Estimation of Upper Limits on Human Radiation Absorbed Doses from Carbon-11-Labeled Compounds

S. John Gatley

Chemistry Department, Brookhaven National Laboratory, Upton, New York

Radiation absorbed dose estimates for short-lived PET tracers are commonly based on biodistributions in rodents which (because of more rapid distribution and other species differences) may have limited relevance to humans. The initial purpose of this study was to estimate an intravenously injectable quantity of ^{11}C which could not, on a priori grounds, exceed regulatory limits on radiation absorbed doses for individual organs. Upper limits on organ cumulative activities were estimated by assuming that ^{11}C-labeled compounds are instantaneously distributed in the blood plasma, and then transfered solely and irreversibly to a single organ. The rate-constant (min^{-1}) for each organ was taken to be its fractional cardiac output, since the plasma volume of 3 liters is recirculated each minute. The method was extended by using measured time courses of radioactivity in human arterial plasma available from previous PET studies with several ^{11}C compounds in place of the assumption that the injected radioactivity was initially instantaneously distributed throughout the plasma. Calculations for ^{11}C L-deprenyl, cogentin, cocaine, N-methylspiperone, putrescine and 2-deoxy-D-glucose, assuming transfer limited to a single organ, gave the kidneys rather than the thyroid as critical organ in each case. The upper-limit self-doses were 140, 210, 320, 360, 450 and 750 mrad/mCi, respectively, indicating that 34, 24, 15, 14 and 6.5 mCi, respectively, could be administered in a single PET study. These results suggest a strategy for human studies with ^{11}C-labeled compounds: a preliminary study at the 3.5-mCi level would yield ^{11}C arterial plasma data which could in turn be used to give a refined upper limit on radiation absorbed doses. For many ^{11}C compounds, this strategy would demonstrate that sufficient radioactivity could be injected to give acceptable human PET images and would avoid the death of animals for biodistribution studies.

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The generally accepted limitations on radiation absorbed doses by adult subjects in medical experiments involving administration of a radioactive substance are: for a single administration, 3 rad to the whole body, active blood forming organs, lens of the eye or gonads, or 5 rad to other organs; for annual or cumulative doses, 5 rad to one of the sensitive organs or 15 rad to the other organs (*1*). Investigators and local committees (e.g., Institutional Review Board and Radioactive Drug Research Committee (RDRC)) must be satisfied that these limits are not exceeded. RDRC approvals of studies with ^{11}C compounds are frequent in institutions with PET research groups. Commonly, human dose estimates are made on the basis of biodistribution studies in mice or rats. However, because of the more rapid distribution in rodents (*2*), and other species differences, such studies are probably of only limited applicability to humans. PET experiments in large animals suffer from the problem that subjects must be anesthetized which limits the relevance to conscious humans. Furthermore, obtaining kinetic data for all major organs involves several administrations of ^{11}C tracer per animal, and partial volume effects complicate accurate uptake measurements in small organs such as adrenals. Similar considerations presumably explain the paucity of published studies of dosimetry of PET tracers using human data (*3–8*).

Intravenously administered ^{11}C tracers are almost invariably relatively lipophilic receptor-binding compounds or enzyme inhibitors, or substrates for tissue transport or metabolic processes, which are expected to undergo rapid widespread distribution through the body. Carbon-11-labeled compounds have a short physical half-life (20.4 min), and are produced by methods which preclude longer-lived radionuclidic contaminants (*9*). Physical decay makes a large contribution to tissue clearance, so that prolonged irradiation of slowly clearing tissues does not occur. The purpose of this study was to determine if "theoretical" calculation of an intravenously injectable activity of ^{11}C which could not exceed the regulatory limits was possible. The obvious worst-case assumption of immediate deposition of the entire injected amount of ^{11}C in a single organ, with clearance only by physical decay, naturally gives very high doses to small organs. However, since small organs receive a smaller fraction of the cardiac output, delivery of tracer is retarded compared to major organs. Delayed delivery significantly reduces the area under the time-activity curve when a nuclide of very short half-

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For correspondence or reprints contact: S. John Gatley, Chemistry Dept., Brookhaven National Laboratory, Upton, NY 11973.

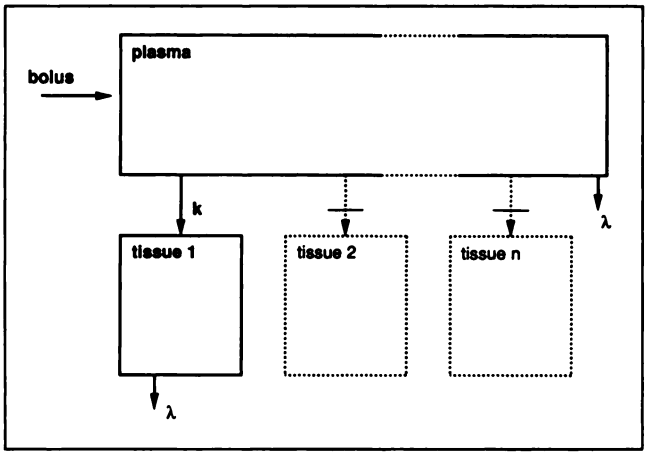

FIGURE 1. Compartmental Model 1 represents the essence of the approach used in this manuscript. Following bolus intravenous injection, radioactivity is instantaneously distributed in the plasma which can then be transferred to a single organ only with rate constant k. Physical decay is represented by λ. Calculations were also made for several labeled compounds using Model 1 with the measured time course of radioactivity in human arterial blood plasma as input.

