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Research Article

Optimization of the Therapeutic Index by Adjustment of the Rate of Drug Administration or Use of Drug Combinations: Exploratory Studies of Diuretics

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The purpose of this investigation was to explore theoretically certain strategies for optimizing the therapeutic index of drugs and to assess these strategies experimentally with two diuretics. Diuretic agents allow dosing rate flexibilities because the temporal profile of diuretic action can vary considerably as long as the total diuretic effect per day is the same. They can also be used in combination. Experiments were designed to determine if the therapeutic index of furosemide and hydrochlorothiazide can be optimized by administering one or the other at a certain rate or by administering the two drugs together in a certain ratio and at a certain rate. Male Lewis rats received one or the other drug, or combinations of the two, by i.v. infusion at different rates. Several timed urine collections were made under steady-state conditions, with excreted urine replaced volume for volume by i.v. lactated Ringer's solution. The urine flow rates and the urinary excretion rates of the diuretics and of Na^+ and K^+ were determined. The relationship between the diuretic effect of either of the two drugs given alone and the respective drug excretion rate could be described by the Hill equation. The ratio of urine flow rate to K^+ excretion rate exhibited a marked dependence on hydrochlorothiazide excretion rate (highest ratio at high excretion rates), whereas the K^+/Na^+ excretion rate ratio was constant over a wide range of hydrochlorothiazide excretion rates. There was no significant change of these ratios with changing excretion rate of furosemide. Infusion of the two diuretics in combination of different ratios and at different combined rates under steady-state conditions revealed proportionality between the urinary excretion rates of Na^+ and urine over a wide range and a decreasing K^+/urine excretion rate ratio with increasing urine flow rate. Hence, a favorable increase in the Na^+/K^+ excretion rate ratio was attained with increasing urine flow rate. These experiments and computer simulations demonstrate in principle the feasibility of optimizing the therapeutic index by appropriate selection of a drug's dosing rate or by dosing a combination of two drugs at an appropriate ratio and rate.

KEY WORDS: hydrochlorothiazide; furosemide; Na^+, K^+; diuretic effect.

INTRODUCTION

The aim of drug therapy is clinical efficacy with relative safety. For this reason, prescribers prefer drugs that have a favorable therapeutic index. This property, reflected by the ratio of the intensities of therapeutic to adverse effects, may not be a constant but rather be dependent on drug concentration. For example, a drug may produce several different types of effects, each with its own characteristic concentration-intensity of effect relationship. Such a case is simulated in Fig. 1 (left panel); the three different relative intensity of effect versus concentration curves can be described by the Hill or sigmoid E_{max} equation (1):

$$E = \frac{E_{max}C^S}{EC_{50}^S + C^S} \quad (1)$$

with the same EC_{50} but different values for the exponent S. In the equation, E is the intensity of the effect, E_{max} is the maximum attainable intensity of effect, C is the drug concentration, EC_{50} is the drug concentration that elicits one-half the intensity of the maximum effect, and S is a constant that defines the sigmoidicity of the relationship. The right panel in Fig. 1 shows the ratio of the intensities of effects A and B and also the ratio of the intensities of effects C and B as a function of drug concentration. Were one to define B as the therapeutic effect and A as well as C as adverse effects, then it is evident that (a) the therapeutic index is drug concentration dependent and (b) this concentration dependence relates to differences in the relevant concentration-intensity of effect relationships.

In the left panel in Fig. 2 are shown simulations of three other relative intensity of effect versus drug concentration curves, differing only in the value of EC_{50}. The drug concentration dependence of the effect intensity ratios A/B and C/B is illustrated in the right panel in Fig. 2. Obviously, there can also be cases in which EC_{50} and S change concurrently. Finally, the effect of a change in E_{max} on the intensity of

