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PHARMACODYNAMIC CONSIDERATIONS IN THE USE OF DIURETICS

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INTRODUCTION

Response to a diuretic is determined by a number of factors that have only recently been more clearly elucidated. The older medical literature for the most part focused upon patients with disease states in whom decreased response, i.e. resistance, occurred, and emphasized studies assessing changes in renal solute handling in the various disease states. These studies, in essence, were directed more toward the pathophysiology of solute retention than toward the pharmacology of the diuretic itself. More recently, with the advent of accurate assays of diuretics in biological fluids (1, 2), studies have addressed additional determinants of diuretic response such as the time course of delivery of diuretic to its site of action (pharmacokinetics) (1, 2), the response to diuretic once it reaches its active site (pharmacodynamics) (3), the interrelationship of the two in determining overall response (4), and aberrations of this relationship that occur in disease (5, 6). The greatest amount of data addressing all the different components of response concerns furosemide. Consequently, it serves as the focal point of this review with general extrapolation to other diuretics throughout. This discussion addresses the site of action of furosemide, how it reaches that site, the dynamics of response to amounts of drug at the site of action, and putative modulators of that response as it applies to clinical conditions of resistance to furosemide.

SITE OF ACTION OF FUROSEMIDE

Diuretics can increase sodium excretion by increasing the filtered load of sodium or by decreasing reabsorption at any of several tubular sites.

Furosemide's effects on glomerular filtration rate are short-lived, if present, and are not important to its overall effects.

The predominant component of sodium reabsorption in the proximal tubule is mediated by carbonic anhydrase (7). Furosemide possesses inhibitory activity to this enzyme but at concentrations that most likely are not achieved in vivo. Net reabsorption of sodium by the proximal tubule is also influenced by hemodynamic factors (8–13). In addition to forces moving sodium and water out of the proximal tubule and into the blood, there is a component of leakage back across the tubular epithelium into the lumen of the proximal nephron. Consequently, net reabsorption of fluid in the proximal tubule includes the amount reabsorbed less the amount that leaks back into the tubular lumen. The amount of backleak is influenced by the peritubular oncotic pressure which, in turn, is related to the relationship between glomerular filtration rate (GFR) and renal blood flow (RBF); namely the filtration fraction, which is equal to GFR divided by RBF:

$$FF = \frac{GFR}{RBF}.$$

The influence of filtration fraction is illustrated in Figure 1. If filtration fraction decreases, a smaller fraction of blood flowing to the kidney is

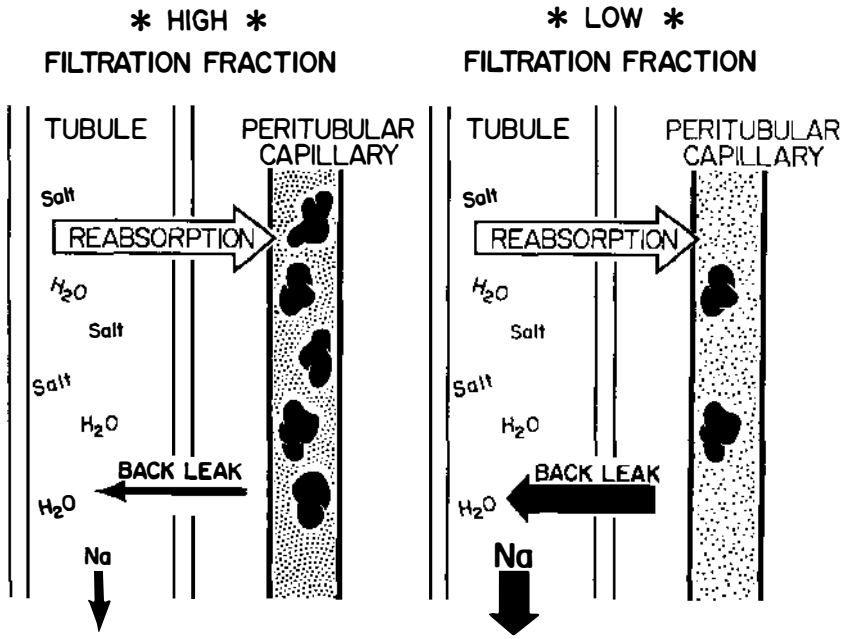

Figure 1 Schematic diagram of the effect of filtration fraction on peritubular osmotic pressure, back leak, and net reabsorption by the proximal tubule. [Reprinted from (5) with permission].

filtered, causing the protein in the peritubular fluid to be less concentrated; the lower oncotic force maintains less of the reabsorbed fluid outside of the lumen, and as a consequence more backleak occurs. As a consequence, *net* reabsorption decreases. In contrast, if filtration fraction increases, the fraction of blood flowing to the kidney that is filtered has increased, increasing oncotic pressure in the peritubular vascular space and facilitating reabsorption by diminishing backleak. As a consequence, *net* reabsorption of solute will be greater when filtration fraction has increased. It is important to note that changes in filtration fraction can occur either by changes in glomerular filtration rate, changes in renal blood flow, or changes in both. It is the net effect on the ratio of the two which is of overriding importance. All of the loop diuretics described to date are capable of increasing renal blood flow without affecting glomerular filtration rate, particularly when they are administered intravenously (14–18). Consequently, a component of the diuretic effect caused by loop diuretics when administered parenterally may be a result of a hemodynamic component to increase renal blood flow.