life is concerned. We present here calculations based on the concept that injected ^{11}C is instantaneously distributed in the blood plasma and then transferred solely and irreversibly to a single organ. The calculation was repeated for several organs of dosimetric interest using a rate constant determined from literature values of tissue blood flow or percent cardiac output in each case. This process yielded a general set of upper limit organ doses applicable to any ^{11}C compound. Refined organ self-doses were also calculated for several specific ^{11}C compounds using measured human arterial plasma time courses as input to each organ. These upper limit doses were lower than those in the general set, reflecting faster plasma clearance for each of these compounds than obtained in the general model.

METHODS

General Information

Organ weights and the blood contents of organs of standard man were taken from Snyder et al. (*10*); blood content was assumed to be one-tenth the organ weight if values of the former were not listed. Carbon-11 cogentin, cocaine, putrescine, 2-deoxy-D-glucose and L-deprenyl and ^{18}F-N-methylspiperone were prepared as previously described (*11–16*). Traditional dose estimates for 2-deoxy-D-glucose were obtained in a dog study (*3*), and deprenyl dosimetry was based on PET measurements in a baboon. Conservative dose estimates for other compounds were based on the organ distribution in mice at 5 min assuming clearance by decay only.

Upper-Limit Dose Models

Model 1 (Fig. 1) is the central feature of this communication and was used for most tissues. It was assumed that intravenously injected radioactivity was instantaneously distributed throughout the blood plasma, which it could only leave by irreversible trapping in a *single* tissue. Transfer was a first-order process for which the rate-constant, k, was calculated by:

$$k\ (\text{min}^{-1}) = \frac{\text{fractional cardiac output} \times \text{total cardiac output (ml/min)}}{\text{total plasma volume (ml)}}.$$

Since the plasma volume of standard man is 3 liters, and cardiac output is 3 liters of plasma per minute, the value of k for each organ is equal to the organ's fractional cardiac output. For most tissues the values in Guyton (*17*) were used. They are shown in Table 1. Blood flow to the ovaries was assumed to be 0.5 ml g^{-1} min^{-1} (*18,19*). Testicular flow was assumed to be 0.26 ml g^{-1} min^{-1} (*20*). Total gonadal blood flows were calculated by multiplying these values by human organ weights (*10*).

For the urinary bladder, Model 1B was used (Fig. 2), with the kidney and bladder in tandem. The rate constant for kidney-to-bladder transfer was set to 0.2 min^{-1}. This was the average value found by Stabin et al. for kidney-to-bladder transfer of the renal radiopharmaceutical ^{99m}Tc-MAG3 in human studies (*21*). Presumably the value of this transfer constant for a compound designed to trace renal excretion is near the maximum attainable. It was assumed that bladder voiding did not occur.

The hepatobiliary system was treated analogously to the urinary system, with transfer of radioactivity from the liver to both the gallbladder and the small intestine. The approach published by Vestergren for the hepatobiliary radiopharmaceutical (*22*) was used, in which the liver radioactivity was considered as three compartments, A, B and C, containing 30%, 40% and 30% of the ^{11}C, respectively. Transfer from compartments A and B was described by rate-constants (i.e., k_2 values) 0.0153 and 0.001 min^{-1}, respectively, to the gallbladder (35% of liver output) and the small intestine (65% of liver output), respectively. Carbon-11 entering the gallbladder or small intestine was assumed to remain in these organs and decay to completion.

Model 1 was also used to calculate organ doses using representative measured human arterial plasma time-activity curves for several PET radiotracers as inputs to the target tissue, rather than the plasma time-course calculated on the assumption that transfer occurs only to the target tissue. After the last data point (usually 60 min), plasma radioactivity was assumed to decrease only by physical decay. The total plasma volume was assumed to be 3 liters for these calculations.

