An Interpretation of the Hill Equation: Time Course of Diuretic Response after Furosemide Administration in Man

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Response function, which correlates pharmacologic response intensity and the drug concentration, is defined assuming that the biophase (or the site of action) is consisted of the elements responsive to the drug, each of which is in a responding or non-responding state depending on the drug concentration in the biophase.

The Hill equation, which has been widely used without a definite rationale, for correlation between pharmacologic response intensity and drug concentration is revealed as an approximate equation of the response function.

Diuretic data obtained after administration of furosemide and reported previously are used for conformity assessment of the response function.

Keywords — dose-response correlation; response function; Hill equation; furosemide; urine flow rate

Introduction

In our previous study on the disposition of furosemide and diuretic response in man,¹⁾ it was revealed that the cumulative increment of urinary $\text{Na}^+ + \text{K}^+$ excretion (R) and the cumulative amount of furosemide excreted in urine (X_u) are correlated by a Hill-type equation (Eq. 1).

$$R = \frac{R_m X_u^\gamma}{X_{u50}^\gamma + X_u^\gamma} \quad (1)$$

where R_m , X_{u50} and γ are constants.

Pharmacologic response intensity of diuretics at a given time (t) is defined by the increase in urine flow rate or the increase in electrolyte excretion rate (dR/dt) at that moment.

Furthermore, furosemide concentration in the proximal tubule is expressed as $(dX_u/dt)/(\text{GFR} \cdot (1-fR))$.²⁾ Therefore, if the biophase of furosemide is located in the proximal tubule, biophase concentration is represented by the urinary excretion rate of the drug (dX_u/dt), as long as glomerular filtration rate (GFR) and fraction of renal reabsorption (fR) are kept constant.

From the viewpoint of analyzing pharmacologic response intensity as a function of drug

concentration in the biophase, manipulation of Eq. 1 was attempted and Eq. 2 was obtained in the succeeded study.²⁾

$$\frac{dR}{dt} = \gamma \left[\frac{R_m}{X_{u50}} \right] \left[\frac{X_u}{X_u} \right]^{\gamma+1} \left[\frac{R}{R_m} \right]^2 \frac{dX_u}{dt} \quad (2)$$

Assuming $\gamma = 1$, Eq. 2 is reduced to Eq. 3, which shows that the diuretic response intensity (dR/dt) is not only a function of drug concentration in the biophase (dX_u/dt) but also a function of the cumulative pharmacologic response (R).

$$\frac{dR}{dt} = \frac{R_m}{X_{u50}} \left[1 - \frac{R}{R_m} \right]^2 \frac{dX_u}{dt} \quad (3)$$

Time dependent decrease of diuretic response intensity was further confirmed by a so-called clockwise hysteresis of a graph in which urine flow rate (= diuretic response intensity) was plotted against urinary excretion rate of furosemide (= biophase drug concentration).³⁾ And Eq. 4, which correlate urine flow rate ($E(t)$) at a given time (t) and furosemide urinary excretion ($X_u(t)$, $dX_u(t)/dt$), was derived.

$$E(t) = \frac{A \dot{X}_u(t)^\gamma}{Q^{\gamma+1} \dot{X}_u(t)^\gamma} - \frac{A \dot{X}_u(T)^\gamma}{\left\{ \frac{X_u(T)}{X_u(t)} Q \right\}^\gamma + \dot{X}_u(T)^\gamma} \quad (4)$$

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where A , Q , T and γ are constants and dotted $X_u(t)$ represents $dX_u(t)/dt$. The first right side term of Eq. 4 is the Hill term which defines functional relationship between diuretic response intensity and biophase drug concentration. The other term of the right side is a correction term for the time-dependency of diuretic effect.

The Hill equation has been used quite often to express pharmacologic response intensity as a function of biophase drug amount or concentration.⁴⁾ Rationale to use Hill equation, however, has not yet been established. The aim of this report is to present an explanation for using the Hill equation.

