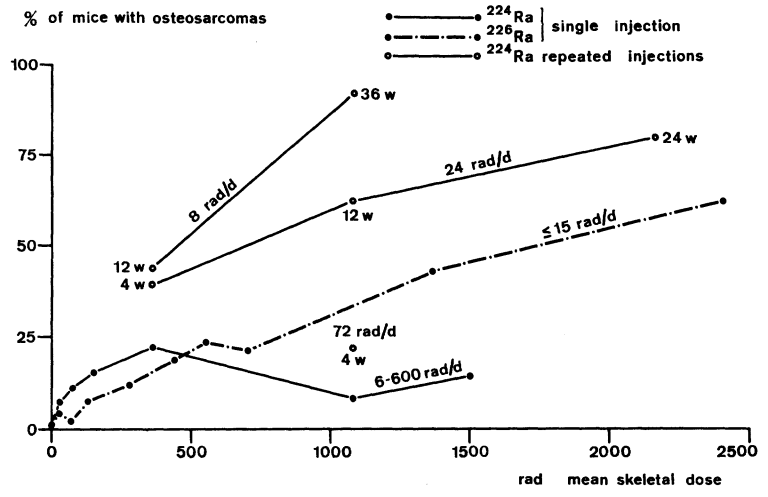

FIG. 1. Incidence of osteosarcomas in mice vs mean total skeletal dose after a single application of ^{224}Ra and ^{226}Ra and after repeated injections of ^{224}Ra. The number of weeks shown at each point refers to the injection span. The dose rates indicated as rad/*d* above the curves are maximum values.

experiments of Finkel *et al.* (*1*). Mean skeletal doses were calculated for ^{224}Ra and ^{226}Ra according Müller (*2*) and Mays *et al.* (*4*), respectively. The ^{226}Ra doses were accumulated until the mean time of bone tumor appearance as reported by Finkel *et al.* (*1*). The two lower curves show osteosarcoma incidences after a single injection of ^{224}Ra with NMRI mice (our own data) and of ^{226}Ra with CF1 mice (*1*). Experimental results from different laboratories have established that the final incidence of osteosarcomas is similar in different mouse strains after incorporation of ^{90}Sr (*5–7*). Therefore we believe that we are justified in postulating a similar relationship for radium as well. For skeletal doses below ca. 500 rad, ^{224}Ra—from a *single* injection—seems to be somewhat more effective than comparable doses of ^{226}Ra. Above this value the relationship is reversed (*2*). This could be explained by the great difference in maximum dose rates (resulting in an "overkilling effect") produced by the two isotopes for obtaining equal skeletal doses by application of only one injection. In experiments with *repeated* (multiple) injections of ^{224}Ra the steepest increase of osteosarcoma incidence with dose was observed in the case where the dose was applied in the smallest increments (0.5 μCi/kg twice weekly up to a 36-week injection span—upper curve in Fig. 1). Higher activities per individual injection resulted in a lower osteosarcoma incidence for the same total dose.

The 1080-rad mean skeletal dose was tested with most variations of the dose–time distribution. Here we saw the osteosarcoma incidence between 15 and 92% increasing with the length of the injection span or, correspondingly, with the lowering of the dose rate.

On the basis of the cumulative radiation dose in the skeleton, the tumor incidence after ^{226}Ra injection was considerably lower than that in most experiments with repeated injections of ^{224}Ra and comparable doses.

TABLE I

Comparison of Dosimetric Data of Experiments with Multiple Injections of ^{224}Ra and Single Injections of ^{226}Ra[a]

Bone tumor incidence		*Injections*			*Total mean skeletal dose*		*Partial ^{226}Ra dose delivered within injection span of corresponding ^{224}Ra experiments*	*Bone tumor incidences per dose unit (%/100 rad)*		
		^{224}Ra		^{226}Ra						
^{224}Ra (%) *a*	^{226}Ra (%) *b*	*Twice weekly* ($\mu Ci/kg$) *c*	*Injection span* (*weeks*) *d*	*single injection* ($\mu Ci/kg$) *e*	^{224}Ra (*rad*) *f*	^{226}Ra (*rad*) *g*	(*rad*) *h*	^{224}Ra $(a\times100)/f$ *i*	^{226}Ra $(b\times100)/g$ *j*	^{226}Ra $(b\times100)/h$ *k*
22	23	4.5	4	1	1080	550	47	2.04	4.18	49
39	43	1.5	4	2.5	360	1375	117	10.83	3.13	37
44	43	0.5	12	2.5	360	1375	274	12.22	3.13	16
62	62	1.5	12	5	1080	2404	549	5.74	2.58	11.3
80	79	1.5	24	10	2160	4380	1890	3.70	1.80	4.2
92	86	0.5	36	20	1080	7939	5208	8.52	1.08	1.7

[a] Data by Finkel *et al.* (*1*), based on similar percentages of induced bone tumors (osteosarcoma).