Mathematical Operations

Cumulative activities ($\tilde{A}$) for activities (Act.) instantaneously deposited and then decaying to completion in organs were calculated by:

$$\tilde{A} = \frac{\text{Act.}}{\lambda},$$

where λ is the decay constant for ^{11}C (0.034 min^{-1}). Cumulative activities which would result from restriction of a ^{11}C tracer to the blood pool were calculated by:

$$\tilde{A} = \frac{\text{blood content of organ (ml)}}{\text{Total blood pool}} \times \frac{\text{Act.}}{\lambda}.$$

The solution to the differential equation reflecting radioactivity in the tissue compartment of Model 1 is:

TABLE 1
Maximum Possible Doses For Model 1 or Instantaneous Deposition of Radioactivity Bolus in Tissue

Tissue	S value (mrad/mCi-min)	Cardiac output (%)	Model 1		Deposition in tissue dose (mrad/mCi)
			Cum. Act. (mCi-min/mCi)	Dose (mrad/mCi)	
Adrenals	900	0.5	3.8	3,400	26,000
Bladder	42	n/a	19	800	1,200
Bone surface	2.2	5	18	40	65
Brain	14	14	24	340	410
Gallbladder	140	n/a	0.8	110	4,100
Heart	51	3	14	710	1,500
Kidneys	55	22	25	1,400	1,600
Liver	10	27	26	260	290
Lungs	22	100	n/a	n/a	650
Muscle	0.45	15	24	11	13
Ovaries	1,700	0.11	0.9	1,500	50,000
Red marrow	13	5	18	230	380
Skin	5.7	6	19	110	170
Small intestine	22	n/a	1.5	33	650
Testes	390	0.2	1.6	620	11,000
Thyroid	720	1	6.7	4,800	21,000
Whole body	0.4	100	n/a	n/a	12

$$A(t) = e^{-\lambda t} - e^{-(\lambda + k)t},$$

which is integrated to give:

$$\tilde{A} = \frac{k}{\lambda(\lambda + k)}.$$

Approximate numerical solutions to Model 1 and Model 1B were conveniently obtained using the Microsoft Excel spread sheet program on a Macintosh IIcx computer. Columns and rows represented compartments and time increments (usually 1 min), respectively. For specific solutions, measured human time-course data were placed in the plasma column. For the general solution, the first row of the column representing the plasma contained a unit of radioactivity; other cells were empty. In each row, appropriate fractions were added to and subtracted from columns to simulate physical decay and transfer between compartments. Iterations were carried out for at least 120 min, at which time <2% of an initial activity of ^{11}C remains. Tissue cumulative activities were calculated as:

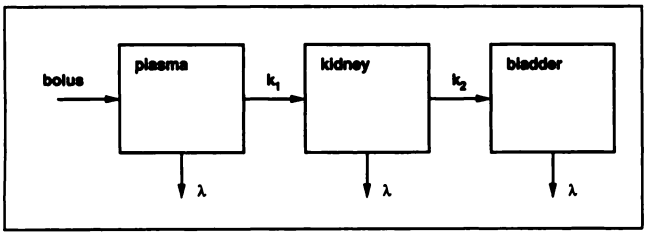

FIGURE 2. Model 1B is a variant of Model 1 in which k_1 represents sole, irreversible transfer of radioactivity from plasma to the kidney and k_2 represents transfer of radioactivity from the kidney to the urinary bladder. A variant of Model 1B (see main text) was used to represent transfer from the liver to the small intestine and gallbladder.

$$\tilde{A} = \sum_{1}^{n} A_i t_i,$$

where Ai and ti were the radioactivity-concentration and time-increment of the ith row, respectively.

Cumulative activities were multiplied by appropriate S values to obtain estimates of tissue self-doses. The S values (shown in Table 1) were those used in MIRD 11 (*23*) or the MIRDOSE program (*24*).

RESULTS

Tissue Dose Estimates Based on Deposition of Radioactivity in Plasma (Model 1)

The results of calculations for Model 1 are shown in Table 1, column 5. Among major organs only the kidney would receive >1 rad/mCi. The thyroid dose was the highest at nearly 5 rad/mCi, followed by: adrenals > ovaries > gallbladder > urinary > bladder > heart > testes > brain.

Dose Estimates Based on Direct Deposition of Radioactivity in Tissues

Calculations are given in Table 1, column 6. Although the dose would be only 12 mrad/mCi for instantaneous distribution throughout the whole body, the heart, kidneys or bladder would receive over 1 rad/mCi from the entire injected radioactivity. Small organs such as adrenals, thyroid and gonads would receive >5 rad/mCi.

Tissue Doses from the Blood Pool

To aid in consideration of doses received by organs other than the target organ in Model 1, dose estimates were also made using the assumption that a ^{11}C compound was restricted to the blood pool; the heart would receive 75

