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ESTIMATED RADIATION DOSAGE IN MAN FROM ADMINISTERED MORPHINE-N-METHYL-C^{14}

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ABSTRACT

Radiation dose to man from administered morphine-N-methyl-C^{14} is estimated using human C^{14} excretion data. Cumulative dosages are calculated assuming 100 μc injected compound and uniform distribution of activity. Kidney radiation dose is also estimated.

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The radiation dosage in man from an administered chemical compound containing carbon-14 may often be estimated from available literature with sufficient accuracy to establish tentative radioactivity dose limits for the use of the particular chemical form of this isotope in normal and cancer subjects. This note presents the calculations and estimations for morphine-N-methyl-C^{14}.

The 24-hour breath and 4-day urine and fecal excretion of carbon-14 from labeled morphine was measured by Elliot *et al.*[1] The average urine, breath, and feces values for the four normal subjects in Elliot's study are used to start our calculation. See Table I. By the end of the fourth day of our study, excretion of radioactivity in the feces had virtually ceased. On the basis of our experience with many other labeled compounds, we presume that only very negligible amounts of radioactivity appear in the feces after this initial period.

Table I

Cumulative excretion data of carbon-14 from morphine-N-methyl-C^{14}

(expressed as percent of injected dose)

Time from administration	Feces	Urine	Breath	Urine Feces, and Breath
12 hr	0.0	53	3.5	56.5
24 hr	4.12	64	4.4	72.5
48 hr	8.01	69	5.7	82.7
72 hr	9.78	71	6.8	87.6
5 d	10.0	72	7.8	89.8
10 d	10.0	72.6	11.3	93.9
20 d	10.0	72.6	12.2	94.8
40 d	10.0	73.0	13.9	96.9
60 d	10.0	73.5	14.8	98.3
100 d	10.0	73.9	14.8	98.7
200 d	10.0	74.4	14.8	99.2

[1] Elliot, Tolbert, Adler, and Anderson, Proc. Soc. Exptl. Biol. Med. **85**, 77 (1954).

The breath excretion of carbon-14, which in Elliot's study was measured through only 24 hours, was extrapolated for this study through 5 days on the assumption that the shape of the breath curve would be similar to that for $C^{14}O_2$ excretion following the administration of glycine-2-C^{14} to man.[2, 3, 4] The glycine data are used in this extrapolation because they are available and probably are a good model. (See later.)

One percent more of radioactivity excretion was allowed for urinary excretion in going from the fourth to the fifth day. We then estimate that the 5-day cumulative excretion of C^{14} from the methyl-labeled morphine is 89.8%, which leaves a body burden of 10.2%.

For the extrapolation of the excretion of the carbon-14 beyond the fifth day we must use some appropriate model, for no data from labeled-morphine studies are available. If we assume that at the end of 5 days there is no more morphine or even labeled morphine derivatives in the body, then the body burden of 10.2% of the injected dose of C^{14} will have been derived from methyl groups, probably obtained from the morphine nitrogen by a transmethylation or oxidation type of reaction. It is not unreasonable to assume that the body carbon pools into which these methyl groups have gone are very similar to the pools into which glycine methylene groups go. On the basis of such an assumption, we can then use the long-term carbon-14 excretion studies that have been made in man with glycine-2-C^{14}. At the end of 5 days 23.4% of a given glycine injection still remains in the body.[3] The ratio 10.2/23.4, and the data in Table II, page 3 of Reference 3, can then be used to estimate continuing breath and urine excretion of C^{14} from an injected dose of morphine-N-methyl-C^{14}. It was in this manner that the remaining data in Table I of this paper were obtained. Fecal excretion was considered negligible after the first 5 days.

Radiation Dose

If we assume that the carbon-14 from the morphine is uniformly distributed throughout the body, then the dose rate will be

$$\text{mrad/day} = \frac{(N)\,(\overline{E_\beta -})\,(\text{erg/ev})\,1000}{(\text{erg/gm/rad})\,(\text{wt. gm})} ,$$

where N = number of betas per day,

$\overline{E_{\beta}-}$ = average energy of C^{14} beta (50, 000 ev),

erg/ev = 1.60×10^{-12} ,

erg/gm/rad = 100.

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[2] Berlin, Tolbert, and Lawrence, J. Clin. Invest. 30, 73 (1951).

[3] Berlin, Tolbert, and Lee, J. Clin. Invest. 32, 1 (1953).

[4] N. I. Berlin and B. M. Tolbert, Proc. Exptl. Biol. Med. 88, 386 (1955).

Table II

Radiation dose rates and cumulative dose derived from 100 μc of morphine-N-methyl-C^{14}

Time (days)	μC in body	mrad/day	Cumulative dose (mrad)
0	100.0	3.66	0.00
1	27.5	1.01	2.08
2	17.3	0.63	2.79
3	12.4	0.46	3.46
5	10.2	0.38	4.45
10	6.1	0.23	5.90
20	5.2	0.19	8.40
40	3.1	0.12	11.1
60	1.7	0.062	12.8
100	1.3	0.048	14.9
200	0.8	0.029	19.2

For a 70-kg man and 100 μC of C^{14} ($N = 3.20 \times 10^{11}$/day) this equation gives a dose rate of 3.66 millirad/day. (The rad is approximately equal to a rep, since the latter is variously taken to be 83 or 93 ergs of radiation energy absorbed per gram of substance.)

