Pharmacokinetic and Pharmacodynamic Studies of Piretanide in Rabbits. III. Sodium and Potassium Excretion under Different Hydrated Conditions

Wei LU, Makiko ENDOH, Kazunori KATAYAMA, Masawo KAKEMI* and Tamotsu KOIZUMI

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama, 930-01, Japan

(Received October 5, 1987)

The diuretic effect of piretanide, one of the loop diuretics, was investigated in three different hydrated conditions, namely well hydrated condition (treatment I), progressive hydropenic condition (treatment II) and complete hydropenic condition (treatment III) in rabbits. Each rabbit received intravenous administration of 1.5 or 15 mg/kg of piretanide and the urine flow rate, the excretion rates of Na and K, plasma concentrations of Na and K, urine osmolarity, plasma concentration of piretanide and urinary excretion of piretanide were determined after administration. The pharmacokinetics of piretanide was not influenced by the hydration state of the body, even in treatment III. The diuretic effect of piretanide evaluated by both urine flow rate (E_{H_2O}) and Na+K excretion rate (E_{Na+K}), was significantly affected by the hydration state of the body. The more the hydropenic state was developed, less amounts of urine or electrolytes were excreted. A pharmacokinetic-pharmacodynamic link model which was proposed in the previous paper was applied to the present experimental results. The result indicated that the diuretic effect, even in the complete hydropenic condition (treatment III), was reasonably described by the model, with minor modifications. The time course of the excretion rate of K (E_K) was not always in parallel with E_{Na+K} , but was dependent on treatments. We found that the K-fraction, which was known as an indicator of the Na-K exchange reaction in the distal tubule, was quantitatively related to E_{Na+K} , using a simple equation. Accordingly, the time course of E_K was also calculated. The result also indicated that time courses of E_K were described reasonably well by the model, regardless of treatments and doses.

Keywords — piretanide; diuretic; pharmacokinetics; pharmacodynamics; hydration; hydropenia; sodium excretion; potassium excretion

Introduction

Recently, extensive investigation has demonstrated that the time course of the pharmacologic effect of diuretics is closely related to the hydration state of the body.¹⁾ The increase in urine flow or the urinary excretion rate of electrolytes after administration of loop diuretics to the normal animals, including man, rapidly decreases unless fluid replacement is made. It has also been reported that the maximum pharmacologic response intensity of the urine flow rate or excretion rates of Na and K after administration of loop diuretics was not always dependent on the dose and that the decline of each pharmacologic response did not always parallel one another.^{2a)} A sudden drop of urine osmolarity^{2b)} and hypokalemia³⁾ as well as fluid and electrolyte imbalance after the loop diuretics adminis-

tration were often reported clinically and these facts indicate that the loop diuretics should be used with caution. However, the quantitative and kinetic aspects of the physiological conditions of the body to diuretics have rarely been investigated.

In previous papers,^{1b,c)} we investigated the effect of piretanide, one of the loop diuretics, under three different physiological conditions, namely, well hydrated, progressive hydropenic and complete hydropenic conditions, in rabbits. The results suggested that the pharmacologic response intensity was decreased in accordance with the hydropenic state which was developed in the body during diuresis. We introduced a pharmacokinetic (PK)-pharmacodynamic (PD) link model to describe the effect of piretanide in the rabbit, and the results obtained revealed that the effect of piretanide on the well hydrated and

* To whom correspondence should be addressed.

progressive hydropenic conditions in rabbits was reasonably described by the model. In the present study, we modified the previous PK-PD model in order to apply the effect of piretanide on rabbits even in complete hydropenic conditions. The purpose of this investigation was to verify the applicability of the modified PK-PD link model to describe piretanide action in three different hydrated conditions in rabbits.

Materials and Methods

Chemicals — Piretanide (Hoechst Japan Ltd., Tokyo), bumetanide (Sankyo Co., Tokyo) and antidiuretic hormone (ADH, [Arg⁸]-vasopressin, Sigma Chemical Co., St Louis, Mo) were obtained commercially and were used without further purification. All other reagents used in the experiment were reagent grade and were also obtained commercially.