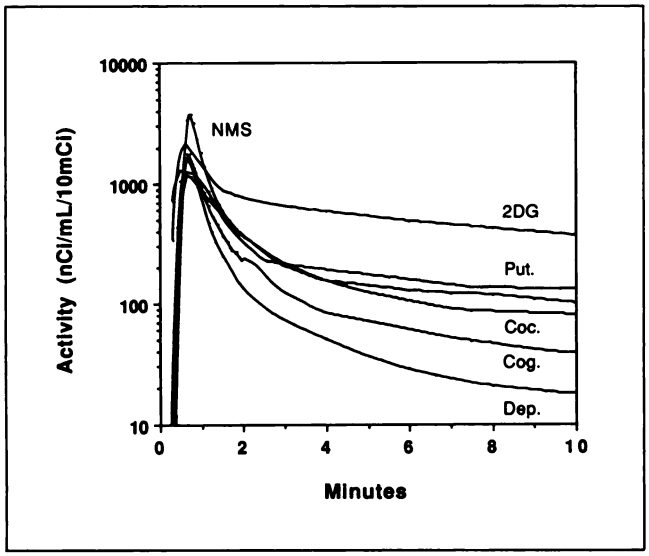

FIGURE 3. Representative time courses in human arterial plasma for several radiotracers. These were used as inputs to Model 1 to generate upper-limit organ radiation absorbed doses specific for the radiotracers. NMS = N-methylspiperone; 2DG = 2-deoxy-D-glucose; Put = putrescine; Coc. = (−)-cocaine; Cog. = cogentin (benztropine); and Dep. = L-deprenyl.

mrad/mCi (59 from the heart chamber contents and 16 from heart tissue), the lungs 48 mrad/mCi, the kidneys 22 mrad/mCi, and other tissues 16 mrad/mCi or less (not shown).

Model 1 with Measured Input Functions

Representative measured human plasma time-activity curves (uncorrected for the presence of labeled metabolites) are shown for several ^{11}C compounds in Figure 3. Doses calculated according to Model 1, but using the data of Figure 3 as model inputs, are given in Table 2, together with conservative dose estimates made on the basis of animal distribution studies. For each ^{11}C compound, the model gave the kidneys as the critical organ with maximum possible self-doses of 140, 210, 320, 360, 450 and 750 mrad/mCi, respectively, for ^{11}C L-deprenyl, cogentin, cocaine, N-methylspiperone, putrescine and 2-deoxyglucose. Calculated doses to the thyroid were lower than for the kidneys for each of these tracers.

Simulated Tissue Time Courses

Figures 4A and B show time-activity curves for thyroid and kidneys calculated according to three sets of assumptions: the general Model 1; Model 1 using human plasma time-activity data for ^{11}C putrescine; and irreversible, instantaneous delivery of radioactivity to the organs. The graphs illustrate the reduction in cumulative activity (i.e., area under the curve) for Model 1 compared to the case for instantaneous delivery, and also that the reduction is greater for an organ receiving a smaller fraction of cardiac output. Additionally they show the further large reduction when the measured plasma data for ^{11}C putrescine were used.

DISCUSSION

In this study we have estimated upper limits for organ ^{11}C radiation absorbed doses using a model in which injected tracer is instantaneously distributed in blood plasma and then delivered irreversibly to a single organ with a rate constant calculated from the literature value of cardiac output for that organ. Our purpose was to determine if "worst case" estimates could be made in order to conservatively plan initial human PET imaging without the need for detailed animal biodistribution studies.

Organ Self-Doses

Carbon-11 has rather benign dosimetry for compounds which are widely distributed, as shown by the total body dose of 12 mrad/mCi (Table 1). Doses for complete decay of all the injected radioactivity in individual organs are obviously large overestimates. However, it is notable that complete and irreversible first-pass extraction of the injected radioactivity by the lungs would still permit administration of 7.7 mCi before exceeding the 5-rad limit. Doses to other major organs, including bone, brain, liver, skin, muscle and bone marrow would also permit administration

TABLE 2
Upper-Limit Doses Calculated Using Measured Arterial Plasma Time-Activity Curves and Model 1 and Conservative Dose Estimates Calculated from Animal Biodistribution Data

	Cocaine		2-deoxy-glucose		Cogentin		Putrescine		L-deprenyl		N-methyl-spiperone*	
Tissue	Model	Mouse	Model	Dog	Model	Mouse	Model	Mouse	Model	Baboon	Model	Mouse
Brain	55	3	130	8	36	33	78	n.d.	25	15	62	<10
Heart	46	9	110	48	30	12	65	7	21	70	52	n.a.
Kidneys	320	51	750	59	210	180	450	180	140	18	360	71
Liver	76	50	180	26	49	87	110	24	34	77	86	43
Thyroid	220	n.d.	520	n.d.	150	<1	310	2	100	n.d.	250	n.a.