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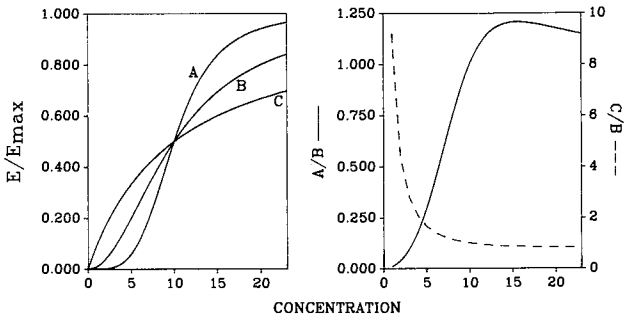

Fig. 1. Effect of the Hill equation exponent S on the relationship between the concentration at the effect site and the ratio of the relative intensities of different pharmacologic effects of a hypothetical drug. Left: Simulated relative effect intensity versus concentration profiles of a drug having three different types of effects (A, B, and C). The Hill equations describing these relationships have the same EC_{50} (10 concentration units) but different S values: four (for A), two (for B), and one (for C). Right: Relationship between the drug concentration and the ratio A/B and C/B, respectively.

effect versus drug concentration relationship, with EC_{50} and S being constant, is simulated in Fig. 3. In this case, the ratio of the intensity of pharmacologic effects does not change with the drug concentration. This is readily shown mathematically by dividing Eq. (1) for effect A by the same equation for effect B:

$$\frac{E_A}{E_B} = \frac{E_{maxA}}{E_{maxB}} \cdot \frac{EC_{50B}^{S_B} + C^{S_B}}{EC_{50A}^{S_A} + C^{S_A}} = \frac{E_{maxA}}{E_{maxB}} \cdot \text{constant} \qquad (2)$$

The subscripts A and B in Eq. (2) refer to the respective pharmacologic effects.

In many situations there are only limited possibilities to select a targeted drug concentration (and a corresponding rate of drug administration) to optimize the therapeutic index. The concentration must be sufficient to achieve a certain intensity of a therapeutic effect such as analgesia or blood pressure reduction. The associated intensity of adverse effects such as respiratory depression or sedation, for example, must be accepted, although the adverse effects may be dose-limiting. Much greater flexibility is available in

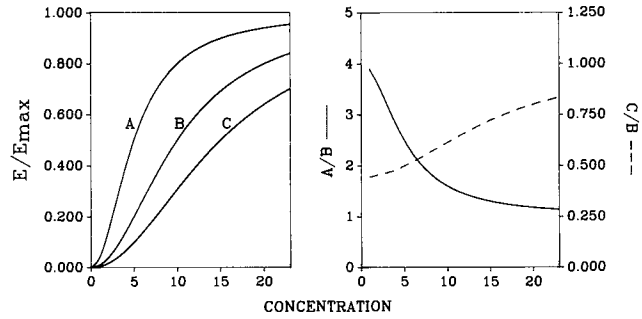

Fig. 2. Effect of the EC_{50} value of the Hill equation on the relationship between the concentration at the effect site and the ratio of the relative intensities of different pharmacologic effects of a hypothetical drug. See the legend to Fig. 1 for additional information. The S value is 2 in all cases and EC_{50} is 5 (for A), 10 (for B), and 15 (for C) concentration units.

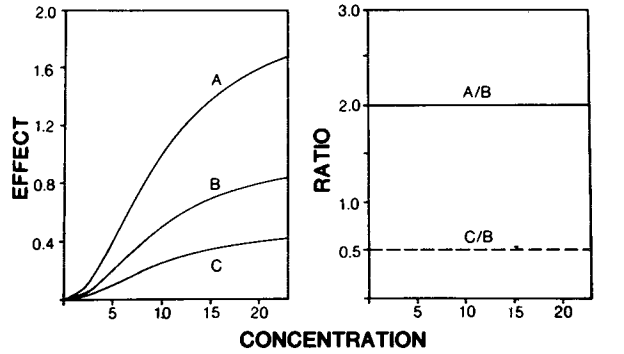

Fig. 3. Effect of the E_{max} value of the Hill equation on the relationship between the concentration at the effect site and the ratio of the relative intensities of different pharmacologic effects of a hypothetical drug. See the legend to Fig. 1 for additional information. The S value is 2 and the EC_{50} is 10 concentration units. The E_{max} is 2 (for A), 1 (for B), and 0.5 (for C) intensity of effect units.