Parenthetically, this vasodilator effect is similar in time course to the effects of parenterally administered loop diuretics to increase systemic venous capacitance (19). This increase in venous capacitance caused by venodilation decreases cardiac preload and thereby decreases left ventricular end diastolic pressure and pulmonary congestion in patients with acute pulmonary edema. This effect occurs prior to any diuretic effect. It has been hypothesized that the diuretic causes release of some vasoactive component from the kidney, causing the venodilation (20). A leading candidate for the vasoactive substance is one of the prostaglandins, particularly prostacyclin, PGI_2, for parenterally administered loop diuretics cause release of prostaglandins by the kidney (21–31).

Loop and thiazide diuretics block chloride reabsorption by the thick ascending limb of the loop of Henle (32). The loop diuretics affect both the medullary and cortical aspects of this segment of the nephron (33–36), whereas the thiazide diuretics affect only the cortical segment (37–40). Since the medullary segment is responsible for generating the concentrated medullary interstitium which, in turn, provides the driving force for reabsorption of water under the influence of antidiuretic hormone, this segment of the nephron is responsible for the capacity of the kidney to concentrate the urine, and interference with its function affects concentrating ability. Similarly, the cortical segment of the thick ascending limb of the loop of Henle is responsible for dilution of the urine, and interference with its function decreases the ability to form a dilute urine.

In summary, furosemide and other loop diuretics cause a natriuresis by effects at two sites. When administered intravenously, they increase renal blood flow and thereby decrease net reabsorption of sodium in the proximal tubule. Quantitatively, their predominant effect, however, is to decrease

chloride reabsorption throughout the thick ascending limb of the loop of Henle. Decreased reabsorption of sodium ensues as a consequence, and a sodium chloride diuresis occurs. Because of the physiologic functions of this nephron segment and its capacity for solute reabsorption, loop diuretics impair the ability to concentrate the urine during dehydration and to dilute the urine in response to a water load, and they are the most potent diuretics in our armamentarium.

ACCESS OF FUROSEMIDE TO ITS SITE OF ACTION

From in vitro and in vivo animal studies, it is clear that all diuretics except triamterene and spironolactone must reach the tubular lumen to be effective (3, 41–43). These diuretics, excluding osmotic agents and amiloride, are all organic acids and are highly bound to serum proteins. As a consequence, they cannot reach the tubular lumen by glomerular filtration, for only a small fraction of the total drug in serum is free in the circulation and can be sieved through the glomerulus. These drugs reach the luminal compartment by being actively secreted from the blood into the urine at the organic acid transport pathway of the straight segment of the proximal tubule (Figure 2). To assess determinants of response to furosemide in man, it was important to determine whether observations in the basic laboratory could be extrapolated to man. Probenecid can be used to permute the relationship between concentrations of furosemide in blood and in urine and, thus, can

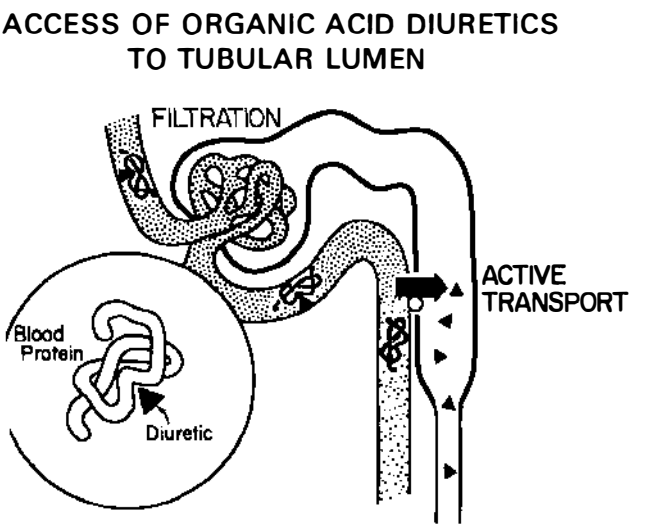

Figure 2 Schematized illustration of route of access to the tubular lumen of a protein bound organic acid diuretic. [Reprinted from (5) with permission].

be used as a tool to assess the importance of blood versus urinary furosemide in determining response. Pretreatment of normal subjects with probenecid decreases both renal and nonrenal clearance of furosemide by half, thereby greatly changing the relationship between blood and urinary furosemide. As shown in Figure 3, this change causes a rightward shift in the relationship between serum concentrations of furosemide and response while having no effect on the relationship between urinary furosemide and response (3). These data confirm that one can extrapolate previous animal data to man, and that urinary furosemide is the best correlate of response.

What then determines access of furosemide and other organic acid diuretics to the urine? Since the sites of action are reached via the organic acid secretory pump at the proximal tubule, the presence of inhibitors of transport will affect access. Inhibitors include co-administered organic acids such as probenecid and accumulated endogenous organic acids of uremia. In patients with mild to moderate renal dysfunction, the accumulated endogenous organic acids decrease access of furosemide to the site of action and alter response, in contrast to the changed response's being a manifestation of decreased nephron mass (44–46). The latter situation becomes predominant only with severe renal impairment.