Values are mrad/mCi.
*N-methylspiperone model values are based on blood plasma data obtained with ^{18}F-labeled material; mouse values are those of Wong et al. (*7*).
n.d. = not determined.
n.a. = not available.

of >10 mCi. However, immediate uptake of the whole injected radioactivity by bladder, heart or kidneys would limit administration to 3 mCi, and complete uptake in small organs would give very high doses. The calculated doses for major organs which take into account time for transfer from blood plasma to tissues (Model 1) are lower than those assuming immediate deposition in each organ, but the kidneys still represent the critical organ and would limit administration to 3.5 mCi. Application of this model gives high doses to small, well-perfused organs such as the adrenals and especially the thyroid which would receive almost 5 rad/mCi. The cumulative activities given by Model 1 for small organs, however, are unrealistically high for several reasons:

1. Some tracer may be retarded during passage through the lungs.
2. Tracer will leave the vasculature in many tissues. Even if it were eventually trapped in a single tissue, it would suffer decay during recirculation, drastically reducing doses from ^{11}C compounds, especially for small organs. It is readily shown that if a ^{11}C compound rapidly distributes in a volume several times that of the blood plasma rather than the plasma alone, then calculated "theoretical" doses to small organs are reduced in a linear, inverse fashion. Carbon-11 compounds selected for PET studies of basic biochemistry and metabolism are typically of low molecular weight and expected to undergo fairly wide distribution. They thus would be very unlikely to yield the thyroid, kidney or bladder uptakes suggested in Table 1.
3. Trapping mechanisms are unlikely to be either 100% efficient or irreversible. Even when tracers are initially well extracted by tissues possessing an "irreversible" trapping mechanism such as phosphorylation or receptor binding, the probability of backflux to the vascular compartment is usually comparable to that of transfer to the trapped compartment. For example, the ratio of trapping-to-backflux rate constants has a maximum value of about 0.5 for ^{18}F-labeled 2-deoxy-2-fluoro-D-glucose, fluoride ion and N-methylspiperone (*25–27*). The situation may be illustrated by the example of radioiodide, which is trapped with very high efficiency in the thyroid. However, about 24 hr are required for accumulation of 25% of an administered bolus (*17*). The discovery of a tracer that fitted Model 1 for a small organ would thus be a major event in nuclear medicine.
4. Some tracer may be associated with erythrocytes, and/or so strongly bound to plasma proteins that not all is available for extraction. In fact, this exposes a contradiction in Model 1, because a tracer could only be restricted to the vasculature if binding to blood components were very tight indeed. In that case, however, *no* organ would be able to extract it with high efficiency. Large reductions in calculated organ doses occur when tracer is unavailable for extraction because of binding in the vascular compartment. The effect is similar to a widespread increase in extraction by tissues.
5. The tracer is likely to undergo metabolism. It is improbable that metabolites and the parent compound would both be trapped in the same tissue and with 100% efficiency.

Total Organ Doses

Calculation of total organ doses would require consideration of a dose to each organ from residual radioactivity in the blood pool. In the extreme case of a blood pool agent (i.e., transfer from plasma to *no* organ) the heart, lungs and kidneys would receive 75, 48 and 22 mrad/mCi, respectively. These dose estimates are a factor of 10 or more smaller than the Model 1 doses for kidneys or thyroid, and blood-pool radioactivity could not change the critical organ or increase the kidney dose estimate.

Doses to other organs from the recipient organ of Model 1 would also be small. From S-value tables it can be calculated that muscle contributes up to 30% of its self-dose to other organs, but this contribution is very small (<10 mrad/mCi) compared with the kidney or thyroid self-doses. The small intestinal (SI) contents-to-large intestinal wall dose is 13% of the SI contents-to-SI wall. Similarly, the kidney-to-adrenal dose is 2.8%, the liver-to-lung dose is 3%, the bladder-to-testes dose is 1.4% and the bladder-to-ovaries dose is 1.7% of the donor organ's self-dose. Thus, a situation where *two* organs extract tracer from plasma, and one of these organs therefore receives a higher dose than if it were the sole recipient organ, cannot occur.

Dose Estimates Using Human Arterial Blood Data

Upper-limit dose estimates were made using Model 1 with arterial plasma data which had been previously obtained for several ^{11}C compounds studied in our laboratory (Table 2). The rationale is that in each time interval the plasma content of tracer sets a limit on the quantity that can be taken up by a tissue. The estimate for N-methylspiperone in Table 2 was made with plasma data for the ^{18}F-labeled compound, since ^{11}C-N-methylspiperone is also a commonly used PET radiopharmaceutical. Plasma curves for N-methylspiperone are probably very similar whether it is labeled with ^{11}C or ^{18}F (*28*), since plasma ^{18}F was >80% unchanged N-methylspiperone at 20 min postinjection (not shown). The highest upper-limit organ doses were obtained for 2-deoxy-D-glucose, where the calculated kidney dose would limit administration to 6.7 mCi (Table 2). It must be emphasized that the actual kidney dose given by 2-deoxy-D-glucose is much lower than implied by Model 1, as indicated by traditional animal distribution studies in dogs (*3*). The purpose of the present calculation was to obtain a quantity of ^{11}C which could not exceed regulatory limits, rather than to estimate the true organ doses. A paradoxical feature of the use of measured arterial blood data with Model 1 is that slow clearance of tracer from the plasma is positively correlated with calculated