the use of diuretics. These drugs can be administered in single or divided doses, at high rates over short periods of time daily, or at lower rates over longer periods of time daily as long as the total diuretic effect per day is adequate. Thus, there is an opportunity to optimize the therapeutic index of diuretics (achieve a high ratio of Na^+ and urine excretion to K^+ excretion) by administering these drugs singly at an appropriate rate or perhaps in combination at an appropriate ratio and total rate. These possibilities have been explored in principle in model studies of the diuretic effects of hydrochlorothiazide and furosemide alone as well as in combination.

MATERIALS AND METHODS

Inbred, male Lewis rats (LEW/CrlBR, Charles River Laboratories, Wilmington, MA), weighing 175 to 200 g when received, were used in this investigation. They had three indwelling cannulas implanted under light ether anesthesia 1 day before the experiment. Silastic cannulas were implanted in the right jugular vein (for drug infusion) and right femoral vein (for replacement of fluid); a PE-60 polyethylene catheter was inserted and fixed in the urinary bladder for continuous urine collection. Most of the bladder and the urethra were ligated to reduce dead space and prevent leakage, respectively.

In the morning of the experiment, food and water were removed, and the rats were weighed and then placed in individual plastic cages. Starting about 1 hr later, three successive timed (15-min) urine samples were obtained. The animals then received an infusion of hydrochlorothiazide, furosemide, or the two drugs in various combinations. Solutions of these drugs were prepared in lactated Ringer's solution, using dropwise addition of sodium hydroxide as necessary to obtain complete dissolution. An initial infusion rate of 0.0206 ml/min for 10 to 15 min was administered as a loading dose and was followed by an infusion rate of 0.0103 ml/min. Collection of three timed (15-min) urine samples commenced after 1 hr (the time found in preliminary experiments to be adequate for achieving steady-state conditions). The infusion rate was increased to 0.0501 ml/min (the next setting on the infusion pump) for 10 to 15 min and was then

reduced to 0.0206 ml/min. Three timed urine collections were made beginning 1 to 1.5 hr after the start of this infusion. The urine was collected in 1.5-ml plastic tubes and the fluid loss (urine volume minus the volume of drug solution infused during the collection period) was replaced during the subsequent collection period by slow i.v. injection of lactated Ringer's solution into the femoral vein. The urine volumes were determined accurately by weighing at the end of the experiment and aliquots were stored at −20°C for assay within 2 weeks.

Concentrations of Na^+ and K^+ in urine were obtained by atomic absorption spectrophotometry (Perkin–Elmer Model 603). The concentrations of furosemide and hydrochlorothiazide were determined by high-performance liquid chromatography as described by Kikkoji *et al.* (2) with minor modifications: the mobile phase of 29% methanol in 0.01 *M* sodium acetate was run at 1 ml/min, ultraviolet detection was at 280 nm, and caffeine (20 μg/ml in pH 5.0 phosphate buffer) was used as the internal standard. Retention times for hydrochlorothiazide, furosemide, and caffeine were about 4.2, 5.2, and 6.3 min.

Pharmacodynamic analysis was performed with the computer program NONLIN (3). Experimentally determined values of the baseline intensity of effect, the apparent E_{max} (the latter defined as the highest observed effect intensity), and the urine, Na^+, K^+, and drug excretion rates served as input and were weighted equally to determine apparent EC_{50} and S values of the modified Hill equation

$$\frac{E}{E_{max}} = \frac{C^S}{EC_{50}^S + C^S} + \frac{E_0}{E_{max}} \qquad (3)$$

where E_0 is the baseline intensity of effect. Simulations were also performed with NONLIN.