Theoretically, decreases in protein binding of organic acid diuretics would allow more to be filtered at the glomerulus and would thereby change the route of access to the site of action. In clinical conditions in which changed binding occurs, namely, azotemia and hypoalbuminemic states of any cause, the increase in unbound drug is not quantitatively important relative to amounts entering the tubule via active secretion (47).

Access of the diuretic to the organic acid secretory site as determined by the amount of blood flowing to it is obviously important, but with furosemide, the avidity of the transport system is so great that considerable decrements in renal blood flow must occur before access to the site of transport becomes limiting.

The most important determinant of how much drug reaches the urinary site of action, then, is the amount of drug circulating in blood. This, in turn, is a function of the bioavailability of the drug after an oral dose, its volume of distribution, and its clearance; i.e. its pharmacokinetics. The pharmacokinetic characteristics of furosemide have been recently reviewed and are not elaborated upon here (1, 2). The important interrelationship between the time course of drug delivered to the site of action and overall response is addressed below (4). One should note that, excepting azotemia, changes in pharmacokinetics of furosemide in disease states are minor relative to altered pharmacodynamics, and cannot account for the resistance to diuretics commonly observed in clinical conditions (6, 47–53).

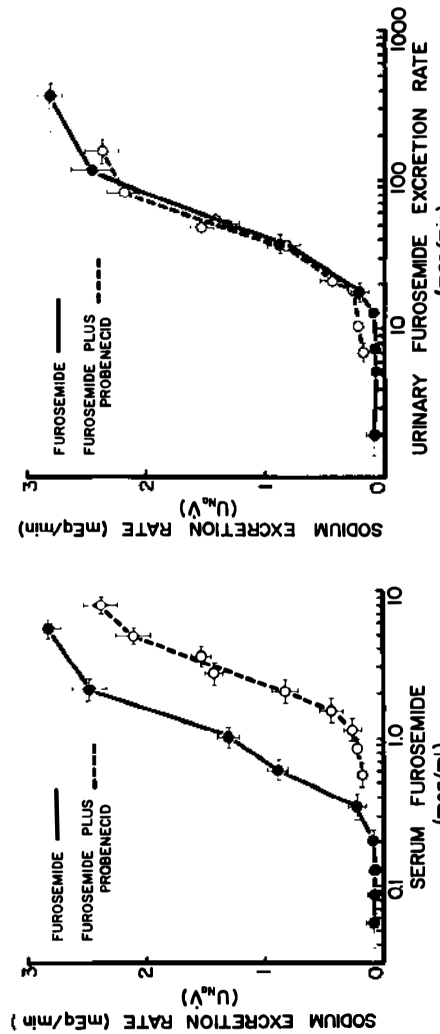

Figure 3 "Dose-response" curves for furosemide after a 40 mg intravenous dose. The left panel depicts the relationship between concentrations of furosemide in serum and response expressed as sodium excretion rate. The right panel depicts the relationship between urinary excretion rate of furosemide and response. [Reprinted from (3) with permission].

PHARMACODYNAMICS OF RESPONSE TO FUROSEMIDE

As shown in Figure 3, the relationship between amounts of furosemide delivered to the urinary site of action and response is characterized by a sigmoid-shaped curve (3). To assess the determinants of response to furosemide, one must relate the pharmacokinetics of furosemide to the pharmacodynamics of response, i.e. the time course of its delivery to the site of action to the "dose-response" curve.

An unexpected finding in previous studies of furosemide was that pretreatment of subjects with probenecid increased the overall natriuretic response from 262 ± 16 to 358 ± 11 mEq/8 hr ($P < 0.005$) (54). Since dose-response curves were identical (see Figure 3) (3), this effect did not occur because of a changed sensitivity of the nephron to furosemide. In addition, the total amount of furosemide delivered into the urine was not different; 19.7 ± 2.2 without probenecid, versus 16.0 ± 1.4 mg/8 hr with probenecid pretreatment ($P = 0.252$) (3). As a consequence, the only factor that could account for this difference in response between the two groups was a changed time course of delivery of furosemide into urine.

A similar phenomenon occurred when comparing overall response to oral versus intravenous dosing of furosemide (4). In our laboratory, 27 subjects who received furosemide intravenously had less than twice the natriuretic response of 21 subjects who received an oral dose (359 ± 43 versus 235 ± 25 mEq/24 hr), despite having delivered almost three times as much drug into the urine (21.2 ± 1.8 versus 7.9 ± 1.6 mg/24 hr). As with the probenecid effect, then, there was a discrepancy between overall response relative to amounts of drug reaching the active site. Changed sensitivity could not account for the observation, for again dose-response curves for the two formulations were superimposable (4). Consequently, as occurred with the probenecid studies, a difference in time course of delivery of drug into the urine was invoked to explain the results.

