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The Fundamental Principles of Compartmental Pharmacokinetics Illustrated by Radiopharmaceuticals Commonly Used in Nuclear Medicine

Continuing Education for Nuclear Pharmacists
And
Nuclear Medicine Professionals

By

Raymond M. Reilly, Ph.D.

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THE FUNDAMENTAL PRINCIPLES OF COMPARTMENTAL PHARMACOKINETICS ILLUSTRATED BY RADIOPHARMACEUTICALS COMMONLY USED IN NUCLEAR MEDICINE

STATEMENT OF LEARNING OBJECTIVES:

The primary goal of this continuing education lesson is to demonstrate the application of commonly used pharmacokinetic methods of analysis to radiopharmaceuticals. A review of pharmacokinetics covering areas such as compartmental analysis, the effects of protein binding on pharmacokinetic parameters, and computerized methods for analyzing data is provided. 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 half-lives, volume of distribution, volume of distribution at steady state, systemic clearance, and renal clearance.

3. When provided with a set of pharmacokinetic data for a radiopharmaceutical, 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 manual 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 pharmacokinetic data and determine the best model.

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INTRODUCTION

Pharmacokinetics describes the changes in drug disposition in the body over time, including the distribution from the site of administration, metabolism and elimination from the body. For most drugs, their disposition is actually inferred by sampling blood, plasma, and urine and measuring changes in drug concentrations in these accessible compartments over time. A model is then constructed which mathematically explains the changes in drug concentrations in these compartments and may also infer changes in drug concentrations in other compartments that are not sampled (i.e. a multi-compartmental model). The radioactive nature of radiopharmaceuticals greatly facilitates the measurement of concentrations in the blood, plasma, and urine compared to other drugs, which normally first require separation and then measurement by high performance liquid chromatography (HPLC) or other chromatographic techniques. However, while changes in radioactivity concentrations are easily measured for radiopharmaceuticals by gamma--scintillation counting, it should be recognized that metabolism can disrupt the presumed 1:1 relationship between the radionuclide pharmacokinetics and that of the radiopharmaceutical. This risk is highly dependent on the stability of the radiochemistry used to link the radionuclide and the carrier molecule for radiopharmaceuticals as well as the length of time over which the radioactivity concentrations are measured. Complexation of radiometals is more stable than radiohalogen substitution, but mechanisms exist for loss of radiometals from radiopharmaceuticals (1-3). Another major advantage of radiopharmaceuticals which is not available for other drugs is that the pharmacokinetics of organ uptake and elimination can be visualized and also quantified by single photon-emission emission computed tomography (SPECT) or by positron-emission tomography (PET). Whole organ pharmacokinetics are used to estimate the mean residence times of radioactivity and from these, the radiation absorbed doses deposited in various tissues following administration of a radiopharmaceutical (4). In addition, the pharmacokinetics of elimination by the kidneys of certain radiopharmaceuticals (e.g. ^{99m}Tc-DTPA or ^{99m}Tc-MAG_3) is used clinically to estimate key physiological parameters such as glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) which are altered in renal disease (5). In the current lesson however, only concentrations of radiopharmaceuticals measured in the blood, plasma or urine will be considered to describe the pharmacokinetics. Whole organ pharmacokinetics and radiation dosimetry will be discussed in a future lesson.

The purpose of this continuing education lesson is to illustrate with examples of radiopharmaceuticals commonly used in nuclear medicine the fundamental principles of pharmacokinetics. Compartmental models and standard pharmacokinetic equations (without their derivation) that describe

radiopharmaceutical disposition in these models will be presented. For the derivation of these equations, the reader is referred to a more comprehensive pharmacokinetic source such as the standard text by Gibaldi and Perrier (6). Although oral, subcutaneous or inhalation routes of administration are possible for radiopharmaceuticals (e.g. oral ^{123}I or ^{131}I for thyroid studies, ^{99m}Tc-sulfur colloid for sentinel lymph node detection, and ^{99m}Tc-labeled aerosols for pulmonary ventilation studies), most radiopharmaceuticals are administered by intravenous (i.v.) bolus. Thus, this route of administration will be the focus of the pharmacokinetic modeling described in this lesson.

COMPARTMENTAL PHARMACOKINETIC ANALYSIS

One approach to analyzing pharmacokinetic data is to construct a mathematical model of the body which consists of one or more connected but separate compartments (Figure 1). The radiopharmaceutical is administered into the central compartment (Compartment 1). Elimination always occurs from Compartment 1, but the radiopharmaceutical may also be transferred to other (peripheral) compartments (Compartments 2 and 3) depending on the model, and returned from these compartments to the central compartment. The rate constants describing the transfer between compartments and the elimination of the radiopharmaceutical are assumed to be first-order, i.e. the rate of transfer and elimination are proportional to the concentration of the radiopharmaceutical in the compartment from which it is being transferred or eliminated:

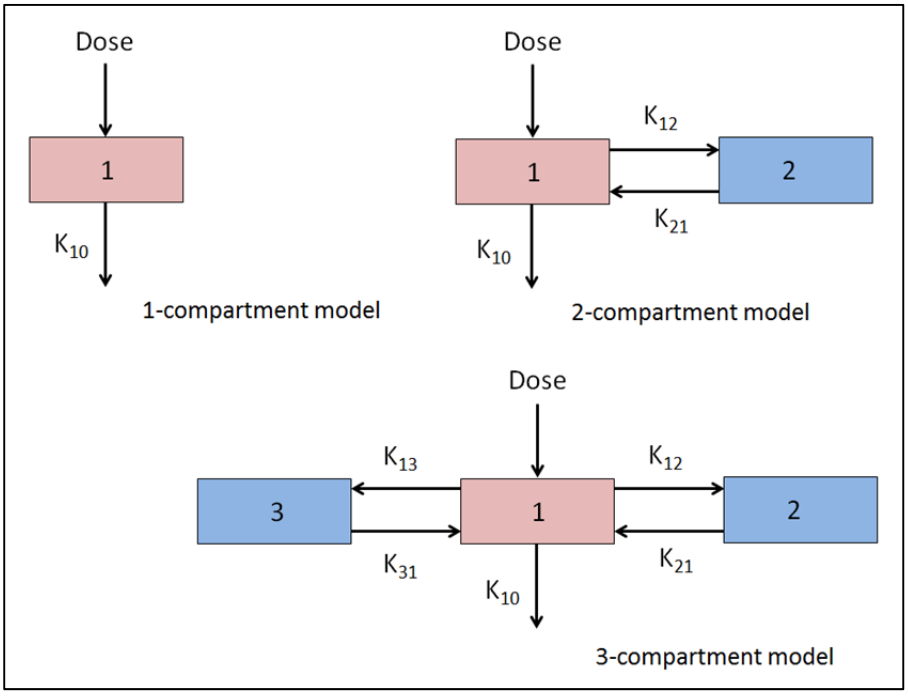

Figure 1. Compartmental pharmacokinetic models.

$$\frac{dC}{dt} = \lambda_z C \qquad \textbf{(Equation 1)}$$

where $\frac{dC}{dt}$ 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 the proportionality constant.

