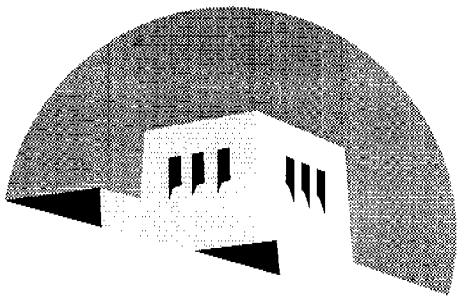

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VOLUME III, NUMBER 2

The Application of Pharmacokinetic Methods to Radiopharmaceuticals

by:

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THE APPLICATION OF PHARMACOKINETIC METHODS TO RADIOPHARMACEUTICALS

STATEMENT OF OBJECTIVES

The primary goal of this continuing education lesson is to demonstrate the application of commonly used pharmacokinetic methods of analysis to radiopharmaceuticals. The course provides a review of pharmacokinetics covering areas such as compartmental analysis, the effects of protein binding on pharmacokinetic parameters, non-compartmental pharmacokinetic analysis and computerized methods for analysing data. Examples are given to illustrate the concepts and the pharmacokinetic characteristics of radiopharmaceuticals currently in clinical use in nuclear medicine.

Upon successful completion of this lesson, the reader should be able to:

1. Describe the various types of compartmental pharmacokinetic models.
2. Define various pharmacokinetic terms such as volume of distribution, volume of distribution at steady state, systemic clearance, renal clearance, mean residence time and mean transit time.
3. When provided with a set of radiopharmacokinetic data, calculate the values for various compartmental pharmacokinetic parameters such as distribution and elimination rate constants, half-lives, volumes of distribution, and systemic and renal clearance.
4. Describe the differences between non-iterative curve fitting and computerized non-linear weighted least squares regression.
5. Compare by statistical methods, two or more different pharmacokinetic models for fitting a set of radiopharmacokinetic data and determine the best model.

Editors note: Due to the complexity of the material contained in this lesson and to assure the author's material is unaltered, the text of this lesson will not be produced in column format.

COURSE OUTLINE

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II. COMPARTMENTAL PHARMACOKINETIC ANALYSIS

- A. One Compartment Pharmacokinetics
- B. Example of One Compartment Pharmacokinetics
- C. Effect of Protein Binding on Elimination of ^{99m}Tc-DTPA
- D. Protein-binding of ^{99m}Tc-DTPA and Other Radiopharmaceuticals

III. MULTI-COMPARTMENT PHARMACOKINETICS

- A. Two-Compartment Pharmacokinetics
- B. Example of Two-Compartment Pharmacokinetics
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- D. Example of Three-Compartment Pharmacokinetics

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- A. Non-Linear Weighted Least Squares Regression
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- A. Example of Calculation of MRT and MTT

VI. SUMMARY

VII. APPENDICES

- A. General Equations for Pharmacokinetic Analysis
- B. Example of a Program in PCNONLIN to Analyse Pharmacokinetic Data

THE APPLICATION OF PHARMACOKINETIC METHODS TO RADIOPHARMACEUTICALS

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INTRODUCTION

Pharmacokinetics describes the time course of drug disposition in the body, including its distribution from the site of administration, its metabolism and its elimination from the body. Due to the radioactive properties of radiopharmaceuticals, these agents offer a unique opportunity to observe their pharmacokinetic characteristics using such non-invasive methods as gamma camera imaging or by sampling blood or urine. Total radioactivity may be measured (as in the case of gamma camera imaging) to demonstrate the biodistribution or pharmacokinetics of the radiolabel. Alternatively, in the case of blood or urine samples, these measurements may be combined with radiochromatography to evaluate the pharmacokinetics of the intact radiopharmaceutical and its metabolites. In the majority of cases, measurement of total radioactivity is sufficient, since most radiopharmaceuticals in clinical use are not metabolized. There are exceptions and *in-vivo* mechanisms have been identified for cleavage of radioiodine, technetium-99m (^{99m}Tc) and indium-111 (^{111}In) from various radiopharmaceuticals (1,2).

The pharmacokinetic properties of radiopharmaceuticals are important in two respects: i) the radiation absorbed dose to the patient from the radiopharmaceutical is not only dependent on the physical properties of the radionuclide but also on the pharmacokinetic characteristics of the radiopharmaceutical (3) and ii) alterations in the normal pharmacokinetic properties of some radiopharmaceuticals may indicate disease processes in an eliminating organ. An example of the latter, is the application of pharmacokinetic methods to determine the clearance of renal imaging radiopharmaceuticals such as ^{99m}Tc-DTPA or ^{131}I-iodohippurate. Reduced clearance of these radiopharmaceuticals may indicate diminished renal function (4).

The purpose of this continuing education lesson is to demonstrate the practical application of pharmacokinetic methods of analysis to data obtained following the administration of radiopharmaceuticals to humans. Specific examples have been chosen with relevance to the practice of nuclear medicine to illustrate the different pharmacokinetic properties of various agents in clinical use. Commonly used pharmacokinetic equations (without their derivations) are presented. For the derivation of these equations, the reader should consult a more comprehensive pharmacokinetic reference (5). Although extravascular administration of radiopharmaceuticals is possible (ie. oral ^{131}I for thyroid studies and inhalation of ^{99m}Tc-DTPA for lung ventilation studies) most radiopharma-ceuticals are administered by i.v. bolus. This is, therefore, the route of administration discussed in this lesson.

COMPARTMENTAL PHARMACOKINETIC ANALYSIS

One approach to analysing pharmacokinetic data is to construct a model of the body which consists of one or more inter-connected but separate compartments (Figure 1). The radiopharmaceutical is administered into the central compartment (compartment 1). It may then be transferred to the other (peripheral) compartments (compartments 2 and 3), return from these compartments to the central compartment and finally be eliminated from the central compartment out of the body. The rate constants

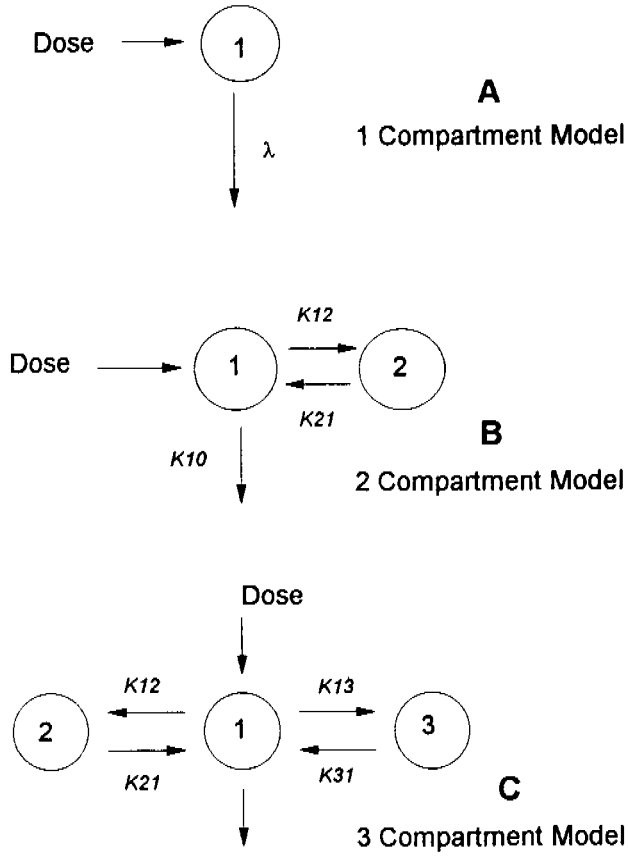
of transfer and elimination are assumed to be first-order (i.e., the rate of transfer is proportional to the concentration in the compartment from which the radiopharmaceutical is being eliminated or transferred):

$$\frac{dC}{dt} = -\lambda_z C$$

(Eq. 1)

where dC/dt is the rate of change in the concentration of the radiopharmaceutical in a particular compartment, C is the concentration in the compartment and λ_z is a proportionality constant.

Figure 1. Various compartmental pharmacokinetic models.



