Notes on the Inverse Gaussian Distribution and Choice of Boundary Conditions for the Dispersion Model in the Analysis of Local Pharmacokinetics

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Abstract □ The dispersion model has been widely used to analyze local pharmacokinetics in the organs and the tissues since the 1980's. However, an ambiguity still remains in selecting the boundary conditions which are necessary to solve the basic equation of the model. In this note, theoretical considerations are given to this problem and we present here some deficiencies of the mixed boundary conditions. It seems that theoretical confusion exists in the literature for the mixed boundary conditions. It is well-known that the solution of the dispersion model with a bolus input is the inverse Gaussian distribution for the mixed boundary conditions. However, it is rarely recognized that the inverse Gaussian distribution requires an open boundary at either the inlet or the outlet. For the analysis of local pharmacokinetics, the use of the classical Danckwerts (or closed) boundary conditions is recommended.

Introduction

To predict in vivo organ clearances from in vitro findings, a mathematical model that assumes certain structured blood flow is indispensable. It has been reported that the convection dispersion model[1,2] and distributed tube model[3,4] are sound models which give appropriate predictions of organ clearance in various situations. These two models afford similar predictions in linear kinetics,[5] but not in nonlinear kinetics.[4−6] This is because the distributed tube model does not assume any micromixing of the blood stream in the bed. In contrast, micromixing is incorporated naturally into the dispersion model.

The dispersion model was proposed by Roberts et al. in the 1980s[1,2] and has been used to analyze local pharmacokinetics in various situations.[7−11] The dispersion model is expressed by a partial differential equation, and to obtain its solution, the entrance and the exit boundary conditions are necessary. A drawback of the dispersion model is an ambiguity in selecting the boundary conditions.[4] Roberts et al. initially chose the Danckwerts (or closed) boundary conditions (DBC) because it satisfies the extremes of the well-stirred and tube model predictions,[1] but later favored the mixed boundary conditions (MBC).[5] MBC have also been preferred by several other investigators.[4,7−9]

The solution for MBC is apparently equivalent to a probabilistic distribution of the rate of first passage of particles moving randomly (as a random walk) that is referred to as the inverse Gaussian distribution.[2] A random walk is a discrete process but is superimposed on a convection flow by limiting the size of the steps and by expanding the basic equation in a Taylor series.[12] Accordingly, MBC has been related to the first passage time.[5] However, there is a pitfall, as will be discussed later.

In this correspondence, theoretical considerations are given to the ambiguity of the boundary conditions of the dispersion model. Some deficiencies of MBC will be discussed. We recommend the use of DBC.

Deficiencies of the Mixed Boundary Condition

The dispersion model is described by a partial differential equation as follows:[1,2]

$$\frac{\partial C}{\partial T} = D_N \frac{\partial^2 C}{\partial Z^2} - \frac{\partial C}{\partial Z} - R_N C \qquad (1)$$

where C is the normalized concentration of a substance at the normalized cross-section Z and at the normalized time T, D_N is the dispersion number, and R_N is the efficiency number. DBC is defined as follows:[2,5,13]

$$C - D_N\, \partial C/\partial Z = C_{in} \text{ at } Z = 0 \text{ for } T \geq 0 \qquad (2)$$

$$\partial C/\partial Z = 0 \qquad \text{at } Z = 1 \text{ for } T \geq 0 \qquad (3)$$

where C_{in} is the concentration in the entering stream. MBC is expressed as follows:[2,5,14]

$$C = C_{in} \qquad \text{at } Z = 0 \text{ for } T \geq 0 \qquad (4)$$

$$C \rightarrow 0 \text{ or } \partial C/\partial Z \rightarrow 0 \text{ as } Z \rightarrow \infty \text{ for } T \geq 0 \qquad (5)$$

The analytical solution of the dispersion model after bolus input with MBC is given by:[2]

$$C(T,Z) = \frac{Z}{2}\left(\frac{1}{\pi D_N T^3}\right)^{1/2} \exp\left(-\frac{(Z-T)^2}{4D_N T}\right) \qquad (6)$$

where the elimination is not considered. As described above, eq 6 also represents the inverse Gaussian distribution.[15]

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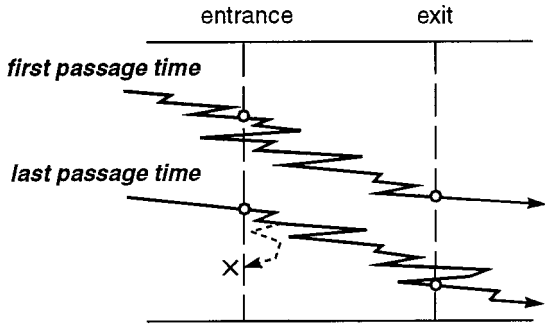

Figure 1—Schematic representation of a first passage time and a last passage time of a particle moving randomly in the bed. The first passage time starts when the particle first enters the bed and continues until it first reaches the exit. The last passage time starts when the particle last leaves the entrance and continues until it exits from the bed, never to return. Note that these sojourn times may include some time spent outside the bed. The dotted line indicates the trajectory of a lost particle in the case of MBC.

