Nagoya J. Med. Sci. 50. 1 ~ 7, 1988

INTRODUCTION TO RADIOTRACER DISPOSITION KINETICS: ANALYSIS BY MATHEMATICAL MODELING

SHUHEI YAMAMOTO, M.D.

Department of Pharmacology and Therapeutics, School of Medicine and Dentistry, State University of New York at Buffalo, 127 Farber Hall, Buffalo, New York 14214, U.S.A.

ABSTRACT

The most prevalent use of a radioactive tracer is to assess specific organ function for diagnostic purpose. This analysis is performed by obtaining a time-activity curve of the tracer and then developing an appropriate mathematical model for disposition kinetics of the tracer. This article provides an introductory guide to several aspects of this method, which has been successfully applied in various experimental and clinical studies.

Key words: Radioisotope, Mathematical model, Pharmacokinetics

INTRODUCTION

A pharmacokinetic analysis of a radioactive tracer is a study of the time course of the tracer's radioactivity *in vivo* by handling the data with appropriate mathematical modeling to permit assessment of organ function for diagnostic or other purposes. This editorial provides an introductory guide to several aspects of this method.

MATHEMATICAL MODELING

Linear pharmacokinetic model

For several radioactive tracers, the time-activity curve is known to fit a polyexponential function. For example, with thallium-201, radioactivity that is polyexponential to time can be obtained by serial imaging[1] (or direct radiation detection) of the heart *in vivo*, by the use of tissue slices,[2] by pump-perfused heart,[3] and by blood counting.[4,5] Generally, the time-concentration curve of a tracer can be obtained by correcting the time-activity curve for its monoexponential physical decay. Because division of a polyexponential function by a monoexponential function still yields a polyexponential function, the time-concentration curve of a tracer that shows a polyexponential time-activity curve can also be expressed polyexponentially.

Disposition kinetics of many drugs, on the other hand, is known to follow a linear, multicompartment model, in which the drug concentration is a polyexponential function of time and its change is independent of the dose administered.[6] (Dose-dependent, nonlinear disposition kinetics is expressed by functions other than polyexponential equations, e.g., the Michaelis-Menten equation.) Therefore, it is possible to apply a linear pharmacokinetic model to the disposition kinetics of a tracer that shows a polyexponential time-activity curve.

In linear pharmacokinetics the model is assumed to be a network of well-stirred compartments

山本秀平　名古屋大学第一内科，第7研究室（国内所属）
Received for Publication November 26, 1987

or tanks of different volumes interconnected with pipes having feed- and drainage-valves. The assumptions of the model are as follows: (1) the drug dissolves within each compartment instantaneously; (2) drug distribution depends on the rate constants between adjacent compartments; and (3) all processes are linear (i.e., dose independent and not saturable). Before entering each cell, the drug must transverse the barriers of capillary wall, interstitial fluid space and cell membrane, each of which exerts a certain resistance to the passage of the tracer. These complex resistances are thus integrated into the rate constants and the sizes of the compartments. But, if the parameters are known, then the drug distribution and its rate of disappearance in each compartment can be determined theoretically.

A radioactive tracer is generally a complex of three elements, i.e., the tracer itself, its stable isotope (carrier), and the labeled molecule. Thus the aforementioned model can be applied to tracer kinetics by further assuming that, within the observation period, the three elements are bound to each other and neither undergo metabolism nor change their physicochemical properties except for radioactive decay.

Since tracer kinetics represents the interplay between the living organism and the tracer, its concentration is affected by the biological property of the organism and the physicochemical property of the tracer. The former includes rates of uptake, metabolism, and elimination of the substance (the atoms or molecules) that forms the pool into which the tracer is distributed. The latter includes molecular size and shape, lipid solubility, polarity, dissolution and diffusion capacities, carrier concentration, and specific activity (radioactivity/mass ratio). The rate constants in a compartment model may be modified by change in any of these properties. But, if a tracer has high specific activity, then none of its physicochemical properties modifies, unlike drugs, the biological properties; i.e., such a tracer will exert no pharmacologic effect. Thereby tracer kinetics reveals the underlying pathophysiological condition (i.e., kinetics of the pool of the labeled biological substance) in terms of radioactivity.

Biological and physical half-lives

In the linear one-compartment model, the amount of drug in the compartment is affected by the rates of its uptake and elimination. These two exponential processes are characterized by (1) **uptake half-life** and (2) **elimination half-life**, respectively, and the time to reach a half value in the elimination phase of its "concentration" curve is called (3) **biological half-life**. In tracer kinetics, while the radioactivity of the tracer is decreasing according to its decay constant, (4) **physical half-life**, the time to reach a half value in the elimination phase of its "time-activity" curve is called (5) **effective half-life**. (Terms (1) and (2) are conceptual, while terms (3) to (5) are empirical.)

