THE DIURETIC EFFECT OF FUROSEMIDE IN RELATION TO ITS DISPOSITION IN MAN

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Experiments concerning the diuretic effect and disposition of furosemide were performed in nine healthy male volunteers. During the test period, each of subject was given 50 ml of water every half an hour. Under this experimental condition, interesting phenomena, such as almost identical duration of diuretic effect independent of given dose and the so-called clockwise hysteresis of the concentration-effect curve were observed. These phenomena revealed that the body water regulation system had intervened in the pharmacodynamics of furosemide. Based on experimental results, a model and a new equation are presented, which describe the quantitative relationship of the drug disposition, the diuretic response and the body water regulatory function.

Keywords — diuretic response; clockwise hysteresis; body water regulation system; Hill's equation; furosemide

INTRODUCTION

The correlation between disposition and diuretic response of furosemide in humans was investigated by supplying 50 ml water every 0.5 h, a rate of water supplement only slightly higher than the ordinary urine flow rate but far lower than the diuretic rate of furosemide. In this experimental condition, the body water regulation system was found to interfere with the pharmacodynamics of diuretics. We demonstrated the time course of the regulatory function, how the regulatory system is interposed on the pharmacokinetic-pharmacodynamic models of a diuretic and how the body water regulatory system is harmonized with the pharmacodynamics of furosemide.

MATERIALS AND METHODS

All the experimental procedures and analytical methods were described in the previous report.1

RESULTS AND DISCUSSION

Dose-Response Relationship

The dose-response curve most often used2) was suitable for the correlation of a given dose and diuretic response of furosemide. A linear correlation between the logarithm of furosemide oral dose and the total diuretic response (urine flow increment) was observed as shown in Fig. 1 (a). Considering the fact that furosemide acts directly on the tubular lumen surface3) and, therefore, the fraction of dose unabsorbed and eliminated non-renally does not share the diuretic effect of furosemide, a more reasonable correlation should be obtained between the total amount excreted unchanged in urine (\(X_u^\infty\)) and the total increment of urine flow (\(V_u^\infty\)) as shown in Fig. 1 (b).

Duration of Diuretic Response

Six volunteer subjects were given furosemide in oral doses of 10, 20, 30 and 40 mg and a bolus intravenous dose of 20 mg and three additional subjects were given oral doses of 5, 10, 20 and 40 mg of the drug, as indicated in Table I. The duration of diuresis in these 42 experiments are listed in Table I. The duration of diuresis after a bolus intravenous injection is defined as the time, after drug administration, at which the urine flow rate is restored to the normal level. For example, if the average urine flow rate observed in 3.0—3.5 h was already reduced to the normal level, then duration of diuresis is regarded as 3.0 h. As for oral administration, the lag time of absorption, which is one of the pharmacokinetic parameters estimated in the previous report, is subtracted from the duration, because a drug does not exert pharmacologic effect before it is

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FIG. 1. Dose–Response Relationship of Furosemide in Man
(a): plot of total increments of urine flow versus administered dose \( r = 0.8662 \). (b): plot of total increments of urine flow versus cumulative amount of furosemide excreted \( r = 0.8897 \).

