Title

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Author

Parker, H.G.

Publication Date

1972

LBL-584 c.1
TID-4500 (59th Ed.)
UC-48 Biology + Medicine

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H. G. Parker
DONNER LABORATORY

January 1972

AEC Contract No. W-7405-eng-48

Printed in the United States of America
Available from
National Technical Information Service
U.S. Department of Commerce
5285 Port Royal Road
Springfield, Virginia 22151
Price: Printed Copy $3.00; Microfiche $0.95

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CALCULATION OF HUMAN BONE AND URINARY ^{18}F CLEARANCE AFTER SINGLE INTRAVENOUS INJECTION

H. G. Parker, M.D., Ph.D.

Donner Laboratory and Lawrence Berkeley Laboratory
University of California
Berkeley, California 94720

ABSTRACT

A two-compartment mathematical model and a detailed method of calculation are presented for determination of bone and urinary ^{18}F clearance from blood of humans following a single intravenous injection of the nuclide. The calculation is part of an assessment of bone blood-flow currently employed as a clinical research procedure. It is based on multiexponential fitting to a three-hour blood activity curve and on measurement of activity in a single cumulative urine sample. The independence of the clearances from some other details of the two-comparment model is stressed, and the computation is simplified, facilitating calculation by hand or by using a very simple computer program. The method also appears useful for measurement of clearances of certain other rapidly-incorporated bone-seeking materials.

INTRODUCTION

In a series of experiments, Van Dyke, Anger, Yano, and Bozzini (1) found that the kinetics of disappearance of ^{18}F from

blood and its uptake in bone can be used to measure bone blood-flow, a previously unobtainable physiological parameter. Fluorine-18 is removed from the circulating blood by the kidney and the bone, and the near 100% efficiency of its removal from the blood on each pass through the bone is the basis for this estimation of the bone blood-flow.

In our early work with the dog, a single-exponential curve appeared to be an adequate approximation of the blood disappearance data. As human data became available, it was evident that the one-compartment mathematical model was inadequate; therefore an examination was made of two-compartment models that could fit the data. Van Dyke et al. (2) describe the measurement of human bone blood-flow, using the two-compartment model upon which we have presently settled. So far, it has been used in 28 human cases and appears to be a useful clinical research technique.

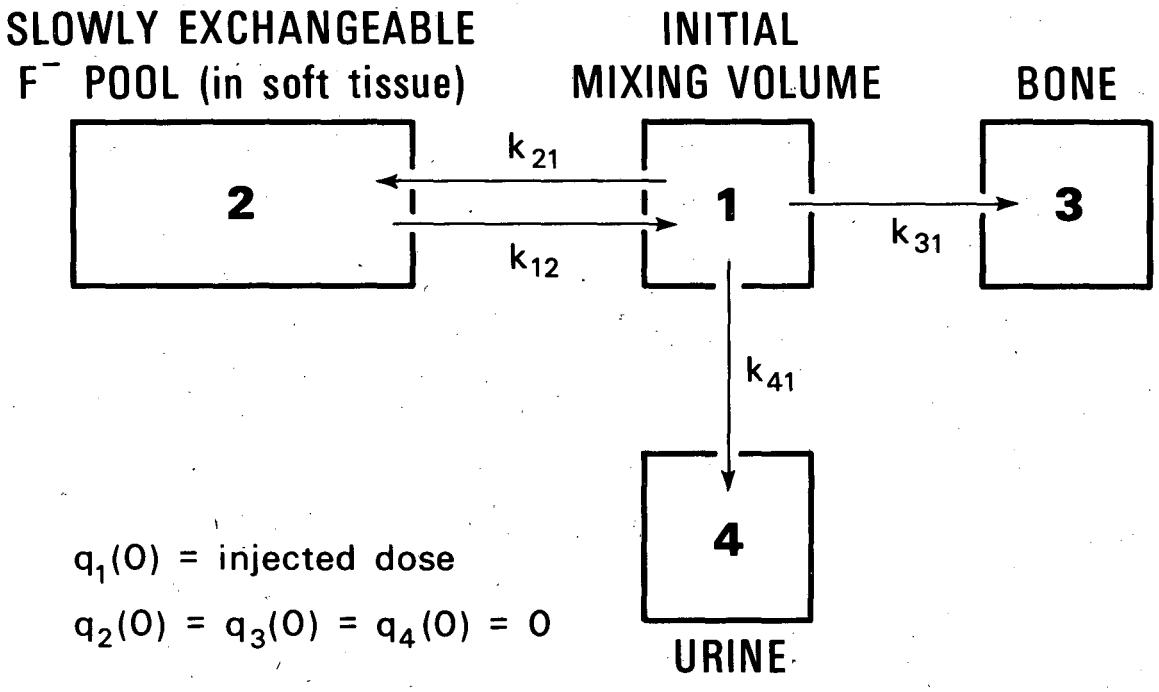
For determining bone blood-flow, bone ^{18}F extraction-efficiency must be known or assumed. The near-100% figure is not obtained from these human cases, but from other considerations (1). The other major portion of the problem is calculation of bone and urinary clearance of ^{18}F from blood in each human case, using the two-compartment model. It is this part of the problem that will be covered here. The assumptions underlying the technique have been described (2), but the calculation has not previously been outlined in mathematical detail.