If a tracer is instantaneously taken up in an organ after intravenous injection, then the relationship among the half-lives (3) to (5) in this model is known to be expressed as follows:

$$1/Te = 1/Tb + 1/Tp,$$

where Te, Tb and Tp are effective, biological and physical half-lives, respectively. This equation, then, should also be applicable to a polyexponential multicompartment model, because the rate of tracer elimination from the system at the terminal phase is limited by the rate constant of the most slowly equilibrating compartment. After equilibration, all the compartments can be considered as one compartment.

In this model, therefore, the biological half-life of the tracer can be calculated, regardless of nuclides, using the tracer's effective and physical half-lives, both of which can be obtained experimentally and in the literature, respectively. To elucidate this equation further, if a tracer has an extremely long physical half-life, its effective half-life substantially represents its biological

half-life. Conversely, if a tracer has an ultrashort physical half-life, e.g., if it has position emitters, its effective half-life is much shorter than its biological half-life and no longer represents the kinetics or biological behavior of the tracer; i.e., the concentration of the tracer decreases slightly even though its radioactivity is decreasing rapidly.

In the previous section the tracer uptake was assumed to be instantaneous; however, this assumption is not realistic. The concentration of the tracer apparently starts from zero, increases, reaches a plateau, decreases and returns to zero. Bolus injection of a tracer is possible, but the compartment barrier is assumed to act on both the uptake and elimination processes. Thus the tracer should have its own finite uptake half-life, although this would not be necessarily the same as the elimination half-life. As a result, two situations arise.

First, if the uptake half-life is shorter than the elimination half-life, then the change in tracer concentration in the compartment will be eventually limited by its rate of elimination (the elimination-rate limited process); the tracer uptake into the compartment is completed at a finite period, while its elimination continues. Thus the tracer remaining within the compartment at this point undergoes elimination according to its elimination half-life. Therefore, the aforementioned equation can be applied and the biological half-life obtained should represent the elimination half-life.

Second, if the uptake half-life is longer than the elimination half-life, then a "flip-flop" phenomenon occurs. Since the tracer is eliminated as soon as it is taken up into the compartment, the rate of its elimination is limited by its uptake process. This means that the biological half-life spuriously coincides with its uptake (and not its elimination) half-life. Therefore, although the equation can still be applied, the biological half-life obtained represents the uptake half-life.

To summarize these two possible situations, the biological half-life can be experimentally determined but may represent either the uptake half-life or the elimination half-life, depending on which of the two is longer. The problem might be solved, if feasible, by direct injection of tracer into the compartment (e.g., incorporation of the tracer into all the cells of an organ by microinjection). If the two biological half-lives A and B obtained by such procedure and by intravenous administration, respectively, are the same, then B should represent the elimination half-life; if different, then B should represent the uptake half-life, since A unquestionably represents the elimination half-life. But this problem cannot be solved by *a posteriori* reasoning, because such direct injection is virtually impossible.

In either of the aforementioned situations, the time required to reach maximal radioactivity in the compartment will be prolonged to some extent. Generally, the more slowly a tracer is taken up, the longer it takes for the tracer to reach its maximal radioactivity in the organ. If both the uptake and physical half-lives are the same, then an almost steady-state radioactivity will be obtained immediately and will be maintained until the tracer uptake is completed. And, no matter how long the physical half-life of a tracer is, its radioactivity will decrease unless the tracer is permanently trapped in the body.

Distribution space of tracer

Drug distribution space, i.e., apparent volume of drug distribution, can be calculated by extrapolating the slowest component of the drug's exponential time-concentration curve to time zero, provided that the diffusion of the drug in the body is much more rapid than its elimination from the body (elimination-rate limited process, as described). Similarly, the distribution space of a tracer can be calculated from the tracer's time-activity curve. If the tracer uptake is slow while its elimination is rapid (uptake-rate limited process, as described), then analysis after single injection is impossible; however, analysis will be possible if the tracer is continuously infused

throughout the observation period to compensate for its elimination. In either event, the analysis may be useful in understanding various pathophysiological conditions.

Furthermore, the multiple-tracer method may permit simultaneous measurement of the volume or mass of several body compartments as well as assessment of the size of compartments that are difficult to measure directly, e.g., the intracellular compartment, by use of appropriate tracers. Repetitive measurements on the same subject may allow evaluation of pathophysiological variations in the body composition and their modification by drugs.