### TABLE I. Duration \(^{a)} \) of Diuretic Response

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 i.v.</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.5</td>
<td>3.0</td>
<td>3.0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3.08 ± 0.20</td>
</tr>
<tr>
<td>5 p.o.</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2.92</td>
<td>2.88</td>
<td>3.89</td>
<td>3.21 ± 0.59</td>
<td></td>
</tr>
<tr>
<td>10 p.o.</td>
<td>2.85</td>
<td>2.41</td>
<td>2.94</td>
<td>3.0</td>
<td>2.91</td>
<td>3.38</td>
<td>1.84</td>
<td>2.83</td>
<td>2.86</td>
<td>2.78 ± 0.43</td>
</tr>
<tr>
<td>20 p.o.</td>
<td>3.86</td>
<td>2.88</td>
<td>2.88</td>
<td>2.86</td>
<td>2.96</td>
<td>3.42</td>
<td>1.86</td>
<td>3.33</td>
<td>4.85</td>
<td>3.21 ± 0.82</td>
</tr>
<tr>
<td>30 p.o.</td>
<td>3.92</td>
<td>3.38</td>
<td>3.27</td>
<td>3.86</td>
<td>2.41</td>
<td>2.89</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3.29 ± 0.58</td>
</tr>
<tr>
<td>40 p.o.</td>
<td>2.85</td>
<td>3.93</td>
<td>4.43</td>
<td>2.86</td>
<td>3.36</td>
<td>2.87</td>
<td>2.84</td>
<td>3.35</td>
<td>3.90</td>
<td>3.38 ± 0.59</td>
</tr>
</tbody>
</table>

Total average duration 3.147 ± 0.587

\(^{a)} \) Duration is expressed in hours.

### TABLE II. Variance Analysis of Results Presented in Table I

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Sum of squares</th>
<th>Degrees of freedom</th>
<th>Mean sum of squares</th>
<th>( F )-ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between dose levels</td>
<td>1.9284</td>
<td>5</td>
<td>0.38567</td>
<td>1.13502</td>
</tr>
<tr>
<td>Within dose levels</td>
<td>12.2323</td>
<td>36</td>
<td>0.33979</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>14.1607</td>
<td>41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{a)} \) Influence of dose levels on duration of diuretic effect is not significant, since \( F \)-ratio, \( F_{35}^{2} \) (0.05) = 2.4851.

Absorbed.

From Table I, it is apparent that durations of diuresis were all close to 3 h (average of 42 durations is 3.15 ± 0.59 h), irrespective of dose given.
or route of administration. The analysis of variance showed no significant differences \((p = 0.05)\), as shown in Table II.

In general, the duration of the drug effect increased with the increase in the dose administered, because the time at which the drug concentration in the biophase which was reduced to the minimum effective concentration (MEC) was prolonged.\(^2\) By doubling the dose, the duration was prolonged for about another one half-life of drug elimination. The fact that almost identical durations of diuresis were observed with furosemide of different doses implied that as the dose and effect increased, the resistance of the body to diuresis also increased for protection against great losses of body water.

**Time Dependent Dose–Response Relationship**

In most oral experiments, the increments of urine flow rates were plotted against the corresponding furosemide excretion rates and the phenomenon of the clockwise hysteresis\(^4\) was observed as shown in Fig. 2. Figure 2 revealed that the diuretic response intensity corresponded to the identical drug excretion rate was higher in the absorption phase than that in the elimination phase.

Nine volunteer subjects were administered 3 levels of furosemide (10, 20 and 40 mg in solution) and at the midpoint of each urine collection period, the diuretic rate was plotted against the logarithm of furosemide excretion rate. The results are shown in Fig. 3. There was a linear correlation between the diuretic rate and the logarithm of the corresponding renal excretion rate of furosemide in each of the urine collection periods, but the slope of the regression line decreased as the midpoint of the collection period increased. The results clearly show the decreasing tendency in diuretic intensity for a given concentration of furosemide in the tubule. In Fig. 3, a lower slope of the very first urine collection period indicated that a finite time was required for the drug to enter the biophase and to arrive at equilibrium of distribution. From our results, it is clear that the finite distribution time was relatively short, no longer than 0.375 h.

**A Model for Furosemide Dose–Response Correlation**

It is evident from the above discussion that the diuretic effect of furosemide is related not only to drug disposition but also to time and, therefore, this relationship cannot be described by any of the conventional equations, such as simple straight line, semi-logarithmic, full-logarithmic, logistic or logarithmic logistic (Hill's equation).\(^2,6\) This may be the reason why prior attempts to relate the diuretic effect with pharmacokinetics of furosemide have met with only limited success.\(^6\)

On the basis of the above analyses, we have presented a new model for a more precise description of pharmacokinetics and pharmacodynamics of furosemide in man (Fig. 4). This model is based on four essential hypotheses as follows:
FIG. 3. Time Course of Diuretic Response/ Urinary Excretion Rate of Furosemide Correlation
In each urine collection period, the diuretic responses are plotted against the logarithm of urinary excretion rates of furosemide. \(dX_u/dt\), urinary excretion rate of furosemide. \(dV_u/dt\), diuretic response.