The clearance measurement may at times be useful when extraction efficiency is quite unknown. We have had some success with application of the same model to bone and urinary clearance of other rapidly-incorporated bone-seeking materials. This has permitted a comparison of their bone extraction-efficiency to that for ^{18}F.

THE MODEL

The mathematical model is given in the drawing and equations of Fig. 1. It is worked out entirely in terms of sampling and clearance of whole blood rather than plasma. The very rapid exchange of ^{18}F between plasma and red cells appears to justify such an approximation at this stage of our knowledge. The "initial mixing volume" should be interpreted as some space considerably larger than blood volume and approximately equal to the extracellular volume fluid, with which ^{18}F comes into equilibrium within 6 to 8 min. Reference 2 should be consulted for additional background and justification for the choice of this model. Two other two-compartment models were tested and rejected as less consistent with known facts.

Explicit solutions for the differential equations are not required in order to obtain much of the information of interest -- the clearances in particular -- and this fact is emphasized in the order in which the calculation is set forth below.



$q_1(0)$ = injected dose

$q_2(0) = q_3(0) = q_4(0) = 0$

$$\frac{dq_1}{dt} = k_{12}q_2 - (k_{21} + k_{31} + k_{41})q_1 \qquad (1)$$

$$\frac{dq_2}{dt} = k_{21}q_1 - k_{12}q_2 \qquad (2)$$

$$\frac{dq_3}{dt} = k_{31}q_1 \qquad (3)$$

$$\frac{dq_4}{dt} = k_{41}q_1 \qquad (4)$$

DBL 721-5132

Fig. 1: The compartment-system model and differential equations for calculation of bone and urinary ^{18}F clearance after a single intravenous injection.

FITTING TECHNIQUE

Following a single injection of ^{18}F, blood samples are taken frequently, and a single cumulative urine sample obtained, usually just after completion of the blood sampling at 3 hrs.

The radioactivity of whole blood in net, decay-corrected counts per min per ml is plotted on a semilogarithmic scale against time after injection. Using a "stripping" method, a two-component exponential curve is fitted by hand to the points. The curve formed by these points is usually rather smooth and its terminal portion reasonably straight, so there is little equivocation about finding a terminal slope. This fit often necessitates rejecting a few of the early points -- often before 6 to 8 min in normals -- which would require 3 components for a good fit. (Uncertainty about the best handling of these early points is one of the reasons we have not yet begun least-squares computer fitting of the two-component curve. The hand fit has seemed adequate for our purpose, and has the advantage that it gives one a feeling as to how well two or three components really represent the data.)

From the exponential fitting, one takes the two half-times and two zero intercepts for the calculation shown below. By counting an appropriate standard of the injected dose and an aliquot of the urine, and noting the time from injection to collection of the urine sample, one completes the seven pieces of input data for the following calculation.

THE CALCULATION

Using the above procedure to fit to the blood and urine data, the significant parameters of the model are derived as follows -- in the nomenclature for tracer kinetics of Brownell, Berman, and Robertson (3):

$$c_1 = c_{11}\, e^{-\lambda_1 t} + c_{12}\, e^{-\lambda_2 t}, \tag{5}$$

where c_1 is the curve of the whole-blood ^{18}F concentration in cpm/ml, c_{11} and c_{12} are the two zero intercepts, $\lambda_1 = 0.693/(t_{1/2})_{11}$, and $\lambda_2 = 0.693/(t_{1/2})_{12}$.