Theoreticals

Definition of Response Function, Resp (X)

Response function is derived based on the assumptions: (1) The biophase (or the site of action) is consisted of a number of elements (*e.g.* enzymes, gates, channels *etc.*) responsive to the drug, each of which exists in one of two states, responding or non-responding. (2) There is an equal chance of 1/2 for each element to be in responding or non-responding state. (3) The fraction of the elements which are in the responding state is a log-linear function of the drug concentration in the biophase.

By assumption (2), probability of the condition that r out of total n elements are in responding state is given by Eq. 5.

$$P(r) = \frac{n!}{(n-r)!r!} \left(\frac{1}{2}\right)^n \quad (5)$$

Since $P(r)$ is equal to $P(n-r)$, maximal probability occurs at $r = n/2$, or 50% of the elements are in the responding state. We define that the drug concentration in the biophase at this condition is C_{50} . Supposing that n is large enough, $P(n/2)$ is calculated using Stirling's approximation formula for factorials.⁵⁾

$$P\left(\frac{n}{2}\right) \cong \sqrt{\frac{2}{n\pi}} \quad (6)$$

For the drug concentration in the biophase, C , other than C_{50} , the fraction of the elements responding is defined by assumption (3) as follows:

$$r = \frac{n}{2} + \frac{\sqrt{n}}{\sigma} \log \frac{C}{C_{50}} = \frac{n}{2} + x \quad (7)$$

where σ is a constant.

Applying Stirling's formula⁵⁾ again and after some simplification, we obtain Eq. 8.

$$P\left(\frac{n}{2} + x\right) \cong \sqrt{\frac{2}{n\pi}} e^{-\frac{2x^2}{n}} \quad (8)$$

Simultaneous squeezing and expansion of the coordinates:

$$\begin{aligned} \frac{\sqrt{n}}{2} P\left(\frac{n}{2} + x\right) &\rightarrow Y, \\ \frac{2x}{\sqrt{n}} &\rightarrow X \end{aligned}$$

result in normal function.⁶⁾

$$Y = \frac{1}{\sqrt{2\pi}} e^{-\frac{X^2}{2}} \quad (9)$$

Summing up all the fraction of elements responding, on the drug concentration in the biophase, we finally obtain a response function, which correlates pharmacologic response intensity and drug concentration.

$$\text{Resp}(X) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^X e^{-\frac{y^2}{2}} dy, \quad (10)$$

$$X = \frac{1}{\sigma} \log \left[\frac{C}{C_{50}} \right]$$

As shown in Appendix (A), response function is also defined using error function $\text{erf}(x)$.

$$\begin{aligned} \text{Resp}(X) &= \frac{1}{2} \left\{ 1 + \frac{X}{|X|} \text{erf} \left(\frac{|X|}{\sqrt{2}} \right) \right\}, \\ \text{erf}(x) &= \frac{2}{\sqrt{\pi}} \int_0^x e^{-y^2} dy \end{aligned} \quad (11)$$

Evaluation of the response function is not necessarily easy but one can calculate the error function with ease, applying FILT (Fast Inverse Laplace Transformation) algorithm,⁷⁾ as shown in Appendix (B).

Hill Equation as an Approximation of Response Function

According to the mathematical derivation used in the appendix of reference,⁸⁾ Hill equation, Eq. 12 is rewritten as Eq. 13.

$$E = \frac{E_{\max} C^\gamma}{C_{50}^\gamma + C^\gamma} \quad (12)$$

$$E = \frac{E_{\max}}{2} \left[1 + \tanh \left\{ \frac{\gamma}{2} \ln \left(\frac{C}{C_{50}} \right) \right\} \right] \quad (13)$$

Resemblance between Eq. 11 and 13 is apparent and, as it is said elsewhere that the first approximation of error function is hyperbolic tangent, values of Eq. 11 and 13 are very close if $\gamma = \sqrt{8/\pi} \log e / \sigma = 0.693034/\sigma$ (Fig. 1). Consequently, it is quite probable that drug concentration in the biophase and pharmacologic response intensity are originally correlated by response function but that, owing to its simplicity, the Hill equation has alternatively been used as a sort of experimental equation.