1. The diuretic rate can be correlated with the urinary excretion rate of furosemide because the biophase is in the kidney and the drug concentration in the kidney is proportional to the urinary excretion rate of the drug (Appendix 1).

2. If there is no intervention of the body fluid regulation system, the relationship of the diuretic rate and the corresponding urinary excretion rate can be described by a logarithmic logistic function (Hill’s equation).

3. Negative feedback intensity of the body fluid regulation system is also described by Hill’s equation, in which, the feedback intensity is correlated with the cumulative amount of drug excreted in urine. This is because when more of the drug is excreted in urine, more of the drug has passed through the tubule; the larger the volume of body water lost by the diuretic effect, the more regulation intensity is produced to protect the body from further loss of water.

4. The duration of the diuretic effect is independent of the dose given and is constant.

Mathematical description of the model shown in Fig. 4 is given by Eq. 1.

\[
E(t) = \frac{A X_u(t)}{Q + X_u(t)} - \frac{A X_u(T)}{(X_u(T)/Q)^s + X_u(T)^s}
\]

(1)

FIG. 4. Diagrammatic Representation of a Model Which Includes Furosemide Disposition, Diuretic Response and Body Fluid Regulation
A, absorption site; C, central compartment; P, peripheral compartment; U, urinary excretion; NR, nonrenal elimination; E, drug effect compartment; BRS, body fluid regulation system.
TABLE III.  Adaptability of Dose–Response Equations

<table>
<thead>
<tr>
<th>Eq.</th>
<th>i.v. experiments (n = 6)</th>
<th>p.o. experiments (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S.S.</td>
<td>A.I.C.</td>
</tr>
<tr>
<td>1</td>
<td>0.0026 ± 0.0021</td>
<td>−62.28 ± 11.77</td>
</tr>
<tr>
<td>2</td>
<td>0.2264 ± 0.2268</td>
<td>−18.07 ± 12.82</td>
</tr>
<tr>
<td>3</td>
<td>0.0164 ± 0.0154</td>
<td>−45.07 ± 9.05</td>
</tr>
<tr>
<td>4</td>
<td>0.1433 ± 0.0884</td>
<td>−19.95 ± 8.69</td>
</tr>
<tr>
<td>5</td>
<td>0.0964 ± 0.0632</td>
<td>−22.13 ± 7.74</td>
</tr>
<tr>
<td>6</td>
<td>0.0184 ± 0.0214</td>
<td>−43.29 ± 10.72</td>
</tr>
</tbody>
</table>

Mean ± S.D.

where \(X_u(t), \dot{X}_u(t), E(t)\) are the cumulative amount of drug excreted in urine, the instantaneous urinary excretion rate of drug and the diuretic rate at time \(t\) after drug administration, respectively. \(A, s\) and \(Q\) are parameters of Hill's equation and \(T\) is the cessation time of the pharmacologic effect (duration of diuretic effect). The derivation of Eq. 1 is given in Appendix 2.

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 Eq. 1 and to the following five equations (Eqs. 2–6). The results are summarized in Table III.

Linear equation:

\[
E(t) = SX_u(t) - A
\]  \hspace{1cm} (2)

Semi-logarithmic equation:

\[
E(t) = S \log \dot{X}_u(t) - A
\]  \hspace{1cm} (3)

Full-logarithmic equation:

\[
E(t) = A \dot{X}_u(t)^s
\]  \hspace{1cm} (4)

Logistic equation:

\[
E(t) = \frac{A \exp[\dot{X}_u(t)^s]}{Q + \exp[\dot{X}_u(t)^s]}
\]  \hspace{1cm} (5)

Hill’s equation:

\[
E(t) = \frac{A \dot{X}_u(t)^s}{Q^s + \dot{X}_u(t)^s}
\]  \hspace{1cm} (6)

In the above five equations, \(A, Q\) and \(S\) are relevant parameters; \(\dot{X}_u(t)\) and \(E(t)\) are as defined above.

