Drug or Kidney

DIURETIC RESISTANCE: WHY IT HAPPENS AND WHAT TO DO ABOUT IT

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Introduction

Diuretic resistance is a common clinical problem. In the past, focus has been on the physiologic mechanisms of this phenomenon with little attention to possible pharmacologic mechanisms. This review will emphasize pharmacologic considerations, not to give short shrift to the physiologic, but to offer a different perspective and demonstrate that ultimately the two approaches merge.

1. The Role of Sodium Intake

The rationale for effecting a diuresis in a patient is to create a net negative balance of sodium. Though simplistic, many clinicians often overlook the fact that accomplishing this goal depends not only on causing a natriuresis with a diuretic but also on the magnitude of this effect relative to sodium intake. When a patient presents with florid congestive heart failure and large amounts of peripheral edema, acute therapy often results in a brisk natriuresis with considerable weight loss while the patient is ingesting little or no sodium and receiving no sodium in intravenous preparations. That a net negative sodium balance ensues is obvious to clinician and patient alike.

In contrast, many do not realize during institution of treatment in less severe and dramatic settings and with chronic maintenance therapy with a diuretic that sodium intake can easily offset the natriuretic effects of the diuretic. For example, a recent series of well-performed balance studies have assessed the impact of sodium intake on the ability to achieve a net negative sodium balance (Wilcox et al., 1983; Kelly et al., 1983). Six normal volunteers received 40mg of furosemide per day for 3 days while on either a 20 or 270mEq Na/day diet. During high salt

intake, no negative sodium balance occurred; the cumulative balance over the 3 days being 20±63mEq. In contrast, on the low sodium diet the cumulative balance was -146±8mEq and in this phase of the study a significant decrease of approximately 1Kg in weight occurred. During the phase with high sodium intake, furosemide caused a pronounced, short-lived natriuresis followed by avid sodium retention that matched that lost following the diuretic (Fig 1).

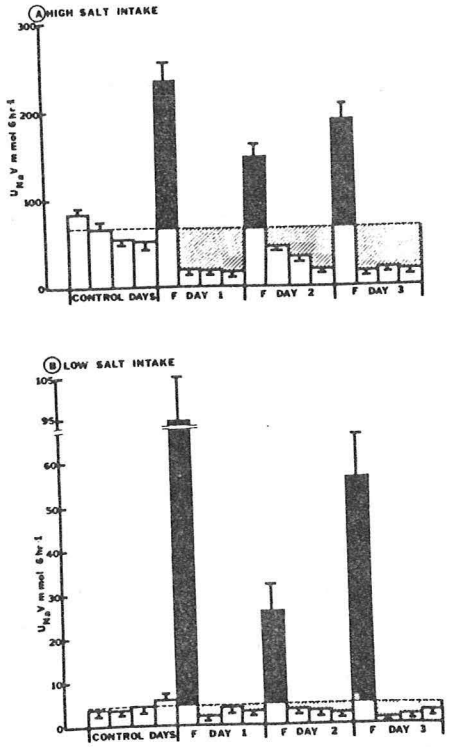


Fig 1: Effects of furosemide on overall sodium balance during both high (upper panel) and low (lower panel) salt intakes. The horizontal dashed line represents intake. Columns above the line represent net loss of sodium while those below the line represent net gain. Columns represent urinary sodium excretion over 6 hours. With the high salt intake the net loss of sodium caused by furosemide (F) is matched by subsequent sodium retention. With low salt intake, sufficient sodium retention cannot occur to match losses and net negative sodium balance ensues. (From Wilcox et al, 1983).

In essence, then, though these studies were performed in normal volunteers, it would appear that a patient can easily ingest sufficient sodium to obviate the sodium loss caused by potent diuretics. Clinically, this could be overcome somewhat by administering the diuretic frequently and thereby lessening the opportunity for compensatory sodium retention to occur. Clearly, however, one must also be aware that a degree of sodium restriction may be necessary, the extent of which most likely will differ among patients. It is important to realize that this form of diuretic failure does not constitute diuretic resistance, for patients respond to the drug as expected. Rather, they have managed to simply overcome the effects of the diuretic by intake of sodium.

How does this compensatory sodium retention occur? During both high and low sodium intakes, renin, angiotensin and aldosterone increase (Wilcox et al., 1983; Kelly et al., 1983). With a high intake of sodium, aldosterone-mediated sodium retention could conceivably account for this phenomenon. However, treatment with captopril in sufficient doses to normalize aldosterone did not prevent the compensatory sodium retention. Volunteers ingesting 270mEq Na/day treated with both furosemide and captopril had a neutral cumulative sodium balance of 42±54mEq (Fig 2) (Kelly et al., 1983). Consequently, an intact renin-angiotensin-aldosterone system is not required for this compensation. Its mechanism remains unexplained. Circulating concentrations of norepinephrine rose and might be causal or contributory; further studies are required to elucidate mechanisms.

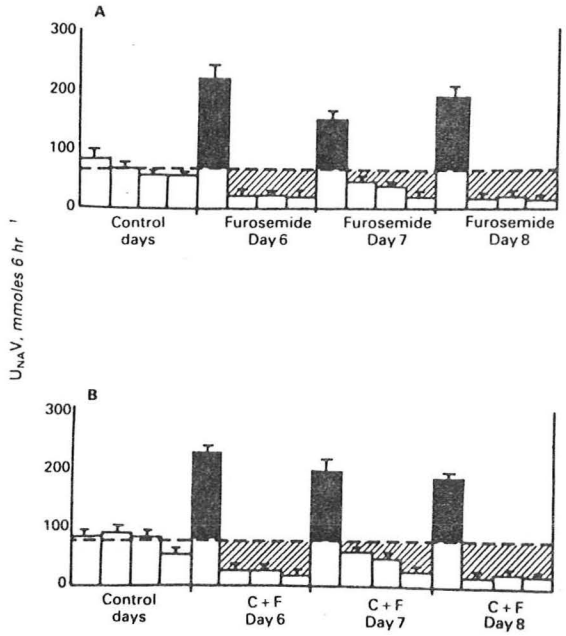


Fig 2: The effects of captopril (panel B) on the overall sodium balance caused by furosemide during a high salt diet. Schematic is as in Figure 1. (From Kelly et al, 1983).