The number of compartments required in the pharmacokinetic model depends partially on the range of plasma concentrations studied. A plot of the plasma concentrations versus time post-injection (p.i.) on semi-logarithmic paper may yield a straight line which suggests that the data could be described by a one-compartment model. However, by taking additional plasma samples shortly after injection, a distribution phase may also be observed which would then require a two-compartment model to adequately describe the data. Likewise, by taking additional samples long after injection, a second elimination phase may also be observed which would require an increase in the number of compartments to three. Table 1 shows the compartmental pharmacokinetic characteristics of several commonly used radiopharmaceuticals in nuclear medicine. The general equations used to calculate

the various pharmacokinetic parameters are given in Appendix I and will be discussed in the remainder of this lesson. Standardized terminology and symbols have been utilized (15).

Table 1. Compartmental Pharmacokinetic Characteristics of Some Common Radiopharmaceuticals in Individual Patients.

Radiopharmaceutical	Application	No. of Compartments	$T1/2\lambda_1$ (h)	$T1/2\lambda_2$ (h)	$T1/2\lambda_3$ (h)	Vc (L)	Vss (L)	CL (mL/min)	Ref.
^{99m}Tc-DTPA	Renal Imaging	1	*na	1.4	na	17.0	na	140	6
		2	0.09	1.4	na	9.7	15.3	131	6
^{131}I-Iodohippurate	Renal Imaging	2	0.04	0.4	na	5.3	10.9	412	7
^{99m}Tc-MAG3	Renal Imaging	2	0.04	0.4	na	3.7	7.0	265	7
^{131}I-B72.3	Immunoscinti-graphy	2	3.7	62.4	na	4.7	5.9	2	8
^{99m}Tc Red Blood Cells (in-vitro label)	Blood Pool Imaging	2	1.0	20.4	na	7.5	11.4	6	9
^{201}Tl Thallous Chloride	Myocardial Imaging	2	0.06	38.7	na	18.2	297	91	10
^{99m}Tc-Sestamibi	Myocardial Imaging	2	0.06	3.0	na	51.4	289	1252	11
^{99m}Tc-HIDA	Hepatobiliary Imaging	2	0.04	0.8	na	8.3	30.2	490	12
^{99m}Tc-Exametazime (HMPAO)	Cerebral Perfusion Imaging	3	0.02	0.8	19.3	19.2	74.6	46	13
^{99m}Tc-MDP	Bone Imaging	3	0.40	2.2	30.1	12.3	124	70	14

*na: not applicable

One-Compartment Pharmacokinetics

The simplest compartmental model is the one-compartment model (Figure 1A). Single compartment pharmacokinetics is exhibited by a radiopharmaceutical which demonstrates a single disposition phase (i.e., a straight line) when the plasma concentrations are plotted versus time p.i. on semi-logarithmic paper. The volume of this compartment (volume of distribution) is V_c. Elimination processes may include a combination of renal and non-renal (e.g., hepatobiliary) elimination of intact radiopharmaceutical or metabolism by the liver and other organs. The rate of elimination is described by the rate constant, λ_z . Renal elimination is associated with the rate constant k_e , non-renal elimination with the rate constant k_{nr} and metabolism with the rate constant k_m. These constants are related to λ_z as follows:

$$\lambda_z = k_e + k_{nr} + k_m$$

(Eq. 2)

The elimination from the plasma of a radiopharmaceutical which exhibits compartmental pharmacokinetics may be described by the following general equation :

$$C = \sum_{i=1}^{z} C_i e^{-\lambda_i t}$$

For a one-compartment model:

$$C = C(0)\, e^{-\lambda_z t}$$

(Eq. 3)

where C is the concentration of the radiopharmaceutical at time t, $C(0)$ is the plasma concentration at $t = 0$ and λ_z is the elimination rate constant.

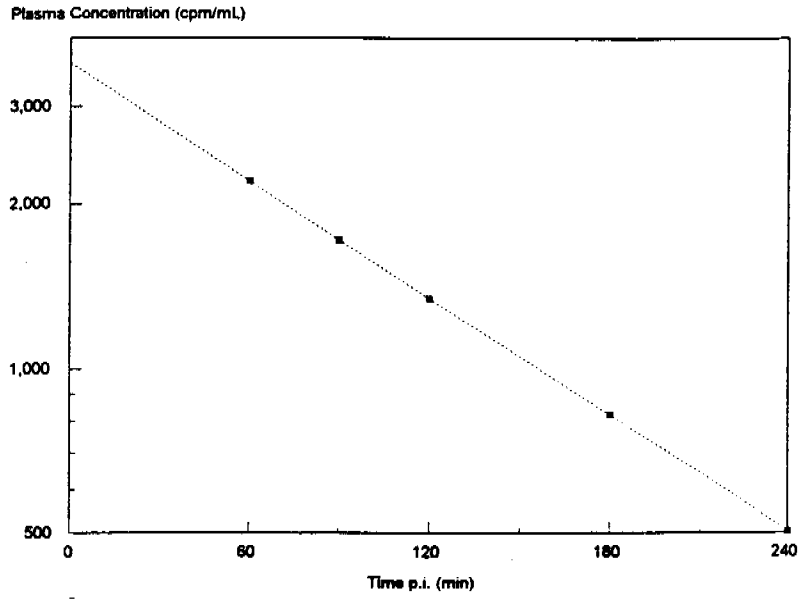
Example of one-compartment pharmacokinetics

^{99m}Tc-DTPA is a radiopharmaceutical used for renal function studies, which may be characterized by one or two-compartment pharmacokinetics depending on the range of plasma samples taken. The plasma concentrations of ^{99m}Tc at various times after injection of a dose of 3.7 MBq (6.05 X 10^7 cpm) of ^{99m}Tc-DTPA in a 70 kg patient are shown in Table 2 (6).

Table 2. Worksheet for ^{99m}Tc-DTPA Plasma Data

Time p.i. (min)	Plasma Concentration (cpm/mL)	Log Plasma Concentration
60	2203	3.34
90	1721	3.23
120	1346	3.13
180	827	2.91
240	503	2.70

Figure 2. Elimination of ^{99m}Tc-DTPA from the Plasma after i.v. Injection



A plot of the decay-corrected plasma concentrations versus time p.i. on semi-logarithmic paper (Figure 2) demonstrates only a single disposition phase suggesting that the data may be adequately described by a one-compartment model. The log of the plasma concentration is calculated (Table 2) and linear regression is performed on these log values versus time p.i. to obtain parameter values for the log function describing the elimination of the radiopharmaceutical:

$$LogC = LogC(0) - \frac{\lambda_z t}{2.303}$$

(Eq. 4)

In this example, linear regression on the log plasma concentration versus time p.i. yielded the following equation:

$$LogC = 3.55 - 0.00356\,t \quad (r = -0.999)$$

The slope of this line is:

$$-0.00356 = \frac{-\lambda_z}{2.303}$$

(Eq. 5)

Therefore, the elimination rate constant:

$$\lambda_z = (2.303)(0.00356)$$

$$= 0.00820\ \text{min}^{-1}$$

The general equation for half-life is given by :

$$t_{1/2\lambda_i} = \frac{0.693}{\lambda_i}$$

For a one-compartment model:

$$t_{1/2\lambda_z} = \frac{0.693}{\lambda_z}$$

(Eq. 6)

$$= \frac{0.693}{0.00820\text{min}^{1}}$$

$$= 84.5\ \text{min}$$

The plasma concentration at t = 0 min is given by,

$$LogC(0) = 3.55$$

$$C(0) = 3548\,cpm/mL$$

The equation describing the plasma concentration of ^{99m}Tc-DTPA versus time in this patient using a one-compartment model is therefore:

$$C = 3548e^{-0.00820t}\,cpm/mL$$

The general equation for volume of distribution of the central compartment is:

$$V_c = \frac{D_{i.v.}}{\sum_{i=1}^{n} C_i}$$

or a one-compartment model:

$$V_c = \frac{D_{i.v.}}{C(0)}$$

(Eq. 7)

$$= \frac{6.05 \times 10^7\,cpm}{3548\,cpm/mL}$$

$$= 17{,}052\,mL$$
$$= 17.05\,L$$

Plasma volume can be estimated from the patient's weight (16):

$$V_p = (0.065\,L/kg)(70\,kg)$$

$$= 4.55\,L$$

The volume of distribution of ^{99m}Tc-DTPA is obviously much larger than the plasma volume, which indicates that the radiopharmaceutical is widely distributed in the body.