To probe the mechanism of this effect, our laboratory used the concept of the ratio of sodium to furosemide excretion to describe the efficiency of the diuretic (4). This ratio has been used by others, though in a somewhat different context, to describe the influence of indomethacin on the response to furosemide in the dog (49), and to describe the interaction between probenecid or spironolactone and furosemide in man (55). Applying this efficiency approach to the actual dose-response curve to furosemide allowed mathematical derivation (by taking the first derivative of the Hill equation) of the determinants of maximum efficiency:

$$\text{Amount with Maximum Efficiency} = [c^b(b-1)]^{1/b}$$

where b is the slope factor of the dose-response curve and c is the amount of drug causing half-maximal response (ED_{50}). This quantitative derivation allowed comparison between dosing regimens in terms of the relationship between the actual time course of delivery of drug to the active site and that amount with maximal efficiency.

The amount of urinary furosemide with maximum efficiency derived from the preceeding equation (21.5 μg/min) was considerably less than the ED_{50} (69.8 μg/min) for furosemide. Therefore, the importance of the time course of delivery in determining overall response was the manner in which delivery of drug to its active site related to a value at the relatively low end of the steep portion of the dose-response curve.

Figure 4 depicts the time course of urinary furosemide excretion after oral and intravenous dosing relative to the amount of furosemide with maximum efficiency (4). After oral administration, amounts of furosemide more persistently approached that amount with maximal efficiency; thus, during the summated time course of response, overall natriuresis was greater relative to total amounts of drug delivered to the active site. Similarly, pretreatment with probenecid caused a counterclockwise shift in the time course curve with less overall deviation from the amount with maximum efficiency (see Figure 5). Cumulative areas of deviation of the different study groups are quantified in the figures. Oral administration and pretreat-

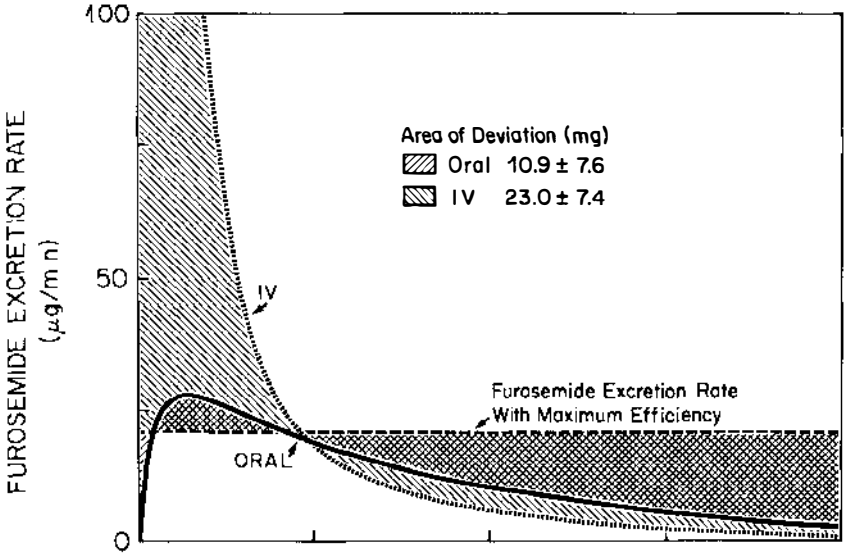

Figure 4 Time course of urinary excretion of furosemide after intravenous (stippled line) and oral (solid line) dosing demonstrating the relationship to the amount of furosemide with maximum efficiency (dashed line). Shading depicts the areas of deviation from the amount with maximum efficiency, quantified and compared for individual cures. [Reprinted from reference (4) with permission].

