論　　文

# A Multi-sinusoidal Compartment Model as an Alternative to the Dispersion Model for Hepatic Extraction Kinetic Analysis

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## Abstract

The analysis of hepatic availability or hepatic extraction ratio as a function of hepatic blood flow and intrinsic clearance is important to estimate first-pass effects and oral bioavailability for pre-systemically-eliminating drugs. The dispersion model can afford more accurate analysis of hepatic availability than the other conventional models (well-stirred model, parallel-tube model). However, the model is rather complicate. In the present study, a simpler model was derived by assuming the sinusoidal space in the liver as a number of well-stirred compartments sequentially connected through the hepatic blood flow (multi-sinusoidal compartment model). In comparison with the other models, this model demonstrated hepatic outflow profiles very similar to those obtained by the dispersion model. It gave a simpler equation for hepatic availability, and improved the inaccuracy of the well-stirred model or the parallel tube model. The number of compartments, around 3, for this model corresponded to the dispersion number, 0.33, which has been reported to give the best fit to the rat hepatic outflow in the dispersion model. Similarly, the number of compartments, around 5 corresponded to the dispersion number, 0.17, which has been reported to give the best fit to the human hepatic elimination kinetics in the dispersion model.

**Keywords**: hepatic availability; hepatic extraction ratio; intrinsic clearance; hepatic blood flow; total body clearance; hepatic outflow; well-stirred model; parallel tube model; dispersion model; multi-sinusoidal compartment model

## INTRODUCTION

The analysis of hepatic availability ($F_h$) or hepatic extraction ratio ($E_h$) as a function of hepatic blood flow ($Q_h$) and intrinsic clearance ($Cl_{int}$) is important to estimate first-pass effects and oral bioavailability for pre-systemically-eliminating drugs. Various models for hepatic elimination kinetics such as well-stirred model,[1] parallel-tube model,[1] dispersion model[2] etc, have been developed.

The well-stirred model has received most attention.[1] It assumes the sinusoidal space as a single well-stirred compartment and gives a simple equation for hepatic extraction ratio, $E_h=Cl_{int}/(Q_h+Cl_{int})$. From this equation, important information on pharmacokinetics can be derived. When $Cl_{int}$ is far larger than $Q_h$, the total body clearance after intravenous administration ($Cl_t$) is approximated to $Q_h$. On the other hand, when $Cl_{int}$ is far smaller than $Q_h$, $Cl_t$ is approximated to $Cl_{int}$. However, the total body clearance after oral administration ($Cl_t/f$) is always equal to $Cl_{int}$. This may not be necessarily true.

According to the well-stirred model,[1] a single bolus intra-portal-venous injection gives a hepatic outflow profile with decay of a first order rate ($Q_h+Cl_{int}$) and maximal concentration at time zero. However, this is not realistic in the light of the experimental data on rat hepatic outflow profiles[2]: bolus injection to isolated perfused rat liver demonstrated the hepatic outflow

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profiles with maximal concentration around 8 seconds. Thus the well-stirred model has been thought to underestimate $E_h$ for rapid elimination, due to the assumption of shorter residence of drug solutes in the liver. On the other hand, the parallel-tube model assumes sinusoidal perfusion. Unlike the well-stirred model, it has been thought to overestimate $E_h$ for rapid elimination, due to the assumption of longer residence of drug solutes in the liver.

The dispersion model[2] is based on the residence time distribution of drug solutes in the liver which can be determined by distribution number ($D_N$). Therefore, it can afford more accurate analysis of $E_h$. However, the equation of $E_h$ is complicate.

In the present study, a simpler model was proposed by assuming the sinusoidal space in the liver as a number of well-stirred compartments sequentially connected through the hepatic blood flow.

A similar model has been reported.[3] However, there has been little information on kinetic. Therefore, in the present study, equations for $F_h$, $E_h$, and hepatic outflow concentration were derived, and the hepatic outflow pattern and $F_h$ calculated by these equations were compared with those calculated in the dispersion model. The usefulness of the model was also tested by the simulation of the actual hepatic outflow profiles in rat[4] and the $F_h$[5] and the $Cl_t/f$[6,7] after administration of pre-systemically-eliminating drugs in human.

## METHORDS

### Description of Multi-sinusoidal Compartment Model

The multi-sinusoidal compartment model is derived by assuming that the sinusoidal space in the liver is expressed as a number of well-stirred compartments sequentially connected through the hepatic blood flow; each sinusoidal compartment connects with its own drug eliminating or non-eliminating tissue compartments through drug distribution; each sinusoidal compartment behaves similarly as a compartment assumed in well-stirred model, so that the drug concentration is homogenous inside the compartment (Fig. 1).