Animal Experiments — Male albino rabbits (Shizuoka Laboratory Animal Center, Hamamatsu, Japan) weighing 3.6 to 4.1 kg were used in the experiment. Piretanide was dissolved in isotonic sodium chloride solution (JP XI, Otsuka Pharmaceuticals, Tokyo, Japan) and was administered *via* the right marginal auricular vein within 30 s, in a dose level of 1.5 or 15 mg/kg. The diuretic effect of piretanide was investigated under three different hydrated conditions in the rabbit.

(a) Well Hydrated Condition (Treatment I): The rabbits received a constant rate of infusion of isotonic Ringer's solution at the rate of 100 mg/h before and after piretanide administration. After reaching a steady-state urine flow, piretanide was administered. The amount of the body fluid which was lost during diuresis was replaced by infusing Ringer's solution at exactly the same rate with the urine flow using an extra infusion pump.

(b) Progressive Hydropenic Condition (Treatment II): The rabbits also received a constant rate of infusion of isotonic Ringer's solution in the same manner as in treatment I; however, no compensatory infusion was made after piretanide administration.

(c) Hydropenic Condition (Treatment III):

The rabbits received a simultaneous constant infusion of hypertonic saline solution (804 mOsm/l, at the rate of 50 ml/h) and ADH (33.2 mU/kg/h) under urethane anesthesia. After reaching the steady-state urine flow, piretanide was administered, and the infusion was continued until the end of the experiment. The urine samples were collected through a urinary catheter indwelling in the bladder (treatments I and II) or through the ureteral cannula (treatment III). The blood samples were withdrawn from the left marginal auricular vein. Details of the experimental procedure for the animal treatment were described previously.^{1b,c)}

Analytical Methods — Plasma and urinary concentrations of piretanide were determined by a high performance liquid chromatography (HPLC) method,^{1b)} and the sodium and potassium concentrations in plasma and urine were assayed by flamephotometry.^{1c)} The osmolarity of plasma and urine was determined by a freezing-point depression method.^{1c)}

Data Analysis — The concentration-time or amount-time data were analyzed by a non-linear regression program based on the algorithm of Gauss-Newton and Berman^{1b)} using a PDP11/34 mini-computer (Digital Equipment Corp., Maynard, Mass). The weighing value and the condition of convergency were as described in previous reports.^{1b,c)}

Theoretical

(1) Pharmacokinetic Model

Plasma concentrations and urinary excretion rates of unchanged piretanide after i.v. administration in rabbits were described by a linear three compartment open model as shown in following equations.

$$C_p = \sum_{i=1}^3 C_i e^{-\lambda_i t} \quad (1)$$

$$\frac{dX_u}{dt} = C_p CL_r \quad (2)$$

Where C_p is the plasma concentration of piretanide, C_i and λ_i are the constant and the rate constant of linear compartment model, respectively, dX_u/dt is the urinary excretion rate and

Fig. 1. Diagrammatic Representation of the PK-PD Link Model

CL_r is the renal clearance of piretanide. The concentration of piretanide in the hypothetical effect compartment is described by Eq. 3.

$$D = k_{eo} \sum_{i=1}^3 C_i \frac{(e^{-\lambda_i t} - e^{-k_{eo} t})}{k_{eo} - \lambda_i} \quad (3)$$

Where k_{eo} is the elimination rate constant from the hypothetical effect compartment.^{1b)} Schematic representation of the model is shown in Fig. 1.