Table I shows more-detailed data on the dose distributions with time as a basis for the comparison of the osteosarcomogenic effectiveness of a single injection of ^{226}Ra and that of multiple injections of ^{224}Ra. Considering the fractionation experiments with multiple injections of ^{224}Ra, the time of dose delivery played an important role. Consequently, for comparison the total doses after a single injection of ^{226}Ra have been given (i) until the appearance of the tumor, corresponding to Fig. 1 (column g), and (ii) as partial dose for the corresponding time period of the ^{224}Ra injection span (column h). If we compare the efficiency per dose unit, we find higher values for repeated applications of ^{224}Ra (column i) than for single applications of ^{226}Ra (column j) as related to total doses. But the partial doses of ^{226}Ra, within the corresponding ^{224}Ra injection span (column h), seemed to be more effective only for the shorter periods, decreasing to comparable values at 24 weeks, and are obviously lower (by a factor as high as 5) for the 36-week time span (column k).

For periods shorter than 24 weeks, the later additional irradiation dose in the ^{226}Ra experiment seemed to increase the tumor risk further. The higher efficiency of dose protraction over 36 weeks in the ^{224}Ra experiment is much more clear, if we consider that a ^{226}Ra experiment that also delivers nearly 1000 rad to the bone within 36 weeks (i.e., ca. 5 μCi ^{226}Ra/kg) results in only 62% osteosarcomas.

For a possible explanation of the results we discuss the following biological aspects. In the case of a single injection of ^{226}Ra the main portion of the total activity is deposited within a very limited part of the osteogenic tissue that is mineralized at the time of injection. Afterward the spatial distribution of the activity changes to some extent by the continuous process of bone remodeling (also by the process of bone growth in mice before 12 weeks of age). In the case of repeated injections of ^{224}Ra the individual amounts of injected activity will be distributed over many fractions of newly formed osteogenic tissue. Therefore the portion of irradiated osteogenic tissue on the bone surface (i.e., the number of irradiated dividing cells) will be larger in the case of repeated injections of ^{224}Ra than after a single injection of ^{226}Ra. A similar conclusion was also reached by Mays (*8*), who compared effects of repeated injections of ^{224}Ra with those of the long-lived bone-"surface-seeker" plutonium.

All these phenomena occur after small amounts of fractionally injected ^{224}Ra (i.e., at low dose rates), which may result in the killing of a few osteogenic cells per unit time. Under these conditions the remodeling activity and growth will be nearly normal, and the number of surviving irradiated cells will be larger. With regard to ^{226}Ra, comparable experimental results in mice after fractionated injection are lacking.

As a practical consequence for radiation protection, it should be taken into account that skeletal doses after chronic incorporation of short-lived α-emitters may be even more hazardous than after acute incorporation of a long-lived α-emitting radionuclide.

RECEIVED: August 18, 1975; REVISED: May 28, 1976

REFERENCES

1. M. P. Finkel, B. O. Biskis, and P. B. Jinkins, Toxicity of ^{226}Ra in mice. In *Radiation-Induced Cancer* (A. Ericson, Ed.), pp. 369–391. International Atomic Energy Agency, Vienna, 1969, STI/PUB/228.
2. W. A. Müller, Studies on short-lived internal α-emitters in mice and rats. I. ^{224}Ra. *Int. J. Radiat. Biol.* **20**, 27–38 (1971).
3. W. A. Müller, W. Gössner, O. Hug, and A. Luz, Late effects after incorporation of the short-lived α-emitters ^{224}Ra and ^{227}Th in mice. *Health Phys.*, in press.
4. C. W. Mays, T. H. Cochran, and W. S. S. Jee, Radium and radon retention in mice. *Health Phys.* **9**, 615–619 (1963).
5. L. M. van Putten, M. J. de Vries, Strontium-90 toxicity in mice, *J. Natl. Cancer Inst.* **28**, 587–603 (1962).
6. A. Nilsson, Dose-dependent carcinogenic effect of radiostrontium. In *Radiation-Induced Cancer*, pp. 173–182. International Atomic Energy Agency, Vienna, 1969. [Available as STI/PUB/228 from UNIPUB, Inc., P.O. Box 433, Murray Hill Station, New York, N. Y. 10016.]
7. M. P. Finkel, P. J. Bergstrand, B. O. Biskis, The latent period, incidence, and growth of Sr-90-induced osteosarcomas in CF1 and CBA mice. *Radiology* **77**, 269–281 (1961).
8. C. W. Mays, Estimated risk from ^{239}Pu to human bone, liver and lung. In *Biological Effects of Low-Level Radiation*, Vol. II, pp. 373–384. International Atomic Energy Agency, Vienna, 1976. [Available as STI/PUB/409 from UNIPUB, Inc., P.O. Box 433, Murray Hill Station, New York, N. Y. 10016.]