### Nomenclatures

N represents the number of compartments as shown by broken boxes, each of which consists of a sinusoidal compartment, a hepatic tissue compartment and a metabolic compartment shown by solid boxes; $C_t$,

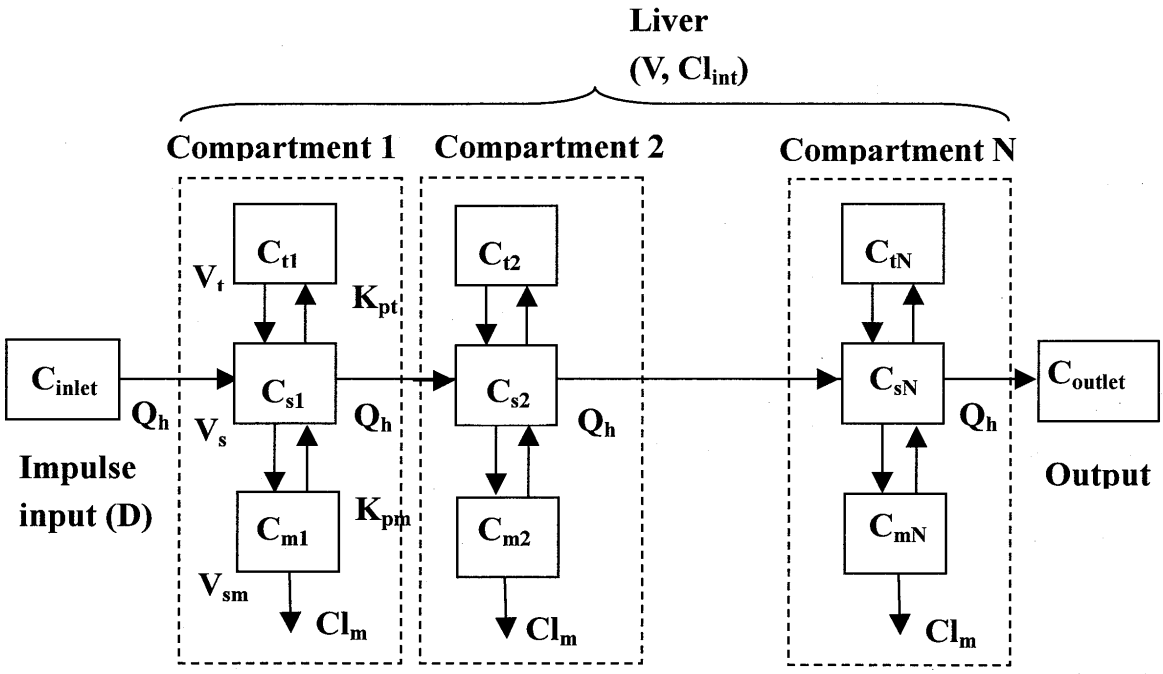


Figure 1. Illustration of multi-sinusoidal compartment model for hepatic extraction after single perfusion by impulse input.

$C_s$ and $C_m$ represent drug concentrations in a hepatic tissue compartment, in a sinusoidal compartment and in a metabolic compartment, respectively; $Q_h$ represents the hepatic blood flow rate; $Cl_s$ represents a drug clearance from a metabolism compartment; $K_{pt}$ and $K_{pm}$ represent constants of drug distribution equilibrium between a tissue compartment and a sinusoidal compartment, and between a metabolism compartment and a sinusoidal compartment, respectively; $V_t$, $V_s$ and $V_m$ represent volumes of a tissue compartment, a sinusoidal compartment, and a metabolic compartment, respectively; D, $Cl_{int}$, and V represent dose, hepatic intrinsic clearance, apparent hepatic distribution volume, respectively.

### Assumptions

(i) In the Nth sinusoidal compartment, the outflow of drug toward the next sinusoidal compartment occurs at the rate equal to the product of the sinusoidal drug concentration ($C_{sN}$) and the hepatic blood flow rate ($Q_h$).

(ii) The influx of drug from the preceding sinusoidal compartment (compartment N-1) occurs at the rate equal to the product of the drug concentration of the outflow ($C_{s(N-1)}$) and the hepatic blood flow rate ($Q_h$).

(iii) The drug distribution to a hepatic tissue compartment or to a metabolic compartment occurs so rapidly that equilibrium is reached instantaneously.

(iv) The drug elimination occurs at a rate proportional to the concentration of the drug in a sinusoidal compartment ($C_{sN}$).