Interpretation of Eq. 4 by Using Response Function

Equation 4 is rearranged to Eq. 14. The bracketed term in the right side of Eq. 14 represents, although seemingly complex, time dependent decrease in pharmacologic response intensity, which is unity at $t=0$ and becomes null at $t=T$.

$$E(t) = \frac{A \dot{X}_u(t)^\gamma}{Q^\gamma + \dot{X}_u(t)^\gamma} \left[1 - \frac{X_u(t)^\gamma \left[1 + \left\{ \frac{Q}{\dot{X}_u(t)} \right\}^\gamma \right]}{\left\{ \frac{X_u(T)}{\dot{X}_u(T)} Q \right\}^\gamma + X_u(t)^\gamma} \right] \quad (14)$$

If $\{Q/(dX_u/dt)\}^\gamma$ is small enough com

Fig. 1. Comparison of Hill Function and Response Function

Solid curve, response function; dotted curve, Hill function.

pared with unity, the second term in the right hand brackets is another Hill function of cumulative urinary excretion of the drug or the cumulative drug concentration in the biophase.

The time dependent decrease in diuretic response intensity is considered a result of the diuretic response itself. Enhanced elimination of body fluid and electrolytes caused by a diuretic resulted, in turn, decreased response to the drug. Therefore, the time-dependent correction term is better expressed by using cumulative diuretic response, rather than cumulative excretion of the drug, as Eq. 15. In Eq. 15, two Hill terms of Eq. 14 are replaced by response functions. The bracketed term is unity at $t=0$ and decreases monotonously with time.

$$E(t) = E_{\max} \text{Resp}(X) \{1 - \text{Resp}(Y)\} \\ X = \frac{1}{\sigma_1} \log \left\{ \frac{\dot{X}_u(t)}{\dot{X}_{u50}} \right\}, \quad (15) \\ Y = \frac{1}{\sigma_2} \log \left\{ \frac{\int_0^t \dot{X}_u(t) dt}{\dot{X}_{u50}} \right\}$$

Methods

Compatibility assessment of Eq. 15 was carried out using diuretic data obtained after administration of furosemide and reported previously.⁹ Since the diuretic response intensity $E(t)$ was determined by increase in urine flow rate dV/dt , Eq. 15 is written as Eq. 16, where V is cumulative increase in urine output.

$$\frac{dV(t)}{dt} = \dot{V}_\infty \text{Resp}(X) \{1 - \text{Resp}(Y)\} \quad (16) \\ X = \frac{1}{\sigma_1} \log \left\{ \frac{\dot{X}_u(t)}{\dot{X}_{u50}} \right\}, \quad Y = \frac{1}{\sigma_2} \log \left\{ \frac{V(t)}{V_{50}} \right\}$$

Applying Runge-Kutta method,¹⁰ Eq. 16 was integrated numerically for evaluation of $V(t)$. For adaptation of Eq. 16 to the observed data and parameter estimation, a non-linear least squares program FKDM which is based on the algorithm of Berman *et al.*¹¹ was used on a personal computer (NEC, PC-9801/RA).

Estimation of $dX_u(t)/dt$ was performed by Eqs. 17 and 18 for intravenous and oral drug administration, respectively, with parameter values tabulated in the reference.⁹

$$\frac{dX_u(t)}{dt} = \frac{k_r D}{\alpha - \beta} \left\{ (\alpha - k_{21}) e^{-\alpha t} + (k_{21} - \beta) e^{-\beta t} \right\} \quad (17)$$

$$\frac{dX_u(t)}{dt} = FDk_r k_a \left[\frac{(\alpha - k_{21})}{(k_a - \alpha)(\alpha - \beta)} e^{-\alpha(t-t_L)} \quad (t \geq t_L) \right. \\ \left. + \frac{(k_{21} - \beta)}{(\alpha - \beta)(k_a - \beta)} e^{-\beta(t-t_L)} - \frac{(k_a - k_{21})}{(k_a - \alpha)(k_a - \beta)} e^{-k_a(t-t_L)} \right] \quad (18)$$

$$\frac{dX_u(t)}{dt} = 0 \quad (t < t_L)$$

Results and Discussion

Time Dependent Concentration-Response Relationship

The declines in urinary excretion rates of furosemide and increments of urine flow rate after administration of 20 mg (i.v.) and 40 mg (p.o.) of the diuretic to human are shown in Figs. 2 and 3, respectively. A nonlinear least-squares computer fit of the data was obtained. The equations which were fit to the data of urinary excretion rate and increment of urine flow rate are