(2) Pharmacodynamic Model on the Excretion Rate of Na + K

The relationship between the excretion rate of Na and K and the concentration of piretanide in the effect compartment was described by Hill's equation with basal effect, as shown in Eq. 4.

$$E_{Na+K,j} = f_j \left(E_0 + \frac{E_{max} D^r}{ED_{50}^r + D^r} \right) (j = 2, \text{ or } 3) \quad (4)$$

Where $E_{Na+K,j}$ is the diuretic effects of piretanide, expressed by the sum of the sodium and potassium excretion rates and j is the treatment number (1: treatment I, 2: treatment II, 3: treatment III). E_{max} is the maximum effect, ED_{50} is a hypothetical biophase concentration at 50% of maximum effect, E_0 is the basal value of the excretion rate of Na + K and r is the Hill's constant. f_j is the modification factor in respect to the hydration state of the body.

(3) Calculation of the Modification Factor f_j

The modification factor f_j is closely related to

the water balance in the body, and it is expressed by a Langmuir type equation, as follows.

$$f_j = 1 - \frac{K_1 CE_{H_2O,j}}{K_2 + CE_{H_2O,j}} (j = 1, 2 \text{ or } 3) \quad (5)$$

Where $CE_{H_2O,j}$ is the net loss of water in the body during the experiment and K_1 and K_2 are the constants. In the case of treatment I, there is no net loss or gain of water before and after piretanide administration, therefore f_1 is assumed to be unity. In the case of treatment II, $CE_{H_2O,2}$ is expressed by Eq. 6.

$$CE_{H_2O,2} = \int_0^t (E_{H_2O,2} - \text{Inf}_2) dt \quad (6)$$

Where Inf_2 is the infusion rate of Ringer's solution, $E_{H_2O,2}$ is the excretion rate of water (urine flow rate) during piretanide administration. Inf_2 is constant during treatment II. As shown in Fig. 2, the relationship between urinary excretion rate of Na + K and urine flow rate is linear over a wide range tested, and therefore, $E_{H_2O,2}$ is expressed by Eq. 7.

$$E_{H_2O,2} = A_2 + B_2 E_{Na+K,2} \quad (7)$$

Where B_2 and A_2 are the slope and the intercept of the graph, respectively.

In treatment III, the f value is calculated by Eq. 8.

$$CE_{H_2O,3} = \int_0^t (E_{H_2O,3} - \text{Inf}_3) dt + K_3 (T + t) \quad (8)$$

Where K_3 is a proportionality constant reflecting the effect of ADH and hypertonic saline infusion and T is the duration of the infusion before piretanide administration. Accordingly $K_3 T$ reflects the hydropenic condition of the body before medication, in treatment III. Inf_3 in Eq. 8 represents the infusion rate of hypertonic saline. Since the slope and intercept of the graph of the urinary excretion rate of Na + K *versus* urine flow rate relationship in treatment III was significantly different from that in treatment II, $E_{H_2O,3}$ is calculated by Eq. 9.

$$E_{H_2O,3} = A_3 + B_3 E_{Na+K,3} \quad (9)$$

Fig. 2. The Relationship between Urine Flow Rate and Excretion Rate of Na + K

I: treatment I, II: treatment II, III: treatment III. Each value shown is the mean $\pm$ S.E. and the solid lines in the figures are the regression lines. Each of the slope (B) and intercept (A) are as follows; I: $B = 8.06$ ml/meq $A = -9.08$ ml/h, II: $B = 8.06$ ml/meq $A = -9.08$ ml/h, III: $B = 6.47$ ml/meq $A = -20.4$ ml/h.

Where B_3 and A_3 are the slope and the intercept of the graph, respectively.

(4) Pharmacodynamic Model on the K-Fraction

The effect of piretanide on the K-fraction, which is defined by the fraction of potassium urinary excretion rate divided by sum of the excretion rates of sodium and potassium, is described by Eq. 10.

$$E_{K/(Na+K),j} = f'_j \left(\frac{K_4}{E_{Na+K,j}} \right)^{K_5} \quad (j=1, 2 \text{ or } 3) \quad (10)$$

Where K_4 and K_5 are constants and f'_j is another modification factor referred to the hydration state of the body, which is calculated by Eq. 11.

$$f'_j = 1 - \frac{K_6 CE_{H_2O,j}}{K_7 + CE_{H_2O,j}} \quad (j = 1, 2 \text{ or } 3) \quad (11)$$

Where K_6 and K_7 are the constants. In the case of treatment I, f'_1 value is unity because $CE_{H_2O,1}$ is considered to be zero. By definition, urinary excretion rate of potassium is calculated by Eq. 12.