It should be noted, however, that the probabilistic distribution of first passage times of a random walk becomes the inverse Gaussian distribution where the inlet boundary is open.[12] The situation of MBC is distinct from the first passage time because its inlet is not open as indicated by eq 4. In reality, MBC is equated to the last passage times.[12] As shown in Figure 1, these two sojourn times are different but apparently equivalent because the time for roaming on the inlet in the first passage times corresponds to that for the outlet in the last passage times.

The dispersion assumed in the dispersion model represents mixing of the blood streams flowing through the microcapillaries in the tissue.[5] Accordingly, dispersion occurs within the tissue but must end at the boundaries. In this instance, both the first and the last passage times are inappropriate because an open boundary is postulated. As MBC is the last passage time, the dispersion is assumed across the exit,[10] which is physiologically irrelevant because the blood never returns from the distal vessels.

Another deficiency of MBC is that it cannot properly control the transfer of mass across the inlet. The peculiarity is obvious for a bolus case. The total mass of the drug is given by integration of eq 6:

$$\int_0^\infty C(T,Z)\,dZ = \{1 + \mathrm{erf}(\alpha^{1/2}/2)\}/2 + (\pi\alpha)^{-1/2}e^{-\alpha/4} \quad (7)$$

where $\alpha = T/D_N$. Equation 7 takes a minimum value of 1 when $\alpha \to +\infty$, namely $T \to +\infty$ and/or $D_N = 0$, but scatters to $+\infty$ as α or T approaches 0. It implies that the mass retained in the bed becomes infinity at the time of injection (Figure 2).

It is generally agreed in the field of chemical engineering that the correct boundary conditions are those that show the flux

$$\phi = C - D_N \partial C/\partial Z \quad (8)$$

to be continuous at the boundary.[12] Since the differential term in eq 8 is ignored for the inlet of MBC (eq 4), the implicit flux occurs when $\partial C/\partial Z \neq 0$ at $Z = 0$. This is the reason for the excessive mass in eq 7. The mass is increased explosively at the time of injection when $\partial C/\partial Z$ becomes $-\infty$ at the inlet and then evaporates gradually after the injection when $\partial C/\partial Z > 0$.

Availability predictions of the dispersion model at steady-state for any boundary conditions in linear kinetics have been reported (eqs 6 and 7 in reference 16). However, they are irrelevant for MBC. If $\partial C/\partial Z$ is less than zero at the inlet of MBC, which occurs when $R_N > 0$, the mass needs to be pored into the bed more than the flow rate allows to satisfy eq 4. This is impossible. In other words, MBC does not have a reasonable solution for steady-state conditions when $R_N > 0$ because of the improper inlet definition.

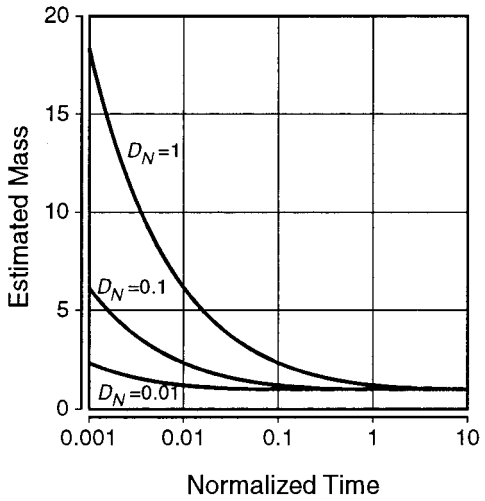

Figure 2—Overestimation of mass retained in the bed by the dispersion model with the mixed boundary condition after bolus input. Note that the mass must be 1.0 independently of time or dispersion number (D_N). The mass is calculated by eq 7.

Danckwerts Boundary Condition

DBC is a necessary consequence of the restrictions for mass conservation and discontinuity of mixing at the boundary.[17] This is currently the most physiological assumption for the solutes that are carried by the bloodstream in the organ, because micromixing of the blood never occurs across the boundaries. In the future, however, DBC might be reexamined for unnatural discontinuities at the boundaries. Continuous or stepwise change of dispersion has been considered theoretically.[18,19] These conditions are advantageous to simulate the real dynamics in the organ, although they are inapplicable to the current analyses because the change of the dispersion in the organ is unknown.