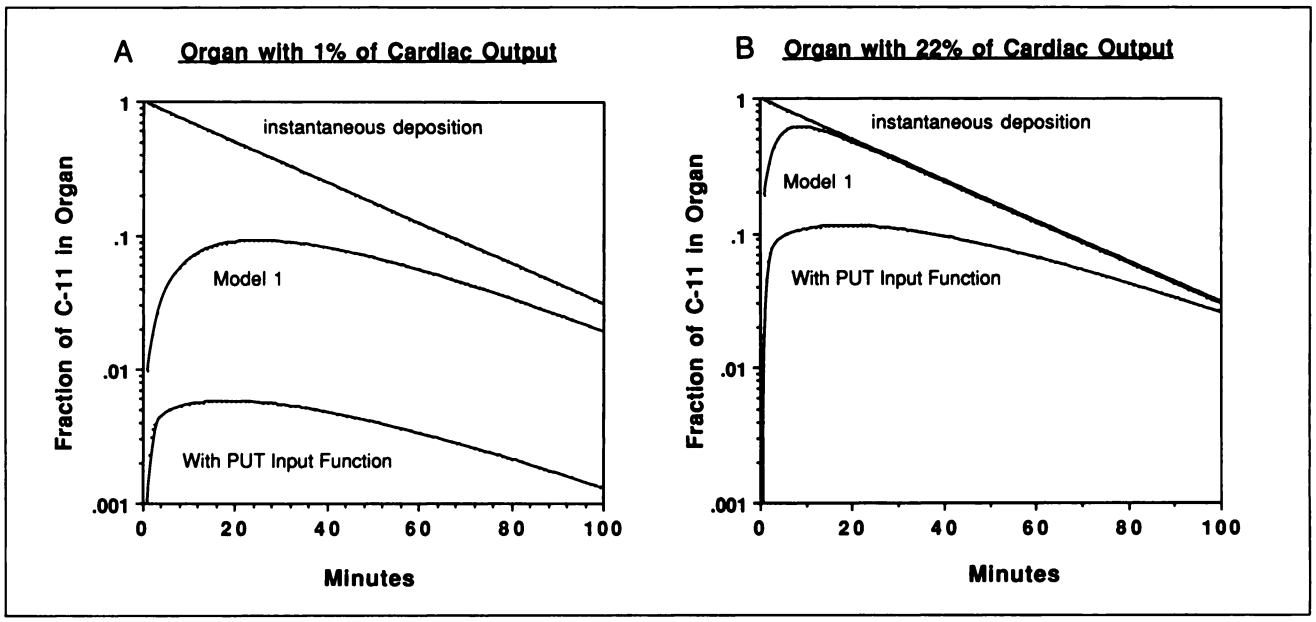

FIGURE 4. Calculated tissue time-activity curves. (A) Curves generated using general Model 1 and Model 1 with the putrescine input function for an organ which receives 1% of the cardiac output (i.e., it represents the thyroid). (B) Similar simulations for an organ receiving 22% of the cardiac output (i.e., representing the kidneys). The graphs also show the time-course obtained assuming irreversible and instantaneous deposition of ^{11}C directly into an organ. The ordinate gives the fraction of administered radioactivity in the organ.

organ doses, whereas a negative correlation is expected in practice because labeled compounds clearly cannot accumulate in tissues unless they leave the plasma. In the extreme case of a ^{11}C compound totally confined to the plasma, use of the arterial input function with Model 1 would yield a dose of over 8 rad/mCi for the kidneys, nearly three times that calculated for complete decay of the administered activity in the kidneys.

In spite of the limitations of Model 1, it can yield useful results when used with human arterial plasma data. Thus for three of the tracers in Table 2, ^{11}C-cocaine, cogentin and L-deprenyl, Model 1 showed that >15 mCi could be administered without exceeding regulatory limits, while maximum injectable activities of N-methylspiperone and putrescine would be 13.9 and 11 mCi, respectively. For many novel ^{11}C compounds, these activities would give images of acceptable quality to address specific hypotheses.

Preliminary PET Studies with Carbon-11 Compounds

From the above considerations it may be argued that it is physiologically impossible for 1-mCi injections to give doses to small organs that are within an order of magnitude of the 5 rad given by Model 1 for the thyroid. However, it is suggested that the 3.5 mCi implied by the upper-limit dose for kidney be accepted as a maximum injected activity for an initial study with a novel ^{11}C compound. Such a study would allow measurements of urinary and blood-plasma radioactivity, as well as transaxial scanning of probable critical organs and rectilinear scanning to search for unexpected accumulations of ^{11}C. These data would then permit more accurate dose estimates to be made.