Fig. 2. Time Course of Diuretic Response to Furosemide and Urinary Excretion Rate of Furosemide (Subject 3, Dose 20 mg i.v.)

The solid curve represents the results of least squares computer-fitting of observed data to Eq. 16, while the dotted line shows calculated values of Eq. 17. Pharmacokinetic parameters obtained are as follow: Parameters for Eq. 17 $D=20.0$ mg, $V_c=4.6190$ l, $k_{12}=1.3293$ h⁻¹, $k_{21}=1.3810$ h⁻¹, $Cl_s=5.8966$ l/h, $Cl_r=5.5285$ l/h. Parameters for Eq. 16 $\dot{V}_\infty=1.2417$ l/h, $X_{u50}=2.3738$ mg/h, $\sigma_1=0.1365$, $V_{50}=0.6740$ l, $\sigma_2=0.3143$

Fig. 3. Time Course of Diuretic Response to Furosemide and Urinary Excretion Rate of Furosemide (Subject 5, Dose 40 mg p.o.)

The solid line represents the results of least squares computer-fitting of observed data to Eq. 16, while the dotted line shows calculated values of Eq. 18. Pharmacokinetic parameters obtained are as follow: Parameters for Eq. 18 $D=40.0$ mg, $F=0.8425$, $t_L=0.1367$ h, $V_c=2.9485$ l, $k_a=1.9705$ h⁻¹, $k_{12}=1.3726$ h⁻¹, $k_{21}=1.1047$ h⁻¹, $Cl_s=5.3276$ l/h, $Cl_r=4.3201$ l/h. Parameters for Eq. 16 $\dot{V}_\infty=1.4741$ l/h, $X_{u50}=3.6163$ mg/h, $\sigma_1=0.1874$, $V_{50}=1.4807$ l, $\sigma_2=0.3201$

Fig. 4. Clockwise-Hysteresis Relationship between Diuretic Response and Urinary Excretion Rate of Furosemide (Subject 5, Dose 40 mg p.o.)

The solid curve represents the results of least squares computer-fitting of observed data to Eq. 16. The dotted line shows computer simulation for dose of 20 mg with the same parameter values. Pharmacokinetic parameters are as shown in the caption of Fig. 3.

Eqs. 17 (i.v.), 18 (*p.o.*) and 16, respectively. The parameters which were obtained for each set of the data are shown in the respective figure captions. The solid lines of Figs. 2 and 3 represent the computer least-squares fit to the respective data.

The increments of urine flow rates were plotted against the corresponding furosemide excretion rates as shown in Fig. 4. The clockwise hysteresis of the Fig. 4 represents the time dependent decrease in diuretic response.

A Model for Furosemide Concentration-Response Correlation

In the previous study,³⁾ the experimental data of six subjects with bolus intravenous injection of furosemide (20 mg) and the data of nine subjects with oral doses of 5, 10, 20, 30 and 40 mg of furosemide were subjected to computer-fitting of 6 equations. The results clarified that Eq. 4, which includes the body regulatory function, describes the relationship of diuretic effect and disposition of furosemide in man more accurately than the other equations.

The same data were utilized once again for assessment of Eq. 16. The results are summarized in Table I. Parameters involved in Eq. 4 are A , Q and γ . Those in Eq. 16 are V_∞ , V_{50} , σ_1 and σ_2 . Although the number of model parameters is one more, the number of observed data is 10. Therefore, residual sum of squares (SS) value less than 81.87% of the original SS value demonstrates smaller AIC¹²⁾ value and the better conformity of Eq. 16 with the observed data.