In Table II the data are presented for morphine-N-methyl-C^{14} on the radiation dose rate and cumulative dose derived from 100 μC of carbon-14. In Fig. 1 the dose-rate curve is given. It can be seen that, on the basis of the calculations we have made, the radiation dose from 100 μC of this C^{14}-labeled morphine is quite small; the dose rate falls to the level of natural and cosmic radiation in about 10 days.

The most serious error in these calculations probably arises from our assumption of uniform distribution of carbon-14. After the first 5 days, such an assumption is probably fairly valid, for glycine-2-C^{14} studies in mice have shown uniform radioactivity distribution within a factor of about ±2.[3, 5, 6]

[5] G. L. Nardi, The Fate of C^{14} in the Tissues of Mice after Administration of C^{14} Methyl-labeled Glycine, UCRL-257, Jan. 1949.

[6] G. L. Nardi, Science 111, 362 (1950).

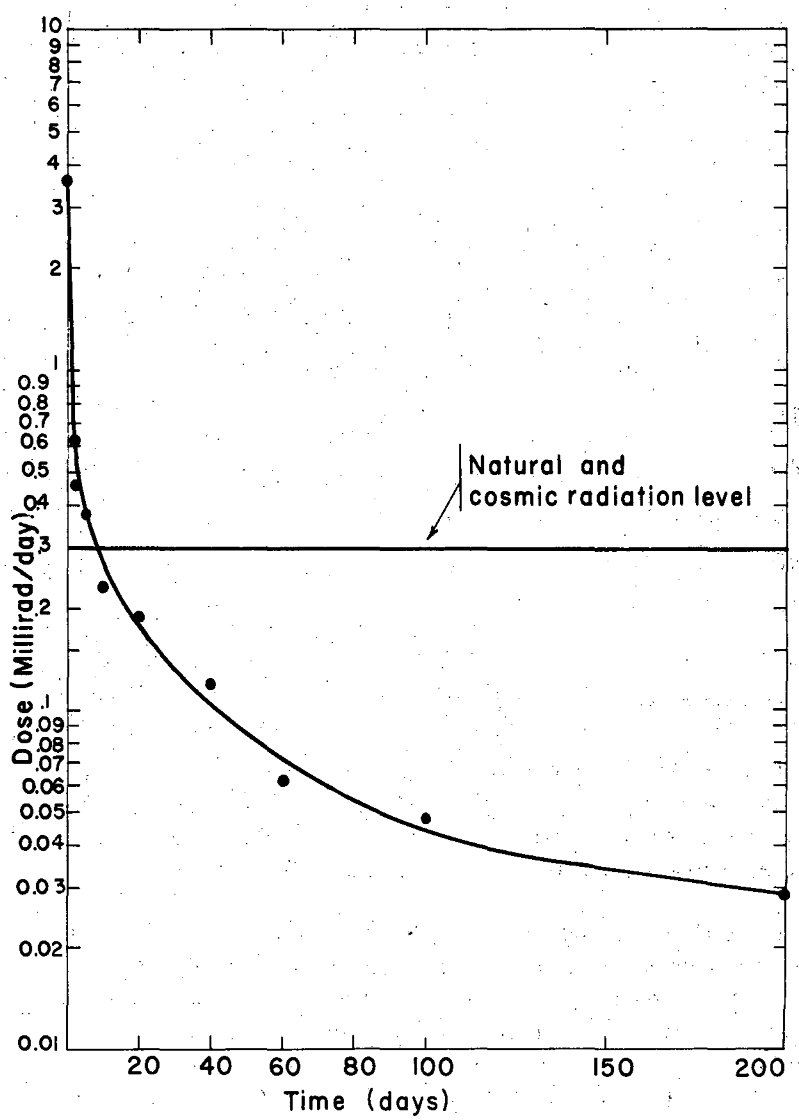

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Fig. 1. Calculated daily dose rate from 100 μC of morphine-N-methyl-C^{14} in a 70-kg man given in a single iv dose. Uniform distribution of radioactivity is assumed, and data after the first few days are based on glycine-2-C^{14} experiments.

During the first day or so there should be an appreciable concentration of activity in the kidneys, bladder, intestines, liver, and gall bladder. Of these organs, the kidneys would get the most irradiation, both because they are small glands and because much activity is excreted via this pathway.

The weight of the kidneys in a normal adult is about 1/240 of the body weight,[7] or about 290 g. Urinary output is about 1500 ml a day. The fluid volume of the kidney, if the same as that of the rest of the body, is about 150 ml, or about 1/10 of the urine output. Assuming that the radioactivity concentration in the kidney is the same as in the urine, about 1/10 of the daily excretion of activity could be in the kidney at one time. The fraction probably is less. Using the data of Table I, we see that 53% of a given dose is excreted in the urine in the first 12 hours. For a 100-μC injected dose, this corresponds to a rate of ~100 μC/24 hrs and means that 10 μC will be in the kidneys at all times during the first 12 hours, which would produce an integrated dose of 44 millirads in 12 hours. The activity excreted in the second 12 hours will give about 10 millirads, to make the total dose to the kidneys in the first day some 54 millirads. After the first day, the dose rate to the kidneys drops rapidly.

By way of comparison, we would like to point out that the presently accepted weekly tolerance dose for continuous exposure to whole-body radiation is set at 100 mrep.

This work was done under the auspices of the U. S. Atomic Energy Commission.

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[7] Henry Gray, Gray's Anatomy, C. M. Goss, Ed., 25th ed. (Lea and Febiger, Philadelphia, 1948), p. 1264.