Then we obtain the following:

$$V_1 = \frac{q_1(0)}{c_{11} + c_{12}} \quad \text{where } q_1(0) \text{ is the injected dose,} \tag{6}$$

$$\text{Total clearance (ml/min)} = \frac{q_1(0)}{\frac{c_{11}}{\lambda_1} + \frac{c_{12}}{\lambda_2}} \tag{7}$$

$$\text{Renal clearance (ml/min)} = \frac{q_4(t_u)}{\frac{c_{11}}{\lambda_1}(1 - e^{-\lambda_1 t_u}) + \frac{c_{12}}{\lambda_2}(1 - e^{-\lambda_2 t_u})} \tag{8}$$

where t_u is the time of urine collection and $q_4(t_u)$ is the total amount of radioactivity (cpm) collected in the single cumulative urine sample.

Finally,

$$\text{Bone clearance (ml/min)} = \text{Total clearance} - \text{renal clearance.} \tag{9}$$

If desired, the rate constants of the kinetic model (Fig. 1) are obtained as follows:

Let $b = \lambda_1 + \lambda_2$ and $c = \lambda_1 \lambda_2$.

Let $P_1 = \frac{c_{11}}{c_{11} + c_{12}}$, and $P_2 = \frac{c_{12}}{c_{11} + c_{12}}$.

Then $k_{12} = P_1 \lambda_2 + P_2 \lambda_1$, (10)

$$k_{41} = \frac{\text{renal clearance}}{V_1}, \quad (11)$$

$$k_{31} = \frac{c}{k_{12}} - k_{41}, \quad (12)$$

and $k_{21} = b - k_{12} - k_{31} - k_{41}$.

The steady-state assumption for the exchange of solutions in which ^{18}F is dissolved, provides the value of $V_2 = \frac{k_{21} V_1}{k_{12}}$. (14)

The schema given in Table I can serve as the worksheet for a programmed hand method, or as an aid to the simple computer programming required to carry out the above calculations. Even with this sytem the hand calculation is tedious and error-prone compared to computer methods; the latter are highly recommended, if available. Care should be taken to carry more significant figures than are desired in the final result.

DISCUSSION

A straightforward solution of the differential equations 1 through 4 would be the simplest way to derive equations for all the results set forth above, but it is not the simplest way to calculate the clearances, nor does it give as clear an indication, as does the above calculation, of what assumptions are really

TABLE I

Calculation Schema of ^{18}F Clearances

Enter C1:	First intercept (cpm/ml)
Enter T1:	First half-time (min)
Enter C2:	Second intercept (cpm/ml)
Enter T2:	Second half-time (min)
Set D = C1 + C2	D:
Enter ID:	Injected dose (cpm)
Set V1 = ID/D	V1: Mixing vol. (ml)
Set L1 = 0.693/T1	L1:
Set L2 = 0.693/T2	L2:
Set I1 = C1/L1	I 1:
Set I2 = C2/L2	I2:
Set TC = ID/(I1 + I2)	TC: Tot. clearance (ml/min)
Enter TU:	Time of urine sample (min)
Enter QU:	Total cpm in urine sample
Set E1 = 1 - EXP(-L1*TU)	E1:
Set E2 = 1 - EXP(-L2*TU)	E2:
Set RC = QU/(I1*E1 + I2*E2)	RC: Renal clearance (ml/min)
Set BC = TC - RC	BC: Bone clearance (ml/min)

Optional portion -- for rate constants of the model:

Set B = L1 + L2	B:
Set C = L1*L2	C:
Set P1 = C1/D	P1:
Set P2 = C2/D	P2:
Set K12 = P1*L2 + P2*L1	K12:
Set K41 = RC/V1	K41: Frac. turnover rates (min^{-1})
Set K31 = C/K12 - K41	K31:
Set K21 = B - (K12 + K31 + K41)	K21:
Set V2 = K21*V1/K12	V2: Vol. of comp. 2 (ml)

necessary for each stage of the calculation. As set forth here, the calculation emphasizes the independence of the clearances from the specifics of the particular two-compartment model chosen to approximate the invariants of the data. Indeed, if warranted, the clearances could be calculated based on the same general considerations regarding the invariant area under the blood curve (see below), without any exponential fitting. For renal clearance, the exponential fitting may be regarded as a mere mathematical convenience. For total clearance, the fitting also provides a necessary decision as to the probable course of the blood curve extrapolated beyond the available data.

In equation 7 the total clearance from the labile pool made up of the combination of compartments 1 and 2 is obtained simply by finding the formula for the reciprocal of the area under the two-component exponential blood curve, normalized to the fraction of the injected dose per milliliter. This is synonymous with the reciprocal of the mean time that the ^{18}F spends in any one milliliter of the labile pool. In unpublished work we have shown that use of this area gives the correct result for total clearance from any such labile pool made up of all the regions that are in reversible exchange with one another, in any stationary and conservative linear system. In the case of this particular model, the clearance calculation can be verified by comparison with the result obtained by solving the differential equations of the model and finding

$(k_{31} + k_{41})V_1$.