The number of compartments required or even feasible in the pharmacokinetic model depends on the range of times over which plasma or blood concentrations are sampled and the number of data points available for modeling. A plot of the plasma or blood concentrations vs. time post-injection on a semi-logarithmic scale may yield a straight line which suggests that the data are described by a 1-compartment pharmacokinetic model. However, if additional samples are taken shortly after injection, a distribution phase may be observed which may then be better modeled by a 2-compartment model. Similarly, if additional samples are obtained beyond the originally sampled last time point, a second elimination phase may be observed which could then require a 3-compartment model for describing the pharmacokinetics. Nonetheless, it is always advisable to employ the least number of compartments that adequately describe the pharmacokinetics of the radiopharmaceutical to avoid over-interpreting the data ("Principle of Parsimony"). Table 1 shows the compartmental pharmacokinetics of several commonly used radiopharmaceuticals in nuclear medicine. The standard pharmacokinetic equations used to estimate the parameters shown will be discussed in this lesson.

Table 1

COMPARTMENTAL PHARMACOKINETIC MODELS FOR COMMON RADIOPHARMACEUTICALS

Radiopharmaceutical	*Model*	[a] $T_{1/2}\lambda_1$ *(h)*	$T_{1/2}\lambda_2$ *(h)*	$T_{1/2}\lambda_3$ *(h)*	V_1 *(L)*	V_{ss} *(L)*	CL_s *(mL/min)*	*Ref.*
^{99m}Tc-DTPA	1	1.4	-	-	17.0	-	[b] 40	(7)
^{99m}Tc-MAG$_3$	2	0.04	0.4	-	3.7	7.0	265	(7)
^{99m}Tc-red blood cells	2	1.0	20.4	-	7.5	11.4	6	(8)
^{201}Tl thallous chloride	2	0.06	38.7	-	18.2	297	91	(9)
^{99m}Tc-sestamibi	2	0.06	3.0	-	51.4	289	1252	(10)
^{99m}Tc-exametazime	3	0.02	0.8	19.3	19.2	74.6	46	(11)
^{99m}Tc-medronate	3	0.40	2.2	30.1	12.3	124	70	(12)

[a] Symbols shown are: $T_{1/2}$ λ_1 (half-life of the first phase); $T_{1/2}$ λ_2 (half-life of the second phase); $T_{1/2}$ λ_3 (half-life of the third phase); V_1 (volume of distribution); V_{ss} (volume of distribution at steady-state), CL_s (systemic clearance) [b] This was in a patient with poor renal function. Normally, clearance (CL) of ^{99m}Tc-DTPA should be similar to the glomerular filtration rate which is 80-120 mL/min.

1-COMPARTMENT PHARMACOKINETICS

The simplest compartmental model is the 1-compartment model (Figure 1). 1-compartment pharmacokinetics is exhibited by a radiopharmaceutical which demonstrates a single disposition phase (i.e. a straight line) when the blood or plasma concentrations are plotted vs. time post-injection on a semi-logarithmic scale (Figure 2). The volume of this one compartment is known as the volume of distribution of the central compartment (V_1).

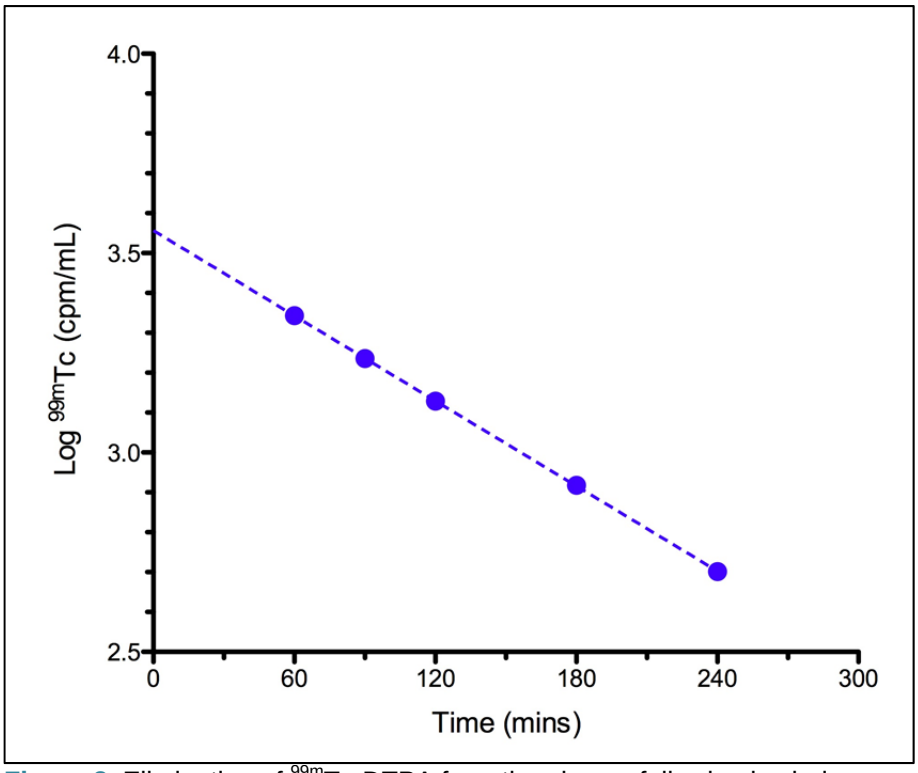

Figure 2. Elimination of ^{99m}Tc-DTPA from the plasma following i.v. bolus injection.

Elimination of the radiopharmaceutical from this compartment may occur through a combination of renal or hepatic elimination or by metabolism and subsequent elimination of radioactive metabolites. The rate of elimination is described by the micro-rate constant, $K_{10,}$ which is also equivalent to the macro-rate constant, $\lambda_{1,}$ for a 1-compartment model. Renal elimination is described by the rate constant, k_e, non-renal elimination by the constant, k_{nr}, and metabolism by the constant, k_m. These constants are related to λ_1 as follows:

$$\lambda_1 = k_e + k_{nr} + k_m \qquad \textbf{(Equation 2)}$$

The elimination from the blood or plasma of a radiopharmaceutical which exhibits compartmental pharmacokinetics is described by the following general equation:

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

For a 1-compartment model:

$$C = C_0 e^{-\lambda_1 t} \qquad \textbf{(Equation 3)}$$

where C is the concentration of the radiopharmaceutical at time, t, C_0 is the concentration at t = 0 and λ_1 is the elimination constant.

^{99m}Tc-DTPA – An example of 1-compartment pharmacokinetics

^{99m}Tc-DTPA is a radiopharmaceutical used for assessment of renal function which is characterized by 1, 2 or 3-compartment pharmacokinetics, depending on the range of times used for sampling the plasma. The plasma concentrations vs. time for an i.v. injected dose of 6.05×10^7 cpm of ^{99m}Tc-DTPA in a 70 kg patient are shown in Table 2 (7). A plot of the decay-corrected plasma concentrations vs. time post-injection on a semi-logarithmic scale (Figure 2) demonstrates only a single disposition phase suggesting that this data may be described by a 1-compartment model. Note that decay-corrected values are used to model the *biological* (i.e. pharmacokinetic) elimination of the radiopharmaceutical. Non-decay corrected values model the *effective* elimination of the radiopharmaceutical which takes into account both biological elimination and radioactive decay.