RESULTS

At the beginning of the experiment, the body weight of the rats was 228 ± 20 g (mean ± SD; n = 32). About 6 to 7 hr later, at the end of the experiment, the body weight was 223 ± 19 g, representing a weight loss of 2.34 ± 1.17%. The experimental studies were conducted in random order with respect to the diuretic treatment on 7 days between June 1 and July 18.

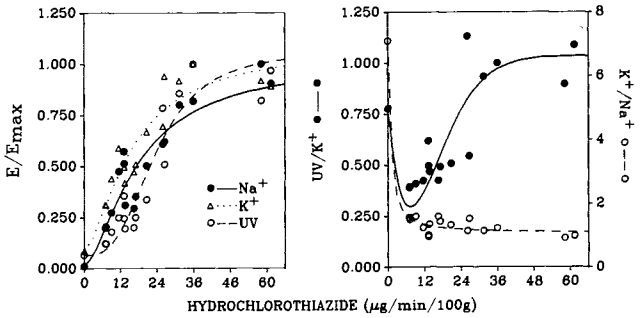

Fig. 4. Pharmacodynamics of the diuretic effects of hydrochlorothiazide in rats. Left: Relationship between relative diuretic effects and the urinary excretion rate of hydrochlorothiazide in three rats, each of which provided several timed urine samples while receiving infusions of the drug at two different rates. UV, urine flow rate. The curves were fitted to the data by nonlinear least-squares regression analysis based on the Hill equation. The parameters of the equations are listed in Table I. Right: Relationship between the urinary excretion rate of hydrochlorothiazide and the ratio of UV/K^+ and K^+/Na^+, respectively. The curves are the relationships derived from the drug excretion rate versus diuretic effect curves in the left panel. The symbols are the experimental data.

The results of the hydrochlorothiazide study are summarized in Fig. 4. Urine flow rate and the urinary excretion rates of Na^+ and K^+ increased with increasing urinary excretion rate of hydrochlorothiazide. The experimental data are well described by the Hill equation; the apparent Hill parameter values are listed in Table I. These parameter values were used to "predict" the relationship between the urine flow rate/K^+ ratio and the hydrochlorothiazide excretion rate as well as the relationship between the K^+/Na^+ ratio and the hydrochlorothiazide excretion rate. The experimentally obtained ratio values are in good agreement with the predicted relationships (Fig. 4). They show that the clinically most favorable UV/K^+ ratio (i.e., a high value) and the most favorable K^+/Na^+ ratio (a low value) are obtained at relatively high urinary excretion rates of hydrochlorothi-

Table I. Observed and Derived Hill Equation Parameters for the Diuretic Effects of Furosemide and Hydrochlorothiazide in Rats

Treatment	Parameter	Urinary excretion rate, $min^{-1} \cdot 100\ g^{-1}$		
		Urine, ml	Na^+, μEq	K^+, μEq
None	E_0[a]	0.0051	0.104	0.196
Furosemide	E_{max}[b]	0.0949	8.91	1.82
	EC_{50}[c]	0.806 ± 0.056	0.704 ± 0.054	0.832 ± 0.039
	S[d]	2.05 ± 0.18	1.76 ± 0.19	1.89 ± 0.11
	r[e]	0.954	0.932	0.975
Hydrochlorothiazide	E_{max}	0.0767	8.31	2.31
	EC_{50}	23.8 ± 1.5	17.8 ± 1.4	15.8 ± 1.1
	S	3.02 ± 0.32	1.58 ± 0.15	1.57 ± 0.13
	r	0.943	0.913	0.917

[a] Geometric mean of six rats whose urinary excretion rates were determined before drug administration.
[b] The maximum observed effect.
[c] Urinary excretion rate of the drug ($\mu g\ min^{-1} \cdot 100\ g^{-1}$) at 50% of maximum observed effect; mean ± SD.
[d] Exponent; mean ± SD.
[e] Correlation coefficient.