Tracer dose

If the specific activity of a tracer is high, then the radioactivity per unit weight of organ per administered dose of tracer in each organ of interest does not vary with the dose administered; i.e., the shape of the time-activity curve does not change according to the dose. Thus any parameters derived from the curve should be independent of the dose, regardless of the linearity of the model. Since the dose of a tracer required for its kinetic or static analysis is much smaller than the whole pool of atoms or molecules into which it is distributed, and since a tracer generally has no pharmacologic effect, it is understandable that its kinetics would not change even if an administered dose were varied tenfold or more. Generally the optimal dose to administer and the optimal time of counting are determined by a trade-off among quality of the data (i.e., certainty of the counting rate), unwanted radiation (particularly in human studies) and cost, each of which is roughly proportional to the dose.

Extraction ratio and clearance

These parameters are also used in pharmacokinetics. In tracer kinetics, their measurement requires either implantable radiation sensors or blood sampling by arterial and venous cannulation; therefore, precise data are obtained at the expense of technical difficulties and possible disturbance of physiological conditions. Extraction ratio (E) is defined as the percentage of a drug extracted from the arterial blood in a single passage through a vascular bed. Clearance (C) is defined as the virtual blood volume required to account for the drug taken up by the organ in a unit time. Therefore,

$$C = Q \times E = Q \times (A-V)/A = Q \times (Ca-Cv/\exp(-(1n(2)/Tp) \times T))/Ca,$$

where A and V are arterial and venous blood concentrations of the drug, respectively; Ca and Cv are arterial and venous blood radioactivities (cpm/unit volume), respectively; Tp = physical half-life; T = time spent by the tracer to pass through the organ; and Q = organ blood flow. If T is relatively small compared with Tp, then $E = (Ca-Cv)/Ca$.

Capillary clearance theory

In the previous section, the efficiency of tracer uptake as well as its elimination was discussed in terms of half-life, extraction ratio and clearance. In any organ this efficiency may be considered a function of the capillary bed, i.e., its blood flow rate, its permeability to the tracer and its surface area, each of which can modulate the organ radioactivity independently (capillary clearance theory of Renkin, 1959).[7]

Accordingly, the rate of tracer uptake would be mainly limited by the organ blood flow or by the capillary permeability to the tracer, depending on whether the permeability is extremely high or extremely low, respectively. For example, tracers that are totally taken up by an organ during the first pass, i.e., tracers in the forms of microspheres, are used for estimation of regional blood flow as a fraction of cardiac output. Thus the radioactivity is a measure of blood flow only when both capillary permeability and its surface area are not the rate-limiting factors.

The myocardial uptake of thallium was once considered to be limited only by coronary blood flow. (Thallium scintigraphy has been used for assessment of myocardial ischemia because the ion disappears rapidly from the blood after intravenous injection, its extraction ratio in the first pass exceeding 80 percent.[5]) But recent studies report that thallium uptake is also modulated by other factors, e.g., the activity of sarcolemmic Na^+, K^+-adenosine triphosphatase (ATPase) itself[8,9,10] or other possible ionic transport mechanisms,[11] which would indirectly represent myocardial capillary permeability. Clinically, this implies that the amount of myocardial thallium uptake may be altered by factors other than coronary blood flow when the flow is high, i.e., at peak exercise.

Thus the factors that reportedly affect myocardial thallium uptake can be summarized according to this theory as follows: **(1)** modulation of coronary blood flow by (a) increase (exercise, isoproterenol, pressure change[12]) or decrease (beta-blocker[13]) in cardiac output or (b) dilatation (dipyridamole,[14] calcium-antagonists,[15] adenosine) or constriction (ergonovine) of coronary arteries; **(2)** change in capillary permeability or efficiency of ionic exchange by (a) alkalinization of blood pH (IV bicarbonate,[16] hyperventilation), (b) inhibition of sarcolemmic Na, K-ATPase (glucose/insulin,[17] digitalis glycoside,[3,11] diphenylhydantoin[18]), or (c) cell degeneration of miscellaneous causes (cardiomyopathy); and **(3)** change in the capillary surface area to myocardial volume ratio by increase (hypertrophy[19]) or decrease (myocardial infarction and cardiomyopathy of miscellaneous causes) in the volume of intact myocardium. Moreover, many other factors reportedly affect the quality of the thallium image, e.g., background activity (fasting,[20] drugs that affect pulmonary vessels[21]), photon attenuation by breast contribution,[22] etc.