The systemic or total body clearance of ^{99m}Tc-DTPA (*CL*) is the volume of plasma (or blood) from which the radiopharmaceutical is completely eliminated per unit time. The clearance can be calculated from plasma concentration versus time data as follows:

$$CL = \lambda_z V_c$$

(Eq. 8)

$$= (0.00820\,\text{min}^{-1})(17{,}052\,mL)$$
$$= 139.8\,mL/\text{min}$$

Alternatively, the clearance can be calculated from the area under the plasma concentration versus time curve (*AUC*) and the injected dose as follows :

$$CL = \frac{D_{i.v.}}{AUC}$$

(Eq. 9)

The general equation for *AUC* is:

$$AUC(0 \rightarrow \infty) = \sum_{i=1}^{n} \frac{C_i}{\lambda_i}$$

For a one-compartment model:

$$AUC = \frac{C(0)}{\lambda_z}$$

(Eq. 10)

$$= \frac{3548 cpm/mL}{0.00820 \text{min}^{-1}}$$

$$= 432,682 \frac{cpm \cdot \text{min}}{mL}$$

Substituting the values for the *Di.v.* and *AUC* into Eq. 9 gives an estimate of the systemic clearance:

$$CL = \frac{6.05 \times 10^7 cpm}{432682 cpm \cdot \text{min}/mL}$$

$$= 139.8 \, mL/\text{min}$$

The renal clearance (CL_R) of a radiopharmaceutical is the volume of plasma (or blood) flowing through the kidneys from which the radiopharmaceutical is completely eliminated per unit time. A renal clearance which is less than the glomerular filtration rate (GFR) in the patient suggests that the radiopharmaceutical may be reabsorbed in the renal tubules whereas a renal clearance much higher than GFR suggests tubular secretion. Renal clearance, however, cannot exceed renal blood flow. Renal clearance can be calculated from plasma and urinary excretion data as follows:

$$CL_R = \frac{\Delta A_e / \Delta t}{C_m}$$

(Eq. 11)

where ΔA_e is the amount of the radiopharmaceutical excreted in the urine over the time interval Δt and C_m is the concentration of the radiopharmaceutical in the plasma at the mid-point of the time interval (t_m). The urinary excretion data for ^{99m}Tc-DTPA in this patient is shown in Table 3.

Table 3. Worksheet for ^{99m}Tc-DTPA Urinary Excretion Data

Time Interval (Δt) (min)	t_m	Amount Excreted in Urine (ΔAe) (cpm)	Urinary Excretion Rate ($\Delta Ae/\Delta t$) (cpm/min)	C_m (cpm/mL)
0-60	30	2.27×10^7	3.78×10^5	2885
6-120	90	1.35×10^7	2.25×10^5	1721
120-240	180	0.65×10^7	1.08×10^5	827

If we consider the time interval, t = 60-120 min (t_m = 90 min),

$$CL_R = \frac{13,500,000\ cpm/\ 60 min}{1721\ cpm/\ mL}$$

$$= 131\ mL/min$$

Eq. 11 may be rearranged as follows:

$$\frac{\Delta A_e}{\Delta t} = CL_R \cdot C_m$$

Since renal clearance may vary slightly over the time course of the radiopharmaceutical in the body, a more accurate estimate may be obtained by plotting $\Delta A_e/\Delta t$ versus C_m. The slope of the line (obtained by linear regression) is then equal to the renal clearance (CL_R). A plot of $\Delta A_e/\Delta t$ vs. C_m for ^{99m}Tc-DTPA in this patient is shown in Figure 3.

Linear regression yielded the following equation:

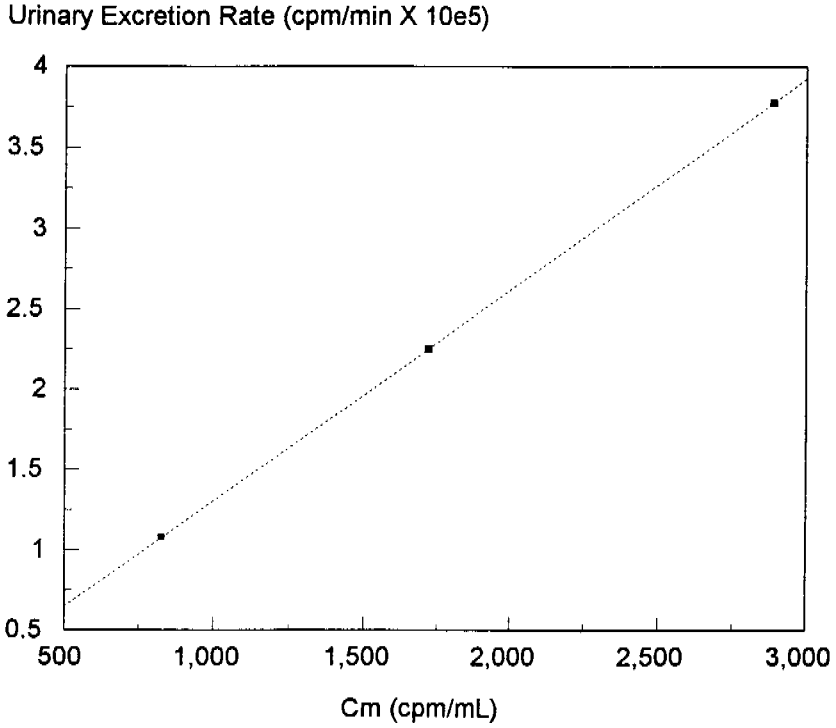
$$\frac{\Delta A_e}{\Delta t} = 131 \cdot C_m$$

The renal clearance of ^{99m}Tc-DTPA in this patient is therefore 131 mL/min. Renal clearance is also related to the volume of distribution by the urinary excretion rate constant, ke:

$$CL_R = k_e V_c$$

(Eq. 12)

Figure 3. Urinary excretion rate of ^{99m}Tc-DTPA versus plasma concentration.



The urinary excretion rate constant (*ke*) can therefore be calculated once CL_R and V_c are known:

$$k_e = \frac{CL_R}{V_c}$$

$$= \frac{131 mL/min}{17,052 mL}$$

$$= 0.00768\ min^{-1}$$

The fraction of the radiopharmaceutical which is ultimately excreted unchanged in the urine [A_e (∞)] is given by the ratio of the renal clearance to the systemic clearance (or by the ratio of the urinary excretion rate constant *ke* to the elimination rate constant λ_z). Fraction excreted in the urine:

$$= \frac{CL_R}{CL} = \frac{k_e}{\lambda_z}$$

(Eq. 13)

$$= \frac{131 mL/min}{139 mL/min} = \frac{0.00768 min^{-1}}{0.00820 min^{-1}}$$

$$= 0.94$$

Since ^{99m}Tc-DTPA is only eliminated by glomerular filtration and is not eliminated by other means such as metabolism or hepatobiliary elimination, then it is expected that the renal clearance will be essentially identical to the systemic clearance and therefore the fraction eliminated unchanged will approach one. Furthermore, since ^{99m}Tc-DTPA is only eliminated by glomerular filtration, its clearance can be used as a measure of GFR in the patient.

Although it is widely recognized that GFR decreases with age in adults, it is also lower in infants and children, possibly related to a smaller volume of distribution (V_c) or slower rate of elimination (λ_z) (17). The normal GFR in young adults is approximately 100-130 mL/min. However, the GFR (as measured by the clearance of ^{51}Cr-EDTA) in infants and children ranges from 15 mL/min up to 1 year of age to 80 mL/min in children 10-15 years old (17). This illustrates that the normal CL of a radiopharmaceutical may be affected by the age of the patient.