TABLE I. Comparison of Pharmacologic Response Intensity of Piretanide after i.v. Administration in Rabbits with Different Hydrated Conditions ^{a)}

	1.5 mg/kg			15 mg/kg		
	I	Treatment II	III	I	Treatment II	III
I_{H_2O}	5.92 ± 1.10	0.454 ± 0.645	0.458 ± 1.08	17.5 ± 4.46	3.10 ± 0.93	7.45 ± 2.54
I_{Osm}	5.90 ± 0.33	1.20 ± 0.20	-1.20 ± 0.45	15.8 ± 2.07	3.25 ± 0.68	1.46 ± 0.77
I_{Na}	4.65 ± 0.47	1.24 ± 0.81	-0.430 ± 0.525	14.0 ± 2.3	4.53 ± 0.95	1.86 ± 0.53
I_K	3.75 ± 1.99	0.435 ± 0.560	0.616 ± 0.763	7.54 ± 0.86	2.52 ± 0.62	3.27 ± 0.54

^{a)} Each value of the data is shown as the mean $\pm$ S.D. and the number of animals used in each treatment is indicated as shown in the legend of Fig. 3.

TABLE II. List of Basal Values in Three Different Hydrated Conditions in Rabbits

	Treatment I and II ^{a)}	Treatment III ^{b)}
$E_{H_2O}^0$ (ml/h)	82.8 ± 14.4	31.8 ± 19.2 ^{c)}
E_{Osm}^0 (mOsm/h)	24.1 ± 3.5	20.2 ± 10.3
E_{Na}^0 (meq/h)	9.31 ± 1.24	8.37 ± 4.93
E_K^0 (meq/h)	1.08 ± 0.20	0.378 ± 0.162 ^{c)}

^{a)} Each value of the data is shown as the mean ± S.D. ($n=16$).
^{b)} Each value of the data is shown as the mean ± S.D. ($n=8$).
^{c)} $p < 0.001$.

$$E_{K,j} = E_{K/(Na+K),j} E_{Na+K,j} \quad (j=1, 2 \text{ or } 3) \quad (12)$$

Results and Discussion

Table I shows the comparison of the pharmacologic response intensities among three different experimental conditions after i.v. administration of piretanide in rabbits. The pharmacologic response intensity up to 6 h after the administration (I) was calculated by Eqs. 13 through 16, as the area under the relative pharmacologic effect-time curve.

$$I_{H_2O} = \int_0^6 \frac{E_{H_2O} - E_{H_2O}^0}{E_{H_2O}^0} dt \quad (13)$$

$$I_{Osm} = \int_0^6 \frac{E_{Osm} - E_{Osm}^0}{E_{Osm}^0} dt \quad (14)$$

$$I_{Na} = \int_0^6 \frac{E_{Na} - E_{Na}^0}{E_{Na}^0} dt \quad (15)$$

$$I_K = \int_0^6 \frac{E_K - E_K^0}{E_K^0} dt \quad (16)$$

Where E_{Osm} , E_{Na} and E_K are the urinary excre-

Fig. 3. Effect of Piretanide on the Concentrations of Plasma Na and K

○, plasma Na concentration (meq/l); □, plasma K concentration (meq/l). Upper figures represent 1.5 mg/kg dose studies and the lower figures represent 15 mg/kg dose studies. Each value shown is the mean ± S.E. and the number of animals used in each treatment is indicated as follows; treatment I: 1.5 mg/kg ($n=3$), 15 mg/kg ($n=3$) treatment II: 1.5 mg/kg ($n=5$), 15 mg/kg ($n=6$), treatment III: 1.5 mg/kg ($n=4$), 15 mg/kg ($n=4$).

tion rates of osmotic substances, sodium and potassium, respectively. The superscript 0 represents the basal value of each response, which was obtained experimentally as the premedication level (before piretanide administration). The basal values of each response are listed in Table II. The I_{H_2O} value in treatment I at 15 mg/kg dose study was the largest and the values in treatments II and III decreased significantly in that order. Similar results were observed in the other pharmacologic response intensities, regardless of dose. These results suggest that the pharmacologic effects after piretanide administration were closely related to the hydration state of the body and that the more the hydropenic state progressed in the body, the more the pharmacologic response intensities decreased.

