Solution of rate constants in pharmacokinetics local model of nuclear medicine*

Cao Guo-Xian, Yu Hui-Xin and Huang Xu-Quan
(*State Key Laboratory of Nuclear Medicine, Jiangsu Institute of Nuclear Medicine, Wuxi 214063*)

Abstract Rate constants are important pharmacokinetic parameters and very useful in study of radiopharmaceuticals, nuclide therapy and internal radiation. In the situation of small number of compartments, solution of rate constants is not too difficult. But with increasing compartment number, the calculation is tending to more complex, which makes solving rate constants very difficult. Therefore, according to a general principle a series of formulae is established to simplify the process of solving rate constants.
Keywords Pharmacokinetics, Local model, Rate constants

1 Introduction

It is obvious that normal pharmacokinetics model, such as the compartment model, can only describe pharmaceuticals' pharmacokinetics in blood but in organs.[1,2] However, nuclear medicine mainly focuses on pharmacokinetics in organs. Therefore, we have put forward the pharmacokinetics local model to describe radiopharmaceuticals' pharmacokinetics for nuclear medicine.[3]

In the situation of small number of compartments, solution of rate constants is not too difficult for either local model or the compartment model. But with the number of compartments being large, the process of solving is becoming very complex. In order to solve the problem, we have established a method, deduced formulae and compiled the computer program to calculate rate constants.

2 Method

Argument related in this paper is limited on the single-dose vein administration central symmetry pattern, which is the main administration pattern in nuclear medicine, because the other patterns can be discussed in the same way.

Pharmaceutical's pharmacokinetics in vivo can be described by a group of differential equations[3]

$$\mathrm{d}D(t) = KD(t) \tag{1}$$

Using Laplace transformation, the solution of these differential equations can be obtained[3]

$$D(t) = AE(t) \tag{2}$$

There is a relationship between matrix A and rate constant K[2]

$$\begin{aligned}
&a_{11} + a_{12} + \cdots + a_{1n} = D_0/V_1 \\
&\frac{a_{11}}{k_{21} - \lambda_1} + \frac{a_{12}}{k_{21} - \lambda_2} + \cdots + \frac{a_{1n}}{k_{21} - \lambda_n} = 0 \\
&\frac{a_{11}}{k_{31} - \lambda_1} + \frac{a_{12}}{k_{31} - \lambda_2} + \cdots + + \frac{a_{1n}}{k_{31} - \lambda_n} = 0 \\
&\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \\
&\frac{a_{11}}{k_{n1} - \lambda_1} + \frac{a_{12}}{k_{n1} - \lambda_2} + \cdots + \frac{a_{1n}}{k_{n1} - \lambda_n} = 0
\end{aligned} \tag{3}$$

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where n is the number of compartments, λ_i the exponential parameter, and A the coefficient matrix.

It should be noted that in Eq.(3) from the second formula to the n-th have similar form, so their roots must be the same. Therefore, if one equation of them is solved, all of n-1 roots can be obtained at the same time, which are $k_{21}, k_{31}, \cdots, k_{n1}$.

In addition, elements a_{ij} of matrix A suit for the following formula[2]

$$\frac{k_{ji}}{k_{ij}-\lambda_j}a_{1j}=a_{ij} \quad (i=2,3,\cdots,n; \quad j=2,3,\cdots,n) \tag{4}$$

According to formula (4), $k_{12}, k_{13}, \cdots, k_{1n}$ can be easily calculated after $k_{21}, k_{31}, \cdots, k_{n1}$ are obtained.

Now we select the second formula in Eq.(3) as an example for evaluation of the equations.

$$\frac{a_{11}}{k_{21}-\lambda_1}+\frac{a_{12}}{k_{21}-\lambda_2}+\cdots+\frac{a_{1n}}{k_{21}-\lambda_n}=0$$

The equation has several singular points which will result in divergence during solving process. It can be changed into

$$a_{11}(k_{21}-\lambda_2)(k_{21}-\lambda_3)\cdots(k_{21}-\lambda_n)+a_{12}(k_{21}-\lambda_1)(k_{21}-\lambda_3)\cdots(k_{21}-\lambda_n)$$
$$+\cdots+a_{1n}(k_{21}-\lambda_1)(k_{21}-\lambda_2)\cdots(k_{21}-\lambda_{n-1})=0 \tag{5}$$

These terms in Eq.(5) can be expanded as

$$a_{11}(k_{21}-\lambda_2)(k_{21}-\lambda_3)\cdots(k_{21}-\lambda_n)$$
$$=a_{11}[k_{21}^{n-1}-\sum_{\substack{i=2\\ i\neq 1}}^{n}\lambda_i k_{21}^{n-2}+\sum_{\substack{i=2\\ i\neq 1\\ j\neq i}}^{n}\lambda_i\lambda_j k_{21}^{n-3}-\cdots+(-1)^{n-1}\prod_{\substack{i=2\\ i\neq 1}}^{n}\lambda_i]$$

$$a_{12}(k_{21}-\lambda_1)(k_{21}-\lambda_3)\cdots(k_{21}-\lambda_n)$$
$$=a_{12}[k_{21}^{n-1}-\sum_{\substack{i=1\\ i\neq 2}}^{n}\lambda_i k_{21}^{n-2}+\sum_{\substack{i=1\\ i\neq 2\\ j\neq i}}^{n}\lambda_i\lambda_j k_{21}^{n-3}-\cdots+(-1)^{n-1}\prod_{\substack{i=1\\ i\neq 2}}^{n}\lambda_i]$$