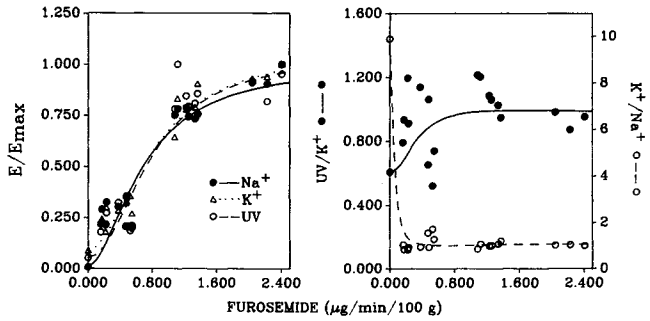

Fig. 5. Pharmacodynamics of the diuretic effects of furosemide in rats. See the legend to Fig. 4 for additional information.

azide. Slow and protracted administration of this diuretic would therefore be undesirable.

Corresponding results for the furosemide study are summarized in Fig. 5 and Table I. Again, the data are well described by the Hill equation, but unlike the case with hydrochlorothiazide, the relative effect versus drug excretion rate curves for urine flow, Na^+ excretion rate, and K^+ excretion rate almost coincide. Consequently, urine flow rate/K^+ and K^+/Na^+ ratios do not change appreciably with furosemide excretion rate. Based on the apparent EC_{50} values, furosemide is about 30, 25, and 19 times more potent than hydrochlorothiazide with respect to urine, Na^+, and K^+ excretion under conditions of volume-for-volume fluid replacement.

In rats treated with hydrochlorothiazide or furosemide, the urinary excretion rate of Na^+ and K^+ increased with increasing urine flow rate (Fig. 6) under the experimental conditions. The Na^+/K^+ excretion rate ratio was essentially independent of urine flow rate and was considerably higher during furosemide treatment than during treatment with hydrochlorothiazide.

Studies with combinations of hydrochlorothiazide and furosemide were carried out on a total of 26 rats, at two steady-state infusion rates each. The hydrochlorothiazide

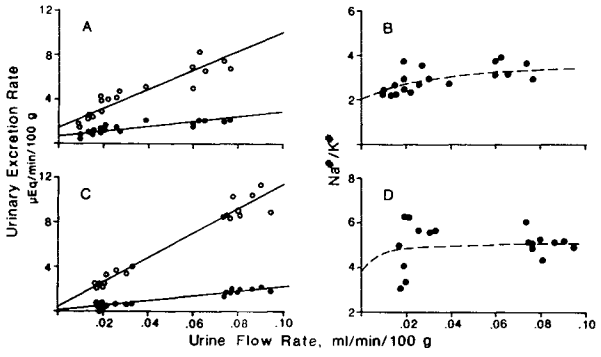

Fig. 6. Left: Relationship between urinary excretion rate of Na^+ (open circles) or K^+ (filled circles) and urine flow rate in rats (three animals for each diuretic) infused with either hydrochlorothiazide (A) or furosemide (C) at two different rates. Three timed urine samples were obtained during each infusion. The solid lines were fitted to the data by linear least-squares regression analysis. Right: Relationship between the Na^+/K^+ excretion rate ratio and the urine flow rate in rats infused with hydrochlorothiazide (B) or furosemide (D). The data points and the theoretical values (dashed lines) are derived from corresponding data points and regression lines in the left panels.

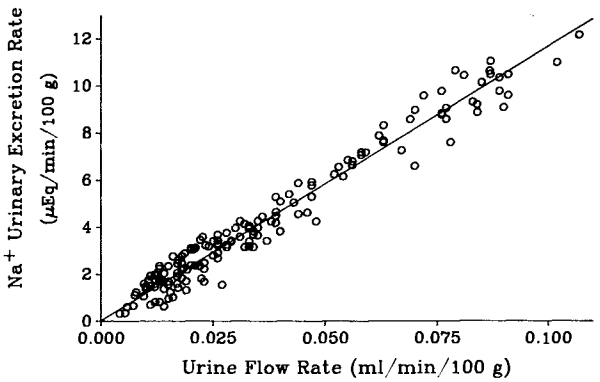

Fig. 7. Relationship between urinary excretion rate of Na^+ and urine flow rate in 26 rats infused with various ratios of furosemide and hydrochlorothiazide at two different rates. Three timed urine samples were obtained during each infusion rate.