### Mass-Transfer Equations with Compartment-1

Mass-transfer with compartment-1 can be expressed as:

$$V_s\frac{dC_{sl}}{dt}+V_t\frac{dC_{tl}}{dt}+V_m\frac{dC_{ml}}{dt}=-(Q_hC_{sl}+Cl_mC_{ml})$$

$$=-\left(Q_hC_{sl}+\frac{Cl_{int}}{N}C_{ml}\right) \quad (1)$$

Under rapid equilibrium,

$C_{tl}=K_{pt}C_{sl}$, $C_{ml}=K_{pm}C_{sl}$,

and $V_s+K_{pt}V_t+K_{pm}V_m=\frac{1}{N}V$

Let $\left(Q_h+\frac{K_{pm}Cl_{int}}{N}\right)\frac{N}{V}=\alpha$

Then,

$$\frac{dC_{sl}}{dt}=-\alpha C_{sl}$$

where $C_{sl}(t=0)=\frac{ND}{V}$ (2)

By Laplace transformation,

$$L(C_{sl})=\frac{ND}{V}\left(\frac{1}{s+\alpha}\right) \quad (3)$$

Then,

$$C_{sl}=\frac{ND}{V}\exp(-\alpha t) \quad (4)$$

### Mass-Transfer Equations with Compartment-N

Mass-transfer with compartment-N can be expressed as:

$$\left(\frac{V}{N}\right)\frac{dC_{sN}}{dt}=Q_hC_{s(N-1)}-\left(Q_h+\frac{Cl_{int}}{N}K_{pm}\right)C_{sN} \quad (5)$$

Then,

$$\frac{dC_{sN}}{dt}=\frac{N}{V}Q_hC_{s(N-1)}-\alpha C_{sN} \quad (6)$$

By Laplace transformation,

$$L(C_{sN})=\left(\frac{NQ_h}{V}\right)L(C_{s(N-1)})\left(\frac{1}{s+\alpha}\right)$$

$$=\left(\frac{NQ_h}{V}\right)L(C_{sl})\left(\frac{1}{s+\alpha}\right)^{N-1} \quad (7)$$

$$=\left(\frac{D}{Q_h}\right)\left(\frac{NQ_h}{V}\right)^N\left(\frac{1}{s+\alpha}\right)^N$$

By inverse transformation,

$C_{sN}=L^{-1}(C_{sN})$

$$=\left(\frac{D}{Q_h}\right)\left(\frac{NQ_h}{V}\right)^N\frac{t^{N-1}}{(N-1)!}\exp(-\alpha t) \quad (8)$$

### $F_h$ and $E_h$ as a Function of $Cl_{int}$ and $Q_h$

The area under the time-dependent hepatic outflow curve ($AUC_{outflow}$) can be expressed as:

$AUC_{outflow}=\int_0^\infty C_{sN}dt$

$$=\left(\frac{D}{Q_h}\right)\left(\frac{NQ_h}{V}\right)^N\frac{1}{(N-1)!}\int_0^\infty t^{N-1}\exp(-\alpha t)dt$$

$$=\left(\frac{D}{Q_h}\right)\left(\frac{NQ_h}{V\alpha}\right)^N\left(\frac{D}{Q_h}\right)\left[1+\frac{1}{N}\left(\frac{K_{pm}Cl_{int}}{Q_h}\right)\right]^{-N} \quad (9)$$

Then, $F_h$ can be expressed as:

$$F_h = \frac{AUC_{outflow}(C_{sN})}{AUC_{outflow}(C_{SN}, Cl_{int}=0)} = \left[1+\frac{1}{N}\left(\frac{K_{pm}Cl_{int}}{Q_h}\right)\right]^{-N}$$

Or

$$F_h = \frac{AUC_{outflow}(C_{sN})}{AUC_{outflow}(C_{SN}, Cl_{int}=0)} = \left[1+\frac{1}{N}\left(\frac{f_B Cl_{int}}{Q_h}\right)\right]^{-N} \quad (10)$$

where $K_{pm}$ is equal to the fraction of unbound drug in the sinusoidal compartment ($f_B$).

Then,

$$E_h = 1-\left[1+\frac{1}{N}\left(\frac{f_B Cl_{int}}{Q_h}\right)\right]^{-N} \quad (11)$$

When N=1, $E_h$ is the same as derived from the well-stirred model:

$$E_h = 1-\left[1+\left(\frac{f_B Cl_{int}}{Q_h}\right)\right]^{-N}$$

On the other hand, when N= infinity, $E_h$ is the same as derived from the parallel-tube model (according to the definition of exponential):

$$E_h = 1-\exp\left(-\frac{f_B Cl_{int}}{Q_h}\right)$$

### Mean Hepatic Resident Time (MHRT)

MHRT can be expressed as:

$$MHRT = \frac{\int_0^\infty tC_{sN}dt}{AUC_{outflow}} = \frac{N}{\alpha} = \frac{VQ_h}{1+\frac{1}{N}\left(\frac{K_{pm}Cl_{int}}{Q_h}\right)} \quad (12)$$

### Equations for $T_{max}$ and $C_{max}$ of Hepatic Outflow

The time ($T_{max}$) at which the hepatic outflow reaches the maximal concentration ($C_{max}$) can be obtained as:

$$\frac{dC_{sN}}{dt} = \left(\frac{D}{Q_h}\right)\left(\frac{NQ_h}{V}\right)^N \frac{t^{N-2}}{(N-1)!}\exp(-\alpha t)[(N-1)-\alpha t] = 0$$