Conclusion

If we assume that sensitivities of each drug-responsive element in the biophase are distribut-

ed normally, it is rational to define the concentration-response relationship by the response function (Eq. 10). It is considered that Hill equation (Eq. 12) which has been widely used for dose-response correlation is merely an approximation of Eq. 10. The value of Eq. 10 defines the sensitivity distribution of the responsive units relative to the drug concentration in the biophase. With biophase concentration of C_{50} , 50% of the units are responding. With concentrations of $C_{50} \times 10^{-\sigma}$ and $C_{50} \times 10^\sigma$, 15.87% and 84.13% of the units are responding, respectively.

Since, however, Eq. 10 is inflexible to mathematical manipulations and Eq. 12 is easier to handle sometimes, we propose to use Eq. 12, when necessary, for computer-fitting of a model *etc.* and to discuss the results converting γ value to σ ($= 0.693034/\gamma$).

The advantage of using Eq. 10 lies in the reproductive property of normal distribution law.¹³⁾ On the case of coadministration of drug A and drug B which share a common biophase, pharmacologic response intensity is estimated logically from the individual pharmacodynamic parameters.

Appendix

A. Expression of Response Function Using Error Function

Equation 1a is same as Eq. 10 in the text.

$$\text{Resp}(x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^x e^{-\frac{y^2}{2}} dy \quad (1a)$$

Conversion of a variable, $y = \sqrt{2} Y$, results: $dy = \sqrt{2} dY$ and

$$\begin{cases} y = -\infty & \longrightarrow & Y = -\infty \\ y = X & \longrightarrow & Y = \frac{X}{\sqrt{2}} \end{cases}$$

Therefore, Eq. 2a is obtained and rearranged as follows:

$$\begin{aligned} \text{Resp}(X) &= \frac{1}{\sqrt{\pi}} \int_{-\infty}^{\frac{X}{\sqrt{2}}} e^{-Y^2} dY \\ &= \frac{1}{\sqrt{\pi}} \int_{-\infty}^0 e^{-Y^2} dY + \frac{1}{\sqrt{\pi}} \int_0^{\frac{X}{\sqrt{2}}} e^{-Y^2} dY \quad (X \geq 0) \\ &= \frac{1}{\sqrt{\pi}} \int_{-\infty}^0 e^{-Y^2} dY - \frac{1}{\sqrt{\pi}} \int_{\frac{X}{\sqrt{2}}}^0 e^{-Y^2} dY \quad (X < 0) \end{aligned} \quad (2a)$$

TABLE I. Adaptability of Response Function (SS Values)

Experiment	Eq. 4	Eq. 16	Ratio
20 mg i.v.	0.0026 ± 0.0019	0.0019 ± 0.0015	0.731
10 mg <i>p.o.</i>	0.0184 ± 0.0147	0.0133 ± 0.0101	0.723
20 mg <i>p.o.</i>	0.0231 ± 0.0086	0.0200 ± 0.0080	0.866
30 mg <i>p.o.</i>	0.0342 ± 0.0100	0.0323 ± 0.0124	0.944
40 mg <i>p.o.</i>	0.0359 ± 0.0116	0.0234 ± 0.0103	0.652

Mean ± S.D. ($n = 6$).