The renal clearance (equation 8) can be obtained from the classic conception of clearance, expressed here as dq_4 = renal clearance $\cdot$ $c_1(t)$ dt. If one further assumes that renal clearance is a function of neither t nor c_1 during the course of the measurement, then straightforward integration of this equation from the time of injection to the time of urine collection yields

$$\text{renal clearance} = \frac{q_4(t_u)}{\int_0^{t_u} c_1 \, dt} .$$

(The denominator of this expression is simply the area under the blood concentration curve from 0 to t_u, another invariant of the data.) When c_1 is substituted from equation 5 and the integration performed, equation 8 is obtained. Essentially the same point of view is expressed by saying that differential equation 4 might be assumed to be true regardless of whether or not the other equations of the model are correct. Equation 4 can be integrated and the value of $k_{41}V_1$, the renal clearance, obtained without solving the rest of the system. Explicit solution of differential equations 1 and 2 is still not necessary at this stage.

If one could wait long enough to measure a good approximation to the total amount of ^{18}F excreted in the urine, this part of the routine calculation would be much simplified. We found, however, that this was not compatible with the short half-life of ^{18}F nor with our method of urine collection.

Equation 9 states the assumption that bone clearance can be obtained simply by subtracting renal from total clearance, that is to say that all extrarenal clearance of the material is bone clearance. This, of course, does not preclude allowing for leakage of the material out of the blood stream and back at rates reasonably fast on the time scale of the experiment, but it does assume that all irreversible removal of material from the labile pool constitutes removal by bone. In the case of ^{18}F the evidence from human scintiphotos and numerous experiments in animals tends to support the basic assumption. If the model is applied to other bone-seekers, it must be done with careful attention to whether or not bone clearance and extrarenal clearance may be safely equated.

Equation 9 is the keystone of the method. It should be realized that it is not limited to this particular two-compartment model, but would be true in any linear model that shows only two irreversible flows out of the above-mentioned labile pool.

A two-compartment model has previously been used for calculating renal clearances from the blood disappearance curve after a single injection (4). The present model bears considerable resemblance to it, but is a bit more complex, requiring urine sampling to fractionate the total clearance obtained from blood sampling into renal and extrarenal clearances. In addition, in presenting the model and the calculations as it is done here, it is

hoped to lay more stress on what assumptions are necessary for each part of the calculation, so that one is not quite so confined to the specifics of a particular two-compartment model; it may be easier to see what would change and what would have to remain invariant if some different model were proposed.

If one is not interested in V_2 or the rates of exchange of ^{18}F between compartments 1 and 2, the calculations shown in equations 10 through 14 may be omitted. To obtain equations 10 through 14, an explicit solution of the pair of differential equations 1 and 2 for q_1 or q_2 was needed. This was done by standard Laplace transform methods. When the coefficients and exponents of the solution were equated to those of the equation for q_1 (V_1 times the value of c_1 from equation 5) and solved for the unknown rate constants, the short sequential calculation shown in equations 10 through 14 was obtained.

It is <u>not</u> assumed that the model can be directly applied to a description of the steady-state movement of nonradioactive fluorine, without additional studies. It is true that the quantity of circulating nonradioactive fluoride (in the microgram/ml range) is large compared to the number of tracer atoms, but some of it may be circulating in a bound form. Our studies of the specific activity of fluorine in serum and urine are limited and inconclusive, so we are not yet ready to apply the model in this way.

The method described here may have application to some other

bone-seeking materials. We have applied it to some and have been able to compare their bone clearances with that of ^{18}F, which is presently our standard for a very efficiently removed material. One must be cautious, however, not only to be sure that the extrarenal clearance can be assumed to be bone clearance and that clearance is constant in the concentration range employed, but that the extrapolation to long post-injection times of the 2-exponential fitting curve is indeed an adequate approximation to the total area under the disappearance curve. It is undoubtedly not an adequate approximation for such slowly removed materials as strontium, calcium and radium, and badly overestimates their clearance.

ACKNOWLEDGMENT

The author gratefully acknowledges the encouragement and support of Dr. Donald Van Dyke, whose work with ^{18}F in bone blood-flow made the present study possible.

This work was performed under the auspices of the U. S. Atomic Energy Commission, and with the support of Grant CA-08370 from the National Cancer Institute of the National Institutes of Health.

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