As shown in the previous papers,^{1b,c)} prominent but temporal increases in E_{H_2O} , E_{Osm} and E_{Na+K} were observed just after piretanide i.v. administration in treatments II and III; however, the pharmacologic effects rapidly decreased thereafter. This phenomenon was reasonably expressed by the effect of the feedback system which was activated by the loss of water and electrolytes from the body during diuresis.^{1b)}

Figure 3 shows the effect of piretanide on the plasma Na and K concentrations in the three different experimental conditions. Plasma Na concentrations after piretanide administration in treatments I and II showed a marginal increase compared to premedication levels; however, they were significantly increased by piretanide administration in treatment III. Plasma K concentrations were not influenced by piretanide administration, regardless of treatments. These results indicate that the concentrations of plasma electrolytes were strictly controlled by the body fluid regulation system in the normal condition (treatments I or II), and that small changes in water or electrolyte contents in the body which were caused by administration of diuretics did not affect plasma concentrations. In treatment III, the basal level of Na was significantly greater than the normal (pre-infusion) level, and the basal level of K was significantly lower than normal level. This fact indicates that the hypertonic saline infusion in treatment III exceeded the controllable range of plasma concentrations of electrolytes, and this might be the reason for the high basal value of plasma Na. The low basal level of plasma K in treatment III might be attributable to the Na-K exchange reac-

Fig. 4. Effect of Piretanide on the Excretion Rate of Na+K in Different Hydration State in Rabbits

Upper figures represent 1.5 mg/kg dose studies and the lower figures represent 15 mg/kg dose studies. Each value shown is the mean $\pm$ S.E. and the number of animals used in each treatment is indicated in the legend of Fig. 3. The solid lines in the figures are the calculated values according to the Eqs. 1 to 9 in the text.

tion in the distal tubule under high Na concentration; however, its precise mechanism is unknown and further investigation is required.

Figure 4 shows the time courses of E_{Na+K} before and after piretanide administration in treatments I, II and III. In each hydration condition, the maximum excretion rate was similar to the two doses used, but the duration of the effect in the 15 mg/kg dose study was much longer than that of the 1.5 mg/kg dose study. The hydration state of the body affected the E_{Na+K} distinctly. The more the hydropenic condition progressed, the less Na + K was excreted.

The time courses of E_K after piretanide administration are shown in Fig. 5. Although the excretion pattern of K in each treatment appeared to be similar to that of Na + K, they were different from each other. In order to clarify the difference, K-fraction in each dose and in each treatment were calculated and were plotted against the respective E_{Na+K} . As shown in Fig. 6 the relationship between E_{Na+K} and K-fraction before (open symbols) and after (closed symbols) piretanide administration showed a hyperbola-like curve, regardless of treatments. The K-fraction values after piretanide administration decreased as the excretion rates of

Na + K increased and their values finally returned to the respective premedication levels. This result indicates that K-fraction was dependent on both E_{Na+K} and the hydration state in the body, and that the Na-K exchange reaction in the distal tubule could not be explained by a simple linear relationship.