Then,

$$t_{max} = \frac{N-1}{\alpha} = (N-1)\left(\frac{VF_h^{1/N}}{NQ_h}\right),\ \alpha = \frac{NQ_h}{VF_h^{1/N}} \quad (13)$$

and

$$C_{sN,max} = \left(\frac{D}{Q_h}\right)\left(\frac{NQ_h}{V}\right)^N \frac{t_{max}^{N-1}}{(N-1)!}\exp\left\{-\left(\frac{NQ_h}{VF_h^{1/N}}\right)t_{max}\right\} \quad (14)$$

### Procedure for Simulation of Hepatic-Outflow Profiles

According to eq. 8, hepatic outflow concentration at a given time is a function of N, D, $Q_h$, V and $\alpha$. The values of D and $Q_h$ are determined by the administration conditions. The value of V is determined as a function of MHRT which is determined by the moment analysis of hepatic outflow profiles. The value of $\alpha$ is determined as a function of $F_h$ which is determined by $AUC_{outflow}$ (eq. 10). Therefore, hepatic outflow profiles can be simulated, by using $F_h$ and MHRT as input data and by assuming a certain value of N.

## RESULTS AND DISCUSSION

### Comparison of Level- and Time-normalized Hepatic Outflow Profiles between Multi-sinusoidal Compartment Model and Dispersion Model

Level-normalized hepatic outflow profiles as a function of normalized time (T) in the dispersion model has been reported,[4]

$$\frac{C_{outflow}(t)}{C_{outflow}(t_{max})} = \frac{C}{C_{max}} = \left(\frac{T_m}{T}\right)^{3/2}\exp\left[\frac{(1-T_m)^2}{4D_N T_m}-\frac{(1-T)^2}{4D_N T}\right]$$

where $T = t/MHRT$ and $T_m = \sqrt{9D_N^2+1}-3D_N$

Similar level- and time-normalized hepatic outflow profiles in the multi-sinusoidal compartment model can be calculated by the following equation:

$$\frac{C_{outflow}(t)}{C_{outflow}(t_{max})} = \frac{C}{C_{max}} = \left(\frac{t}{t_{max}}\right)^{N-1}\exp[\alpha(t-t_{max})]$$

$$= \left(\frac{N}{N-1}\right)^{N-1}\exp(N-1)T^{N-1}\exp(-NT)$$

Level- and time-normalized hepatic outflow profiles calculated by these models using various values of N or $D_N$ were compared (Fig. 2). Both models demonstrated similar hepatic outflow profiles which have a single peak and a lag time depending on the values of N or $D_N$ (when N=infinity or $D_N$=0, the lag time=unity). The profile obtained by assuming $D_N$=0.33 in the dispersion model, which has been reported to give the best fit to the rat hepatic outflow,[4] appears to correspond to that obtained by assuming N=2 in the multi-sinusoidal compartment model. However, this correspondence might not be exact, since the lag time is more weighted than the height in the level-and time-normalized profiles.

### Simulation of Hepatic Outflow Profiles

The simulation of rat-hepatic-outflow profiles of the 5-n-alkyl-5-ethyl barbituric acids homologous series [five compounds: C1 to C5; body weight, 300g (200～400g); D, 0.025mg/rat; $Q_h$ (=perfusion rate),