Possible Incorporation of Other Information into Dose Estimation

In proposing that intravenous injection of 3.5 mCi of a low molecular weight organic ^{11}C tracer could not exceed regulatory dose limitations, we suggest that Model 1 be applied strictly to the major organs, but argue that tracer distribution and likely trapping efficiency allow us to be more relaxed for small organs. In principle, knowledge of the physiology, pharmacology and biochemistry of a ^{11}C-labeled compound could be used to further justify and perhaps extend the relaxation of Model 1. One approach would be to envisage an "other tissues" compartment in reversible connection with the plasma, as shown in Model 3 (Fig. 5). Other information could then be used to estimate values for the new rate constants in Model 3. For example, the brain has a very impermeable capillary endothelium compared with other organs, and PET measurement of tracer extraction by the brain might thus yield a lower limit for extraction by the "other tissues" compartment. In turn, this would permit more refined estimates of upper-limit doses to particular organs.

Other Positron Emitters

The findings of this study may be generalized to positron emitters with half-lives shorter than 20 min, such as ^{13}N (half-life = 10 min), for which Model 1 estimates a dose to the kidneys of 740 mrad/mCi. However, extending the analogy to longer-lived nuclides is problematic, and ^{18}F (half-life = 110 min) gives calculated kidney and thyroid doses of 6,100 and 48,000 mrad/mCi, respectively. The longer mean-life of ^{18}F increases cumulated activities for small organs by prolonging time available for uptake from

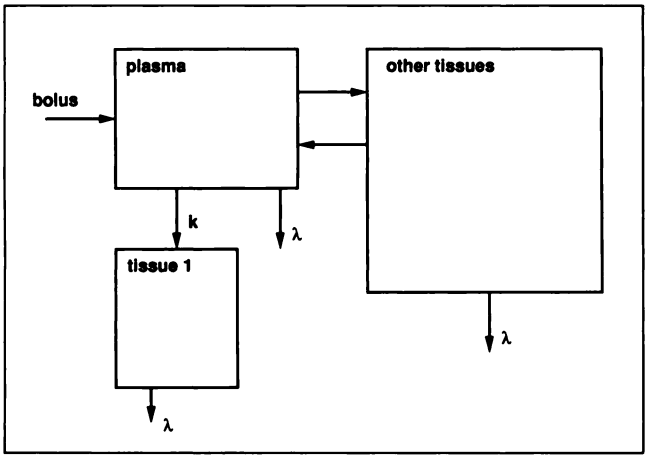

FIGURE 5. Model 2 represents the situation where reversible transfer of radioactivity between plasma and other tissues can occur in addition to irreversible transfer to the tissue of interest.

the plasma. Cumulated activities for both major and minor organs are increased by the longer irradiation time after irreversible trapping. These factors are only partially offset by smaller S values, which result from the lower positron energy of ^{18}F compared to ^{11}C. A "theoretically" acceptable injectable radioactivity of ^{18}F is therefore less than a millicurie.

CONCLUSIONS

Consideration of the short physical half-life of ^{11}C and characteristic physiological distribution times by application of Model 1 shows that 1 mCi of an intravenously injected ^{11}C tracer cannot exceed the dose limit of 5 rad to well perfused small organs such as the thyroid, even if the entire injected radioactivity is eventually accumulated by the organ. Consideration of the general physiology and biochemistry of most ^{11}C compounds likely to be used as PET tracers indicates that the true maximum doses to small organs must in fact be much lower. Application of Model 1 to large organs gave the highest calculated dose to the kidneys. A 5-rad dose to these organs could not be exceeded by administration of 3.5 mCi. Measurements of ^{11}C in arterial plasma and preliminary PET scanning in humans after injection of 3.5 mCi would allow more accurate maximum dose estimates to be made. These would often allow the desired PET studies to be conducted without the need for animal biodistribution studies to obtain dose estimates.

Other issues of regulatory concern such as chemical toxicology, in addition to radiation dosimetry, would of course have to be addressed before human studies could commence.