A major shortcoming of DBC is that its analytical solution is mathematically complex.[2] Yet a solution is possible for linear kinetics with inverse Laplace transformation techniques that are used frequently to solve the two-compartment dispersion model.[7,20,21] In addition, several numerical methods have been introduced to calculate the dispersion model for nonlinear kinetics.[14,22–24] It is now possible to obtain non-steady-state solutions of nonlinear multicompartment dispersion models with any input function.[23]

Practical Considerations

Despite the evident theoretical defects, it must be emphasized that most of the analyses done with MBC in the literature are still relevant because its solution is very similar to that of DBC where the dispersion number is small[5] (especially for $D_N \leq 0.2$). However, the results of some studies need to be interpreted cautiously.

First of all, it must be recognized that MBC offers unrealistically spreading outflow curves at higher D_N. After a bolus dose, the dimensionless variance of the outflow curves for MBC is calculated by:[2]

$$CV^2 = 2D_N \quad (9)$$

Equation 9 implies CV^2 exceeds that for even the well-

stirred situation ($CV^2 = 1$) when $D_N > 0.5$. This overspreading occurs primarily because the excessive mass is transferred to the outlet very rapidly in the early period. Another reason is the long-lasting nature of the curve generated with the open outlet condition. Therefore, it is an error caused by the improper definitions. CV^2 of the dispersion model for DBC is calculated by:[2]

$$CV^2 = 2D_N - 2D_N2(1 - e^{-1/D_N}) \quad (10)$$

in which CV^2 never exceeds 1, increases monotonically as D_N grows, and reaches the well-stirred situation at infinity (refer to Figure 3 in ref 10). All theoretical considerations that relate to the shape of the outflow curves of MBC may have potential problems.

Several investigators simulated availabilities with MBC and DBC for various situations and discussed the difference between the two conditions.[5,25] However, the physiological meaning of the difference is obscure. In linear pharmacokinetics, availability is determined by the residence time distribution of the solute (namely, the shape of the outflow curves),[5] and as Nauman concluded, both open and closed systems afford the same residence time distribution when time spent outside the system boundaries is excluded from the total,[12] which is a reasonable assumption for clearance of drugs. Consequently, availability is independent of boundary conditions for linear kinetics if the conditions are realistic. Unfortunately, MBC is not. The difference between MBC and DBC simply represents the extent of errors raised by MBC. Analogous consideration needs to be paid to interpretation of the dispersion numbers calculated with MBC and DBC.[10]

It is advocated that the extent of intrahepatic mixing is very close to the well-stirred situation because the "mixedness" of solutes is maximized at usual dispersion numbers and then decreases as the dispersion number increases, and this suggestion of maximum mixedness in the liver may explain the discrepancy between the apparent validity of the well-stirred model.[26] In this report, "mixedness" was evaluated based on the relative entropy of the outflow curves predicted by the dispersion model of MBC. However, the curves predicted by MBC may become unrealistic as discussed above. For this reason, the evaluation of "mixedness" seems to be erroneous. The conclusion of this report needs some modification.

In the extended use of the dispersion model, MBC would be more troublesome. In nonlinear kinetics, availability predictions by MBC could be inaccurate because clearance depends on the mass retained in the bed. Moreover, it is difficult to calculate nonlinear differential equations with boundary conditions that do not conserve mass. The assumption of MBC is incompatible with physiologically based pharmacokinetics because organs cannot be connected in a tandem manner due to the requirement of the open outlet.

The inverse Gaussian distribution is frequently adopted as a distribution function for parallel tube models.[4,5,9,10,14,25] From an empirical viewpoint, it is relevant if the model explains real data properly. However, for greatly spreading curves, the appropriateness of the shape needs to be verified because the influence of the improper boundary definitions of its generating function becomes apparent.

The dispersion model has been criticized for its inability to explain the tail part of the dilution curves after bolus input.[8–10] In this instance, the characteristic does not differ between DBC and MBC. However, it seems more reasonable to consider the temporal adsorption of substances to the surface of the vasculature as a possible reason for deviation from the model.[11] If such adsorption occurs, the dilution curve needs to be analyzed with the multicompartment dispersion model[7,23] even for vascular references.

Conclusion

MBC has theoretical deficiencies both at the entrance and the exit. Although analyses performed thus far with MBC are still relevant as approximations in most cases, the use of DBC is recommended to avoid theoretical confusion. Considering the recent progress in the development of numerical methods, the calculation of DBC is not a major problem. When the inverse Gaussian distribution is applied in pharmacokinetic considerations, it should be recognized that an open boundary is assumed at the inlet or the outlet.

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