$$\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots$$

$$a_{1n}(k_{21}-\lambda_1)(k_{21}-\lambda_2)\cdots(k_{21}-\lambda_{n-1})$$
$$=a_{1n}[k_{21}^{n-1}-\sum_{\substack{i=1\\ i\neq n}}^{n}\lambda_i k_{21}^{n-2}+\sum_{\substack{i=1\\ i\neq n\\ j\neq i}}^{n}\lambda_i\lambda_j k_{21}^{n-3}-\cdots+(-1)^{n-1}\prod_{\substack{i=1\\ i\neq n}}^{n-1}\lambda_i]$$

The $n-1$ order higher degree equation about k_{21} can be obtained by summing these coefficients corresponding to each k_{21}^i(i=0, 1, 2, $\cdots$, $n-1$).

We select the third term of the first equation $\sum_{i=2}^{n}\lambda_i\lambda_j k_{21}^{n-3}$ ($i\neq 1$, $j\neq i$) as an example to analyse these coefficients of k_{21}^i. In fact, the coefficient is the sum of some combinations of λ_i and λ_j with $i\neq 1$ and $j\neq i$. It means that two elements are taken from n elements to combine and several combinations are rejected, which are not suitable to the condition, and the other combinations then are summed. Such a combination can be called as conditional combi-

nation. According to this method, we compiled the conditional combination software to calculate coefficients. The other coefficients of k_{21}^{i} are all conditional combinations, and their calculations are similar to the above one.

$k_{21}, k_{31}, \cdots k_{n1}$ can be calculated by terms of Eq.(5) replaced with their expanded forms. Using Eq.(4), k_{12}, k_{13}, $\cdots$, k_{1n} are also obtained.

According to above formulae, we have compiled the computer program named "Rate" with the C language for calculation.

3 Computer program

The computer program "Rate" consists of three parts: PLM[3], COM (combination) and HDE (high degree equation). PLM is used to calculate pharmacokinetic equation, matrix A, λ_i and other data. COM is used to obtain a varied combinations of λ_1, λ_2, $\cdots$, λ_n. HDE is used to calculate rate constants. The process of calculation is: inputting experimental data $\rightarrow$ PLM $\rightarrow$ COM $\rightarrow$ HDE $\rightarrow$ outputting results.

4 Calculation

We used the method to deal with animal (rats) experimental data of ^{125}I-bivalent ligand of practolol (^{125}I-BAP), a myocardial receptor imaging agent, and to calculate the rate constants of the animal experiment. We select a slightly higher compartment number n=4. First, we calculated matrix A and exponential parameters λ_i (i=1$\sim$ 4) by pharmacokinetics local model.[3] Then, using the program, we obtained rate constants k_{i1} and k_{1i}. The results are listed in Table 1.

Table 1 The calculated results of rate constants for ^{125}I-BAP

Time/min	3	5	15	30	60	120	240	480	720
Experimental data*	1.12	0.92	0.53	0.27	0.17	0.13	0.08	0.04	0.02
Calculated data*	1.12	0.92	0.41	0.20	0.13	0.09	0.06	0.02	0.01
Equation	C=1.0005exp(-0.1376t)+0.3692exp(-0.0676t) +0.1178exp(-0.0049t)+0.0400exp(-0.0029t)								
Matrix A	$\begin{pmatrix} 1.0005 & 0.3692 & 0.1178 & 0.0400 \\ -0.2231 & 0.2022 & 0.0158 & 0.0052 \\ -0.5956 & -0.5115 & 0.8629 & 0.2442 \\ -0.0549 & -0.0424 & -0.5606 & 0.6574 \end{pmatrix}$								
λ_i	λ_1 = 0.1376 λ_2=0.0676 λ_3=0.0049 λ_4=0.0029								
Rate constant	k_{12}=0.0111 k_{13}=0.0731 k_{14}=0.0074 k_{21}=0.0879 k_{31} = 0.0149 k_{41}=0.0033								

*Unit is (MBq/g specimens found)/(MBq administered body weight)

5 Summary

The calculation of rate constant in situation of small number of compartments can be done according to some formulae.[1,2] But with increasing compartment number, the calculation is tending to more and more complex, which makes solving rate constants very difficult. Our method based on a general principle simplifies the process of solving rate constants.

Rate constants are very useful in nuclear medicine, such as in study of radiopharmaceuticals, especially imaging agent, in nuclide therapy and in internal radiation. In combination with the local model, they can describe pharmacokinetics action of radiopharmaceutical in blood and in any organ, and provide a lot of useful information to direct our work.

References

1 Gibaldi M, Perrier D. Pharmacokinetics. Second Edition, Revised and Expanded. New York: Marcel Dekker, 1982

2 Liu Chang-Xiao, Liu Ding-Yuan. Introduction of pharmacokinetics (in Chinese). Beijing: China Academic Publishing House, 1984

3 Cao Guo-Xian, Li Wei-Yi, Yu Hui-Xin. Nucl Sci Tech, 1996; 7:170