excretion rate in these studies ranged from 0.883 to 28.0 μg $min^{-1} \cdot 100\ g^{-1}$ and that of furosemide from 0.022 to 1.17 μg $min^{-1} \cdot 100\ g^{-1}$. The (metric) ratio of excretion rates, hydrochlorothiazide/furosemide, ranged from 3.2 to 156. A strong, linear relationship between Na^+ and urine excretion rates was found ($R = 0.98$, $P < 0.001$) with the regression line intercepting at the origin (Fig. 7). The relationship between the excretion rates of K^+ and urine was also apparently linear ($r = 0.82$, $P < 0.001$) but had a significant, positive intercept on the K^+ excretion rate axis (Fig. 8 and Table II). Consequently, the Na^+/K^+ excretion rate ratio increased with increasing urine flow rate (Fig. 9).

To explore the possible effects of total excretion rate of the diuretics and of the furosemide/hydrochlorothiazide excretion rate ratio on the Na^+/K^+ excretion rate ratio independent of urine flow rate, data in a limited urine flow rate range (the intermediate group in Fig. 9) were examined. There was no apparent relationship between these variables. Also, there was no statistically significant difference between the Na^+/K^+ ratios during the first and the second infusion period, based on a total of 73 urine samples which constituted the intermediate group of data in Fig. 9.

The relationships between the urinary excretion rate of Na^+ or K^+ and the urine flow rate in rats treated with either hydrochlorothiazide, furosemide, or combinations of these

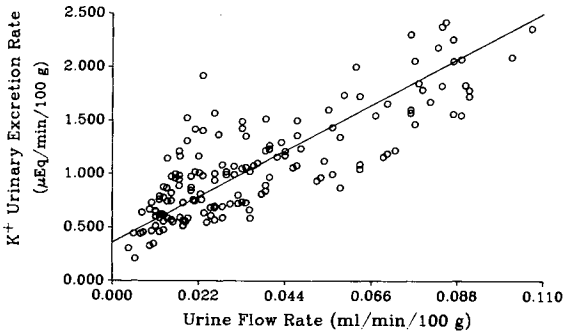

Fig. 8. Relationship between urinary excretion rate of K^+ and urine flow rate in 26 rats infused with various ratios of furosemide and hydrochlorothiazide at two different rates.

Table II. Relationship Between Urine Flow Rate and Urinary Excretion Rate of Na^+ or K^+ in Rats Infused with Hydrochlorothiazide, Furosemide, or Combinations of both Diuretics: Results of Linear Least-Squares Regression Analyses[a]

Parameter[b]	Hydrochlorothiazide	Furosemide	Combinations
No. of urine samples	18	18	156
UV-Na^+			
Slope, μEq/ml	85.8 ± 9.9	109 ± 3	117 ± 2
Intercept, μEq/min/100 g	1.49 ± 0.35	0.427 ± 0.178	0.018 ± 0.082
Correlation coefficient	0.921	0.978	0.982
UV-K^+			
Slope, μEq/ml	21.7 ± 4.0	21.3 ± 1.0	19.5 ± 0.9
Intercept, μEq/min/100 g	0.737 ± 0.142	0.112 ± 0.054	0.359 ± 0.039
Correlation coefficient	0.876	0.966	0.824
Na^+/K^+ ratio at UV = 0.10 ml/min/100 g	3.46	5.07	4.98

[a] Regression analyses of data in Figs. 6–8. Mean ± SD.
[b] UV, urine flow rate; Na^+, sodium excretion rate; K^+, potassium excretion rate.

two diuretics are compared in Table II. There were no striking differences between treatments.