Effect of protein binding on elimination of ^{99m}Tc-DTPA

Considerable discussion has taken place in the nuclear medicine literature concerning the variable amount of protein binding exhibited by different formulations of ^{99m}Tc-DTPA and its effect on measuring GFR with this agent (18-21). Since the protein bound agent cannot be filtered at the glomerulus, its rate of elimination could be assumed to be negligible over the time course that GFR measurements are made. Only the free ^{99m}Tc-DTPA would be eliminated from the plasma by glomerular filtration. However, if only total radioactivity measurements are made for plasma samples, then the elimination rate will appear slower than is in fact the case, due to the contribution from the persistent protein bound radioactivity. The clearance of free ^{99m}Tc-DTPA (CL_f) will then be given by:

$$CL_f = \frac{CL}{f_u}$$

(Eq. 14)

where, f_u is the fraction of ^{99m}Tc-DTPA which is not bound to plasma proteins and CL is the apparent clearance of the radiopharmaceutical (i.e., total of free and protein-bound radioactivity). Using the example of the patient described above, if the ^{99m}Tc-DTPA formulation exhibited 10% protein-binding (i.e., f_u = 0.90), although the apparent clearance (CL) would be 125.8 mL/min, the clearance of the free agent (CL_f) would still be:

$$CL_f = \frac{CL}{f_u} = \frac{125.8\ mL/\min}{0.9}$$

$$= 139.8\ mL/\min$$

The apparent clearance would obviously under-estimate GFR in this patient by 14 mL/min. Other pharmacokinetic parameters are also affected by protein-binding including λ_z, $C(0)$ and V_c. As previously mentioned, λ_z is decreased due to the persistence of the protein-bound fraction; $C(0)$ is increased and V_c is decreased. The effect of increased protein-binding is to decrease V_c until eventually it is equivalent to the plasma volume (V_p) in the patient. The effect of increasing percentages of protein binding on the pharmacokinetic parameters associated with the elimination of ^{99m}Tc-DTPA from the plasma for the patient described in the example above is given in Table 4. Ultrafiltration of plasma samples to remove the protein bound fraction and measurement of the radioactivity contained in the protein-free ultrafiltrate can eliminate the errors associated with measurement of GFR when protein binding may be a factor (21,22).

Table 4. Effect of protein binding on pharmacokinetic parameters associated with ^{99m}Tc-DTPA.

	Pharmacokinetic Parameter				
Protein Binding (%)	λz (min^{-1})	C(0) (cpm/mL)	Vc (L)	Apparent CL (mL/min)	GFR error (mL/min)
0	0.00820	3548	17.05	139.8	0
1	0.00817	3570	16.95	138.4	-1.4
5	0.00808	3680	16.44	132.8	-7.0
10	0.00796	3829	15.80	125.8	-14.0
15	0.00783	3988	15.17	118.8	-21.0

Protein-binding of ^{99m}Tc-DTPA and other radiopharmaceuticals

Protein-binding of radiopharmaceuticals can be measured by several techniques including gel-filtration chromatography, trichloroacetic acid precipitation, dialysis and ultrafiltration of plasma samples. Different values are obtained depending on the technique, with generally lower percentages of protein binding observed by dialysis and gel filtration than by the other techniques (23,24). It is hypothesized that gel filtration and dialysis may disrupt the association between a fraction of the radioactivity and the plasma protein. These techniques therefore measure only irreversibly protein-bound radioactivity (19,23,24). The protein binding of radiopharmaceuticals ranges from negligible values (<5%) for ^{201}Tl and ^{99m}Tc-DTPA (10,20,24) to as high as 79-90% for ^{99m}Tc-MAG_3 (7,4-26). Various plasma proteins appear to be involved in this process (24). α_1-Antitrypsin is responsible for binding ^{99m}Tc-exametazime, ^{99m}Tc-glucoheptonate, ^{99m}Tc-DTPA, ^{99m}Tc-pyrophosphate and ^{99m}Tc-iminodiacetic acid compounds. Albumin is the main protein involved in binding ^{99m}Tc-MDP and ^{99m}Tc-DMSA whereas ^{99m}Tc-MAG_3 is primarily bound to α_2-globulin.

MULTI-COMPARTMENT PHARMACOKINETICS

A radiopharmaceutical which exhibits a discernible distribution phase followed by an elimination phase when the plasma concentrations are plotted versus time p.i. on semi-logarithmic paper is characterized by multi-compartment pharmacokinetics. Two or three compartment models are the most common (Figure 1B and 1C).

Two-compartment pharmacokinetics

After administration of the dose by i.v. bolus into the central compartment (compartment 1), there is distribution of the radiopharmaceutical from the central compartment to a peripheral compartment (compartment 2). It is important to remember that these compartments do not represent actual anatomical regions (i.e., plasma and tissues) but rather only represent components of a mathematical model which is useful for describing the pharmacokinetics of the radiopharmaceutical. Nevertheless, the central compartment is assumed to contain the blood and tissues which are well-perfused whereas the peripheral compartment is assumed to contain those tissues which are less well-perfused. However, these compartments may also represent concentration-dependent binding processes which may occur with plasma proteins or tissues. The volume of the central and peripheral compartments is V_c and V_2 respectively. V_2 is defined in terms of V_c by:

$$V_2 = V_c[\,1 + k_{12}/\,k_{21}]$$

The total volume of both compartments is *Vss* (volume of distribution at steady-state). The constants k_{12} and k_{21} describe the rates of transfer of the radiopharmaceutical from compartment 1 to compartment 2 and from compartment 2 to compartment 1, respectively. Elimination is assumed to occur from compartment 1 and is associated with the rate constant k_{10}. As before,

$$k_{10}=k_e+k_{nr}+k_m \qquad \text{(See Eq 2, P 5)}$$

The elimination from the plasma of a radiopharmaceutical which exhibits two-compartment pharmacokinetics may be described by the following biexponential equation:

$$C=C_1e^{-\lambda_1 t}+C_2e^{-\lambda_2 t}$$

(Eq. 15)

where C is the concentration of the radiopharmaceutical at time t, λ_1 is the overall rate constant associated with the distribution phase, λ_2 is the overall rate constant associated with the elimination phase (note: this is different than k_{10}) and C_1 and C_2 are coefficients.

Example of two-compartment pharmacokinetics

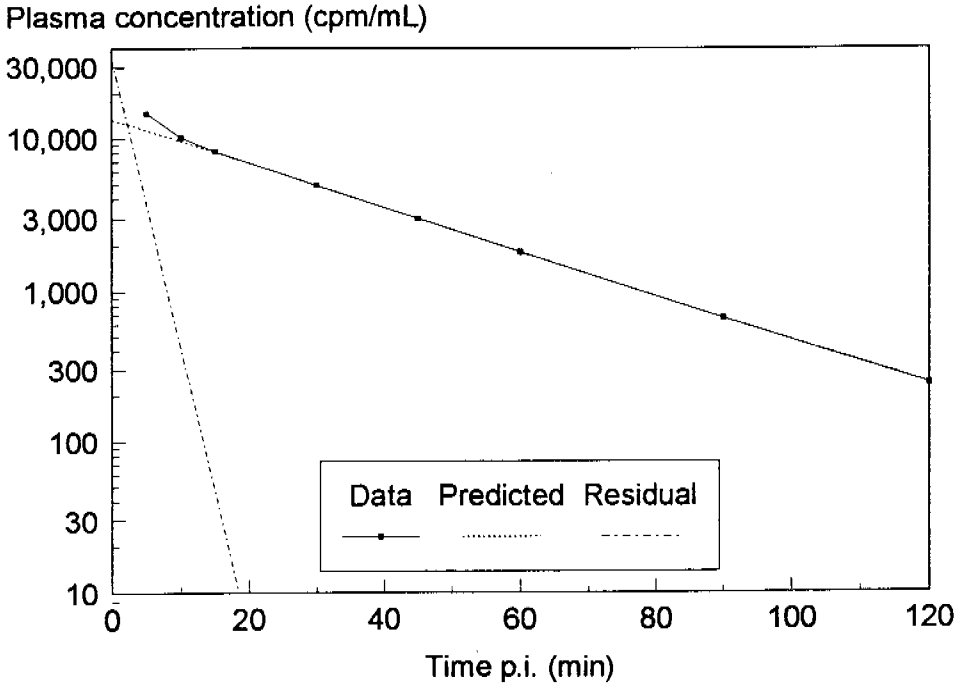
^{99m}Tc-MAG$_3$ (a renal imaging agent) is an example of a radiopharmaceutical which exhibits two-compartment kinetics. A worksheet is presented in Table 5 which shows the process of curve-stripping necessary to determine the parameters associated with the elimination of ^{99m}Tc-MAG$_3$.

Table 5. Worksheet for ^{99m}Tc-MAG$_3$ Plasma Data.

Time p.i. (min)	Plasma Conc. (cpm/mL)	Log Plasma Conc.	Predicted Plasma Conc. (cpm/mL)	Residual (cpm/mL)	Log Residual
5	14762		11416	3346	3.52
10	10188		9661	527	2.72
15	8216		8175	41	1.61
30	4913	3.69	4955		
45	2977	3.47	3003		
60	1803	3.26	1820		
90	665	2.82	668		
120	242	2.38	245		

The first step is to plot the plasma concentrations versus time p.i. on semi-logarithmic paper to determine if the data exhibits multi-exponential pharmacokinetics. In this example (Figure 4) there are two distinct phases suggesting that the data may be described by a biexponential function (i.e., two compartment model).