Overall, the important clinical lesson from these data is that in patients who are not achieving a negative sodium balance, the tendency is to focus on lack of response to the diuretics due to either pharmacologic factors or because of the severity of the patients disease. It is also important to be aware of the possible role of sodium intake in determining overall response to the diuretic.

2. Determinants of Normal Response to a Loop Diuretic

2.1 Importance of Urinary Furosemide

From in vitro and in vivo animal studies, it is clear that loop diuretics must reach the tubular lumen to be effective (Burg, 1976; Odlind, 1979ab, Odlind and Beermann, 1980). These diuretics 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 via the organic acid transport pathway of the straight segment of the proximal tubule (Odlind, 1979ab). To assess determinants of normal response to furosemide in man, it was important to determine whether observations in the basic laboratory were extrapolable to man. Probenecid can be used to permute the relationship between concentrations of furosemide in blood and in urine and, thereby, 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 (Homeida et al., 1977; Honari et al., 1977; Chennavasin et al., 1979). As shown in Figure 3, so doing has no effect on the relationship between urinary furosemide and response (Chennavasin et al., 1979). These data confirm the ability to extrapolate previous animal data to man, and that urinary furosemide is the best correlate of response.

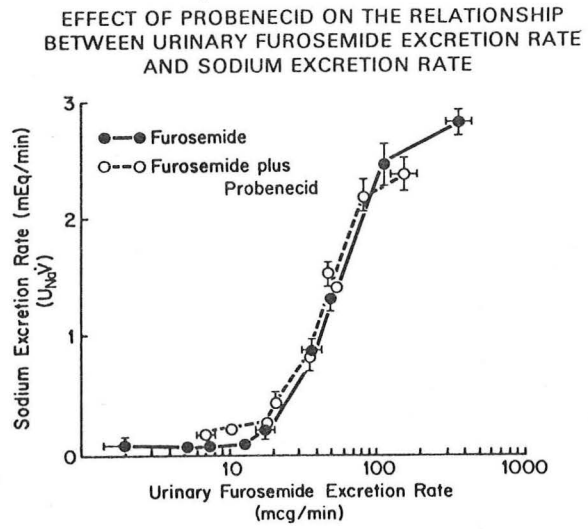


Fig 3: Lack of effect of probenecid on the relationship between urinary furosemide excretion and response assessed as sodium excretion rate. (From Chennavasin et al, 1979).

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. As will be discussed in greater detail subsequently, in patients with mild to moderate renal dysfunction resistance to furosemide is most likely caused by accumulation of endogenous organic acids which decrease access of furosemide to the site of action and alter response. This mechanism is in contrast to the changed response being a manifestation of decreased nephron mass (Rose et al., 1976abc). The latter becomes predominant only with severe renal impairment.

Theoretically, decreases in protein binding of loop diuretics would allow more to be filtered at the glomerulus and thereby change the route of access to the site of action. In clinical conditions in which changed binding occurs; namely, azotemia in which competitors to binding displace the drug and in hypoalbuminemic states of any cause in which the capacity for binding decreases, the increase in unbound drug is not quantitatively important relative to amounts entering the tubule via active secretion (Rane et al., 1978).

Access of the diuretic to the organic acid secretory site should also be determined by the amount of blood flowing to the proximal nephron. Hence, changes in renal blood flow might influence the amount of drug reaching the tubular lumen. However, the avidity of the transport system for loop diuretics appears to be 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 and their possible role in diuretic resistance will be discussed subsequently as specific clinical conditions are considered. It is important to note, however, that the critically important determinant of diuretic response in man is a function of drug reaching the urinary site of action. Any change in serum concentrations of diuretic are only important as they affect that appearing in the urine.

Most clinicians would predict that the total amount of drug appearing in the urine would be a determinant of response since larger doses result in increased diuresis. However, few would have predicted that the time course of its appearance in urine is also an important determinant. Recent work has demonstrated this to be the case.

2.2 Importance of the Time Course of Drug Delivery to the Site of Action

An unexpected finding in previous studies of furosemide was that pretreatment of normal subjects with probenecid increased the overall natriuretic response from 262±16 to 358±11mEq/Na 8 hr ($P<0.005$) (Brater, 1978). Since "dose-response" curves were identical (Fig 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±1.4mg/8 hr with probenecid pretreatment ($P=0.252$). As a consequence, the only factor which 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 has been noted when comparing overall response to oral versus intravenous dosing of furosemide (Branch et al., 1977; Kaojarern et al., 1982). 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±25mEq/Na 24 hr) despite having delivered almost three times as much drug into the urine (21.2±1.8 vs 7.9±1.6mg/24 hr) (Kaojarern et al., 1982). 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. 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, we used the concept of the ratio of sodium to furosemide excretion to describe the efficiency of the diuretic (Kaojarern et al., 1982). 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 (Data et al., 1978) and to describe the interaction between probenecid or spironolactone and furosemide in man (Homeida et al., 1977). 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 (21.5μg/min) was considerably less than the ED_{50} (69.8μg/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 (Kaojarern et al., 1982). After oral administration, amounts of furosemide more persistently approached that amount with maximal efficiency; thereby 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 (Fig 5) (Brater, 1983). Cumulative areas of deviation of the different study groups are quantified in the figures. Oral administration and pretreatment 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.