Table 2

WORKSHEET FOR ^{99M}TC-DTPA PHARMACOKINETIC DATA		
Time Post-Injection (mins)	***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

The logarithm of the plasma concentration is calculated (Table 2) and linear regression performed on these log values vs. the time post-injection to obtain parameter values for the following function describing the elimination of the radiopharmaceutical:

$$Log\ C = Log\ C_0 - \frac{\lambda_1 t}{2.303} \qquad \textbf{(Equation 4)}$$

Note that many software programs can now perform non-linear fitting of pharmacokinetic data which does not require logarithmic transformation of the data, but for illustration purposes, the classical approach using such transformations will be employed. Later in this lesson, non-linear fitting of

pharmacokinetic data using such software is described. In this example, linear regression on the log plasma concentration vs. time curve yielded the following equation:

$$Log\ C = 3.55 - 0.00356\ t\ (r = -0.999)$$

The slope of this line is:

$$-0.00356 = \frac{\lambda_1}{2.303} \qquad \textbf{(Equation 5)}$$

Therefore, the elimination rate constant is:

$$\lambda_1 = (2.303)(0.0356) = 0.00820\ \text{min}^{-1}$$

The equation for half-life ($T_{1/2}$) for a 1-compartment model is:

$$T_{1/2} = \frac{0.693}{\lambda_1} \qquad \textbf{(Equation 6)}$$

$$T_{1/2} = \frac{0.693}{0.00820\ min^{-1}} = 84.5\ min$$

The plasma concentration at t = 0 minutes is:

$$Log\ C_0 = 3.55$$

$$C_0 = 3{,}548\ cpm/mL$$

The equation describing the plasma concentration of ^{99m}Tc-DTPA vs. time in this patient using a 1-compartment model is therefore:

$$C = 3{,}548e^{-0.0082\ t}\ cpm/mL$$

The general equation for the volume of distribution of the central compartment (V_1) is:

$$V_1 = \frac{D_{i.v.}}{\sum_{i=1}^{n} C_i}$$

For a 1-compartment model:

$$V_1 = \frac{D_{i.v.}}{C_0} \qquad \textbf{(Equation 7)}$$

$$V_1 = \frac{6.05 \times 10^7\ cpm}{3{,}548\ cpm/mL}$$

$$V_1 = 17{,}052\ mL = 17.05\ L$$

The plasma volume (V_p) can be estimated from the patient's weight (i.e. 65 mL/kg) (13):

$$V_p = \left(0.65 \frac{L}{kg}\right)(70\ kg) = 4.55\ L$$

The volume of distribution (V_1) for ^{99m}Tc-DTPA is much larger than the plasma volume, which indicates that the radiopharmaceutical is widely distributed in the body (i.e. outside the plasma volume).

The systemic (total body) clearance of ^{99m}Tc-DTPA (CL_s) is the volume of plasma that is cleared of the radiopharmaceutical per unit time. CL_s can be calculated from the fitted plasma concentration vs. time data as follows:

$$CL_s = \lambda_1 V_1 \qquad \textbf{(Equation 8)}$$

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

$$CL_s = 139.8\ mL/min$$

Alternatively, CL_s can be calculated from the area under the plasma concentration vs. time curve from t=0 to t=infinity ($AUC_{0\text{-}\infty}$) and the injected dose as follows:

$$CL_s = \frac{D_{i.v.}}{AUC_{0-\infty}} \qquad \textbf{(Equation 9)}$$

The general equation for $AUC_{0\text{-}\infty}$ is:

$$AUC_{0-\infty} = \sum_{i=1}^{n} \frac{C_i}{\lambda_i}$$

For a 1-compartment model:

$$AUC_{0-\infty} = \frac{C_0}{\lambda_1} \qquad \textbf{(Equation 10)}$$

$$AUC_{0-\infty} = \frac{3{,}548\ cpm/mL}{0.00820\ min^{-1}}$$

$$AUC_{0-\infty} = 432{,}682\ \frac{cpm\ \times\ min}{mL}$$

Substituting the values for $D_{i.v.}$ and $AUC_{0\text{-}\infty}$ into Equation 9 provides an estimate of CL_s:

$$CL_s = \frac{6.05\ \times\ 10^7\ cpm}{432{,}682\ \frac{cpm\ \times\ min}{mL}}$$

$$CL_s = 139.8\ mL/min$$

The renal clearance (CL_R) is the volume of plasma from which the radiopharmaceutical is eliminated per unit time by the kidneys. For a radiopharmaceutical that is eliminated entirely by the kidneys, a CL_R which is less than the glomerular filtration rate (GFR) suggests that the radiopharmaceutical is reabsorbed in the renal tubules whereas a CL_R which is higher than the GFR suggests that the agent is secreted by the renal tubules. CL_R can be calculated from the amount of the radiopharmaceutical excreted into the urine in a defined interval and the plasma concentration at the mid-point of this interval as follows:

$$CL_R = \frac{\Delta A_e/\Delta t}{C_m} \qquad \textbf{(Equation 11)}$$

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 at the mid-point of the interval (t_m). The urinary excretion data for ^{99m}Tc-DTPA in the patient is shown in Table 3.

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If we consider one of the time intervals in Table 3 (i.e. t = 60-120 mins; t_m = 90 mins):

$$CL_R = \frac{13{,}500{,}000\ {}^{cpm}/_{60\ mins}}{1{,}721\ cpm/mL}$$

$$CL_R = 131\ mL/min$$

Table 3

Worksheet for ^{99m}Tc-DTPA Urinary Excretion Data				
Time Interval, (Δt) (mins)	**Mid-Point (t_m) (mins)**	**Amount excreted in the urine (ΔA_e) (cpm)**	**Urinary excretion rate ($\Delta A_e/\Delta t$) (cpm/min)**	**Concentration at mid-point (C_m) (cpm/mL)**
0-60	30	2.27×10^7	3.78×10^5	2,885
60-120	90	1.35×10^7	2.25×10^5	1,721
120-240	180	0.65×10^7	1.08×10^5	827

Equation 11 may be re-arranged as follows:

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

Since CL_R may vary slightly over the different time intervals used to measure excretion of the radiopharmaceutical, a more accurate estimate may be obtained by plotting $\Delta A_e/\Delta t$ vs. C_m. The slope of the resulting line obtained by linear regression is then equivalent to 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:

$$\frac{\Delta A_e}{\Delta t} = 131\ mL/min \times C_m$$

CL_R of ^{99m}Tc-DTPA in this patient is therefore 131 mL/min. Renal clearance is also related to the volume of distribution (V_1) by the urinary excretion rate constant, k_e:

$$CL_R = k_e \times V_1 \qquad \textbf{(Equation 12)}$$

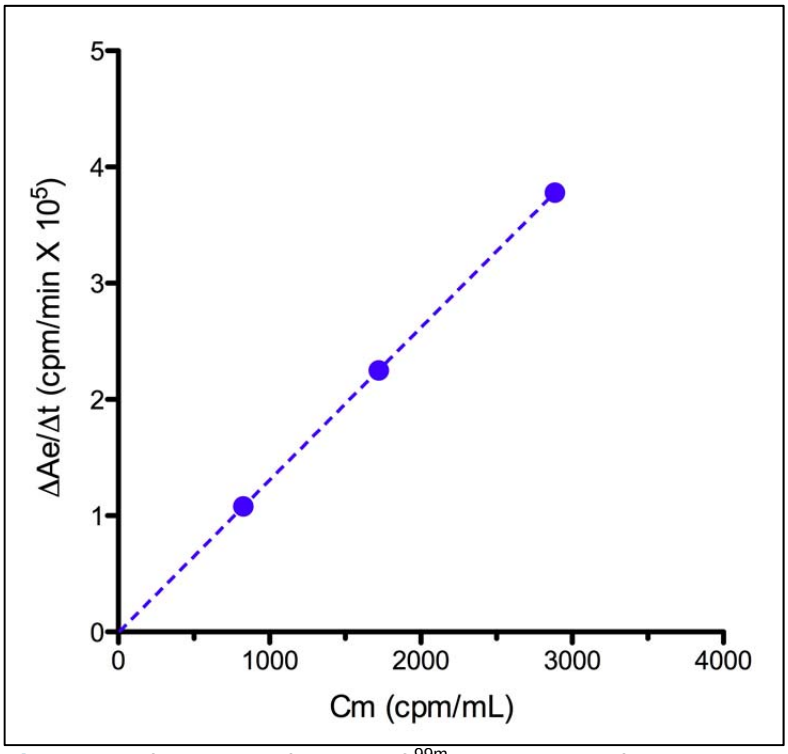

Figure 3. Urinary excretion rate of ^{99m}Tc-DTPA vs. plasma concentration.

The urinary excretion rate constant, k_e can thus be calculated once CL_R and V_1 are known:

$$k_e = \frac{CL_R}{V_1} = \frac{131\ mL/min}{17{,}052\ mL} = 0.00768\ min^{-1}$$

The fraction of the dose of the radiopharmaceutical which is ultimately excreted in the urine, $A_e(\infty)$ is given by the ratio of CL_R to CL_s or by the ratio of k_e to the elimination rate constant, λ_1.

$$Fraction\ excreted\ in\ the\ urine = \frac{CL_R}{CL_s} = \frac{k_e}{\lambda_1} \qquad \textbf{(Equation 13)}$$

$$Fraction\ excreted\ in\ the\ urine = \frac{131\ mL/min}{139\ mL/min} = \frac{0.00768\ min^{-1}}{0.00820\ min^{-1}}$$

$$Fraction\ excreted\ in\ the\ urine = 0.94$$

Since ^{99m}Tc-DTPA is predominantly eliminated by the kidneys and is not eliminated by non-renal routes to any significant extent, it is expected that CL_R will be essentially equivalent to CL_s, and therefore the fraction of the dose eliminated in the urine should be approximately one.

The CL_R of ^{99m}Tc-DTPA is used to estimate GFR in patients since its elimination is almost entirely by glomerular filtration. The GFR in young adults is 100-130 mL/min but declines with age. Also, it is lower in infants and children ranging from 15 mL/min up to 1 year of age to 80 mL/min in children 10-15 years old (14). Thus, the CL_R of ^{99m}Tc-DTPA and other radiopharmaceuticals that are similarly eliminated by glomerular filtration will be affected by the age of the patient.

Effect of Protein Binding on the Elimination of ^{99m}Tc-DTPA

The extent of protein binding of ^{99m}Tc-DTPA can affect its accuracy in estimating GFR since the protein-bound radiopharmaceutical cannot be filtered at the glomerulus (15-17). Only free, non-protein bound ^{99m}Tc-DTPA is eliminated from the plasma by glomerular filtration. If only total radioactivity measurements are made for plasma samples, then the elimination rate will appear slower than is truly the case, due to the contribution from the persistent protein-bound fraction. The clearance of free ^{99m}Tc-DTPA (CL_f) will then be given by:

$$CL_f = \frac{CL_s}{f_u} \qquad \textbf{(Equation 14)}$$

where f_u is the fraction of ^{99m}Tc-DTPA which is not bound to plasma proteins and CL_s is the apparent clearance of the radiopharmaceutical (note that since ^{99m}Tc-DTPA is eliminated entirely by renal excretion, $CL_s = CL_R$). Using the example of the patient described above, if the ^{99m}Tc-DTPA formulation exhibited 10% plasma protein-binding (i.e. $f_u = 0.90$), although the apparent CL_s would be 125.8 mL/min, the true CL_s of the free ^{99m}Tc-DTPA would be:

$$CL_f = \frac{CL_s}{f_u} = \frac{125.8\ mL/min}{0.9} = 139.8\ mL/min$$

The apparent clearance would underestimate the GFR in this patient by 14 mL/min. Other pharmacokinetic parameters are also affected by protein-binding. The persistence of the protein-bound radioactivity in the plasma decreases the elimination rate constants (λ), increases the C_0 value and

decreases the volumes of distribution (V_1 and V_{ss}). The effect of increasing protein-binding for ^{99m}Tc-DTPA on pharmacokinetic parameters for the above described patient is shown in Table 4. Ultrafiltration of plasma samples to remove the protein-bound fraction and measurement of radioactivity in the protein-free ultrafiltrate can eliminate errors associated with measurement of GFR in cases in which protein-binding is problematic (18).

Table 4

Effect of Protein-Binding on Pharmacokinetic Parameters for ^{99m}Tc-DTPA and on the Error in GFR Measurement

	Pharmacokinetic Parameter				
Protein Binding (%)	***λ_1 (min-1)***	***C_0 (cpm/mL)***	***V_1 (L)***	***Apparent CL_s (mL/min)***	***GFR Error (mL/min)***
0	0.00820	3,548	17.05	139.8	0
2	0.00817	3,570	16.95	138.4	-1.4
5	0.00808	3,680	16.44	132.8	-7.0
10	0.00796	3,829	15.80	125.8	-14.0
15	0.00783	3,988	15.17	118.8	-21.0

Protein-Binding of ^{99m}Tc-DTPA and Other Radiopharmaceuticals

Protein-binding of radiopharmaceuticals in plasma samples can be measured by several techniques including size-exclusion chromatography (SEC), trichloroacetic acid (TCA) precipitation, dialysis, and ultrafiltration. Different values are obtained depending on the technique, with generally lower percentages of protein binding measured by dialysis and SEC than by the other techniques (19). It is proposed that SEC may disrupt the association between a proportion of the radioactivity and the plasma protein. These techniques, therefore, only measure irreversibly protein-bound radioactivity. The protein binding of radiopharmaceuticals ranges from negligible (<5%) for ^{201}Tl thallous chloride and ^{99m}Tc-DTPA (most formulations) to as high as 79-90% for ^{99m}Tc-MAG_3 (19). Various plasma proteins appear to be involved. The plasma protein, α_1-antitrypsin is responsible for binding ^{99m}Tc-exametazime, ^{99m}Tc-glucoheptonate, ^{99m}Tc-DTPA, and ^{99m}Tc-iminodiacetic acid agents. Albumin is the main plasma protein involved in binding ^{99m}Tc-medronate (^{99m}Tc-MDP) and ^{99m}Tc-DMSA, whereas ^{99m}Tc-MAG_3 is primarily bound to α_2-globulin.