Figure 4. Elimination of ^{99m}Tc-MAG3 from the plasma after i.v. injection.



Curve stripping is now performed to determine the macroconstants λ_1 and λ_z and the coefficients C_1 and C_z. The log of the plasma concentration is calculated for the last five data points and linear regression is performed on these log values versus time p.i. to obtain parameter values for the log function describing the elimination phase:

$$Log\,C = Log\,C_z - \frac{\lambda_z t}{2.303}$$

In this example, linear regression on log plasma concentration versus time p.i. yielded the following equation:

$$Log\,C = 4.13 - 0.0145\,t \quad (r = -0.999)$$

The slope of this line is:

$$-0.0145 = \frac{-\lambda_z}{2.303}$$ (See Eq 5, P 7)

Therefore, the elimination phase rate constant:

$$\lambda_z = (2.303)(0.0145)$$

$$= 0.0334\ min^{-1}$$

The elimination phase half-life is given by:

$$t_{1/2\lambda_z} = \frac{0.693}{\lambda_z}$$ (See Eq 6, P 7)

$$= \frac{0.693}{0.0334\ \text{min}^{-1}}$$

$$= 20.7\ \text{min}$$

The value for C_z is determined by setting t = 0 min in Eq. 4:

$$Log\,C = Log\,C_z = 4.13$$

$$C_z = 13{,}417\ cpm/mL$$

The residuals (i.e., the difference between the measured plasma concentration and the concentration predicted by the equation describing the elimination phase) are now calculated for the remaining three data points. The log of the residual values is then taken and linear regression is performed on these log values versus time p.i. to obtain the values for the parameters for the log function describing the distribution phase:

$$Log\,C = Log\,C_1 - \frac{\lambda_1 t}{2.303}$$ (See Eq 4, P 7)

In this example, linear regression on the log residuals versus time p.i. yielded the following equation:

$$Log\ C = 4.53 - 0.191\ t\ (r = 0.996)$$

The slope of the line describing the distribution phase is:

$$-0.191 = \frac{-\lambda_1}{2.303}$$ (See Eq 5, P 7)

Therefore, the distribution phase rate constant:

$$\lambda_1 = (2.303)(0.191)$$
$$= 0.439\ \text{min}^{-1}$$

The distribution phase half-life is given by:

$$t_{1/2\lambda_1} = \frac{0.693}{\lambda_1}$$ (See Eq 6, P 7)

$$= \frac{0.693}{0.439\,\text{min}^{-1}}$$

$$= 1.6\ \text{min}$$

The value for C_1 is determined by setting t = 0 min in Eq. 4:

$$Log\ C = Log\ C_1 = 4.53$$
$$C_1 = 33{,}625\ cpm/mL$$

The equation describing the plasma concentration of ^{99m}Tc-MAG$_3$ versus time in this patient is obtained by substituting the values for C_1, C_2, λ_1 and λ_2 into Eq. 15:

$$C = 33{,}625e^{-0.439t} + 13{,}417e^{-0.0334t}\ cpm/mL$$

The microconstants, k_{12}, k_{21} and k_{10} may be calculated as follows:

$$k_{21} = \frac{C_1\lambda_2 + C_2\lambda_1}{C_1 + C_2}$$

(Eq. 16)

$$= \frac{(33{,}625\,cpm/mL)(0.0334\,\text{min}^{-1}) + (13{,}417\,cpm/mL)(0.439\,\text{min}^{-1})}{(33{,}625 + 13{,}417)\,cpm/mL}$$

$$= 0.149\ \text{min}^{-1}$$

$$k_{10} = \frac{\lambda_1\lambda_2}{k_{21}}$$

(Eq. 17)

$$= \frac{(0.439\,\text{min}^{-1})\,(0.0334\,\text{min}^{-1})}{0.149\,\text{min}^{-1}}$$

$$= 0.0984\ \text{min}^{-1}$$

$$k_{12} = \lambda_1 + \lambda_2 - k_{21} - k_{10}$$

(Eq. 18)

$$= 0.439 + 0.0334 - 0.149 - 0.0984\ \text{min}^{-1}$$
$$= 0.225\ \text{min}^{-1}$$

The volume of the central compartment (V_c) is calculated as follows:

$$V_c = \frac{D_{i.v.}}{C_1 + C_2}$$

(Eq. 19)

$$= \frac{1.21 \times 10^8 cpm}{(33,625 + 13,417)\ cpm/mL}$$

$$= 2572\ mL$$

The general equation for volume of distribution at steady-state ($Vss = V_1 + V_2$) is:

$$V_{ss} = \frac{D_{i.v.} \sum_{i=1}^{n} \frac{C_i}{\lambda_i^2}}{\left(\sum_{i=1}^{n} \frac{C_i}{\lambda_i}\right)^2}$$

(Eq. 20)

$$= \frac{D_{i.v.} \sum_{i=1}^{n} \frac{C_i}{\lambda_i^2}}{(AUC)^2}$$

Therefore, for ^{99m}Tc-MAG$_3$:

$$V_{ss} = \frac{1.71 \times 10^8 cpm \left[\frac{33625 cpm/mL}{(0.439 min^{-1})^2} + \frac{13417 cpm/mL}{(0.0334 min^{-1})^2}\right]}{[33625 cpm/mL/(0.439) min^{-1} + 13417 cpm/mL/(0.0334) min^{-1}]^2}$$

$$= 6450\ mL$$
$$= 6.45\ L$$

Alternatively, the *Vss* may be calculated from *Vc* and the microconstants k_{12} and k_{21}:

$$V_{ss} = V_c(1 + k_{12}/k_{21})$$

(Eq. 21)

$$= 2572\ mL\ [1 + (0.225/0.149)]$$

$$= 6546\ mL$$

$$= 6.55\ L$$

Since, $Vss = V_c + V_2$, therefore,

$$V_2 = 6546 - 2572\ mL$$

$$= 3.97\ L$$

The relatively small volume of distribution of ^{99m}Tc-MAG$_3$ compared to ^{99m}Tc-DTPA (*Vss* of 6.5 versus 17.0 L, respectively) suggests that this radiopharmaceutical is not as widely-distributed in the body. This may be a consequence of the much higher protein-binding characteristics of ^{99m}Tc-MAG$_3$ compared to ^{99m}Tc-DTPA (79-90% versus <5%, respectively). The volume of distribution of ^{99m}Tc-MAG$_3$ has also been found to be smaller than that of ^{131}I-iodohippurate [the conventional agent used to measure renal tubular function (7,25)].

The systemic clearance of ^{99m}Tc-MAG$_3$ is given by the following equation:

$$CL = k_{10} \cdot V_c$$ (See Eq 8, P 8)

$$= (0.0984\ min^{-1})(2572\ mL)$$
$$= 253.1\ mL/min$$

As described for the one-compartment model, an alternative way of calculating *CL* is:

$$CL = \frac{D_{i.v.}}{AUC}$$ (See Eq 9, P 9)

The *AUC* may be calculated as follows:

$$AUC = \frac{C_1}{\lambda_1} + \frac{C_2}{\lambda_2}$$

(Eq. 22)

$$= \frac{33,625\ cpm/mL}{0.439\ min^{-1}} + \frac{13,417\ cpm/mL}{0.0334\ min^{-1}}$$

$$= 76,594 + 401,706\ cpm.min/mL$$

$$= 478,300\ cpm.min/mL$$

Substituting into Eq. 9 gives:

$$CL = \frac{1.21 \times 10^8\ cpm}{478,300\ cpm.\ min/mL}$$

$$= 252.9\ mL/min$$

Since the renal clearance of ^{99m}Tc-MAG$_3$ exceeds GFR (100-130 mL/min), this indicates that the radiopharmaceutical is secreted by the renal tubules.

A radiopharmaceutical such as ^{131}I-iodohippurate, which is both filtered at the glomerulus and secreted

so avidly by the renal tubules that its clearance approaches renal blood flow, can be used to evaluate renal function in a patient by estimating the effective renal plasma flow (ERPF) (4). Although the clearance of ^{99m}Tc-MAG$_3$ is lower than that of ^{131}I-iodohippurate, its clearance is proportional to ^{131}I-iodohippurate clearance and, therefore, may be used to estimate ERPF indirectly (4).