DISCUSSION

The ability to produce a wide range of temporal profiles of drug concentrations in biological fluids via rate-controlled drug administration has added a new dimension to pharmacotherapy. Effective utilization of this capability requires a thorough characterization and understanding of the relationship between drug concentration and the intensity of therapeutic as well as adverse effects. It can be readily shown (Figs. 1 and 2) that the therapeutic index of a drug, as reflected by the ratio of intensities of its therapeutic and adverse effects, is not necessarily a constant for that drug but that it can be a variable depending on drug concentration and (as our experimental results and those of others have demonstrated) certain physiologic factors such as urine flow rate in the case of a diuretic. The proximate therapeutic effects of diuretics (particularly the enhanced excretion of Na^+ and water) as well as the adverse effects (especially the increased excretion of K^+) are readily quantifiable and make this class of drugs particularly suitable for model experiments to explore the potential usefulness of optimizing the rate of drug administration or of employing drug combinations for maximizing the therapeutic index.

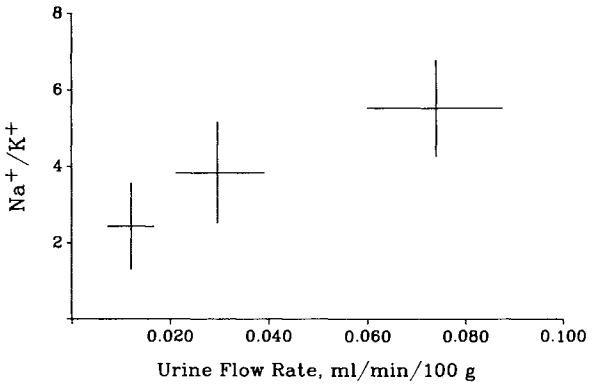

Fig. 9. Relationship between Na^+/K^+ excretion rate ratio and urine flow rate in 26 rats that received infusions of furosemide and hydrochlorothiazide in different ratios and at different rates. The vertical and horizontal bars represent one standard deviation in both directions. The Na^+/K^+ excretion rate ratios are significantly different from one another by one-way analysis of variance ($P < 0.001$) followed by Newman–Keuls multiple-comparison test ($P < 0.05$).

Hydrochlorothiazide and furosemide, the two diuretics used in this investigation, have different mechanisms (sites) of action (4–6). The two agents are used therapeutically in combination when furosemide alone is not sufficiently effective (7,8). They act from the luminal side of the nephron and therefore exhibit a better correlation between diuretic effect and urinary excretion rate of drug than between diuretic effect and drug concentration in plasma (6,9–11). The intensity of diuretic effects is a function not only of the drug concentration at the site of action but of the state of hydration and the electrolyte status of the body (11–13). Pronounced interlaboratory differences in the results of pharmacodynamic studies of diuretics occur because of differences in water and electrolyte replacement. Unless such replacement occurs throughout the course of an experiment, results will be variable (12) and suggestive of acute tolerance development (10), i.e., the "diuretic braking phenomenon" (13), which describes the condition of less diuresis with continuing water and electrolyte depletion of the animal or human subject (12). Particularly in animal studies, the extent of dehydration during some diuretic studies has been profound and caused rapid and substantial loss of body weight. For example, female Wistar rats lost 15% of their body weight within 2 hr after i.v. injection of a large dose of furosemide without replacement of voided urine volume (14). Such animals, weighing 200–220 g, lost 4.5 ± 1.4% of body weight within 4.5 hr even without the administration of a diuretic and with the administration of normal saline solution at a rate of 1.5 ml/hr (15). In our investigation the body weight loss was only 2.3 ± 1.2% due to continuous, volume-for-volume replacement of voided urine with an electrolyte solution containing Na^+, K^+, Ca^{2+}, Cl^-, and lactate. This very minor loss occurred via other than renal routes, i.e., pulmonary, metabolic, etc.