Therefore, tracer kinetics is modified by drugs that affect either blood flow, permeability or surface area of the capillary. Conversely the effect of drugs on these three factors may be studied by tracer kinetics in terms of the size and renewal rate (half-life) of the compartments. A major advantage of the use of tracer kinetics is that it permits simultaneous determination of drug effect on the fractions of cardiac output delivered to various organs. Use of an appropriate tracer permits the evaluation of selective effects of drugs on the circulation in specific regions. For example, the effects of various catecholamines on the circulation may be compared and some may alter fractional tracer uptake in particular organs, whereas others may not.

This theory assumes no pathophysiological blood shunt and thus no competition between the bypass and the functional capillary bed for the available blood. If such a shunt exists, then the more the shunt flow, the more the ratio of capillary surface area to blood flow, assuming that total blood flow and capillary surface area do not change whether or not the shunt is open. If the amount of shunt flow is substantial, then tracer extraction by the organ should eventually reach a plateau.

Shortcomings of radiotracer kinetics

Although tracer kinetics offers many possibilities, several points must also be stressed. Interpretation of the results obtained may not be simple from the following standpoints.

(1) A compartment model in pharmacokinetics is usually developed by curve fitting of the time-concentration data of the blood; but because of the limitations of this approach, the model can be no more complex than a two-compartment open model for estimation of the parameters with reasonable accuracy. Furthermore, the fitting is simply a mathematical tool that does not yield much knowledge as to how the compartments are biologically related. Moreover, this analysis does not reveal the size or pathophysiological state of any one organ. In fact, even the definition of "compartment" itself is arbitrary. Great caution is thus required in interpreting physiologically the parameters measured. The model may in effect permit comparison of the data when a single factor is varied, e.g., the presence or absence of a drug, but the model is still

an arbitrary simplification. Thus the possibility of a systematic error, difficult to assess, always exists. (2) If the tracer complex rapidly undergoes either metabolism or *in vivo* decomposition during the observation period, then the observed distribution is not that of the tracer and, inevitably, it is difficult to understand the underlying biological mechanisms. (3) If the tracer happens to be highly taken up in one organ and is not distributed homogeneously within each compartment, then its apparent distribution space is spuriously increased. (4) If this method is used to study the influence of a drug, the steady state in the body may be disrupted by the drug. Thus one must always confirm that a new steady state has been reached after the drug is administered. If not, this method is not advantageous unless the subject is to be used as his own control. (5) At least six or seven serial images of the organ of interest will be required for precise calculation of parameters; clinically, this is not always feasible. If direct tissue counting is to be employed, then serial needle biopsies or, in animal studies, sacrifices at varying times postinjection are necessary. In the latter method the calculation is based on average values, which have a margin of uncertainty due to individual variation. This makes the measured parameters less precise than in the method using a single subject, in which the results are obtained before proceeding to statistical calculations (variance, etc.) to compare them with those in different subject groups, e.g., drug-pretreated and control groups.

CONCLUSION

Use of radiotracer kinetics has the important advantage of general applicability to living, intact subjects under physiological conditions or under the effect of a drug. Moreover, administration of a tracer and *in vivo* counting or collection of some biological specimen such as blood are relatively simple tasks. Nevertheless, the methods of analysis are diverse, ranging from simple determination of the distribution space of a tracer to a kinetic study involving numerous compartments. With attention to proper data collection and application of appropriate mathematical models, this type of study offers considerable promise of increasing our knowledge of pathophysiology, pharmacology and related fields.

ACKNOWLEDGEMENT

The author thanks Professor Edward A. Carr, Jr., Department of Pharmacology and Therapeutics, School of Medicine, State University of New York at Buffalo, for a helpful discussion and critique of this paper.

REFERENCES

1) Okada, R.D. and Boucher, C.A.: Differentiation of viable and nonviable myocardium after acute reperfusion using serial thallium-201 imaging. *Am. Heart. J.*, **113**, 241–250 (1987).
2) Llaurado, J.G., Madden, J.A., Meade, R.C. and Smith, G.A.: Distribution of thallium-201 injected into rats following stress: Imaging, organ to plasma uptake ratios, and myocardial kinetics. *J. Nucl. Med.*, **19**, 172–177 (1978).
3) Carlin, R.D. and Jan, K.: Mechanism of thallium extraction in pump perfused canine hearts. *J. Nucl. Med.*, **26**, 165–169 (1985).
4) Schelbert, H.R., Ashburn, W.L., Chauncey, D.M. and Halpern, S.E.: Comparative myocardial uptake of intravenously administered radionuclides. *J. Nucl. Med.*, **15**, 1092–1100 (1974).
5) Okada, R.D., Jacobs, M.L., Daggett, W.M., Leppo, J., Strauss, H.W., Newell, J.B., Moore, R., Boucher, C.A., O'Keefe, D. and Pohost, G.M.: Thallium-201 kinetics in nonischemic canine myocardium. *Circula-*