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REFERENCES

1. Food and Drug Administration. Part 361—Prescription drugs for human use generally recognized as safe and effective and not misbranded: drugs used in research. *Fed Reg* 1990;21:200–205.
2. McAfee JG, Subramanian G. Interpretation of interspecies differences in the biodistribution of radioactive agents. *Third international radiopharmaceutical dosimetry symposium.* Oak Ridge, TN; 1980.
3. Christman DR. Tissue distributions of radiopharmaceuticals labeled with positron emitters and problems in relating them to human studies. *Third international radiopharmaceutical dosimetry symposium.* Oak Ridge, TN; 1980.
4. Harvey J, Firnau G, Garnett ES. Estimation of the radiation dose in man due to 6-[^{18}F]fluoro-L-DOPA. *J Nucl Med* 1985;26:931–935.
5. Jones SC, Alavi A, Christman DR, Montanez I, Wolf AP, Reivich M. The radiation dosimetry of 2-[F-18]-fluoro-2-deoxy-D-glucose in man. *J Nucl Med* 1982;23:613–618.
6. Mejia AA, Nakamura T, Masatoshi I, Hatazawa J, Masaki M, Watanuki S. Estimation of absorbed doses in humans due to intravenous administration of fluorine-18-fluorodeoxyglucose in PET studies. *J Nucl Med* 1991;32:699–706.
7. Wong DF, Bice AN, Beck T, Dannals RF, Links JM, Wagner HN Jr. Considerations for dosimetry calculations with neuroreceptor binding radioligands. *Fourth international radiopharmaceutical dosimetry symposium.* Oak Ridge, TN; 1986.
8. Lockwood AH. Absorbed doses of radiation after an intravenous injection of N-13 ammonia in man. *J Nucl Med* 1980;21:276–278.
9. Fowler JS, Wolf AP. *The synthesis of carbon-11, fluorine-18, and nitrogen-13-labeled radiotracers for biomedical applications.* Washington, DC: U.S. Department of Energy; 1982.
10. Snyder WS, Cook MJ, Nasset ES, Karhausen LR, Parry-Howells G, Tipton IH. *Report on the task group on Reference Man. ICRP publication 23.* Oxford: Pergamon Press; 1975.
11. Dewey SL, MacGregor RR, Bendriem B, et al. Mapping muscarinic receptors in human and baboon brain using [N-^{11}C-Methyl]-benztropine. *Synapse* 1990;5:213–223.
12. Fowler JS, Volkow ND, Wolf AP, et al. Mapping cocaine binding in human and baboon brain in vivo. *Synapse* 1989;4:371–377.
13. Gatley SJ, Ferrieri RA, Fowler JS, MacGregor RR, Wolf AP. Rapid radiochemical and radiochemical quality control of [^{11}C]putrescine. *Appl Radiat Isotopes* 1993;44:765–767.
14. MacGregor RR, Fowler JS, Wolf AP, Shiue C-P, Lade RE, Wan C-N. A synthesis of ^{11}C-2-deoxy-D-glucose for regional metabolic studies. *J Nucl Med* 1981;22:800–803.
15. MacGregor RR, Halldin C, Fowler JS, et al. Selective, irreversible in vivo binding of [^{11}C]clorgyline and [^{11}C]-L-deprenyl in mice: potential for measurement of functional monoamine oxidase activity in brain using positron emission tomography. *Biochem Pharmacol* 1985;34:3207–3210.
16. Arnett CD, Fowler JS, Wolf AP, Shiue C-Y, McPherson DW. Fluorine-18-N-methylspiroperidol: the radioligand of choice for PETT studies of the dopamine receptor in human brain. *Life Sci* 1985;36:1359–1366.
17. Guyton AC. *Textbook of medical physiology.* Philadelphia: W.B. Saunders; 1968:279–300.
18. Jorgensen JC, Sejrsen P. Neuropeptide Y reduces ovarian blood flow in the rabbit. *Peptides* 1990;11:451–454.
19. Waddell BJ, Bruce NW, Dharmarajan AM. Changes in ovarian blood flow and secretion of progesterone and 20 alpha-hydroxypregn-4-en-3-one on day 16 and the morning and afternoon of day 22 of pregnancy in the rat. *Biol Reprod* 1989;41:990–996.
20. Myren CJ, Einer JN, Bennett P. The physiology of the testes in the Gottingen mini pig. *Z Versuchstierkd* 1989;32:183–187.
21. Stabin M, Taylor A, Eshima D, Wooter W. Radiation dosimetry for technetium-99m-MAG3, technetium-99m-DTPA and iodine-131-OIH based on human biodistribution studies. *J Nucl Med* 1992;33:33–40.
22. Vestergren E, Jacobsson L, Mattsson S, et al. Biokinetics and dosimetry of Tc-99m HMPAO in children. *Fourth international symposium on radiopharmaceutical dosimetry.* Oak Ridge, TN; 1991.

23. Snyder WS, Ford MR, Warner GG, Watson SB. *MIRD pamphlet no. 11: "S," absorbed dose per unit cumulated activity for selected radionuclides and organs.* New York: Society of Nuclear Medicine; 1975.
24. Stabin MG. *MIRDOSE.* Oak Ridge, Tennessee: Oak Ridge Associated Universities; 1984.
25. Hawkins RA, Choi Y, Huang SC, et al. Evaluation of the skeletal kinetics of fluorine-18 fluoride ion with PET. *J Nucl Med* 1992;33:633–642.
26. Logan J, Wolf AP, Chiue C-Y, Fowler JS. Kinetic modeling of receptor ligand binding applied to positron emission tomographic studies with neuroleptic tracers. *J Neurochem* 1987;48:73–83.
27. Reivich M, Kuhl D, Wolf AP, et al. The (^{18}F) fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ Res* 1979;44:127–137.
28. Fowler JS, Arnett CD, Wolf AP, et al. A direct comparison of the brain uptake and plasma clearance of *N*-[^{11}C]methylspiroperidol and [^{18}F]-*N*-methylspiroperidol in baboon using PET. *Int J Nucl Med Biol* 1986;13:281–284.