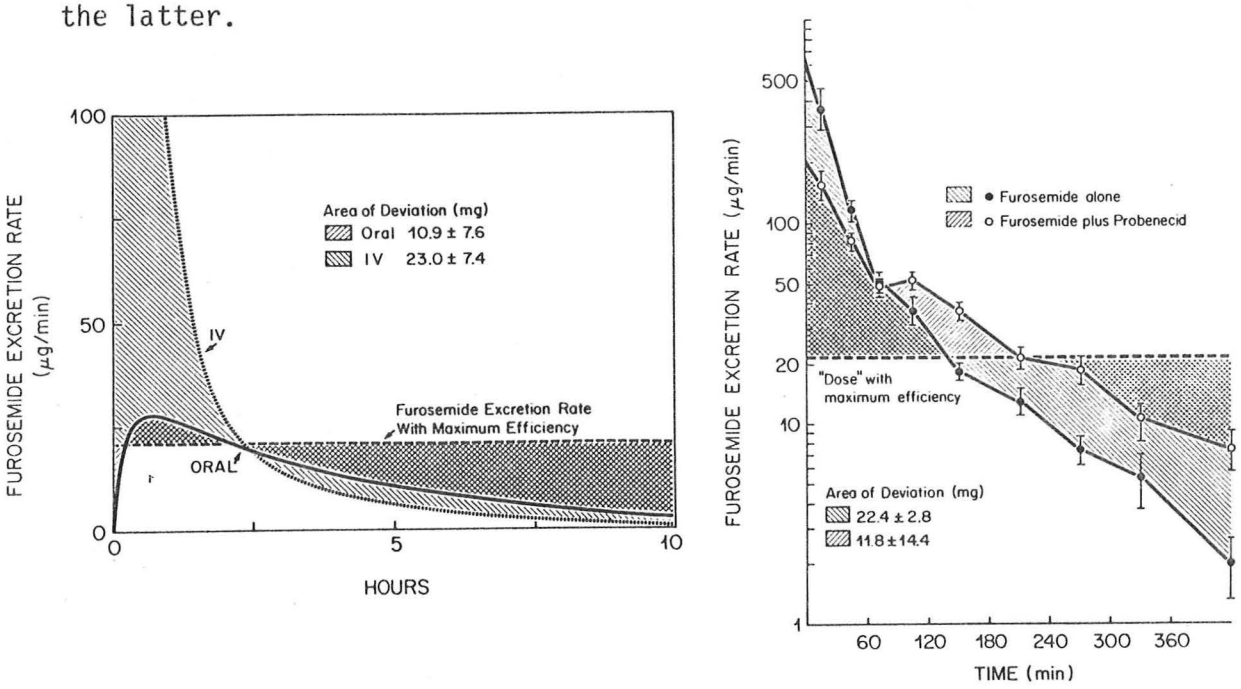


Fig 4: Time course of urinary furosemide after oral and intravenous dosing. Shading depicts the deviation from the urinary amount of furosemide calculated to be maximally efficient with the area of this deviation quantified in the figure. (From Kaojarern et al, 1982).

Fig 5: Effect of probenecid on the deviation of urinary furosemide from the maximally efficient amount. Schematic is as in Figure 4. (From Brater, 1983).

An extrapolation of these data is that patients should respond better to a continuous infusion of furosemide than to bolus administration. Subsequently, this potential strategy will be discussed for patients refractory to large doses of diuretics.

In summary, the determinants of response to furosemide are as shown in Table I. From a pharmacokinetic perspective, overall response 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, curve.

TABLE I. DETERMINANTS OF RESPONSE TO FUROSEMIDE

Pharmacokinetic Determinants
- Total amount of drug reaching the urine
  - Dose
  - Amount absorbed if given by mouth
  - Capacity for active secretion at the proximal tubule
- Time course of delivery of drug into the urine
  - Capacity for active secretion

Pharmacodynamics of response - the concentration versus 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 consider all these determinants of response which have only recently become more fully elucidated.

3. Clinical Conditions of Diuretic Resistance

3.1 Nonsteroidal Anti-inflammatory Drugs

The effect of nonsteroidal anti-inflammatory drugs (NSAID's) to decrease the natriuretic response to loop diuretics is a good example of using a pharmacologic approach to probe the mechanisms of diuretic resistance and also to provide insight into the physiologic role of renal prostaglandins (PG's). Clinically, on the other hand, this drug interaction is of minor importance, for its magnitude is small and can be readily overcome by increased doses of diuretic.

Initial observations that treatment with indomethacin decreased the natriuretic response to furosemide lead to speculation that endogenous PG's might be mediators (or at least modulators) of the effects of loop diuretics (Patak et al., 1975). A host of studies followed using a variety of methods, most of which arrived at the same conclusion (for review, see Anderson et al., 1976; Dunn and Hood, 1977; Dunn and Zambraski, 1980; Gerber et al., 1982; Lee et al., 1976; Levenson et al., 1982; Stokes and Kokko, 1980). During the early pursuit of this area of research, however, a key potential mechanism of the interaction was often overlooked; namely, indomethacin and other NSAID's are organic acids which could compete with loop diuretics for active transport into the lumen. Thereby, the NSAID's could decrease access of furosemide and other loop diuretics to the site of action and decrease response by this drug-drug interaction. Any effect on PG's could, in fact, merely represent an epiphenomenon.

Consequently, we and others have gathered data assessing potential pharmacologic determinants of diuretic response in the setting of administration of NSAID's. Table II shows the effect of several different NSAID's on the natriuretic response to furosemide (Chennavasin et al., 1980; Brater et al., 1985) documenting minor quantitative differences in the effect but that all are qualitatively similar. Table III shows the lack of effect of these NSAID's on total amounts of furosemide appearing in urine. Consequently, the interaction cannot be accounted for by a decrease in the amount of diuretic reaching the active site.

TABLE II. EFFECT OF VARIOUS NSAID'S TO DECREASE RESPONSE TO 40 mg OF INTRAVENOUS FUROSEMIDE

(From Chennavasin et al., 1980; Brater et al., 1985)

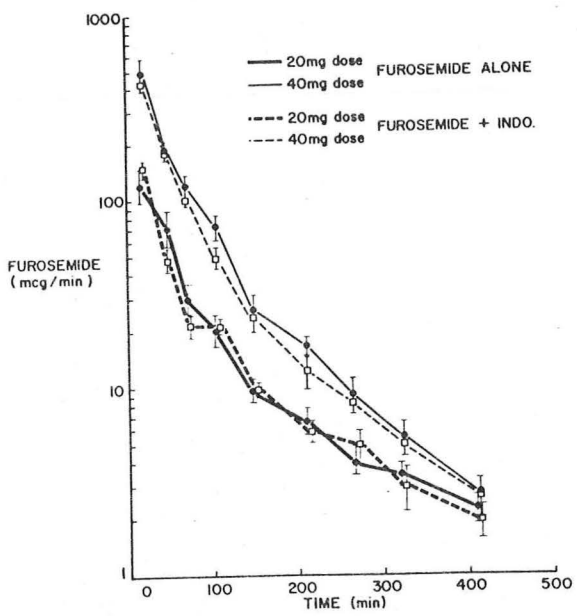
Drug	% Decrease in Sodium Excretion
Ibuprofen	32
Indomethacin	30
Naproxen	14
Sulindac	26

TABLE III. EFFECT OF NSAID'S ON URINARY FUROSEMIDE EXCRETION (40 mg IV DOSE)

(From Chennavasin et al., 1980; Brater et al., 1985)

Drug	Urinary Furosemide Excretion (mg)	
	Placebo	Furosemide
Ibuprofen	21±1	21±1
Indomethacin	20±2	19±2
Naproxen	21±1	24±1
Sulindac	21±1	20±1

Competition of NSAID's for secretion of furosemide might affect the time course of delivery of the diuretic into urine without changing the total amount. Figure 6 shows that indomethacin and Figure 7 that ibuprofen, naproxen and sulindac do not affect the time course of drug delivery. Consequently, a pharmacokinetic interaction cannot explain the effect of NSAID's on response to furosemide.