Three-compartment pharmacokinetics

Analogous to two-compartment pharmacokinetics, in the case of a three-compartment model (Figure 1C), the radiopharmaceutical is administered by i.v. bolus into a central compartment (compartment 1). The radiopharmaceutical then distributes reversibly into two peripheral compartments (compartments 2 and 3) and is finally eliminated from the central compartment. Other three-compartmental model designs which involve elimination from peripheral compartments are possible but they cannot be distinguished from that shown in Figure 1C, from a mathematical standpoint. The volume of the central compartment is V_c and that of the peripheral compartments is V_2 and V_3. The microconstants k_{12}, k_{21}, k_{13} and k_{31} describe the rates of transfer between the central and peripheral compartments. The elimination from the plasma of a radiopharmaceutical which exhibits three-compartment pharmacokinetics may be described by the following triexponential equation:

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} + C_z e^{-\lambda_z t}$$

(Eq. 23)

where C is the concentration of the radiopharmaceutical at time t, λ_1 is the rate constant associated with the distribution phase, λ_2 and λ_z are the rate constants associated with the two elimination phases and C_1, C_2 and C_z are coefficients.

Example of three-compartment pharmacokinetics

^{99m}Tc-MDP which is used for bone-scanning in nuclear medicine, is an example of a radiopharmaceutical which exhibits three-compartment pharmacokinetics (14). Similar to the analysis of two-compartment data, a process of sequential curve stripping is performed on the plasma concentration versus time data to obtain the values for the coefficients and rate constants. The following triexponential equation was determined for the elimination of ^{99m}Tc-MDP from the plasma:

$$C = 78{,}825\, e^{-1.63} + 15{,}411\, e^{-0.320} + 4{,}365\, e^{-0.0230}\ cpm/mL$$

The various half-lives are calculated using the same general formula as before:

$$t_{1/2i} = \frac{0.693}{\lambda_i}$$ (See Eq 6, P 7)

Using this formula, the half-lives of the distribution and two elimination phases were 0.4, 2.2 and 30.1 hours respectively. The volume of the central compartment is given by:

$$V_c = \frac{D_{i.v.}}{C_1 + C_2 + C_z}\ mL$$

(Eq. 24)

$$= \frac{1.21 \times 10^9\ cpm}{(78{,}825 + 15{,}411 + 4{,}365)\ cpm/mL}$$

$$= 12{,}272\ mL$$

$$= 12.27\ \text{L}$$

The general equation for volume of distribution at steady state is:

$$V_{ss} = \frac{D_{i.v.} \sum_{i=1}^{n} \frac{C_i}{\lambda_i^2}}{AUC^2}$$ (See Eq 20, P 18)

The AUC is calculated similarly as before:

$$AUC = \frac{C_1}{\lambda_1} + \frac{C_2}{\lambda_2} + \frac{C_z}{\lambda_z}$$ (See Eq 22, P 19)

$$= \frac{78,825}{1.63} + \frac{15,411}{0.320} + \frac{4,365}{0.0230}\ cpm.\ h/\ mL$$

$$= 286{,}301\ cpm.h/mL$$

The values for AUC and the other parameters are now substituted into Eq. 20 to calculate Vss:

$$V_{ss} = \frac{1.21 \times 10^9 cpm [(78,825/1.63^2) + (15,411/0.320^2) + (4365/0.0230^2)\ cpm.\ h^2/\ mL]}{(286,301)^2 cpm^2.\ h^2/\ mL^2}$$

$$= 124{,}465\ mL$$

$$= 124.5\ \text{L}$$

The very large volume of distribution of ^{99m}Tc-MDP may reflect its adsorption to the bone matrix (a characteristic which makes the radiopharmaceutical useful for bone scanning).

The clearance of ^{99m}Tc-MDP may be calculated as before using Eq.9:

$$CL = \frac{D_{i.v.}}{AUC}$$ (See Eq 9, P 9)

$$= \frac{1.21 \times 10^9 cpm}{286,301\ cpm.\ h/\ mL}$$

$$= 4226\ mL/\text{h}$$

$$= 70.4\ mL/\text{min}$$

COMPUTERIZED NON-LINEAR REGRESSION ANALYSIS

Non-linear weighted least squares regression

The analysis of pharmacokinetic data presented so far in this lesson has involved the fitting of sums of exponentials to the data by a process of non-iterative curve-stripping. Although curve-

stripping can yield good initial estimates of the parameter values and estimate the order, n, of the model (i.e., one versus two versus three compartments), it works best for large numbers of data points with low noise which are sampled over a wide range of times (27). This is rarely the case in pharmacokinetic studies with radiopharmaceuticals. The problems associated with curve stripping are that i) errors in estimating parameters are propagated into the estimates of subsequent parameters, ii) it is often difficult to distinguish separate disposition phases in the plasma concentration versus time curve and iii) quantification of the errors involved in estimating parameters is not possible (27).

Non-linear regression analysis is a superior process than non-iterative curve-stripping because it recognizes that there is error involved in parameter estimation:

$$z\,(t) = y\,(t, p) + e\,(t)$$

where, $z\,(t)$ is the observed value, $y\,(t, p)$ is the model-predicted value (which depends on the value of a parameter, p) and $e\,(t)$ is the random error associated with fitting the model to the data. Since the errors involved in fitting the model to the data are random, they have a mean value E = 0 and variance = σ^2.

Weighted least squares (WLS) regression generates an estimate $\hat{p}$ that minimizes the weighted sum of squared differences between the observed and the model-predictions, $y\,(t_i\,\hat{p})$. This is also known as the weighted residual sum of squares (*WRSS*):

$$WRSS(\hat{p}) = \sum_{i=1}^{N} w_i[\,z(t_i) - y(t_i\hat{p})\,]^2$$

where w_i is a weighting factor for the individual differences between the model-predicted and observed values. The weighting factor utilized depends on an *apriori* knowledge of the variance in the analytical errors in the data. In general, w_i is customarily assigned a value of $1/\sigma^2$. Since the standard deviation in counting radioactivity in plasma samples is equal to the square root of the counts (28):

$$\sigma = \sqrt{z(t_i)}$$

then,

$$w_i = 1/z(t_i)$$

If w_i is set to 1, then unweighted or ordinary least squares regression (OLS) is performed.

Several computer software packages are available for non-linear regression analysis of pharmacokinetic data. These include CONSAAM (29), SIMP (30), PCNONLIN (31) and ADAPT (32). These programs iteratively vary the estimated values of parameters until a minimum WRSS is achieved. After a particular model has been fit to the data by non-linear WLS, it is necessary to check the "goodness of fit" of the model. The goodness of fit can be evaluated by i) examining a plot of the observed data and model predictions versus time for obvious poor fitting of the data and ii) plotting the weighted residuals versus time. This latter plot should demonstrate a uniformly wide band of randomly scattered points (Figure 5A). Non-randomness of the residuals (e.g., a series of positive residuals followed by a series of negative residuals, Figure 5B) may indicate unanticipated noise, an error in the model selection or failure of the WLS algorithm to converge to the best fit.

Selection of the best model

The "principle of parsimony" dictates that the model with the fewest number of parameters that fits the data, should be selected. The Akaike criterion (AIC) and the Schwartz criterion (SC) have been devised to compare the fit of different models on the same data using this principle.

For constant variance error,

$$AIC = WRSS + 2P$$
$$SC = WRSS + P.Ln(N)$$

For constant coefficient of variation error:

$$AIC = N.Ln(WRSS) + 2P$$
$$SC = N.Ln(WRSS) + P.Ln(N)$$

where, P is the number of parameters in the model and N is the number of data points. The smaller the value of the AIC or SC, the better the fit of the model to the data.