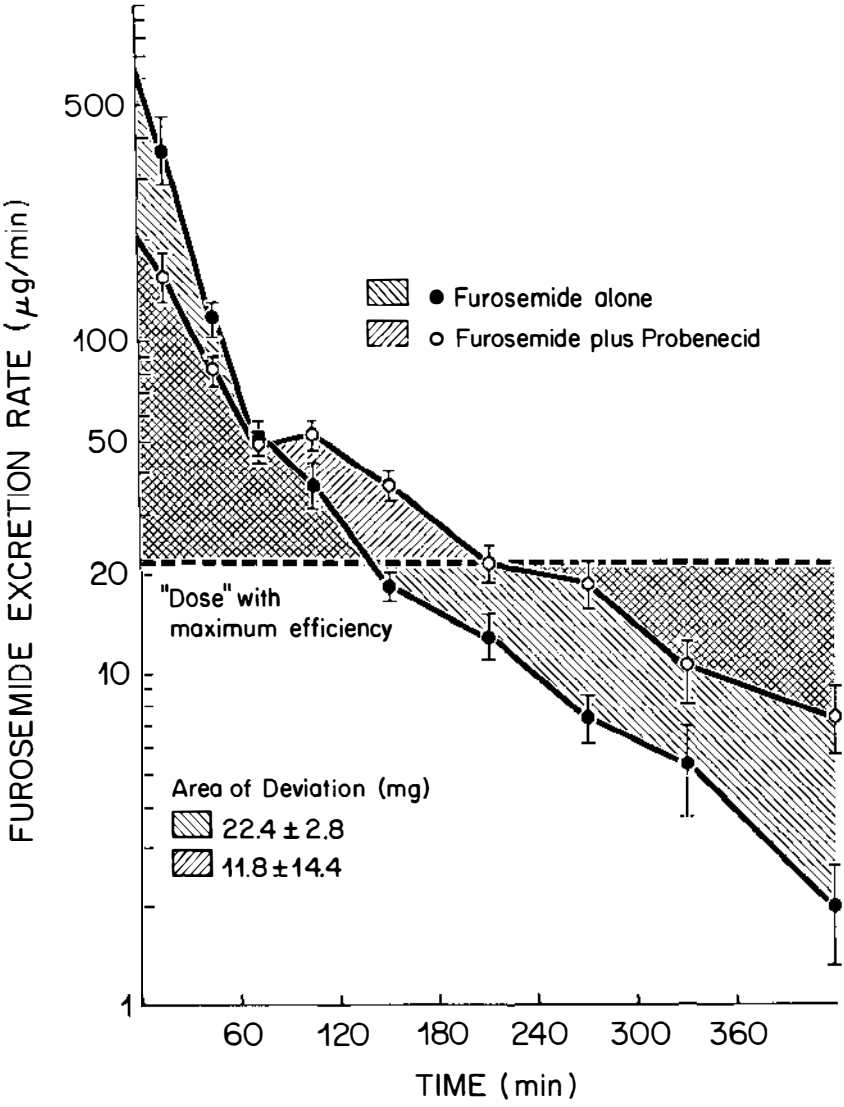

Figure 5 Time course of urinary excretion of furosemide without (solid symbols) and with (open symbols) pretreatment with probenecid. Shading depicts the areas of deivation from the amount with maximum efficiency (dashed line).

ment with probenecid markedly decreased deviation from the amount of diuretic having maximum efficiency. In contrast, there was considerably less or no impact when assessing the relationship of the time course of delivery to the ED_{50}. For furosemide, then, the influence on cumulative response of the time course of delivery of drug to the urinary site of action was more

importantly related to the derived value with maximum efficiency than it was to the ED_{50}, though the former is only one-third the latter.

In summary, from a pharmacokinetic perspective the overall response to furosemide, and presumably other diuretics, is a function of the total amount of drug with access to the site of action, which will be determined by dose of drug, its quantitative absorption, and the capacity of the organic acid transport pump to deliver drug from blood into urine. In addition, overall response is determined by the time course of drug delivery to the site of action, a function of drug clearance, which for organic acid diuretics is again a function of the organic acid transport pathway.

From a pharmacodynamic perspective, overall response is also independently affected by the dose-response curve, as is readily illustrated by the effect of indomethacin (48, 49). Pretreatment of normal subjects with indomethacin changes the dose-response curve to furosemide (see Figure 6) (48) without affecting the total amount or the time course of delivery of furosemide into the urine. Such pretreatment decreased the sodium excretion caused by 40 mg of intravenous furosemide from 262 ± 16 to 183 ± 18 mEq/8 Hr ($P < 0.02$). Clearly, then, overall response is a function of the dose response curve.

It is apparent from the data discussed above that response to diuretics is a function of the relationship between the pharmacokinetics of the drug and its pharmacodynamics. Evaluating either is, in itself, of only marginal value. In using these drugs, in assessing reasons for abnormal response, and in devising therapeutic strategies for overcoming resistance, one must con-

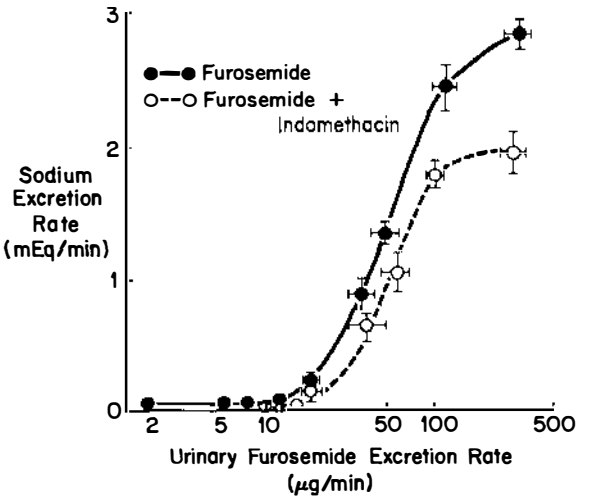

Figure 6 Effect of indomethacin on the dose-response relationship to furosemide. [Reprinted from (48) with permission].

sider all these determinants of response, which have only recently become more fully elucidated.

Visualizing the interplay of these factors is difficult. However, the relationships essentially constitute a three-dimensional matrix, as depicted in Figure 7, in which dose is depicted on the X-axis, response on the Y-axis, and time on the Z-axis. The time-course of a sigmoid-shaped curve can thus be defined. Its two-dimensional projection on the time-versus-response axis then defines the curve of the time course of response; the area under this latter curve represents cumulative response.

Figure 8 depicts the effect of probenecid of changing the pharmacokinetics (i.e. the time course) of furosemide without affecting pharmacodynamics. In the three-dimensional depiction, the probenecid effect causes a rotation of the sigmoid-shaped curve. The two-dimensional projection illustrates the concomitant change in the time course of response and subsequent effect on cumulative response.