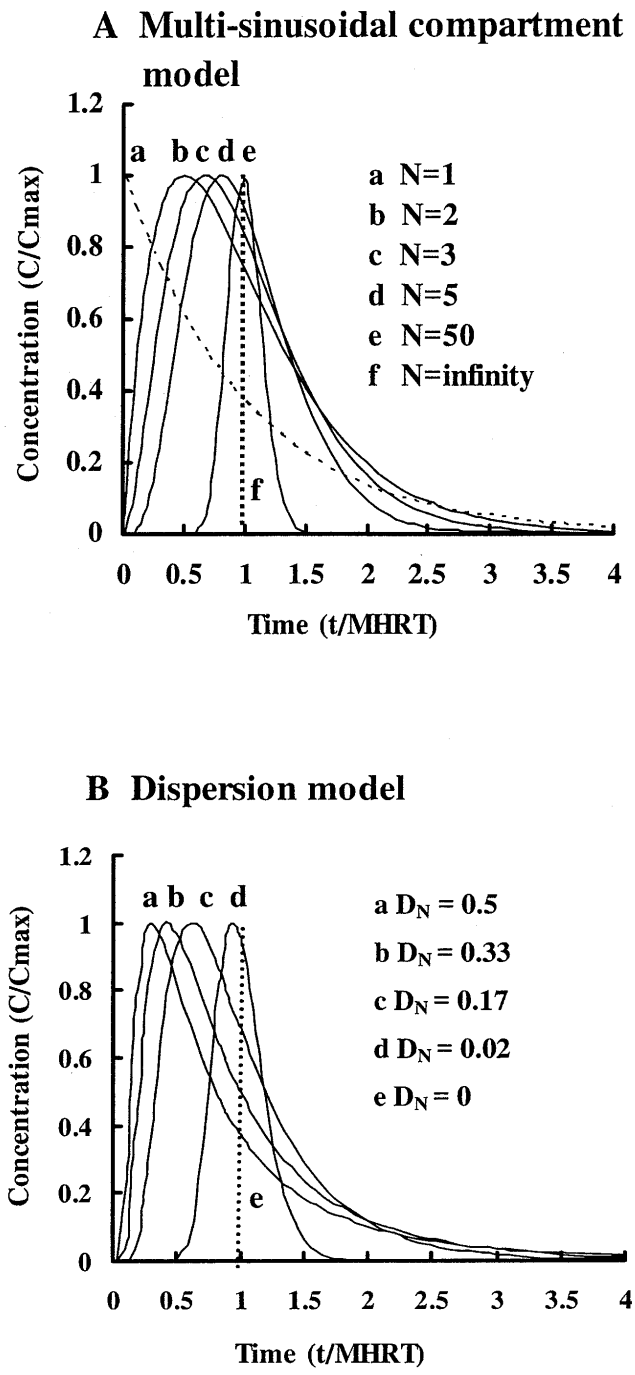


Figure 2. Comparison of level- and time-normalized outflow profiles between multi-sinusoidal compartment model and dispersion model.

0.25mL/sec] by the dispersion model, has been reported.[4] According to the report, the value for $D_N$=0.33 gave the best fit. In the present study, similar simulation was performed by the multi-sinusoidal compartment model. Upon calculation of the hepatic outflow profiles, the reported values of $F_h$ and MHRT which were obtained by the moment analysis of the original experimental data were used as the input data. This condition was the same as in the dispersion model.

Table 1 Calculated values for $t_{max}$, $C_{max}$ and V in the simulation of rat-hepatic-outflow profiles of 5-n-alkyl-5-ethyl barbituric acids homologous series by assuming various values of N.

| Compounds | $F_h$ | MHRT(sec) | $t_{max}$ (sec) | | | |
|---|---|---|---|---|---|---|
| | MA[a)] | MA | Exp | N=2 | N=3 | N=5 |
| C1 | 0.95 | 32 | 16 | 16 | 21 | 25 |
| C2 | 0.93 | 42 | 21 | 21 | 28 | 33 |
| C3 | 1.06 | 66 | 33 | 33 | 44 | 52 |
| C4 | 0.83 | 100 | 50 | 50 | 66 | 80 |
| C5 | 0.46 | 144 | 72 | 72 | 96 | 115 |

a) Moment analysis

| $C_{max}$ (mg/mL) | | | | V (mL/liver) | | | |
|---|---|---|---|---|---|---|---|
| Exp | N=2 | N=3 | N=5 | MA | N=2 | N=3 | N=5 |
| 2.70 | 2.18 | 2.41 | 2.89 | 0.97 | 0.74 | 0.73 | 0.73 |
| 2.02 | 1.62 | 1.79 | 2.16 | 1.19 | 0.98 | 0.97 | 0.96 |
| 1.54 | 1.18 | 1.30 | 1.56 | 1.63 | 1.44 | 1.47 | 1.48 |
| 0.77 | 0.61 | 0.67 | 0.81 | 2.73 | 2.49 | 2.41 | 2.35 |
| 0.32 | 0.23 | 0.25 | 0.31 | ND | ND | ND | ND |

The calculated values for $t_{max}$, $C_{max}$ and V are shown in comparison with the experimentally-obtained values in Table 1.

With respect to the fit to the experimentally-obtained values of $t_{max}$, N=2 was suggested to give the best result. With respect to the fit to the experimentally-obtained values of $C_{max}$, a value between N=3 and N=5 was suggested to give the best result. However, with respect to the simultaneous fit to the experimentally-obtained values of $t_{max}$ and $C_{max}$, a value around N=3 was suggested to give the best result.

The values of V estimated at different N values were not much different and similar to the values estimated by the moment analysis as well as the dispersion model. In the report,[4] the relationship between the hepatic distribution coefficients and the lipophilicities of the compounds were analyzed. In the present study, similar relationship was obtained (the data not shown).

The simulated outflow profiles by assuming N=3 are shown in Figure 3. These seem to be comparable to the actual outflow profiles, although the lag times are

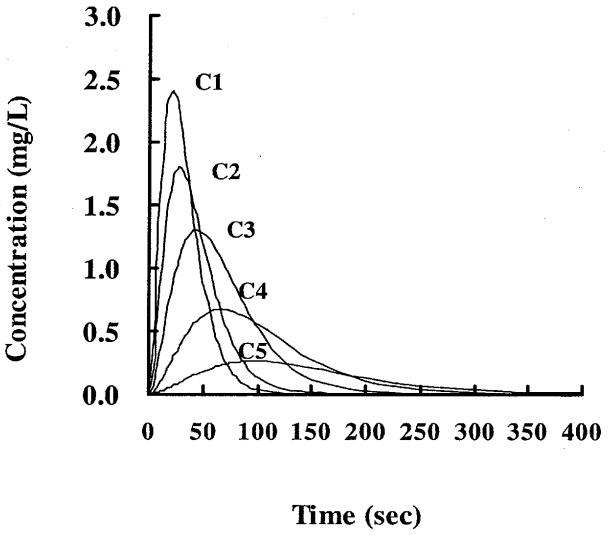


Figure 3. Simulation of the outflow profiles for n-alkyl-5-ethyl barbituric acids by multi-sinusoidal compartment model (at N=3).