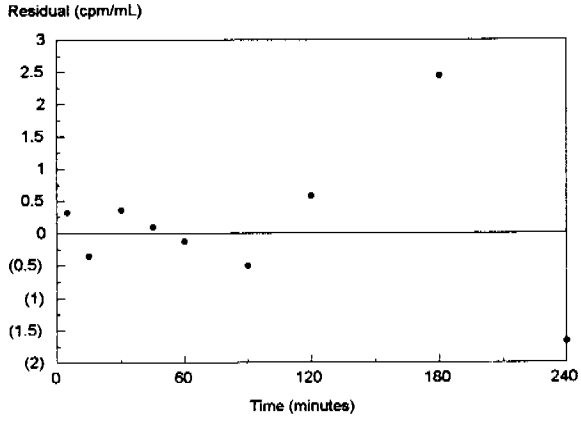
A comparison of the fit of different models to the same data may also be made by a F-test on the WRSS using the null hypothesis that there is no difference between the model with lower order ($n-1$) and that with higher order (n):

$$F = \frac{(WRSS_{n-1} - WRSS_n)/2}{WRSS_n/df_n}$$

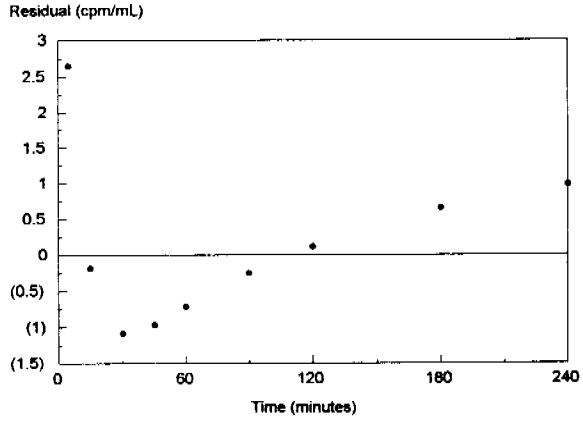
$$df_n = N - 2n$$

Lower order models are sequentially rejected until $F(2, df_n)$ has a $P<0.05$. This model then has the minimum order consistent with the data which cannot be distinguished from those of higher order.

Figure 5. Plot of residuals versus time post-injection for ^{99m}Tc-DTPA data when fitted to a two compartment model (A) or a one compartment model (B).



A



B

Example of computerized non-linear regression of pharmacokinetic data

An example of a simple program in PCNONLIN to analyse radiopharmacokinetic data following administration of ^{99m}Tc-DTPA is shown in Appendix II. The data was weighted by $1/z(ti)$. Three different models (one, two and three compartment) were fit to the data and compared (Table 6). The AIC and SC are much higher for the one compartment model ($n=1$) than for the two or three compartment models ($n=2$ or 3). Furthermore, a F-test comparing the one and two compartment models is highly significant ($P>0.05$). These findings indicate that the two compartment model is much better at fitting the data than the one compartment model. The F-test comparing the two and three compartment models shows no significant difference ($P<0.05$) between the two models in fitting the data. However, following the "principle of parsimony" the model with the lower number of parameters (i.e., the two compartment model) should be used to fit the data. This is confirmed by the slightly lower AIC and SC for the two versus the three compartment model. Therefore, in this patient, a two-compartment model is the best model to describe the elimination of ^{99m}Tc-DTPA.

Table 6. Comparison of Pharmacokinetic Models for ^{99m}Tc-DTPA.

Order of Model (n)	WRSS	AIC	SC	F	df	P
1	301374	117.54	115.74	-	-	-
2	20.9850	35.39	31.79	35,901.0	(2,5)	>0.05
3	20.9866	39.39	33.99	-0.000114	(2,3)	<0.05

NON-COMPARTMENTAL PHARMACOKINETIC ANALYSIS

Certain pharmacokinetic parameters for radiopharmaceuticals do not necessarily require the assignment of a particular compartmental model to the data. These include the mean residence time (MRT), clearance (CL) and volume of distribution at steady state (Vss). The MRT is the time taken for 63.2% of the radiopharmaceutical to be eliminated from the body by biological processes only. This also corresponds to the "average" time that any individual molecule of a radiopharmaceutical remains in the body. Note however, that this is different than the term, mean residence time (τ) for the radiopharmaceutical used in radiation dosimetry calculations. In this latter case, τ is the average time taken for a radiopharmaceutical to be eliminated by *both* radioactive decay and biological processes (3). Nevertheless, the concepts are similar. The plasma concentration versus time curve may be regarded as a statistical distribution curve (5). The area under this curve (AUC) is known as the zero moment:

$$AUC=\int_0^\infty Cdt$$

The area under the first moment curve (AUMC) is the area under the plasma concentration X time versus time curve:

$$AUMC=\int_0^\infty tCdt$$

The MRT is:

$$MRT = \frac{AUMC}{AUC}$$

(Eq. 25)

The MRT may be calculated from the AUMC and AUC as shown above, thus not requiring specification of a particular compartmental model. AUMC may be calculated as follows:

$$AUMC = \sum_{i=1}^{n} \frac{C_i}{\lambda_i^2}$$

(Eq. 26)

AUC may be calculated using Eq. 22:

$$AUC = \sum_{i=1}^{n} \frac{C_i}{\lambda_i}$$ (See Eq 22, P 19)

Note that calculation of AUC by Eq. 22 and AUMC by Eq. 25 requires that the elimination rate constants (λ_i) be known and therefore a polyexponential function must be fit to the data. However the assignment of a specific compartmental model is not actually required, only mathematical fitting of the data. Alternatively these areas may be calculated by simpler methods such as the Trapezoidal Rule (5).

The MRT may also be calculated from the Vss and CL (33):

$$MRT = \frac{V_{ss}}{CL}$$

(Eq. 27)

In addition to the MRT, a mean transit time (MTT) for a radiopharmaceutical may be calculated. This is the average time spent by an individual molecule in a compartment before being transferred to another compartment. For a one-compartment model, the mean transit time in the central compartment (MTTc) is the same as the MRT, but for a two-compartment model, MTTc is given by the following equation (33):

$$MTTc = \frac{1}{k_{10} + k_{12}}$$

(Eq. 28)

Various other mean time parameters may also be calculated including mean residence and transit times in the central and peripheral compartments. The paper by Kong and Jusko (33) gives a detailed description of the calculations involved for a two-compartment model.

Clearance is also a parameter not requiring specification of a particular model but can be calculated simply from a knowledge of the injected dose and the AUC as previously discussed:

$$CL = \frac{D_{i.v.}}{AUC}$$ (See Eq 9, P 9)

Furthermore, the volume of distribution at steady state may be calculated by rearranging Eq. 26 once the MRT and CL are known:

$$V_{ss} = CL \cdot MRT$$ (See Eq 27, P 25)

Example of calculation of MRT and MTT

Using ^{99m}Tc-MAG$_3$ as an example,

$$AUMC = \sum_{i=1}^{n} \frac{C_i}{\lambda_i^2}$$ (See Eq 26, P 25)

$$= \frac{33,625\ cpm/mL}{(0.439\ \text{min}^{-1})^2} + \frac{13,417\ cpm/mL}{(0.0334\ \text{min}^{-1})^2}$$

$$= 12{,}201{,}618\ cpm.\text{min}^2/mL$$

$$AUC = \sum_{i=1}^{n} \frac{C_i}{\lambda_i}$$ (See Eq 22, P 19)

$$= 478{,}300\ cpm.\text{min}/mL$$

$$MRT = \frac{AUMC}{AUC}$$ (See Eq 25, P 25)

$$= \frac{12,201,618\ cpm.\ \text{min}^2/mL}{478,300\ cpm.\ \text{min}/mL}$$

$$= 25.5\ \text{min}$$

Therefore, the average time spent by a ^{99m}Tc-MAG$_3$ molecule in this patient is approximately 25 minutes.

$$MTT = \frac{1}{k_{10} + k_{12}}$$ (See Eq 28, P 25)

$$= \frac{1}{(0.0984 + 0.225)\ \text{min}^{-1}}$$

$$= 3.1\ \text{min}$$

The average time spent by an individual ^{99m}Tc-MAG$_3$ molecule in a single passage through the central compartment is only 3.1 minutes.

SUMMARY

The pharmacokinetic characteristics of radiopharmaceuticals may be described by constructing a compartmental model of the body. The parameters describing this model may be determined by a process of noniterative curve-fitting or by computerized non-linear least squares regression. Compartmental parameters include distribution and elimination rate constants and half-lives, volumes of distribution and clearances. Noncompartmental pharmacokinetic characteristics such as mean residence and mean transit times may be determined from the area under the plasma concentration versus time curve or the area under the moment curve.