In contrast, Figure 9 depicts the effect of indomethacin, which alters the pharmacodynamics and thereby changes the sigmoid-shaped curve without affecting the time-course of delivery of drug to the site of action. The effect on cumulative response is obvious from the two-dimensional projection. Assessment of determinants of response, then, requires a three-dimensional analysis.

CLINICAL CONDITIONS OF RESISTANCE TO DIURETICS

Though the data are fragmentary, insight is available into the determinants of response to diuretics in some disease states.

Patients with azotemia often require large doses of potent diuretics to achieve a response. One might presume that the diuretic resistance in these patients occurs because of decreased glomerular filtration of solute. However, as noted above, a series of studies have demonstrated that a primary cause of diuretic resistance in patients, short of end stage renal failure, is that accumulated endogenous organic acids of uremia block the active transport pathway for organic acid diuretics, preventing their access to sites of action (44–46). As a consequence, exceedingly large doses are required to deliver enough diuretic into the tubular lumen to cause a response. Needless to say, this tactic is used at the expense of very high serum concentrations of potentially toxic diuretics, accounting for the increased incidence of ototoxicity in such patients. Studies have shown a delayed time course of drug delivery in patients with decreased renal function (47, 54, 56–59), but none assess the dose-response relationship or how it relates to changes in pharmacokinetics.

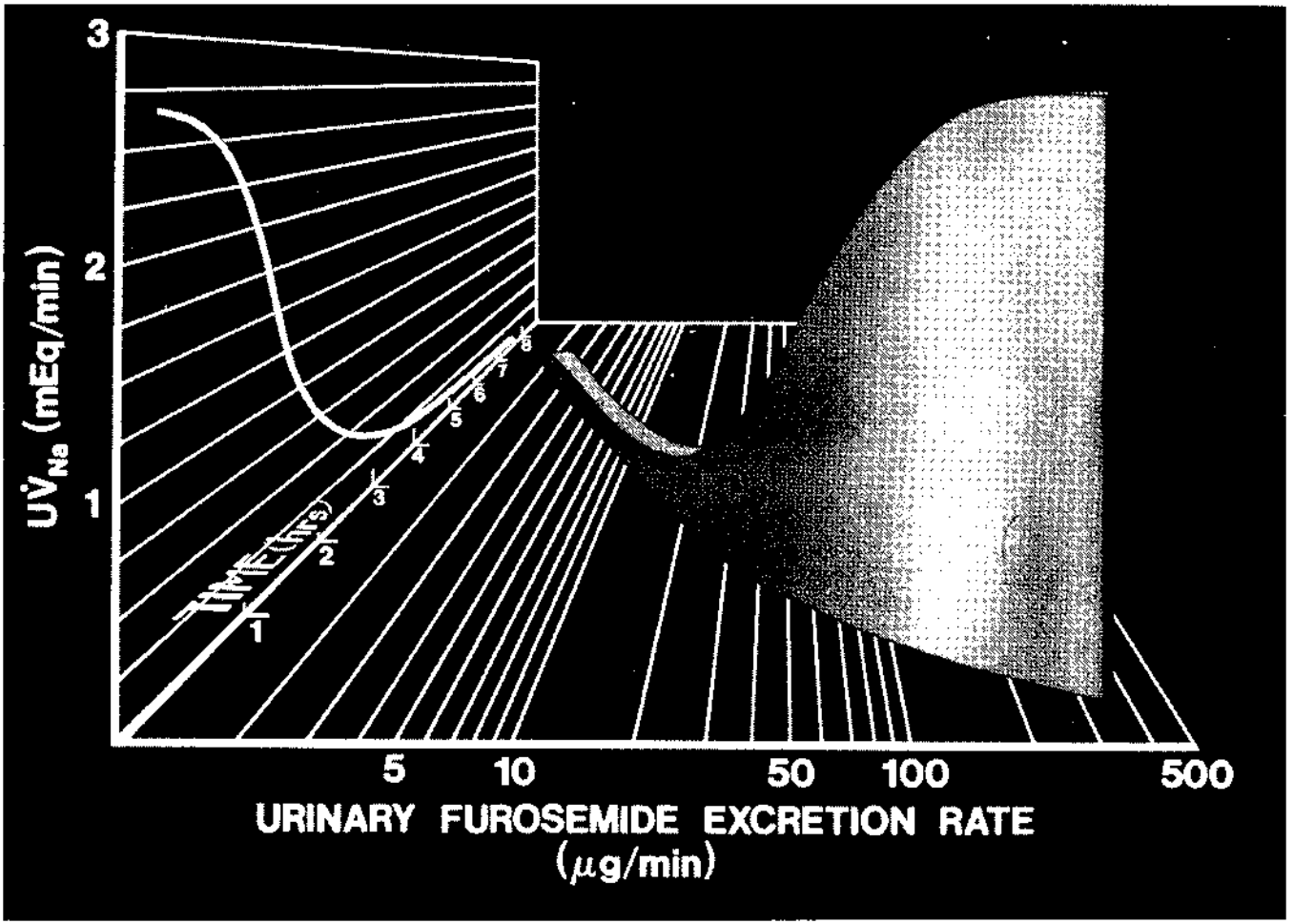

Figure 7 Three-dimensional depiction of the determinants of response to furosemide with the X-axis representing dose, the Y-axis response, and the Z-axis time. The two-dimensional projection on the time versus response axes represents the curve of the time course of response,