The pharmacodynamics of diuretic effects have been characterized by the Hill equation (10,16). One problem in doing that, also encountered in the present investigation, is the determination of the E_{max} values. They depend very much on the state of hydration and electrolyte status. More-

over, furosemide is a high-ceiling diuretic and its natriuretic effect does not level off even at a huge (480 mg/kg) dose of the drug (14). Consequently, the E_{max} value has been defined as the magnitude of the most pronounced diuretic effects observed under the experimental conditions (16). Inasmuch as the Hill equation parameters EC_{50} and S change with changing E_{max} values, the values reported in Table I are apparent rather than "real" and serve only descriptive functions, primarily the simulation of UV/K^+ and K^+/Na^+ excretion rate ratio values in this investigation (Figs. 4 and 5). These simulations revealed a pronounced dependence of the UV/K^+ ratio on the urinary excretion rate of hydrochlorothiazide. The K^+/Na^+ ratio was essentially independent of the hydrochlorothiazide excretion rate except at very low rates (Fig. 4). On the other hand, the diuretic effect curves of furosemide were almost coincident and therefore there was almost no change of UV/K^+ and K^+/Na^+ ratios with furosemide excretion rate (Fig. 5).

Unlike Christensen *et al.* (14), Chimizu *et al.* (17) found that the excretion rate of urine and Na^+ reached a maximum during the i.v. infusion of furosemide at a rate of 10 mg/kg/hr following a priming dose of 10 mg/kg in male Sprague–Dawley rats weighing about 300 g. Injection of an additional bolus dose of furosemide, 5 mg/kg, during the infusion did not increase the excretion rates beyond the rates achieved by the infusion alone. The rats excreted furosemide at a steady-state rate of about 8 μg/min/100 g, which is more than three times the highest rate in our study of male Lewis rats weighing about 230 g. The highest urine excretion rate observed by Shimizu *et al.* (17), about 120 μl/min/100 g body weight, is similar to the highest rate observed in our study, i.e., 95 μl/min/100 g (Table I). On the other hand, the highest Na^+ excretion rate observed by Shimizu *et al.* (17), about 16 μEq/min/100 g, is appreciably higher than our 8.9 μEq/min/100 g. Although these comparisons are limited by strain and experimental differences, they indicate the need for caution in assuming that our apparent Hill equation parameters are equal to the actual parameter values for the pharmacologic effects under investigation.

Attempts were made to confirm reports of a synergistic (supra-additive) pharmacodynamic interaction between thiazides and loop diuretics (18) by isobolographic analysis (19) of the hydrochlorothiazide–furosemide data. The isobolograms (not shown) were too scattered for definitive analysis but are consistent with a synergistic interaction. Other investigators have reported a strong, linear relationship between the urine flow rate and the sum of the Na^+ and K^+ excretion rates (but not with either Na^+ or K^+ excretion rate individually) in furosemide-treated rats, whereas in humans there is a linear relationship between urine flow rate and Na^+ excretion rate (20). In our investigation of hydrochlorothiazide-furosemide combinations, there was an excellent linear relationship between urine flow rate and Na^+ excretion rate in rats (Fig. 7), whereas the K^+ excretion rate showed more scatter and a nonlinear segment (apparent positive intercept on the K^+ excretion rate axis) at low rates (Fig. 8). Consequently, the Na^+/K^+ excretion rate ratio, representing a therapeutic index for diuretics, increased with increasing urine flow rate (Fig. 9). Apparently, it is not necessary to use a combination of the two diuretics to achieve this therapeutic advantage. It has been demonstrated with furosemide alone. An examination of the data recently reported by Sjöström *et al.* (12), who administered an infusion of furosemide at 8 mg/hr to healthy men without fluid replacement and then after rehydration with normal saline solution, indicates an increase in the Na^+/K^+ excretion rate ratio from 3.9 ± 2.4 at a urine flow rate of 4.3 ± 2.0 ml/min to 14.9 ± 2.5 at a flow rate of 23.1 ± 6.7 ml/min.

In summary, selection of an appropriate rate of drug administration, use of drug combinations [including the well-known use of antikaliuretics such as triamterene (21) with a thiazide diuretic which is not discussed here], and manipulation of the state of hydration are potential means for achieving greater selectivity in pharmacologic action and thereby for increasing the efficacy and safety of diuretic drugs.

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