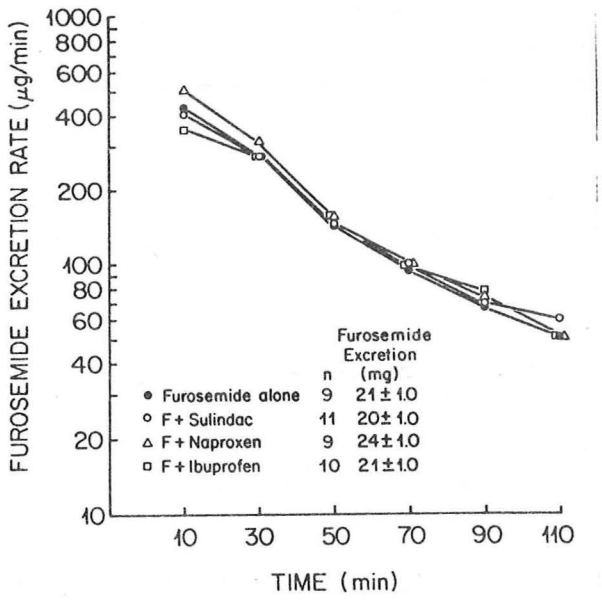


Fig 6: Lack of effect of indomethacin on the time course of urinary excretion of furosemide. (From Chennavasin et al, 1980).

Fig 7: Lack of effect of sulindac, naproxen or ibuprofen on total and time course of urinary excretion of furosemide. (From Brater et al, 1985).

This interaction, then, must represent a pharmacodynamic one which can be confirmed by assessing the relationship between urinary furosemide and sodium excretion; i.e., a "dose"-response curve. This relationship is shown for indomethacin in Figure 8 and for ibuprofen, naproxen and sulindac in Figure 9, demonstrating that all of these NSAID's have the same qualitative effect to blunt the response to furosemide (Chennavasin et al., 1980; Brater et al., 1985).

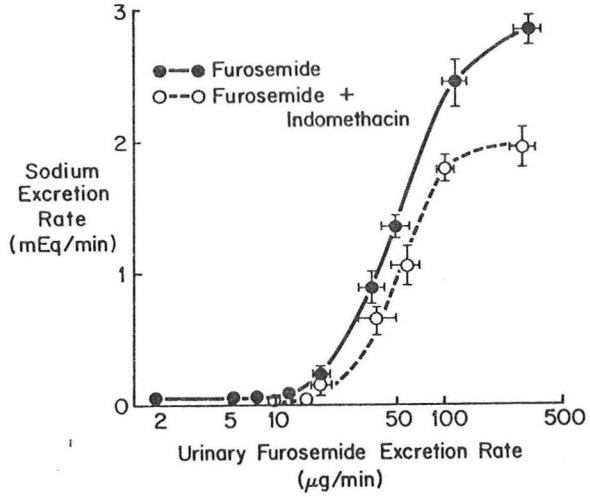


Fig 8: Effect of indomethacin on the relationship between urinary furosemide and response. (From Chennavasin et al, 1980).

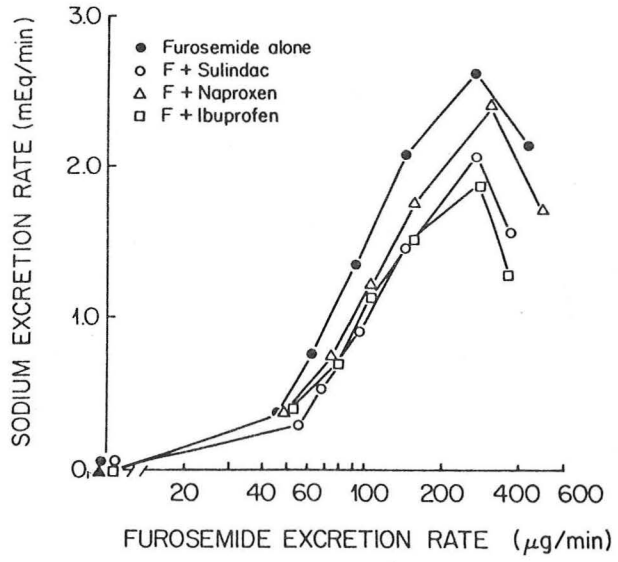


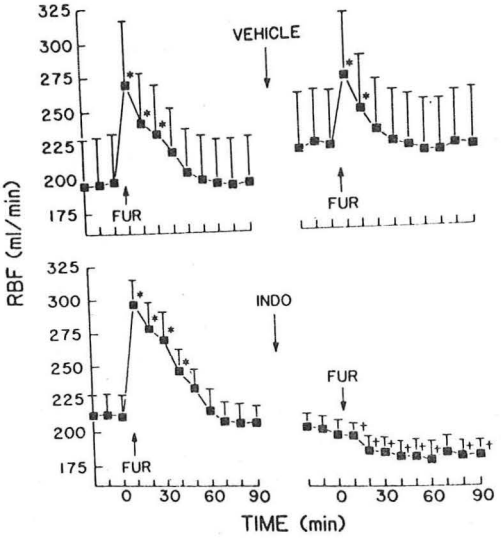
Fig 9: Effect of sulindac, naproxen, and ibuprofen on the relationship between urinary furosemide and response. (From Brater et al, 1985).