For subject 5 after oral administration of 40 mg furosemide, the relationships of \(E(t)\) and \(\dot{X}_u(t)\) and time course of \(E(t)\) were simulated by Eqs. 1 and 6 (Hill's equation), respectively (Figs. 2 and 5).

From Table III, Figs. 4 and 5, it is clear that Eq. 1 which includes the body regulatory function describes the relationship of diuretic effect and disposition of furosemide in man more accurately than other experiential equations.

CONCLUSION

In our experiments with furosemide, the subjects were supplied small amounts of water in the entire experimental period. In this experimental condition some interesting phenomena, such as a clockwise hysteresis and an identical duration of pharmacologic effect, independent

![FIG. 5. Time Course of Diuretic Response to Furosemide (Subject 5, Dose 40 mg p.o.)](image)

The solid curve represents the results of least squares computer-fitting of Eq. 1 of observed data, while dotted line shows results of fitting to Hill's equation. Pharmacokinetic parameters are as shown in the caption of Fig. 2.
of the given dose, were observed. These phenomena revealed that the body regulatory system intervened in the pharmacodynamics of furosemide. Taking into consideration the influences of the body regulatory system, an equation was derived which characterized the time course of the body regulation function as well as of drug effect, simultaneously. The quantitative correlation of diuretic response and disposition of furosemide in man can be satisfactorily described by the equation.

APPENDIX 1

Based on a report by Arita et al., 7) the proximal tubular load of a drug (GFR · C) is the sum of the amounts filtered (GFR · Pt) and the net amount secreted (S). Consequently, the following equation describes the concentration of the drug in the proximal tubule,

\[ C = P_t + S/GFR \]  

(1a)

where \( C \) is the tubular drug concentration, \( P_t \) is plasma concentration of unbound drug, \( S \) is secretion rate of drug in the tubule and GFR is the glomerular filtration rate.

For urinary excretion rate, the following equation is derived,

\[ \frac{dX_u}{dt} = (GFR · P_t + S) (1 - f_e) \]  

(2a)

where \( dX_u/dt \) represents urinary excretion rate of drug and \( f_e \) is the fraction of drug reabsorbed in the proximal tubule.

From Eqs. 1a and 2a, the final equation which describes the relationship of tubular drug concentration and urinary excretion rate of drug is obtained,

\[ C = \frac{1}{(1 - f_e) · GFR} \frac{dX_u}{dt} \]  

(3a)

From Eq. 3a, it is obvious that \( C \) is proportional to \( dX_u/dt \) provided \( f_e \) and GFR are constant. Therefore, \( dX_u/dt \) is a good measure for drug concentration in the tubule.

APPENDIX 2

According to hypotheses 1, 2 and 3 in the text, the relationship of \( E(t) \), \( X_u(t) \) and \( \dot{X}_u(t) \) is assumed by Eq. 4a.

\[ E(t) = \frac{A_1 \dot{X}_u(t)^s}{Q_1^s + \dot{X}_u(t)^s} - \frac{A_2 X_u(t)^s}{Q_2^s + X_u(t)^s} \]  

(4a)

In the right-hand side of Eq. 4a, the first term is a Hill's equation representing the drug effect and the second term is another Hill's equation describing the body regulative function. The first term minus the second term yields the apparent net effect \( E(t) \). \( A_1, A_2, Q_1, Q_2 \) and \( S \) are relevant parameters of the two Hill's equations. We assumed the \( s \)'s of the two Hill's equations are identical for simplicity.