somewhat deviated from the actual ones. Wesiger et al reported N around 8 gave the best fit to the thyroxine uptake by perfused rat liver in a similar model.[3] However, this value might not be realistic.

### Plots of $F_h$ versus $f_BCl_{int}/Q_h$

The comparison of $F_h$ versus $f_BCl_{int}/Q_h$ plots for pre-systemically-eliminating drugs among the well-stirred model, the parallel tube model and the dispersion model, was reported.[5] For drugs exhibiting $f_BCl_{int}/Q_h$ larger than 1 such as lidocaine, propranolol, etc, $D_N$=0.17 in the dispersion model well predicted $F_h$ in human. In the present study, similar plots were performed by using the multi-sinusoidal compartment model and they were compared with those obtained by the dispersion model. For calculation of $F_h$ as a function of $f_BCl_{int}/Q_h$ in the multi-sinusoidal compartment model, eq. 10 was used, whereas in the dispersion model, the following equation was used:

$$F_h = \frac{4a}{(1+a)^2\exp\left[\frac{(a-1)}{2D_N}\right]-(1-a)^2\exp\left[-\frac{(a+1)}{2D_N}\right]}$$

where

$$a = \left[1+4D_N\left(\frac{f_BCl_{int}}{Q_h}\right)\right]^{1/2}$$

Plots of $F_h$ versus $f_BCl_{int}/Q_h$ at different values of N in the multi-sinusoidal compartment model are shown in comparison with the dispersion model in Figure 4.

Like the results shown by the report[5], $F_h$ in any model was shown to decrease from unity with increase of $f_BCl_{int}/Q_h$, although the decrease was negligible at $f_BCl_{int}/Q_h$ smaller than 0.1. At $f_BCl_{int}/Q_h$ larger than 1, the rate of the decrease was different depending on N or

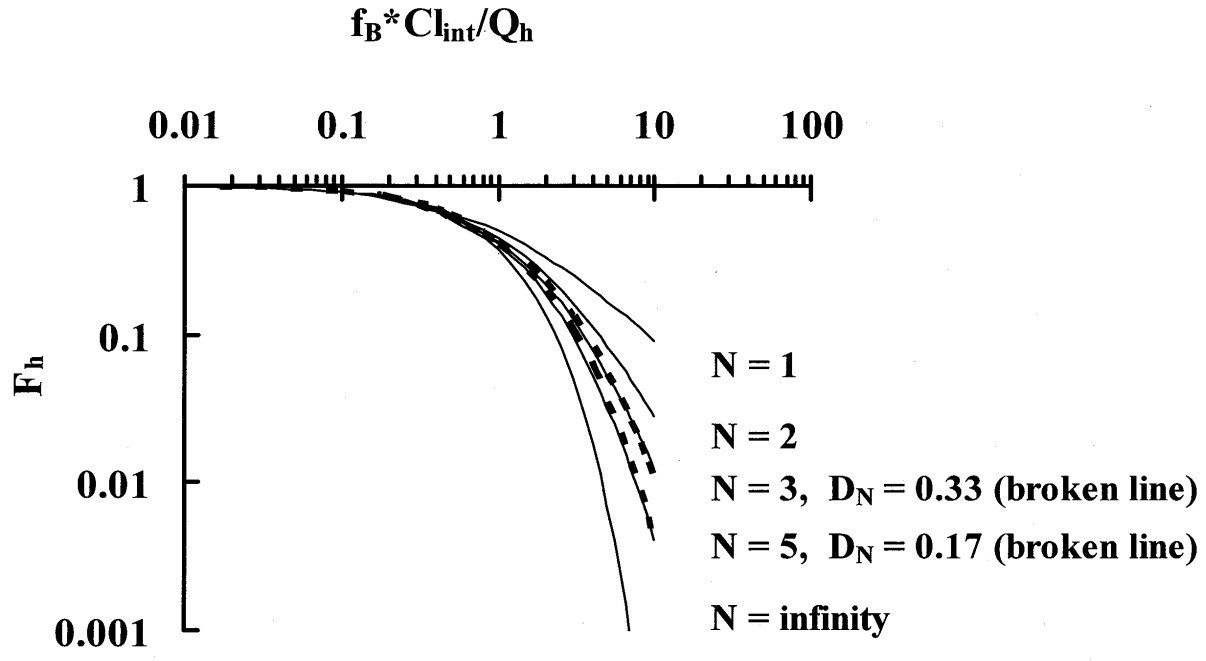


Figure 4. Comparison of $F_h$ versus $f_BCl_{int}/Q_h$ plots between multi-sinusoidal compartment model and dispersion model. The plots for the compounds were based on the graphic presentation in Ref. 5.