What is the mechanism of this pharmacodynamic interaction? Renal PG's are known to play a potential role in renal hemodynamics and in tubular sodium homeostasis (for review, see Clive and Stoff, 1984; Dunn and Zambraski, 1980; Dunn, 1984; Garella and Matarese, 1984; Gerber et al., 1982; Levenson et al., 1982; McGiff and Wong, 1979). In turn, administration of loop diuretics causes both increases in renal blood flow and blocks tubular sodium reabsorption both of which contribute to the overall natriuresis caused by these agents (Bourland et al., 1977; Burg, 1976; Dikshit et al., 1973; Kirkendall and Stein, 1968; Puschett and Goldberg, 1968; Tattersfield et al., 1974). Consequently, inhibition of renal PG's by NSAID's in the setting of administration of a loop diuretic could result in a decrease in the natriuretic effect by affecting the hemodynamic component of response, the tubular component or a combination.

A number of studies have documented that NSAID's can block the increase in renal blood flow caused by loop diuretics (Gerber and Nies, 1980ab, 1981; Halushka et al., 1979; Williamson et al., 1974, 1975ab, 1978; Bailie et al., 1975; Blasingham et al., 1980; Data et al., 1978; Henrich et al., 1978; Kirschenbaum, 1977). That this is the predominant mechanism by which NSAID's affect the response to furosemide has recently been confirmed by Nies et al (1983).

Prior studies from their group had shown that the peripheral vasodilating effect of furosemide did not occur in sodium replete subjects and that its occurrence in sodium deprived subjects could be blocked by indomethacin (Gerber and Nies, 1980b). Hence, this hemodynamic effect was mediated by PG's, and it could be suppressed physiologically by sodium repletion. This finding led to studies more specifically assessing

renal hemodynamics (Nies et al., 1983). In sodium-depleted dogs, furosemide increased renal blood flow and as expected caused a striking natriuresis. Administration of indomethacin in this setting totally blocked the increment in renal blood flow (Fig 10) and decreased peak sodium excretion by 26%. In contrast, in sodium repleted dogs, furosemide did not increase renal blood flow and administration of indomethacin had no effect on either renal hemodynamics or furosemide-induced natriuresis (Fig 11). Consequently, indomethacin had no effect on the tubular response to furosemide implying that the mechanism of the NSAID-loop diuretic interaction is blockade of the renal hemodynamic effect of the diuretic by inhibition of PG synthesis. Recently, this mechanism has been confirmed in a group of patients with cirrhosis in whom acetylsalicylic acid decreased response to furosemide by blocking its renal hemodynamic effect (Planas et al., 1983).



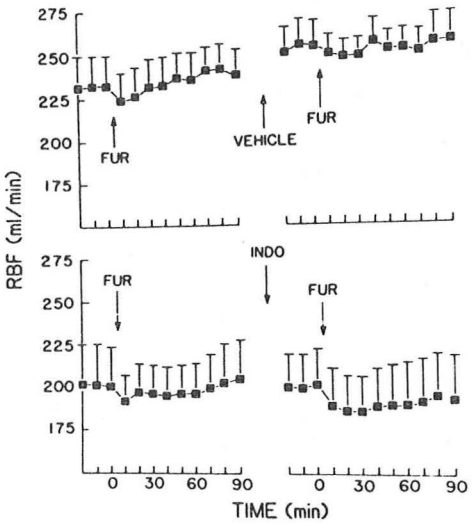


Fig 10: Effects of intravenous furosemide to increase renal blood flow in sodium depleted dogs (left panel) and the blockade of this effect with indomethacin (right panel). (From Nies et al, 1983).

Fig 11: Lack of effect of furosemide or of indomethacin on renal blood flow in sodium replete dogs. (From Nies et al, 1983).

In summary, the NSAID-loop diuretic interaction is pharmacodynamic rather than pharmacokinetic in nature. Its mechanism is the blockade by the NSAID of increases in renal blood flow mediated by increases in PG's which are in turn caused by of the loop diuretics. Clinically, this can be compensated for by increasing the dose of the diuretic.

3.2 Renal Disease

3.2.1 Renal Insufficiency

Patients with azotemia often require large doses of loop 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 previously, a series of studies have suggested that a primary cause of diuretic resistance in patients short of end stage renal failure is decreased access of drug to the site of action (Rose et al., 1976abc). As a consequence, large doses may be required to deliver enough diuretic into the tubular lumen to cause a response. This strategy is simply using principles of mass action. Two mechanisms exist by which secretion of furosemide might be reduced in azotemia: 1)by decreased renal blood flow, less furosemide reaches secretory sites and/or 2)accumulated endogenous organic acids block transport. The studies by Rose et al. (1976abc) in dogs and in man showed the renal clearance of furosemide to be decreased in moderate uremia more so than that of tetra-ethylammonium (TEA) but similar to that of para-amino-hippurate (PAH). The latter is an organic acid avidly secreted at the proximal nephron and subject to competition from endogenous organic acids of uremia. On the other hand, TEA, is an organic base that is also avidly secreted. Since accumulated acids do not compete for its secretion, it becomes a better index of renal blood flow in azotemia

than does PAH. Since effects of uremia on the renal clearance of furosemide were comparable to effects on clearance of PAH, and since both were diminished to a considerably greater extent than clearance of TEA, it is clear that a major limitation of access of furosemide into the urine is diminished secretion rather than due to decreased renal blood flow.

The effect of the decline in renal clearance of furosemide is to decrease both total amounts of drug reaching the urine and to delay the time course of its appearance (Rane et al., 1978; Andreasen et al., 1978; Beermann et al., 1977; Cutler et al., 1974). Presumably, the tubule responds normally to diuretic reaching the active site, though no data have been published to fully substantiate this hypothesis. That it is correct, however, is suggested by recent studies in the elderly.

The inexorable decline in renal function in the elderly results in decreased delivery of total amounts of furosemide into urine and to decreased response (Andreasen et al., 1983, 1984; Kerremans et al., 1983). In a group of normal elderly patients, the renal clearance of furosemide is approximately half that of young patients (Table IV).

TABLE IV. EFFECT OF AGE ON RENAL CLEARANCE (ml/min) OF FUROSEMIDE (MEAN ± SEM)

Young	Elderly	Reference
114±33	75±9	Andreasen et al., 1983
	40±18	Kerremans et al., 1983

These values are comparable to those of patients with mild to moderate renal insufficiency. Despite decreases in global renal function, these patients respond normally to amounts of furosemide reaching the urine (Kerremans et al., 1983; Andreasen et al., 1984) (Fig 12).