MULTI-COMPARTMENTAL PHARMACOKINETICS

A radiopharmaceutical which exhibits a discernible distribution phase followed by one or more elimination phases when the blood or plasma concentrations are plotted vs. time post-injection on a

semi-logarithmic scale is characterized by multi-compartmental pharmacokinetics. A 2-compartmental model or 3-compartmental model (Figure 1) may be used to fit the disposition of the radiopharmaceutical in these instances.

2-COMPARTMENT PHARMACOKINETICS

In the case of a radiopharmaceutical which is characterized by 2-compartment pharmacokinetics, there is distribution from the central compartment (Compartment 1) to a peripheral compartment (Compartment 2) following administration of the dose by i.v. bolus injection. It is important to appreciate that these compartments do not represent actual anatomical spaces (i.e. blood or plasma and extravascular tissues) but rather represent components of a mathematical model that is useful for describing the pharmacokinetics of the radiopharmaceutical. Nevertheless, the central compartment is assumed to include the blood or plasma from which the radiopharmaceutical is ultimately eliminated whereas the peripheral compartment is assumed to contain well-perfused tissues from which the radiopharmaceutical must be transferred to the central compartment for subsequent elimination. The volumes of the central and peripheral compartments are denoted as V_1 and V_2, respectively. V_2 can be estimated as follows:

$$V_2 = V_1\left[1 + \frac{k_{12}}{k_{21}}\right]$$

The micro-constant k_{12}, describes the rate of transfer of the radiopharmaceutical from Compartment 1 to Compartment 2. The micro-constant k_{21}, describes the rate of transfer from Compartment 2 to Compartment 1. Elimination of the radiopharmaceutical always occurs from Compartment 1 and is described by the micro-constant k_{10}, which is the sum of all elimination rate constants as before [see Equation 2]:

$$k_{10} = k_e + k_{nr} + k_m$$

The total volume of all compartments is known as the volume of distribution at steady-state (V_{ss}).

The elimination from the blood or plasma of a radiopharmaceutical which exhibits 2-compartment pharmacokinetics may be described by the following bi-exponential equation:

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \qquad \textbf{(Equation 15)}$$

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
- C_1 and C_2 are coefficients. λ_1 and λ_2 are also known as the macro-constants which differentiate them from the micro-constants (k_{10}, k_{12} and k_{21}) described earlier.

^{99m}Tc-MAG$_3$ – An example of 2-compartment pharmacokinetics

^{99m}Tc-MAG3 is an example of a radiopharmaceutical which exhibits 2-compartment pharmacokinetics. A worksheet is provided in Table 5 which shows the process of "curve stripping" required to determine the pharmacokinetic parameters associated with the elimination of ^{99m}Tc-MAG$_3$ from the plasma following i.v. bolus injection of a dose of 1.21×10^8 cpm.

Table 5

Worksheet for ^{99m}Tc-MAG$_3$ Pharmacokinetic Data					
Time post-injection (mins)	***Plasma Concentration (cpm/mL)***	***Log Plasma Concentration***	***Predicted Concentration (cpm/mL)***	***Residual Concentration (cpm/mL)***	***Log Residual Concentration***
5	14,762		11,416	3,346	3.52
10	10,188		9,661	527	2.72
15	8.216		8,175	41	1.61
30	4,913	3.69	4,955		
45	2,977	3.47	3,003		
60	1,803	3.26	1,820		
90	665	2.82	668		
120	242	2.38	245		

The first step is to plot the plasma concentrations vs. time on a semi-logarithmic scale to determine if the data exhibits multi-compartmental pharmacokinetics. In this example (Figure 4), there are two distinct phases suggesting that the data may be described by a bi-exponential function (i.e. a 2-compartment model).

Curve stripping is now performed to estimate the macro-constants λ_1 and λ_2, and the coefficients C_1 and C_2. The logarithm of the plasma concentration is calculated for the last five data points (from t=30 mins

to t=120 mins) and linear regression is performed on these log values vs. time to obtain the parameter values for the log function describing the elimination phase (see Equation 4):

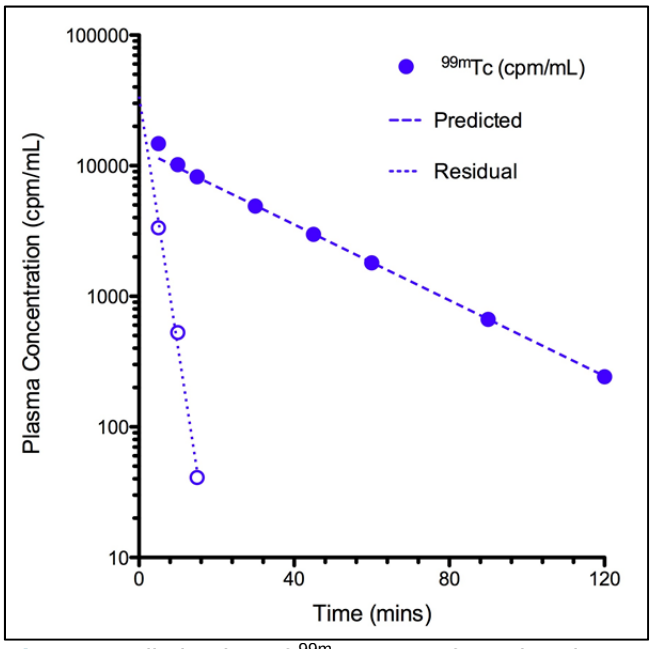

Figure 4. Elimination of ^{99m}Tc-MAG$_3$ from the plasma following i.v. bolus injection showing predicted and residual values.

$$Log\ C = Log\ C_2 - \frac{\lambda_2 t}{2.303}$$

In this example, linear regression on the log plasma concentration vs. time values yielded the following equation:

$$Log\ C = 4.13 - 0.0145\ t\ (r = -0.990)$$

The slope of this line (see Equation 5) is:

$$-0.0145 = \frac{-\lambda_2}{2.303}$$

Therefore, the elimination phase rate constant is:

$$\lambda_2 = (2.303)(0.0145) = \ 0.0334\ min^{-1}$$

The elimination phase half-life (see Equation 6) is given by:

$$T_{1/2} = \frac{0.693}{\lambda_2} = \frac{0.693}{0.0334\ min^{-1}} = 20.7\ min$$

The value for the coefficient, C_2 is obtained by setting t = 0 min in Equation 4:

$$Log\ C = Log\ C_2 = 4.13$$

$$C_2 = 13{,}489\ cpm/mL$$

The residuals are the differences between the measured plasma concentrations and the concentrations predicted by the curve fitting and are now calculated for the three remaining data points (i.e. t=5, 10 and 15 mins). The logarithm of the residual values is then calculated and linear regression performed on these log values vs. time to obtain the parameters for the log function describing the distribution phase (see Equation 4):

$$Log\ C = Log\ C_1 - \frac{\lambda_1 t}{2.303}$$

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

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

The slope of the line describing this distribution phase (see Equation 5) is:

$$-0.191 = \frac{-\lambda_1}{2.303}$$

Therefore, the distribution phase rate constant is:

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

The distribution phase half-life is given by:

$$T_{1/2} = \frac{0.693}{\lambda_1} = \frac{0.693}{0.439\ min^{-1}} = 1.6\ min$$

The value for the coefficient, C_1 is obtained by setting t = 0 min in Equation 4:

$$Log\ C = Log\ C_1 = 4.53$$
$$C_1 = 33{,}884\ cpm/mL$$

Finally, the equation describing the plasma concentration of ^{99m}Tc-MAG3 vs. time in this patient is obtained by substituting the values for C_1, C_2, λ_1 and λ_2 into Equation 15:

$$C = 33{,}884\ e^{-0.439\ t} + 13{,}489\ e^{-0.0334\ t}\ cpm/mL$$

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

$$k_{21} = \frac{C_1\lambda_2 + C_2\lambda_1}{C_1 + C_2}$$ **(Equation 16)**

$$k_{21} = \frac{\left(33{,}884\frac{cpm}{mL}\right)(0.0334\ min^{-1}) + (13{,}489\frac{cpm}{mL})(0.439\ min^{-1})}{33{,}884 + 14{,}489\ cpm/mL} = 0.145\ min^{-1}$$

$$k_{10} = \frac{\lambda_1\lambda_2}{k_{21}}$$ **(Equation 17)**

$$k_{10} = \frac{(0.439\ min^{-1})(0.0334\ min^{-1})}{0.145\ min^{-1}} = 0.101\ min^{-1}$$

$$k_{12} = \lambda_1 + \lambda_2 - k_{21} - k_{10}$$ **(Equation 18)**

$$k_{12} = 0.439 + 0.0334 - 0.145 - 0.101 = 0.226\ min^{-1}$$

The volume of the central compartment (V_1) is calculated as follows:

$$V_1 = \frac{D_{i.v.}}{C_1 + C_2} \qquad \textbf{(Equation 19)}$$

$$V_1 = \frac{1.21 \times 10^8\ cpm}{(33{,}884 + 13{,}489)\ cpm/mL} = 2{,}554\ mL$$

The general equation for the volume of distribution at steady-state, $V_{ss} = V_1 + V_2$ is:

$$V_{ss} = \frac{D_{i.v.} \sum_{i=1}^{n} \frac{C_i}{\lambda_i^2}}{(\sum_{i=1}^{n} \frac{C_i}{\lambda_i})^2} = \frac{D_{i.v.} \sum_{i=1}^{n} \frac{C_i}{\lambda_i^2}}{(AUC_{0-\infty})^2} \qquad \textbf{(Equation 20)}$$

Therefore, V_{ss} for ^{99m}Tc MAG_3 is:

$$V_{ss} = \frac{1.21 \times 10^8\ cpm \left(\frac{33{,}884 \frac{cpm}{mL}}{(0.439\ min^{-1})^2} + \frac{13{,}489 \frac{cmp}{mL}}{(0.0334\ min^{-1})^2} \right)}{\left(\frac{33{,}884 \frac{cpm}{mL}}{0.439\ min^{-1}} + \frac{13{,}489 \frac{cpm}{mL}}{0.0334\ min^{-1}} \right)^2}$$

$$V_{ss} = 6{,}414\ mL$$

Alternatively, and more simply, the V_{ss} can be calculated from V_1 and the microconstants k_{12} and k_{21} as follows:

$$V_{ss} = V_1 \left(1 + \frac{k_{12}}{k_{21}}\right) \qquad \textbf{(Equation 21)}$$

$$V_{ss} = 2{,}554\ mL \left(1 + \frac{0.226}{0.145}\right) = 6{,}534\ mL$$

Since, $V_{ss} = V_1 + V_2$, then:

$$V_2 = 6{,}534 - 2{,}554\ mL = 3{,}980\ mL$$

The relatively smaller volume of distribution of ^{99m}Tc-MAG3 compared to ^{99m}Tc-DTPA (i.e. Vss = 6,534 mL vs. 17,052 mL, respectively) suggests that this radiopharmaceutical is not as widely

distributed in the body. This may be due to the much higher protein-binding of ^{99m}Tc-MAG$_3$ compared to ^{99m}Tc-DTPA (79-90% vs. less than 5%, respectively) (20).

The systemic clearance, CL_s for ^{99m}Tc-MAG$_3$ is estimated from the following equation:

$$CL_s = k_{10}V_1 = (0.101\ min^{-1})(2{,}554\ mL) = 257.9\ mL/min$$

Alternatively, CL_s may be calculated from the $AUC_{0\text{-}\infty}$ as follows (see Equation 9):

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

The $AUC_{0\text{-}\infty}$ can be calculated as follows:

$$AUC_{0-\infty} = \frac{C_1}{\lambda_1} + \frac{C_2}{\lambda_2} \qquad \textbf{(Equation 22)}$$

$$AUC_{0-\infty} = \left(\frac{33{,}884\ cpm/mL}{0.439\ min^{-1}}\right) + \left(\frac{13{,}489\ cpm/mL}{0.0334\ min^{-1}}\right) = 481{,}046\ cpm.min/mL$$

Substituting into Equation 9 gives:

$$CL_s = \frac{1.21\ \times\ 10^8\ cpm}{481{,}046\ cpm/min/mL} = 251.5\ mL/min$$

Since ^{99m}Tc-MAG$_3$ is eliminated by the kidneys, the renal clearance (CL_R) is equivalent to the systemic clearance (CL_s). The renal clearance of ^{99m}Tc-MAG$_3$ (252 mL/min) exceeds the GFR for a young adult (100-130 mL/min); therefore, this radiopharmaceutical is secreted by the renal tubules in addition to glomerular filtration. A radiopharmaceutical which is filtered at the glomerulus and secreted very efficiently by the renal tubules can be used to estimate the effective renal plasma flow (ERPF). ^{99m}Tc-MAG$_3$ clearance underestimates ERPF but its clearance is proportional to ERPF; therefore, it is used as an indirect measure of this parameter of renal function.

3-COMPARTMENT PHARMACOKINETICS

Analogous to 2-compartment pharmacokinetics, in the case of 3-compartment pharmacokinetics (Figure 1) the radiopharmaceutical is administered by i.v. bolus into the central compartment (Compartment 1). The radiopharmaceutical distributes reversibly into two peripheral compartments (Compartments 2 and 3) and is finally eliminated from the central compartment. The volumes of distribution include those for the central compartment (V_1) and for the two peripheral compartments (V_2 and V_3). The micro-constants, 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 3-compartment pharmacokinetics may be described by the following tri-exponential equation:

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} + C_3 e^{-\lambda_3 t} \qquad \textbf{(Equation 23)}$$

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_3 are the rate constants associated with the two elimination phases, and C_1, C_2 and C_3 are the coefficients.