$D_N$. N of 1 (well-stirred model) showed the smallest decrease rate while N of infinity (parallel tube model) showed the largest one. Numerical values for $F_h$ in typical cases were shown as the followings. When $f_BCl_{int}/Q_h$ =1, the values of $F_h$ at N=1, 3, 5, and infinity in the multi-sinusoidal compartment model were 0.5, 0.421, 0.401, and 0.367, respectively, and the values of $F_h$ at $D_N$= 0.33 and 0.17 in the dispersion model were 0.433 and 0.411, respectively. When $f_BCl_{int}/Q_h$ =5, the values of $F_h$ at N=1, 3, 5 and infinity were 0.166, 0.0527, 0.03125, and 0.00674, respectively and the values of $F_h$ at $D_N$= 0.33 and 0.17 in the dispersion model were 0.054 and 0.034, respectively. When $f_BCl_{int}/Q_h$ =10, the values of $F_h$ at N=1, 3, 5 and infinity were 0.0909, 0.0122, 0.00411, and 0.000000, respectively, and the values of $F_h$ at $D_N$= 0.33 and 0.17 in the dispersion model were 0.009 and 0.003, respectively. From the comparison of $F_h$, $D_N$=0.33 and 0.17 in the dispersion model corresponded to N=3 and 5 in the multi-sinusoidal compartment model, respectively.

This correspondence might be more realistic than that obtained in the comparison of the normalized hepatic outflow profiles above.

### Plots of $Cl_t/f/Q_h$ versus $f_BCl_{int}/Q_h$

Response curves for $Cl_t/f$ to $f_BCl_{int}$, which were calculated in the well-stirred model, the parallel tube model and the dispersion model, have been reported.[6] It was suggested that the well-stirred model showed a linear response, while the parallel tube model and the dispersion model showed non-linear responses. In the present study, similar response curves were calculated, by dividing each parameter with $Q_h$, in the multi-sinusoidal compartment model and the dispersion model. The results were shown in Figure 5.

Like in the literature,[6] the response curve obtained by the well-stirred model showed a straight line with zero intercept, demonstrating the well known theory that $Cl_t/f$ is always equal to $f_BCl_{int}$. On the other hand, the response curves obtained by the parallel tube model and the dispersion model showed a curve where at relatively small $f_BCl_{int}$, the curve was approximated a straight line with a zero intercept, but at relatively large $f_BCl_{int}$, the slope of the curve increased with $f_BCl_{int}$. This tendency was remarkable in the parallel tube model. The curves obtained by assuming N=3 and 5 in the multi-sinusoidal compartment model corresponded to those obtained by assuming $D_N$=0.33 and 0.17, respec-

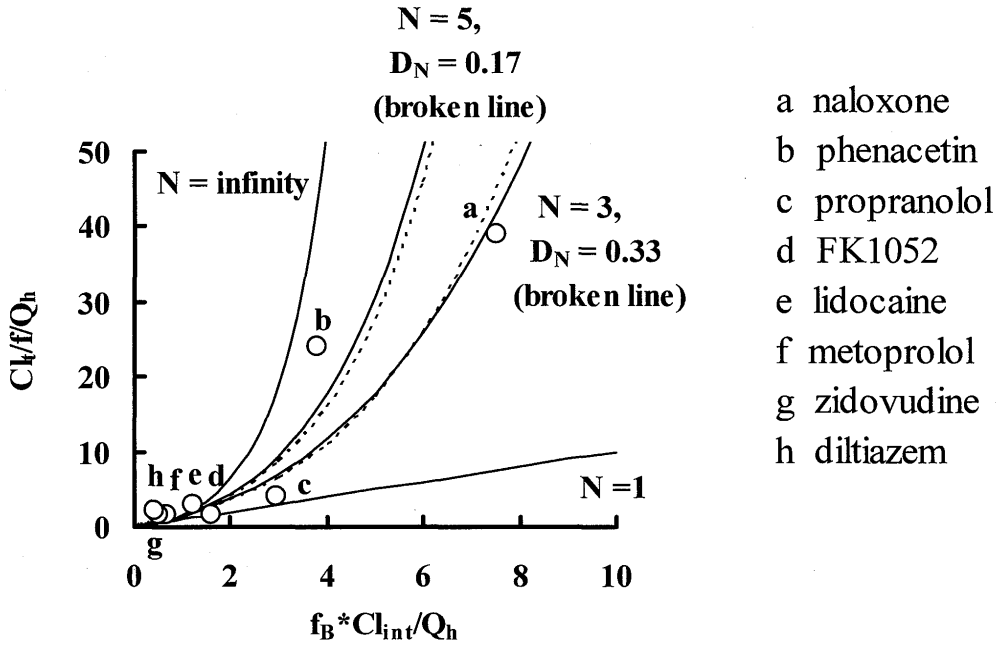


Figure 5. Comparison of $Cl_t/f/Q_h$ versus $f_BCl_{int}/Q_h$ plots between multi-sinusoidal compartment model and dispersion model. The plots for the compounds were based on the dataset shown in Table 2 (Ref. 7).

tively.