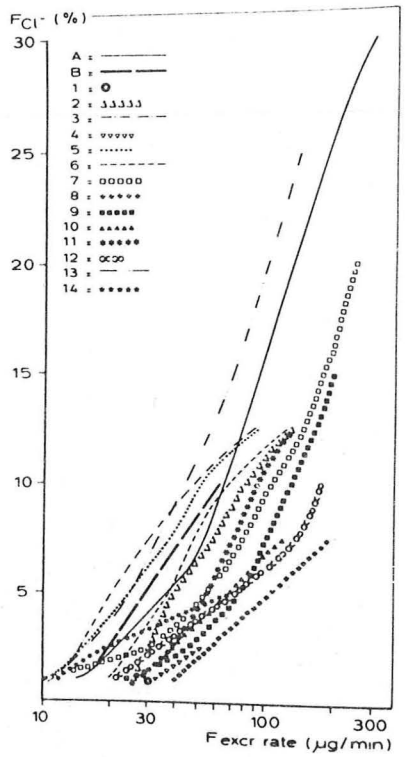


Fig 12: Relationship between urinary furosemide excretion and fractional excretion of chloride. A represents a young normal subject (age 32). The remaining curves represent elderly subjects whose only abnormality is the decreased renal function of aging. (From Kerremans et al, 1983).

In summary, in patients with renal insufficiency, the pharmacodynamics of response are normal. Decreased response appears to occur because of decreased delivery of drug to the site of action. Forcing sufficient amounts of drug into the urine will result in a natriuresis presuming filtration of sodium has not become limiting. In patients requiring large doses of diuretics, the risk of ototoxicity might become limiting. In such cases, use of combination therapy using metolazone or hydrochlorothiazide may be effective by blocking sodium reabsorption at multiple tubule sites (Wollam et al., 1982).

3.2.2 Nephrotic Syndrome

Patients with nephrotic syndrome can require large doses of loop diuretics even if they have a normal (or relatively normal) creatinine clearance. Since their renal function is normal, one would anticipate that their handling of furosemide is also normal. Though some differences in pharmacokinetics occur due to decreased serum protein binding of the drug, both the total amount of diuretic delivered into the urine and its time course are identical to those in normal subjects (Rane et al., 1978; Keller et al., 1982) (Fig 13). Consequently, changes in pharmacokinetics of furosemide do not explain the resistance that occurs in this clinical setting. As one might predict, there is a decrease in the pharmacodynamics of response manifested by an altered "dose"-response curve to furosemide (Fig 14).

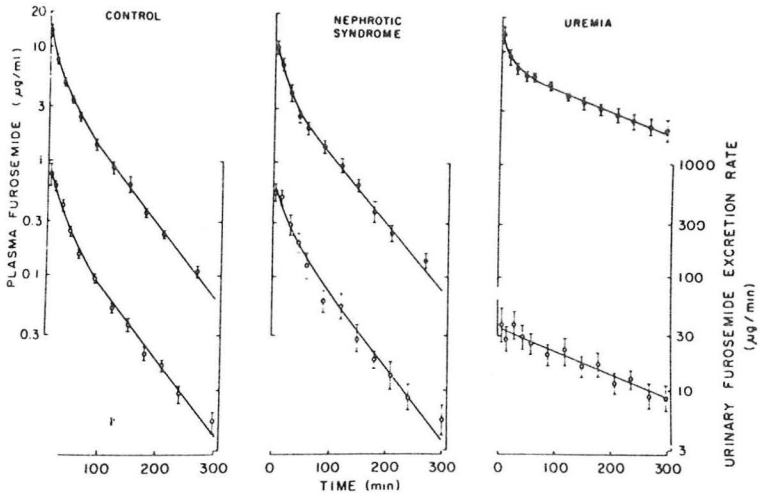


Fig 13: Time course of serum (left axis, solid symbols) and urinary (right axis, open symbols) furosemide in normal subjects and in patients with nephrotic syndrome and uremia. (From Rane et al, 1978).

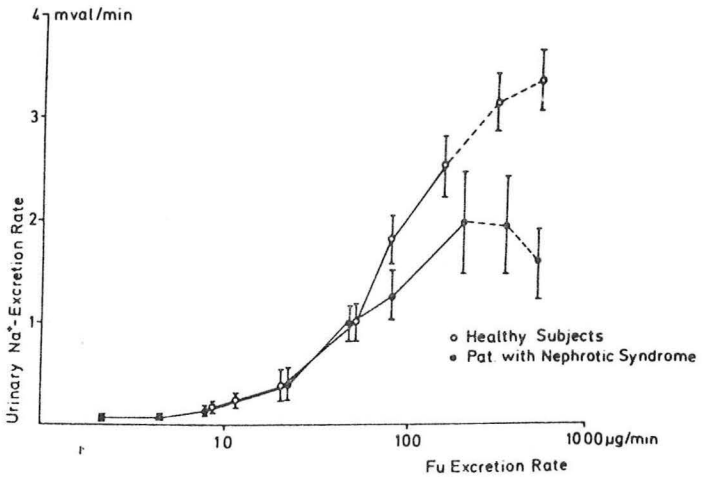


Fig 14: Relationship between urinary furosemide excretion and response in normal subjects compared to patients with nephrotic syndrome. (From Keller et al, 1982).

A potential mechanism for this abnormal response to loop diuretics in nephrotic syndrome has been explored by Green and Mirkin (1980,1981). They rendered rats nephrotic by pretreatment with puromycin aminonucleoside. Sixty to 95% of the furosemide excreted into urine was bound to the urinary protein, making it unable to interact with its nephron site of action. This was reflected by a decrease in responsiveness to furosemide that was indirectly related to the amount of urinary protein (Fig 15). In other words, the greater amount of protein in the urine, the greater amount of diuretic bound, causing less furosemide to be available to exert a pharmacologic effect. One would presume that response of the tubule would be normal if assessed relative to unbound or free amounts of furosemide in urine. This hypothesis has not been tested and is the object of current studies in our laboratory.