Substituting the cessation time of the effect (duration of pharmacologic effect), \( T \) in the variable \( t \) of Eq. 4a, the left-hand side, \( E(t) \) becomes zero, and therefore,

\[ \frac{A_1 \dot{X}_u(T)^s}{Q_1^s + \dot{X}_u(T)^s} = \frac{A_2 X_u(T)^s}{Q_2^s + X_u(T)^s} \]  

(5a)

From hypothesis 4, the duration of the pharmacologic effect is the same if the dose amount is multiplied by \( P^{1/s} \) and Eq. 6a is obtained, which is rearranged as shown as Eq. 7a.

\[ \frac{A_1 \left[ P^{1/s} \dot{X}_u(T)^s \right]}{Q_1^s + \left[ P^{1/s} \dot{X}_u(T)^s \right]} = \frac{A_2 \left[ P^{1/s} X_u(T)^s \right]}{Q_2^s + \left[ P^{1/s} X_u(T)^s \right]} \]  

(6a)

\[ \frac{A_1 P \dot{X}_u(T)^s}{Q_1^s + P \dot{X}_u(T)^s} = \frac{A_2 PX_u(T)^s}{Q_2^s + PX_u(T)^s} \]  

(7a)

The reciprocals of both sides of Eq. 5a yield Eq. 8a, which is rearranged to Eq. 9a.

\[ \frac{1}{A_1} \left[ \frac{Q_1}{\dot{X}_u(T)} \right]^s + \frac{1}{A_1} = \frac{1}{A_2} \left[ \frac{Q_2}{X_u(T)} \right]^s + \frac{1}{A_2} \]  

(8a)

\[ \frac{1}{A_1} \left[ \frac{Q_1}{\dot{X}_u(T)} \right]^s = \frac{1}{A_2} \left[ \frac{Q_2}{X_u(T)} \right]^s + \frac{1}{A_2} - \frac{1}{A_1} \]  

(9a)

Taking reciprocals from both sides of Eq. 7a and rearranging, then, Eq. 10a is obtained.

\[ \frac{1}{A_1} \left[ \frac{Q_1}{P \dot{X}_u(T)} \right]^s + \frac{1}{A_1} = \frac{1}{A_2} P \left[ \frac{Q_2}{X_u(T)} \right]^s + \frac{1}{A_2} \]  

(10a)
Substituting the right-hand side of Eq. 9a into Eq. 10a and the rearrangement yields Eq. 11a.

\[
\frac{1}{A_2} \cdot \frac{Q_2}{X_u(T)} = \frac{1}{A_2} \cdot \frac{1}{A_1} + \frac{1}{A_1} 
\]

\[
\frac{1}{A_2} \cdot \frac{Q_2}{X_u(T)} = \frac{1}{A_2} + \frac{1}{A_1} 
\]  

(11a)

Upon simplification, Eq. 12a is obtained.

\[
\frac{(A_2 - A_1)(P - 1)}{A_1 A_2 P} = 0 
\]  

(12a)

Since \( P \) can represent any positive real number, Eq. 12a is reduced to Eq. 13a.

\[
A_2 = A_1 = A 
\]  

(13a)

Substitution of Eq. 13a in Eq. 8a yields Eq. 14a.

\[
Q_2 = \frac{X_u(T)}{X_u(T)} Q_1 
\]  

(14a)

Substituting Eqs. 13a and 14a into Eq. 4a and setting \( Q_1 = Q \), we obtain Eq. 15a, which is rearranged to yield the final equation identical to Eq. 1.

\[
E(t) = \frac{A X_u(t) s}{Q^s + X_u(t)^s} - \frac{A X_u(t) s}{\frac{X_u(T)}{X_u(T)} Q^s + X_u(t)^s} 
\]  

(15a)

Eq. 1 is defined only within the duration of the pharmacologic effect \( t < T \). If time \( t \) is greater than \( T \), then \( E(t) \) is considered equal to zero.

REFERENCES