In the previous paper,^{1b)} we demonstrated that the diuretic effect of piretanide in both well hydrated (treatment I) and progressive hydropenic (treatment II) conditions in rabbits was reasonably described by a pharmacokinetic-pharmacodynamic link model, including a feedback mechanism in respect to the body fluid depletion. In the present study, the model was modified in order to respond to the effect of piretanide even in the entirely hydropenic condition (treatment III). The solid lines in Fig. 4 through Fig. 6 represent the calculated values according to the model described in the theoretical section, and the parameter values used in the calculation are listed in Table III. Since plasma concentrations of piretanide were not influenced by the hydration state of the body even in the complete hydropenic condition (treatment III),^{1c)} all of the pharmacokinetic parameters were taken from the previous report.^{1b)} The pharma-

Fig. 5. Effect of Piretanide on the Excretion Rate of K in Different Hydration State in Rabbits

Upper figures represent 1.5 mg/kg dose studies and the lower figures represent 15 mg/kg dose studies. Each value shown is the mean $\pm$ S.E. and the number of animals used in each treatment is indicated in the legend of Fig. 3. The solid lines in the figures are the theoretical values calculated by Eq. 12 in the text.

Fig. 6. The Relationship between K-Fraction and E_{Na+K} in Different Hydrated Conditions in Rabbits

○, before piretanide administration; ●, after piretanide administration. Upper figures represent 1.5 mg/kg dose studies and the lower figures represent 15 mg/kg dose studies. Each value shown is the mean $\pm$ S.E. and the number of animals used in each treatment is indicated in the legend of Fig. 3. The solid lines in the figure are the regression lines according to Eq. 10 in the text.

TABLE III. List of Pharmacokinetic and Pharmacodynamic Parameters

Parameter	Estimate $\pm$ S.D.	Parameter	Estimate $\pm$ S.D.
Pharmacokinetic parameters ^{a)}			
C_1 ($\mu\text{g/ml}$)	11.3 ± 3.1	λ_1 (h^{-1})	10.4 ± 2.23
C_2 ($\mu\text{g/ml}$)	0.490 ± 0.30	λ_2 (h^{-1})	2.25 ± 0.95
C_3 ($\mu\text{g/ml}$)	0.017 ± 0.0165	λ_3 (h^{-1})	0.319 ± 0.152
CL_r (ml/h)	1090 ± 108		
k_{eo} (h^{-1})	13.2 ± 4.9		
Hill's constants			
E_0 (meq/h)	7.80 ± 2.21	$E_{\max}$ (meq/h)	49.2 ± 3.9
r	0.660 ± 0.107	ED_{50} ($\mu\text{g/ml}$)	0.170 ± 0.036
Physiological and pharmacodynamic parameters			
K_1	0.580 ± 0.022	K_2 (ml)	99.6 ± 23.3
A_2 (ml/h)	-9.08	B_2 (ml/meq)	8.06
A_3 (ml/h)	-20.4	B_3 (ml/meq)	6.47
K_4 (meq/h)	0.0188 ± 0.0051	K_5	0.340 ± 0.012
K_6	0.569 ± 0.025	K_7 (ml)	1110 ± 300
Parameters in respect to the fluid infusion			
Inf_2 (ml/h)	100.0	Inf_3 (ml/h)	50.0
K_3 (ml/h)	907 ± 676	T (h)	3.50

^{a)} These parameter values were taken from the previous report. ^{1b)}

codynamic parameters in respect to Hill's equation were fundamentally identical with that in the previous report.^{1b)} As shown in each graph, the calculated values were coincided reasonably well with the experimental data.

The relationship between the $CE_{H_2O,j}$ and the f value or the $CE_{H_2O,j}$ and the f' value was expressed by the Langmuir equation, as shown in Eqs. 5 and 11 in the theoretical section, and this model is fundamentally the same as that used in the previous report.^{2b)} In order to describe the relationship between the $CE_{H_2O,j}$ and the f value quantitatively, we examined several equations, such as linear, log-linear and Hill's. The results of curve fitting indicated that Hill's equation gave the smallest value of the sum of the squares, however, the value of Hill's constant tended to be unity. Thus, we used the Langmuir equation instead of Hill's equation, in the series of the investigation. We, therefore, do not claim that this equation is a unique way to describe the relationship between $CE_{H_2O,j}$ and f but this equation can describe the relationship in the simplest manner. Although CE_{H_2O} values instead of CE_{Na+K} values were used in the present study, the time course of f_2 value was similar to that in the previous report.^{1b)}