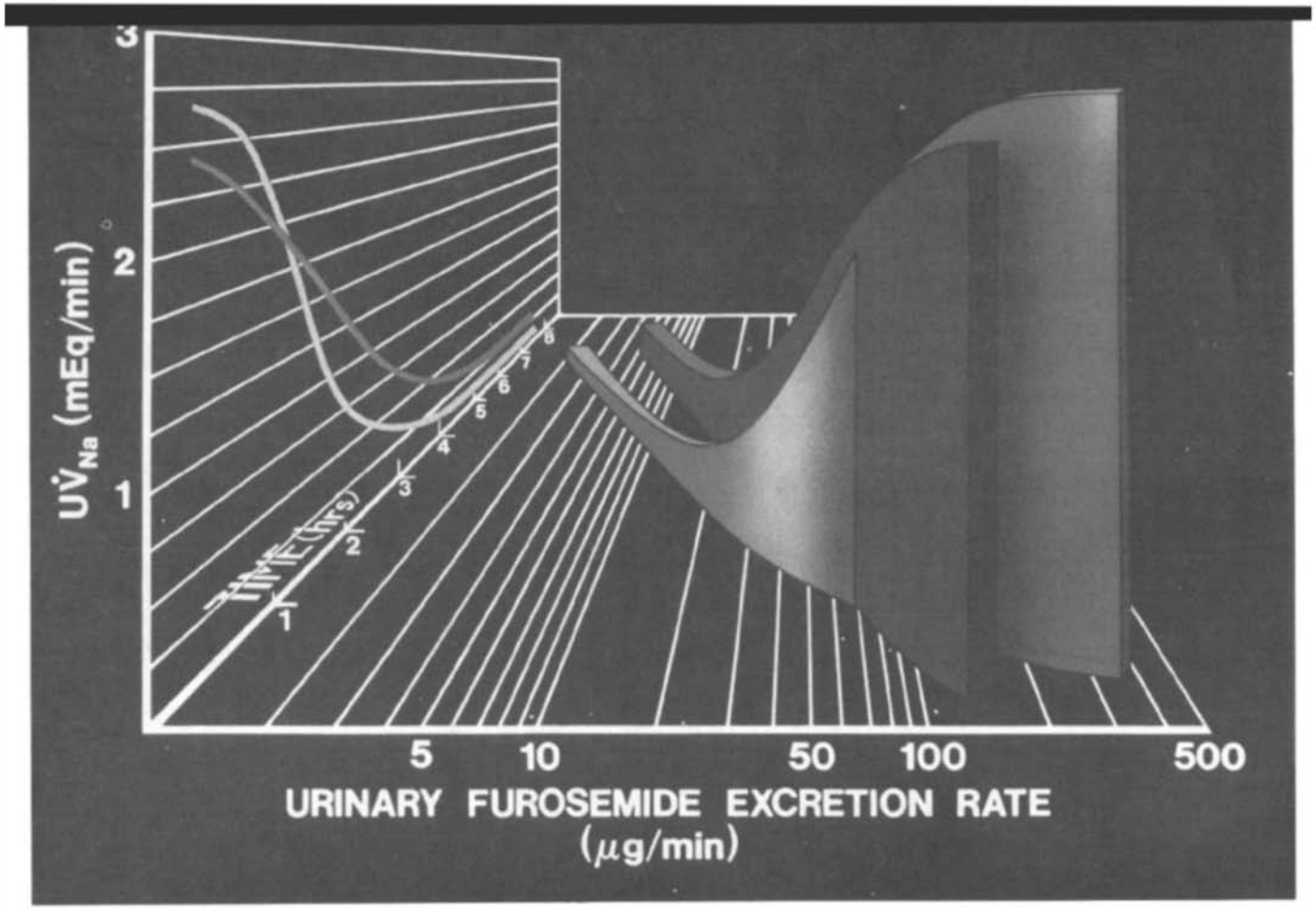

Figure 8 Three-dimensional depiction of the effect of probenecid on the determinants of response to furosemide. See text for discussion.