^{99m}Tc-Medronate (^{99m}Tc-MDP) – An example of 3-compartment pharmacokinetics

^{99m}Tc-medronate (^{99m}Tc-MDP) is an example of a radiopharmaceutical which exhibits 3-compartment pharmacokinetics. Similar to the analysis of 2-compartment data, a process of sequential curve stripping is performed on the plasma concentration vs. time data to obtain the values for the coefficients and the rate constants. The following tri-exponential equation was determined by this process for the elimination of ^{99m}Tc-medronate from the plasma in a patient administered an i.v. bolus dose of 1.21×10^9 cpm/min:

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

The various half-lives are calculated using the same general formula as before (Equation 6):

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

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 distribution of the central compartment is given by:

$$V_1 = \frac{D_{i.v.}}{C_1 + C_2 + C_3}\ mL \qquad \textbf{(Equation 24)}$$

$$V_1 = \frac{1.21 \times 10^9\ cpm}{(78{,}825 + 15{,}411 + 4{,}365)\ cpm/mL} = 12{,}272\ mL$$

The general equation for volume of distribution at steady-state is given by Equation 20:

$$V_{ss} = \frac{D_{i.v.} \sum_{i=1}^{n} \frac{C_i}{\lambda_i^2}}{(\sum_{i=1}^{n} \frac{C_i}{\lambda_i})^2} = \frac{D_{i.v.} \sum_{i=1}^{n} \frac{C_i}{\lambda_i^2}}{(AUC_{0-\infty})^2}$$

The $AUC_{0\text{-}\infty}$ is calculated as before (see Equation 22):

$$AUC_{0-\infty} = \frac{C_1}{\lambda_1} + \frac{C_2}{\lambda_2} + \frac{C_3}{\lambda_3}$$

$$AUC_{0-\infty} = \frac{78{,}825}{1.63} + \frac{15{,}411}{0.320} + \frac{4{,}365}{0.023}\frac{cpm/mL}{h^{-1}} = 286{,}299\ cpm.h/mL$$

$$V_{ss} = \frac{1.29 \times 10^9 \left[\frac{78{,}825}{(1.63)^2} + \frac{15{,}411}{(0.320)^2} + \frac{4{,}365}{(0.0230)^2}\right]\ cpm.h^2/mL}{(286{,}299)^2\ cpm^2.h^2/mL^2} = 132{,}692\ mL$$

The very large V_{ss} of ^{99m}Tc-medronate may reflect its efficient adsorption to the bone matrix which dramatically reduces its concentration in the plasma. This property makes the radiopharmaceutical suitable for bone scanning.

The systemic clearance of ^{99m}Tc-medronate may be calculated as before using Equation 9:

$$CL_s = \frac{D_{i.v.}}{AUC_{0-\infty}}$$

$$CL_s = \frac{1.21 \times 10^9\ cpm}{286{,}299\ cpm.h/mL} = 4{,}226\frac{mL}{h} = 70.4\ mL/min$$

NON-LINEAR FITTING OF PHARMACOKINETIC DATA USING SOFTWARE

The analysis of pharmacokinetic data presented thus far in this lesson involved manual fitting of the 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 inform on the order, *n*, of the model (i.e. 1 vs. 2 vs. 3-compartments), it works best for large numbers of data points with low noise which are sampled over a wide range of times. This is often not the case for pharmacokinetic studies of radiopharmaceuticals. The problems associated with curve stripping include: i) errors in estimating parameters are propagated into estimates of subsequent parameters, ii) it is often difficult to distinguish separate phases in the plasma concentration vs. time curve, and iii) a description of the errors involved in estimating parameters is not possible. Non-linear regression analysis aided by computer software is a superior process than non-iterative analysis because it recognizes that there are errors associated with parameter estimation and attempts to minimize these. Weighted least squares (WLS) regression generates an estimate of these errors ($\hat{p}$) that minimizes the weighted sum of squared differences between the observed value $[z(t)]$ and the model predicted value which includes the error $[y(t;\hat{p})]$. This is known as the weighted residual sum of squares (WRSS):

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

where, *w* is a weighting factor for the individual differences between the model-predicted and observed values. The weighting factor used depends on knowledge of the variance in the analytical errors in the data. If *w* is set to 1, then unweighted least squares regression is performed.

A commonly used computer software package for non-linear regression analysis of pharmacokinetic data is Scientist® (MicroMath, St. Louis, MO). This software iteratively varies the estimated values of parameters until a minimum WRSS is achieved. Initial estimates of the range of values (i.e. estimated value and lower and upper limits) for the parameters in the model need to be provided to aid in convergence of the non-linear regression analysis. After a particular model has been fitted to the data, it is then necessary to check the "goodness of fit". The goodness of fit can be assessed by plotting the

weighted residuals vs. time which should demonstrate a uniformly wide band of randomly scattered points with mean around zero. Non-randomness of the residuals (e.g. a series of positive points followed by a series of negative points) may indicate noise that is not taken into account by the weighting factor, an error in model selection or failure of the regression analysis to converge to the best fit. In general, the model that appears to provide the best fit and has the minimum *WRSS* should be selected. An example of fitting three different models to a data set for ^{99m}Tc-DTPA (expanded from Table 2 to include more points) by Scientist® software is provided in the next section. Non-linear fitting provides estimates of the parameters in the model such as macro- and micro-constants, coefficients as well as volumes of distribution.

Example of computer software fitting of pharmacokinetic data

The expanded data set for ^{99m}Tc-DTPA is shown in Table 6. This table also includes the model-predicted values following fitting by non-linear regression using Scientist® Ver. 3.0 to a 1, 2 or 3-compartment model with i.v. bolus input.

Table 6

Expanded Worksheet for ^{99m}Tc-DTPA Pharmacokinetic Data				
Time Post-Injection (mins)	***Plasma Concentration (cpm/mL)***	***1-Compartment Predicted Concentration (cpm/mL)***	***2-Compartment Predicted Concentration (cpm/mL)***	***3-Compartment Predicted Concentration (cpm/mL)***
5	4700	4371	4226	4424
10	4000	4077	4003	4087
20	3300	3557	3592	3515
30	2900	3114	3223	3055
60	2203	2146	2329	2132
90	1721	1550	1683	1609
120	1346	1184	1216	1281
180	827	819	635	858
240	503	679	331	536

A plot of the observed and model-fitted concentration vs. time data for each of the models is shown in Figure 5 and a plot of the residuals vs. time for each of the models is shown in Figure 6. No weighting was applied for the fitting. The reader is referred to the Scientist® software manual for detailed instructions on the fitting of pharmacokinetic data. Only the interpretation of the model fitting will be discussed in this lesson.