On the other hand, the time course of the f_3 value was different from that of the previous report, because the hyperosmotic saline infusion itself induced a hydropenic state in rabbits. Although a linear relationship between E_{H_2O} and E_{Na+K} still existed during treatment III (as shown in Fig. 2), the relationship between the cumulative amount of Na+K in the body and the development of the hydropenic state during hyperosmotic saline infusion was too complex to explain mathematically. Therefore, in the present study, CE_{H_2O} was approximated by a linear function, shown in Eq. 8. The second term of Eq. 8 reflects the effect of ADH and hyperosmotic saline infusion on the balance of the body water, as a function of time. The calculated curves shown in Fig. 4 described the time courses of E_{Na+K} regardless of treatments and doses. These results indicated that the development of the hydropenic condition caused by ADH and hyperosmotic saline infusion could be approximated by a simple linear equation and

that the effect of the hydropenic condition on the diuretic effect of piretanide in treatment III was fundamentally the same as in treatment II.

The relationship between K-fraction and E_{Na+K} was approximated by a hyperbolic equation, as shown in Eqs. 10 and 11 in the theoretical section. We reported previously that K-fraction could be related to E_{Na+K} using a log-linear function in the furosemide study.⁴⁾ We also applied this log-linear function to the piretanide study; however, the application was not successful. This result indicates that the mode of action of piretanide on the Na-K exchange reaction in the distal tubule might be different from that of furosemide. The precise mechanism of this is unknown and thus requires further investigation. In the calculation of K-fraction, we assumed another modification factor f' (Eq. 11) as shown in the theoretical section. Since the time courses of the effect of hydropenic conditions on E_{Na+K} and $E_{K/(Na+K)}$ were slightly different from each other, this assumption might be appropriate.

In spite of the simplicity of the model employed, the diuretic effect of piretanide in different physiological conditions could be reasonably described by a single PK-PD link model. We trust that the present results using piretanide will be of assistance in the preparation of a better dosage schedule.

References

- 1) a) T. Li, M. G. Lee and W. L. Chiou: Effect of the rate and composition of fluid replacement on the pharmacokinetics and pharmacodynamics of intravenous furosemide, *J. Pharmacokinetic. Biopharm.*, **14**, 495–509 (1986); b) W. Lu, M. Endoh, K. Katayama, M. Kakemi and T. Koizumi: Pharmacokinetic and pharmacodynamic studies of piretanide in rabbits. I. Effect of different hydrated conditions, *J. Pharmacobio-Dyn.*, **10**, 356–363 (1987); c) *Idem*: Pharmacokinetic and pharmacodynamic studies of piretanide in rabbits. II. Effects on the proximal tubules and the loop of Henle, *ibid.*, **11**, 95–105 (1988).
- 2) a) U. B. Olsen: Observation of the early diuretic response after intravenous administration of bumetanide and furosemide in dogs, *Acta Physiol. Scand.*, **93**, 195–201 (1975); b) *Idem*: Indomethacin inhibition of bumetanide diuresis in dogs, *Acta Pharmacol. Toxicol.*, **37**, 65–78 (1975).
- 3) a) A. Alvestrand and J. Bergstrom: The effect of

- HOE118 (piretanide) on muscle electrolytes in normal subjects, *Curr. Ther. Res.*, **25**, 786—790 (1979); *b*) W. Flamenbaum: Diuretic use in the elderly: Potential for diuretic-induced hypokalemia, *Am. J. Cardiol.*, **57**, 38A—43A (1986).
- 4) S. Fukuchi, K. Katayama, M. Kakemi, M. Ueda and T. Koizumi: Biological effect of furosemide in relation to its disposition in rabbits, *Chem. Pharm. Bull.*, **25**, 2217—2224 (1977).