tion, **65**, 70–77 (1982).
6) Wagner, J.G.: Fundamentals of clinical pharmacokinetics. pp.57–120 (1979), Drug Intelligence Publications, Inc., Illinois.
7) Renkin, E.M.: Transport of potassium-42 from blood to tissue in isolated mammalian skeletal muscles. *Am. J. Physiol.,* **197**, 1205–1210 (1959).
8) Delano, M.L., Sands, H. and Gallagher, B.M.: Transport of $^{42}K^+$, $^{201}Tl^+$ and $[^{99m}Tc(dmpe)_2, Cl_2]^+$ by neonatal rat myocyte cultures. *Biochem. Pharmacol.,* **34**, 3377–3380 (1985).
9) Fox, J. and Ciani, S.: Experimental and theoretical studies on Tl^+ interactions with the cation-selective channel of the sarcoplasmic reticulum. *J. Membr. Biol.,* **84**, 9–23 (1985).
10) Ashcroft, F.M. and Stanfield, P.R.: The influence of the permeant ions thallous and potassium on inward rectification in frog skeletal muscle. *J. Physiol.,* **343**, 407–428 (1983).
11) Krivokapich, J. and Shine, K.I.: Effects of hyperkalemia and glycoside on thallium exchange in rabbit ventricle. *Am. J. Physiol.,* **240**, H612–H619 (1981).
12) Grunwald, A.M., Watson, D.D., Holzgrefe, H.H., Jr., Irving, J.F. and Beller, G.A.: Myocardial thallium-201 kinetics in normal and ischemic myocardium. *Circulation,* **64**, 610–618 (1981).
13) van der Wall, E.E., Westera, G., van Eenige, M.J., Scholtalbers, S., Visser, F.C., den Hollander, W. and Roos, J.P.: Influence of propranolol on uptake of radioiodinated heptadecanoic acid and thallium-201 in the dog heart. *Eur. J. Nucl. Med.,* **8**, 454–457 (1983).
14) Gould, K.L.: Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilatation. I. Physiologic basis and experimental validation. *Am. J. Cardiol.,* **41**, 267–278 (1978).
15) Moins, N., Gachon, P., Maublant, J. and Duchene-Marullaz, P.: Comparative study of vascular effects of four calcium antagonists using a multi-organ functional imaging technique with thallium-201. *J. Cardiovasc. Pharmacol.,* **5**, 978–982 (1983).
16) Hetzel, K.R., Westerman, B.R., Quinn, J.L., III, Meyers, S. and Barresi, V.: Myocardial uptake of thallium-201 augmented with bicarbonate: Concise communication. *J. Nucl. Med.,* **18**, 24–25 (1977).
17) Wilson, R.A., Okada, R.D., Strauss, H.W. and Pohost, G.M.: Effect of glucose-insulin-potassium infusion on thallium myocardial clearance. *Circulation,* **68**, 203–209 (1983).
18) Schachner, E.R., Oster, Z.H., Cicale, N.R., Sacker, D.F., Som, P., Atkins, H.L. and Brill, A.B.: The effect of diphenylhydantoin (Dilantin) on thallium-201 chloride uptake. *Eur. J. Nucl. Med.,* **6**, 585–586 (1981).
19) Strauer, B.E., Büll, U. and Bürger, S.: Clinical and experimental analysis of ^{201}Thallium uptake of the heart. *Nuklearmedizin,* **17**, 142–148 (1978).
20) Cavailloles, F., Vitaux, F., Petiet, A. and Vitaux, J.: Thallium uptake in fasted and nonfasted rats. *Eur. J. Nucl. Med.,* **8**, 87–88 (1983).
21) Maublant, J., Gachon, P., Moins, N., Jourde, M. and Duchene-Marullaz, P.: Myocardial imaging in dogs with thallium-201 and the ionophore grisorixin. *J. Nucl. Med.,* **21**, 787–789 (1980).
22) Rabinovitch, M., Suissa, S., Elstein, J., Staniloff, H., Tang, A., Rush, C., Aldis, A., Tannous, R., Turek, M., Addas, A., O'Brien, C., Burgess, J.H. and Rosenthall, L.: Sex-specific criteria for interpretation of thallium-201 myocardial uptake and washout studies. *J. Nucl. Med.,* **27**, 1837–1841 (1986).