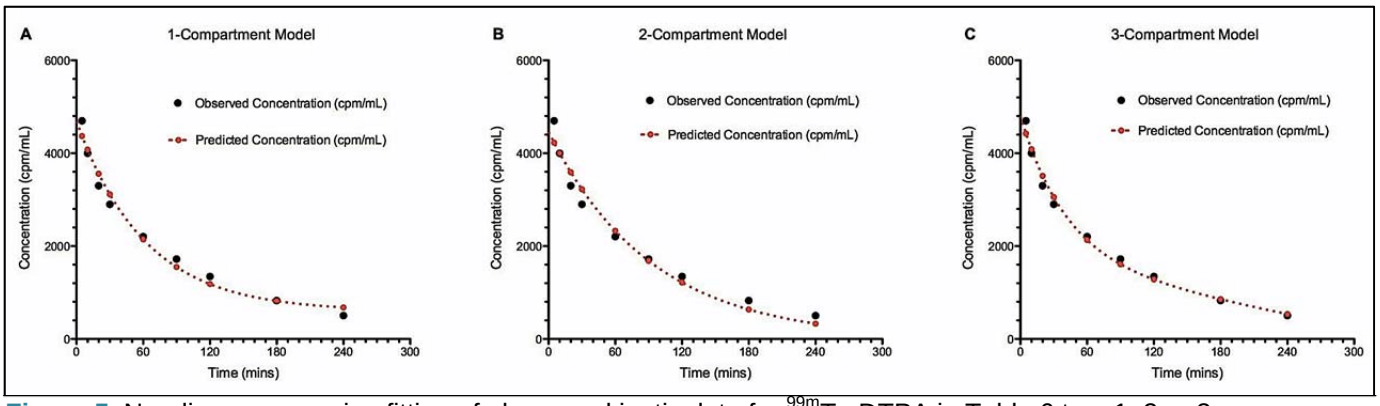

Figure 5. Non-linear regression fitting of pharmacokinetic data for ^{99m}Tc-DTPA in Table 6 to a 1, 2 or 3-compartment model with i.v. bolus input using Scientist® Ver. 3.0 software. The observed concentrations and model-predicted concentrations and fitted lines are shown.

All three models provide a relatively good fit of the data, but it is apparent that the 3-compartment model provides the smallest differences between the observed and the predicted concentrations (Figure 5).

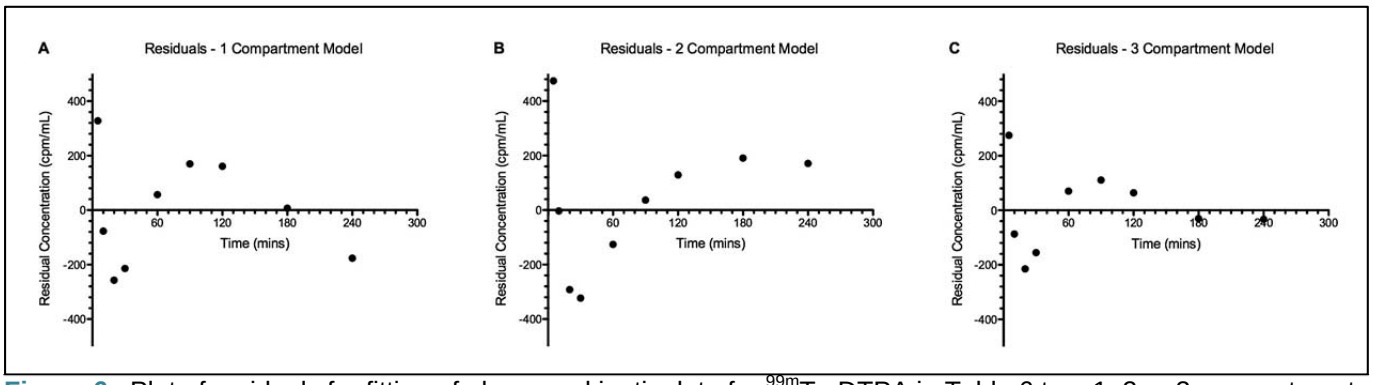

Figure 6. Plot of residuals for fitting of pharmacokinetic data for ^{99m}Tc-DTPA in Table 6 to a 1, 2 or 3-compartment model.

An examination of the residuals (Figure 6) reveals that these are smallest for the 3-compartment model and also more random with a mean around zero. The *WRSS* for the 1, 2 or 3-compartment model fitting was 3.1×10^5, 5.1×10^5 and 1.8×10^5 $(cpm/mL)^2$, confirming that the 3-compartment model provided the best fit of this data.

SUMMARY

The pharmacokinetic characteristics of a radiopharmaceutical may be described by constructing a compartmental model of the body which describes its disposition. The parameters describing this model may be determined by a process of manual non-iterative curve-fitting or, more commonly, by computerized non-linear least squares regression. Compartmental parameters include distribution and elimination rate constants and half-lives, volumes of distribution and clearances.

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ASSESSMENT 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 post injection. 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 2-compartment pharmacokinetics?

    a. $C = C(0)\ t$
    b. $C = C(0)\ e^{-\lambda 1 t}$
    c. $C = C_1 e^{-\lambda 1 t} + C_2 e^{-\lambda 2 t}$
    d. $C = C_1 e^{-\lambda 1 t} + C_2 e^{-\lambda 2 t} + C_3 e^{-\lambda 3 t}$

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 radiopharmaceutical in a patient is 3.5 L and the elimination rate constant is 0.0138 h^{-1}. What is the systemic clearance of the radiopharmaceutical?

   a. 0.8 mL/minute
   b. 8 mL/minute
   c. 20 mL/minute
   d. 48 mL/minute

10. The urinary excretion rate of the radiopharmaceutical 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 (i.e. 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}TI Thallous Chloride
    b. ^{99m}Tc-DTPA
    c. ^{99m}Tc-MAG3
    d. All of the above

13. A complete urine collection was obtained over the first 6 hours in a patient receiving a radiopharmaceutical. The radioactivity in the total urine collection was 2.4×10^8 cpm. The plasma concentrations at 1, 3, 6 and 12 hours were 4,000 cpm/mL, 2,000 cpm/mL, 1,000 cpm/mL and 250 cpm/mL. What was the renal clearance (CL_R)?

    a. 333 mL/min
    b. 260 mL/min
    c. 100 mL/min
    d. 50 mL/min

14. Based on the renal clearance for the radiopharmaceutical in Question # 13, which of the following is true?

    a. The radiopharmaceutical is not extensively eliminated by the kidneys.
    b. The radiopharmaceutical is filtered but reabsorbed by the kidneys.
    c. The radiopharmaceutical is filtered but not secreted by the kidneys.
    d. The radiopharmaceutical is filtered and secreted by kidneys.

15. 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

16. The injected dose of the brain imaging agent described in **question 15** was 1×10^8 cpm. What is the volume of the central compartment?

a. 12.0 L
b. 16.6L
c. 43.5 L
d. 60.1 L

17. Using the information provided to you in **question 15** and **question 16**, 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

18. Using the information provided to you in **question 15**, approximately how much larger would the volume of distribution at steady state be compared to the volume of the central compartment?

a. 1-2 times
b. 3-4 times
c. 5-6 times
d. 10-12 times

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

a. Non-iterative curve stripping
b. Non-linear regression
c. Weighted least squares regression
d. Linear regression

20. Several different models (1, 2 or 3-compartments) were compared for fitting the plasma concentration vs. time data for a radiopharmaceutical. Which of the following would <u>not</u> be important to evaluate the "goodness of fit" of the different models?

a. The weighted or unweighted sum of squares.
b. The apparent fitting of the compartmental equation to the data.
c. The closeness of the fitted parameter values to the initial estimates.
d. The distribution and randomness of the residuals vs. time