Very recently, a set of data on $Cl_t/f$ versus $Cl_{int,ub}$ ($=f_BCl_{int}$) in human have been reported.[9] Plots $Cl_t/f/Q_h$ versus $f_BCl_{int}/Q_h$ with compounds which showed relatively large $Cl_t/f/Q_h$ and $f_BCl_{int}/Q_h$ ($Q_h$= 20 mL/min/kg in human, Table 2) are also shown in Figure 5.

**Table 2 The data set of in vivo intrinsic hepatic clearance and total body clearance for plot of $Cl_t/f/Q_h$ versus $f_BCl_{int}/Q_h$**

| Compounds | $Cl_{int,ub}$,(mL/min/kg) | $Cl_t$(mL/min/kg) |
|---|---|---|
| Lidocaine | 24.61 | 15.0 |
| Metoprolol | 13.87 | 12.1 |
| Naloxone | 150.28 | 19.5 |
| Propranolol | 59.2 | 16.1 |
| FK1052 | 32.38 | 12.2 |
| Phenacetin | 76.01 | 19.2 |
| Zidovudine | 9.87 | 12.4 |
| Diltiazem | 21.67 | 13.3 |

Propranolol, phenacetin and naloxone were shown to be situated on either a curve obtained by N=3 ($D_N$ =0.33) or a curve obtained by N=5 ($D_N$=0.17), or between these curves. This result suggests that the value of N from 3 to 5 in the multi-sinusoidal compartment model as well as the value $D_N$ from 0.17 to 0.33 in the dispersion model is possibly applicable to human. However, in order to determine the values of N or $D_N$ in human, the more accumulated data of $Cl_t/f$ versus $Cl_{int,ub}$ ($=f_BCl_{int}$) for compounds exhibiting relatively large $f_BCl_{int}/Q_h$ is necessary.

### General Consideration

According to the present model, simple equations for $Cl_t/f$ and $f_BCl_{int}/Q_h$ can be derived as:

$$Cl_t/f = \left[-1+\left(1+\frac{f_BCl_{int}}{NQ_h}\right)^N\right]Q_h$$

Or oppositely,

$$f_BCl_{int}/Q_h = N[-1+(1+Cl_t/fQ_h)^{-N}]$$

These equations are useful for analysis of AUC change or $f_BCl_{int}/Q_h$ change due to metabolic drug interaction

According to the well-stirred model, $Cl_t/f$ is always equal to $Cl_{int}$. This leads to a popular relationship for the changing ratio in AUC after concomitant oral administration with an enzyme inhibitor ($R_{AUC}$), namely $R_{AUC}$ = the reciprocal of the changing ratio of the $Cl_{int}$ ($R_{Clint}$). However, if a drug exhibits a relatively large $f_BCl_t/Q_h$, this relationship will not be applicable.

According to the multi-sinusoidal compartment model, $R_{AUC}$ can be expressed as:

$$R_{AUC} = \left[-1+\left(1+\frac{f_BCl_{int}}{NQ_hR_{Clint}}\right)^N\right]\Big/\left[-1+\left(1+\frac{f_BCl_{int}}{NQ_h}\right)^N\right]$$

If a drug exhibits $f_BCl_{int}/Q_h$ = 5 at single administration in human (N=5 in the multi-sinusoidal compartment model) ($F_h$=0.03125) and $R_{Clint}$ is 2, then $R_{AUC}$ will be 4.70, that is 2.35 times as large as $R_{Clint}$. If $R_{Clint}$ is 10 and the other conditions are the same, then $R_{AUC}$ will be 50.8, that is 5.08 times as large as $R_{Clint}$. This means metabolic drug interaction with a drug exhibiting relatively large first pass effect (larger than 97%), will possibly occur in a dramatic way.

## CONCLUSIONS

The multi-sinusoidal compartment model demonstrated hepatic outflow profiles very similar to those obtained by the dispersion model. It gave a simpler equation for $F_h$, and improved the inaccuracy of conventional models such as the parallel tube model and the well-stirred model. The number of N, around 3, for this model corresponded to the number of $D_N$=0.33, which has been reported to give the best fit to the rat hepatic outflow in the dispersion model. Similarly, the number of N, around 5 corresponded to the number of $D_N$=0.17, which has been reported to give the best fit to the human hepatic elimination kinetics in the dispersion model. This model could possibly be an alternative to the dispersion model for hepatic extraction kinetic analysis.

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