Appendix I: General Equations for Pharmacokinetic Analysis

Plasma concentration versus time:

$$C = \sum_{i=1}^{i} C_i e^{-\lambda_i t}$$

Elimination constants and half-lives:

$$\lambda_i = \frac{0.693}{t_{1/2\lambda i}} \qquad t_{1/2\lambda i} = \frac{0.693}{\lambda_i}$$

Volumes of distribution:

$$V_c = \frac{D_i \cdot v}{\sum_{i=1}^{n} C_i} \qquad Vss = \frac{Di.v.\sum_{i=1}^{n} \frac{C_i}{\lambda_i^2}}{\left(\sum_{i=1}^{n} \frac{C_i}{\lambda_i}\right)^2}$$

Clearance and areas under the curve (AUC and AUMC):

$$CL = \frac{D_i \cdot v}{AUC} = \frac{D_i \cdot v}{\sum_{i=1}^{n} \frac{C_i}{\lambda_i}} \qquad AUC(0-\infty) = \sum_{i=1}^{n} \frac{C_i}{\lambda_i}$$

$$CL_R = \frac{\Delta Ae / \Delta t}{C_m} = k_e\ V_c \qquad AUMC = \sum_{i=1}^{n} \frac{C_i}{\lambda_i^2}$$

Mean Residence and mean transit times:

$$MRT = \frac{AUMC}{AUC} \qquad MTT_c = \frac{1}{k_{10} + k_{12}}$$

$$MRT = \frac{V_{ss}}{CL}$$

Appendix II. Example of a program in PCNONLIN to analyse pharmacokinetic data.

```
TITLE
FITTING OF DTPA DATA TO 2 COMPARTMENT
MODEL
MODEL 8
NCON 4
CONS 60551100, 1, 60551100, 0
WEIGHT -1
LOWER ARE 2000, 3000, 0.05, 0.005
UPPER ARE 4000, 5000, 0.2, 0.02
NOBS 9
DATA
5     4786
15    3592
30    2885
45    2501
60    2203
90    1721
120   1346
180   827
240   503
OUTPUT PARM SECO
BEGIN
FINISH
```

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QUESTIONS

1. The elimination of a radiopharmaceutical from the plasma may be described by a pharmacokinetic model involving transfer of the radiopharmaceutical between compartments. Which of the following kinetic processes describes the rate of transfer between the various compartments?

   A. Zero order
   B. First order
   C. Second order
   D. Michaelis-Menten kinetics

2. A straight line is observed when the log of the plasma concentrations of a radiopharmaceutical is plotted versus time postinjection. Which of the following pharmacokinetic models would describe the elimination of the radiopharmaceutical from the plasma?

   A. One compartment model.
   B. Two compartment model.
   C. Three compartment model.
   D. Non-compartmental model.

3. Which of the following equations describes the elimination of a radiopharmaceutical from the plasma exhibiting two-compartment pharmacokinetics?

   A. $C = C(0)\ t$
   B. $C = C\ (0)\ e^{-\lambda z t}$
   C. $C = C_1 e^{-\lambda 1 t} + C_z e^{-\lambda z t}$
   D. $C = C_1 e^{-\lambda 1 t} + C_2 e^{-\lambda 2 t} + C_z e^{-\lambda z t}$

4. Which of the following factors will have the most influence on the selection of a particular type of compartmental model to describe the elimination of a radiopharmaceutical?

   A. The biological characteristics of the radiopharmaceutical.
   B. The number and range of plasma samples obtained.
   C. The physical half-life of the radiolabel.
   D. The physiological function of eliminating organs.

5. The elimination rate constant for a radiopharmaceutical is $0.173\ h^{-1}$. What is the elimination half-life?

   A. 7 minutes
   B. 20 minutes
   C. 4 hours
   D. 6 hours

6. Which of the following is true regarding the volume of distribution?

   A. It cannot exceed plasma volume.
   B. It is affected by protein-binding.
   C. It is the volume of a physiological compartment.
   D. It is very small for radiopharmaceuticals which are tissue-bound.

7. A patient received an intravenous bolus dose of ^{99m}Tc-DTPA (5×10^7 cpm). The plasma elimination of radioactivity was observed to be monophasic when plotted on semi-logarithmic paper, with an estimated C(0) concentration of 5,000 cpm/mL. What is the volume of distribution of ^{99m}Tc-DTPA in this patient?

   A. 3 L
   B. 5 L
   C. 10 L
   D. 25 L

8. Which of the following describes the volume of plasma from which a radiopharmaceutical is completely eliminated from the body per unit time?

   A. Systemic clearance
   B. Hepatic clearance.
   C. Urinary clearance.
   D. Distribution clearance.

9. The volume of distribution of a radiolabelled monoclonal antibody in a patient is 3.5 L and the elimination rate constant is $0.0138\,h^{-1}$. What is the systemic clearance of the monoclonal antibody?

   A. 0.8 mL/minute
   B. 8 mL/minute
   C. 20 mL/minute
   D. 48 mL/minute

10. The urinary excretion rate of the radiolabelled monoclonal antibody described in question 9 is $0.0005\,h^{-1}$. What percentage of the injected dose would be expected to be excreted in the urine?

    A. 0.05%
    B. 1.7%
    C. 3.6%
    D. 27.6%

11. The observed clearance of ^{99m}Tc-DTPA in a patient was 95 mL/minute. If the ^{99m}Tc-DTPA formulation exhibited 15% protein binding, what would be the actual clearance of the free (ie. unbound) ^{99m}Tc-DTPA?

    A. 81 mL/minute
    B. 83 mL/minute
    C. 109 mL/minute
    D. 112 mL/minute

12. Which of the following radiopharmaceuticals is characterized by a high protein-bound fraction?

    A. ^{201}Tl
    B. ^{99m}Tc-DTPA
    C. ^{99m}Tc-MAG3
    D. All of the above.

13. The following equation was found to adequately describe the elimination of a new brain imaging agent from the plasma at time t (minutes post-injection): $C = 6{,}000\,e^{-0.231t} + 2{,}300\,e^{-0.006t}$ cpm/mL. What is the distribution half-life?

A. 2.9 minutes
B. 3.0 minutes
C. 4.3 minutes
D. 115.5 minutes

14. The injected dose of the brain imaging agent described in question 13 was 1 X 10^8 cpm. What is the volume of the central compartment?

A. 12.0 L
B. 16.6 L
C. 43.5 L
D. 60.1 L

15. Using the information provided to you in question 13 and question 14, what is the systemic clearance of the brain imaging agent?

A. 4 mL/minute
B. 47 mL/minute
C. 72 mL/minute
D. 244 mL/minute

16. Using the information provided to you in question 13, approximately how much larger would the volume of distribution at steady state be compared to the volume of the central compartment?

A. 2 times
B. 3 times
C. 5 times
D. 10 times

17. Which of the following pharmacokinetic parameters can not be calculated by non-compartmental analysis?

A. MRT
B. CL
C. V_1
D. Vss

18. Which of the following pharmacokinetic terms describes the time spent by a radiopharmaceutical in a single compartment before being transferred to another compartment?

A. Mean transit time.
B. Mean residence time.
C. Distribution half-life.
D. Elimination half-life.

19. The elimination half-life of a new heart imaging agent was found to be 5 hours. What is its mean residence time?

A. 0.2 hours
B. 3.5 hours
C. 7.2 hours
D. 10.0 hours

20. The clearance of a radiopharmaceutical was found to be 280 mL/minute and the volume of distribution at steady state was determined to be 40 L. What is the MRT for the radiopharmaceutical?

A. 0.4 hours
B. 2.4 hours
C. 3.1 hours
D. 8.6 hours

21. Which of the following terms describes the process of manual curve-stripping of plasma concentration versus time data following administration of a radiopharmaceutical?

A. Non-iterative curve stripping.
B. Non-linear regression.
C. Weighted least squares regression.
D. Ordinary least squares regression.

22. A set of radiopharmacokinetic data has been provided to you for computerized non-linear regression analysis. Which of the following weighting methods for the data points, $z(t_i)$ would be the most appropriate for this type of data?

A. $w_i = 1$
B. $w_i = -1$
C. $w_i = 1/z(t_i)$
D. $w_i = \sqrt{z}\ (t_i)$

23. Which of the following are <u>not</u> computer programs for non-linear regression of pharmacokinetic data?

A. CONSAAM
B. PCNONLIN
C. PC-REDLSN
D. SIMP

24. Which of the following statistical parameters considers the "principle of parsimony" in determining the best model for fitting a set of radiopharmacokinetic data?

A. Akaike criterion
B. F-test
C. t-test.
D. All of the above

25. Using statistical tests and consideration of the AIC and SC, a two-compartment model was found to be the best model for fitting plasma concentration versus time data for ^{131}I-iodohippurate. Which of the following would <u>not</u> be associated with the use of a one-compartment model to fit this data?

A. A smaller SC.
B. A larger AIC.
C. A non-random distribution of weighted residuals versus time
D. Obvious poor fitting of the plasma concentrations versus time