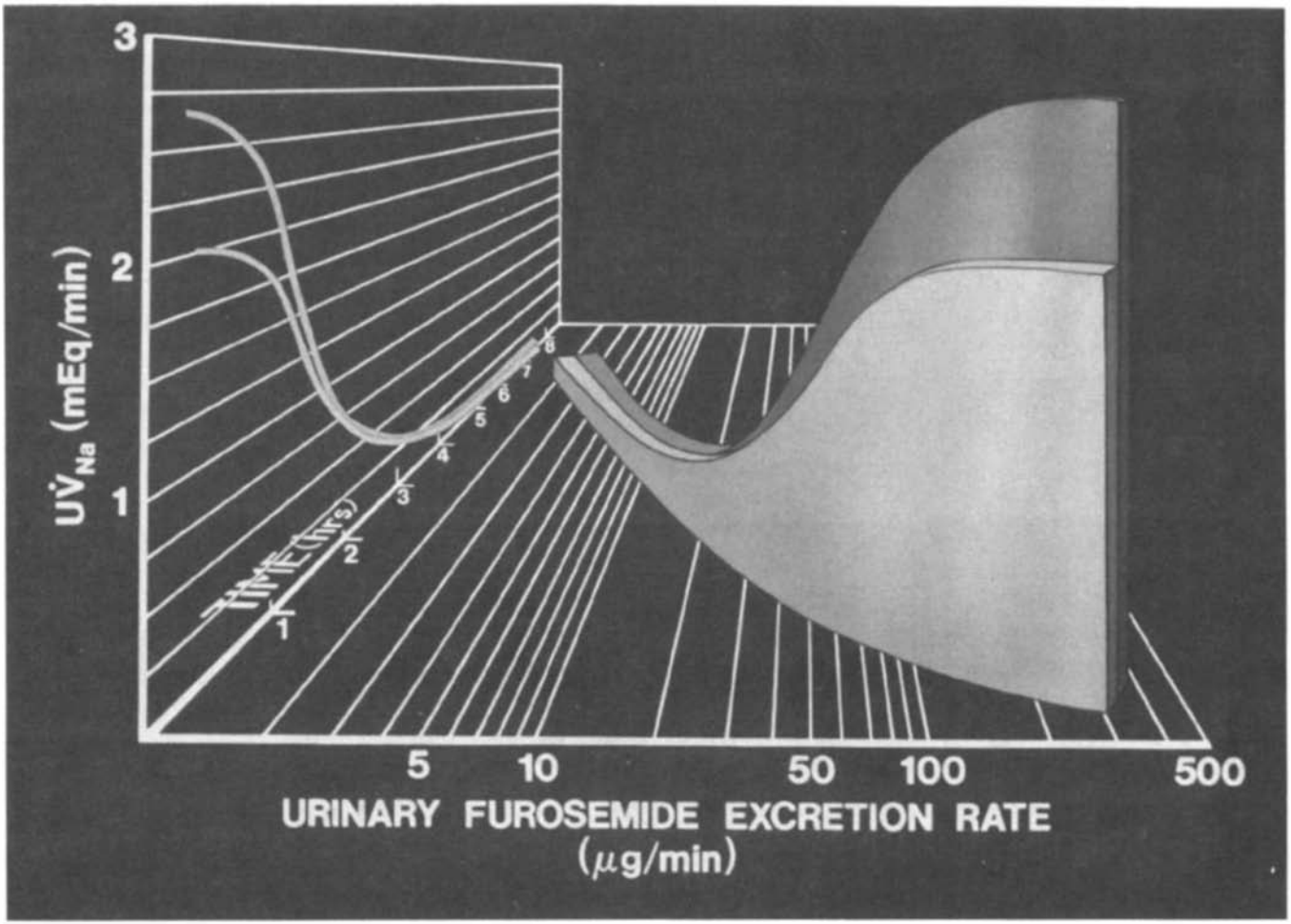

Figure 9 Three-dimensional depiction of the effect of indomethacin on the determinants of response to furosemide. See text for discussion.

Our laboratory has studied some aspects of the determinants of response to furosemide in patients with congestive heart failure (6, 53). The patients we examined manifested a spectrum of severity of disease. The total amount of drug delivered into the urine was the same in these subjects as in normal volunteers. Additionally, the bioavailability or the absorption of furosemide was unchanged in this group of edematous subjects (53). In some patients with decreased renal function, there was a change in the time course of drug delivery into the urine, though this change was slight. In patients with relatively normal renal function there was no difference in the time course of drug delivery. The dose response relationship, however, was markedly changed (6).

No clear-cut pattern of change emerged for these patients with congestive heart failure when all the different patients were assessed (6). It was clear that the dose-response relationship was shifted to the right, but in addition the contour of the relationship was changed. Possible mechanisms for this effect are many and essentially encompass the potential pathophysiologic mechanisms of sodium retention in these disease states. It is unlikely that decrements in glomerular filtration play a predominant role, for most of these patients had near normal glomerular filtration rates. Increases in proximal re-absorption of solute through changes in either hemodynamics or avidity for solute could affect response and might be responsible for these shifts in the dose-response relationship. Similarly, changes in solute processing by the thick ascending limb of the loop of Henle could well be responsible for the observed shifts. This possibility is especially intriguing since furosemide's site of action is the ascending limb of the loop of Henle. It is unlikely that aldosterone excess accounts for the changes observed in our patients, for the sodium to potassium ratio in the urine was no different from that of normal subjects. The mechanisms of this shift obviously require further elucidation.

In summary, there are many candidates for mechanisms of resistance to diuretics, including changes in handling of the diuretics themselves as well as the abnormalities in the dynamics of the response to diuretics that are part and parcel of the pathophysiology of solute retention in the variety of disease states in which resistance to diuretics occurs. Much can be learned with future studies of this subject. A pharmacodynamic approach to diuretic resistance may shed some light on the mechanisms of edema formation and the changes in renal solute handling that occur in edematous disorders. We now have sufficient data delineating the determinants of normal response to diuretics. We must use similar techniques to probe the various common clinical conditions in which abnormal response occurs. So doing will allow a better understanding of the pharmacology of diuretics and of pathophysiology, and will provide more rational therapeutic strategies.

ACKNOWLEDGMENTS

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