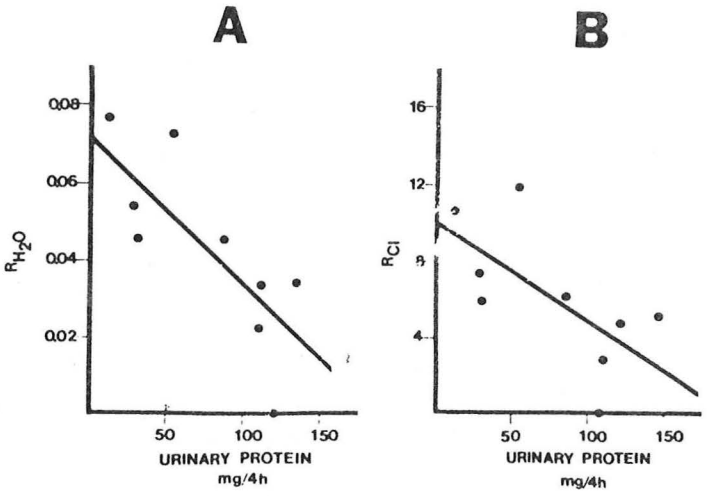


Fig 15: Response to furosemide assessed as diuresis (panel A) or as chloruresis (panel B) as a function of urinary protein. (From Green and Mirkin, 1980).

In summary, resistance to loop diuretics in patients with nephrotic syndrome and relatively normal renal function is pharmacodynamic in nature. The mechanism of this interaction may entail binding of the diuretic to urinary protein. If so, strategies may be developed in the future to cause endogenous displacement from protein binding. In the interim, several other approaches may prove fruitful. Administering large doses of furosemide would result in relatively more unbound drug in the urine causing greater effect. In addition, frequent administration of small doses (though sufficiently large to have some effect individually) could result in a cumulative natriuresis substantial enough to be beneficial. In the extreme this could be accomplished with a continuous intravenous infusion. Lastly, combined use of thiazide diuretics or metolazone would presumably have the same beneficial additive (or even synergistic) effect as occurs in renal insufficiency or in patients with congestive heart failure (see below).

3.3 Hepatic Cirrhosis

Though loop diuretics are infrequently administered to patients with cirrhotic liver disease, when they are used, resistance to their effects is frequent. Minor differences in the pharmacokinetics of furosemide have been observed in this population of patients due to decreased serum protein binding. However, renal handling of the drug appears to be identical to that of normal subjects so that total amounts and the time course of entry of furosemide into urine are not different from normal and cannot explain the resistance that occurs (Allgulander et al., 1980; Sawhney et al., 1981; Keller et al., 1981; Verbeeck et al., 1982; Gonzalez et al., 1982) (Table V) (Figure 16). Moreover, Gonzalez et al. (1982) have explored whether a portion of an administered

dose of furosemide might be sequestered into the ascitic fluid, thereby limiting its access to the kidney. It appears that the diuretic can diffuse into the ascitic compartment, but at most this accounted for only 8% of an administered dose.

TABLE V. RENAL CLEARANCE (ml/min) OF FUROSEMIDE IN CIRRHOSIS (MEAN ± SEM)

Normals	Cirrhotics	Reference
95±10	102±16	Allgulander et al., 1980
106±12	103±14	Sawhney et al., 1981
126±12	118±11	Keller et al., 1981
87±8	66±12	Verbeeck et al., 1982

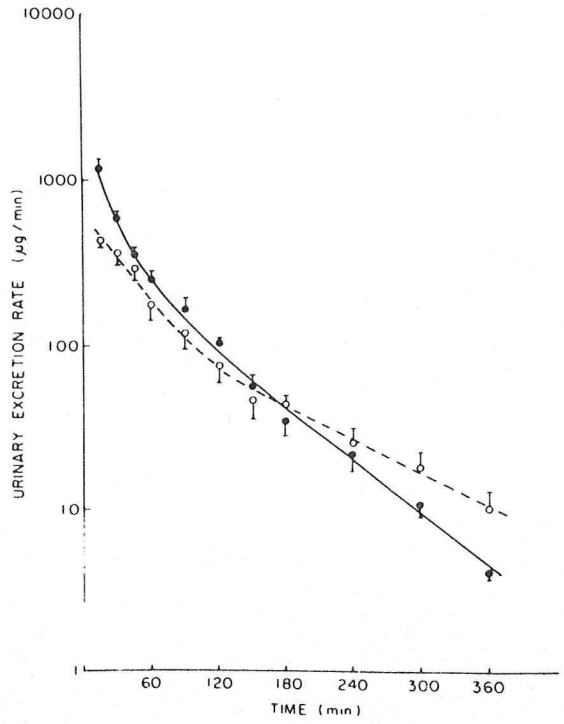


Fig 16: Time course of urinary excretion of furosemide in normal subjects (closed symbols) and in patients with cirrhosis (open symbols). (From Verbeeck et al, 1982).

Consequently, similar to results in patients with nephrotic syndrome, pharmacokinetic mechanisms cannot be invoked as etiologic to diuretic resistance in patients with cirrhosis and a pharmacodynamic mechanism must account for the abnormal response (Fig 17). However, in these patients, the mechanism by which resistance occurs is unclear. It presumably relates to the pathophysiology of sodium retention in this condition.

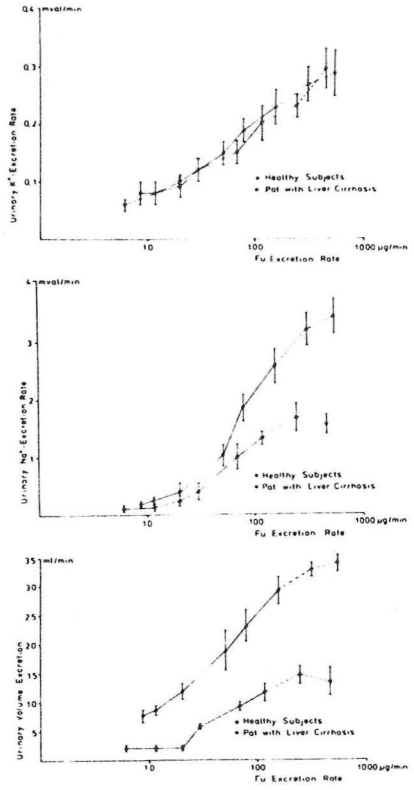


Fig 17: Relationship between urinary furosemide excretion and response assessed as potassium excretion (upper panel), sodium excretion (middle panel) and volume excretion (lower panel) in normal subjects and in patients with cirrhosis. (From Keller et al, 1981).