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*****
* ERROR FUNCTION (FAST INVERSION OF LAPLACE TRANSFORM) *
*          CODED BY T.KOIZUMI          1990.3.28          *
*****
      DEFDBL A-Z
      DIM AMN(10)
      NM=6
      NL=14
      A=7
      AMN(1)=127.0
      AMN(2)=120.0
      AMN(3)=99.0
      AMN(4)=64.0
      AMN(5)=29.0
      AMN(6)=8.0
      AMN(7)=1.0
      PI=3.14159265
10    INPUT "      x =";X
      IF X<=0 THEN STOP
      XN=0.0
      SIGN=1.0
      F1=0.0
      NL1=NL-1
      FOR N=1 TO NL1
          SIGN=-1.0*SIGN
          XN=XN+1.0
          R1=A*4
          J1=(XN-0.5)*PI*4
          GOSUB 100
          F1=F1+J1*SIGN
      NEXT N
      F2=0.0
      FOR N=0 TO NM
          SIGN=-1.0*SIGN
          XN=XN+1.0
          R1=A*4
          J1=(XN-0.5)*PI*4
          GOSUB 100
          F2=F2+SIGN*J1*AMN(N+1)
      NEXT N
      CX=(F1+F2*0.5^(NM+1))*EXP(A)*4
      PRINT USING "##.##      #.#####";X,1-CX
100   GOTO 10
      R2=R1
      J2=J1
      UU=SQR(R1*R1+J1*J1)
      J9=SQR(.5*(UU-R1))
      R1=SQR(.5*(UU+R1))
      IF J1<0 THEN R1=-R1
      J1=J9
      R1=-R1*X
      J1=-J1*X
      UU=EXP(R1)
      R1=UU*COS(J1)
      J1=UU*SIN(J1)
      UU=1/(R2*R2+J2*J2)
      RR=(R1*R2+J1*J2)*UU
      J1=(R2*J1-J2*R1)*UU
      R1=RR
      RETURN
      END

```

Fig. 5. TURBO BASIC Program for Computation of erf(X)

where

$$\frac{2}{\sqrt{\pi}} \int_{-\infty}^{\infty} e^{-Y^2} dY = \frac{2}{\sqrt{\pi}} \int_0^{\infty} e^{-Y^2} dY = \operatorname{erf}(\infty) = 1$$

Consequently, Eq. 3a is obtained.

$$\begin{aligned} \operatorname{Resp}(X) &= \frac{1}{2} \left\{ 1 + \frac{X}{|X|} \frac{2}{\sqrt{\pi}} \int_0^{\frac{|X|}{\sqrt{2}}} e^{-Y^2} dY \right\} \\ \operatorname{Resp}(X) &= \frac{1}{2} \left\{ 1 + \frac{X}{|X|} \operatorname{erf}\left(\frac{|X|}{\sqrt{2}}\right) \right\} \end{aligned} \quad (3a)$$

The final equation is identical to Eq. 11 in the text.

B. Evaluation of Error Function Using FILT Algorithm

Since Laplace transform of $\operatorname{erf}(x/2\sqrt{t})$ is $(1 - \exp(-\sqrt{s}X))/s$, $\operatorname{erf}(X)$ is numerically evaluated using FILT algorithm with $t = 0.25$. A simple program for computation of $\operatorname{erf}(X)$ written in TURBO BASIC is given in Fig. 5 and the computed results are shown in Table II with the approximated values by Eq. 4a¹⁴⁾ as well as the values obtained from the table of error function.¹⁵⁾ The computed values coincide with the values from the table as much as 6 digits.

$$\operatorname{erf}(x) \cong 1 - \frac{1}{(a_0 + a_1x + a_2x^2 + a_3x^3 + a_4x^4 + a_5x^5 + a_6x^6)^{16}} \quad (4a)$$

$a_0 = 1.0000000000$ $a_1 = 0.0705230784$ $a_2 = 0.0422820123$ $a_3 = 0.0092705272$ $a_4 = 0.0001520143$ $a_5 = 0.0002765672$
 $a_6 = 0.0000430638$

TABLE II. Values of Error Function Computed by FILT

X	erf(X)		
	FILT	Eq. 4a	Ref. 15)
0.00	0.0	0.0	0.0
0.05	0.05637218	0.05637172	0.056372
0.10	0.11246306	0.11246272	0.112463
0.20	0.22270266	0.22270274	0.222703
0.40	0.42839259	0.42839241	0.428392
0.60	0.60385664	0.60385584	0.603856
0.80	0.74210148	0.74210102	0.742101
1.00	0.84270114	0.84270104	0.842701
2.00	0.99532235	0.99532252	0.995322
3.00	0.99997792	0.99997774	0.999978

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