In view of the foregoing, what treatment strategies might prove successful? Large doses could result in more time spent at the top of the "dose" response curve. Alternatively, one might also administer frequent small doses. Neither strategy would be successful if the patient had an extremely skewed or suppressed dose response curve and little or nothing would be gained by escalating doses other than toxicity. In such extreme patients, maneuvers must be invoked to either reverse the pathophysiology, such as a peritoneovenous shunt (Bendis et al., 1979) (Fig 18) or to use combinations of diuretics. Both these approaches presumably are successful by increasing delivery of sodium to the site of action at which the loop diuretics have their effect. Further studies are needed to confirm this postulate.

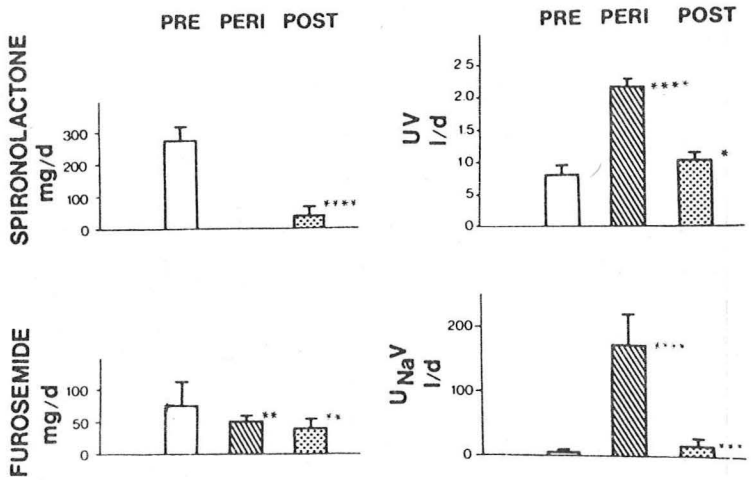


Fig 18: Response to furosemide before, at the time of and after placement of a peritoneovenous shunt in patients with cirrhosis and ascites. In the peri-operative period, smaller doses of furosemide result in greater diuretic and natriuretic responses. (From Blendis et al, 1979).

3.4 Congestive Heart Failure

Patients with congestive heart failure (CHF) probably represent the most common circumstance in which resistance to furosemide is encountered clinically. Many clinicians have presumed that considerable changes in the pharmacokinetics of loop diuretics would occur in such patients, particularly in absorption of drug from the gastrointestinal tract. Edema of the gut, changed intestinal motility and perfusion, and a variety of other factors have been cited as potentially causal of drug malabsorption in CHF (Benet et al., 1976; Benowitz and Meister, 1976). Recent data support some abnormalities of absorption, but their contribution to diuretic resistance remains unclear.

After intravenous dosing of furosemide, the pharmacokinetics are relatively normal. A study from our laboratory demonstrated a trend for decreased total and renal clearance of the diuretic (Brater et al., 1982) (Table VI). However, when these parameters were correlated to creatinine clearance, it was apparent that differences from normal were caused by decreased renal function and that overall the time course of delivery of drug into urine was the same as in normals (Fig 19). Hence, patients with CHF and relatively normal renal function deliver the same amounts of furosemide into the urine over the same time course as do normal subjects. Similar results have been shown with bumetanide (Brater et al., 1984). Consequently, after intravenous dosing resistance to furosemide cannot be explained by pharmacokinetic factors and is caused by changes in the pharmacodynamics of response (Brater et al., 1980) (Fig 20). The pattern of the "dose"-response curve in such patients is similar to that of patients with nephrotic syndrome and with cirrhosis. The mechanism of this change is unknown but presumably represents the pathophysiology of sodium retention in CHF.

TABLE VI. PHARMACOKINETICS OF FUROSEMIDE IN PATIENTS WITH CONGESTIVE HEART FAILURE (MEAN ± SD)

(From Chennavasin et al., 1980)

	Half-Life (min)	Volume of Distribution (L/Kg)	Clearance (ml/min/Kg)	Renal Clearance (ml/min/Kg)
CHF (n=16)	122±64	0.20±0.09	1.40±1.24	0.56±0.70
Normals (n=8)	91±27	0.35±0.34	1.84±1.02	1.05±0.65

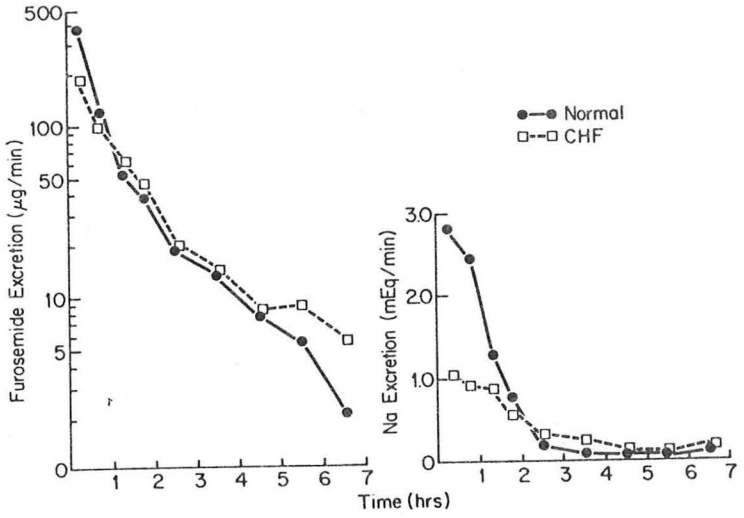


Fig 19: Time course of urinary furosemide excretion (left panel) and response (right panel) in normal subjects and in patients with congestive heart failure (CHF).

As noted previously, many have assumed drugs to be malabsorbed in patients with CHF. However, we and others have shown that the same total amounts of furosemide are absorbed in patients with CHF as in normal subjects with bioavailabilities in 25 normal subjects of 38±20%

compared to 31±12% in CHF (mean ± SD) (Greither et al., 1979; Brater et al., 1982). Hence, an effect of CHF to diminish the total amount of drug absorbed cannot be invoked to explain lack of response to furosemide given by mouth in such patients.

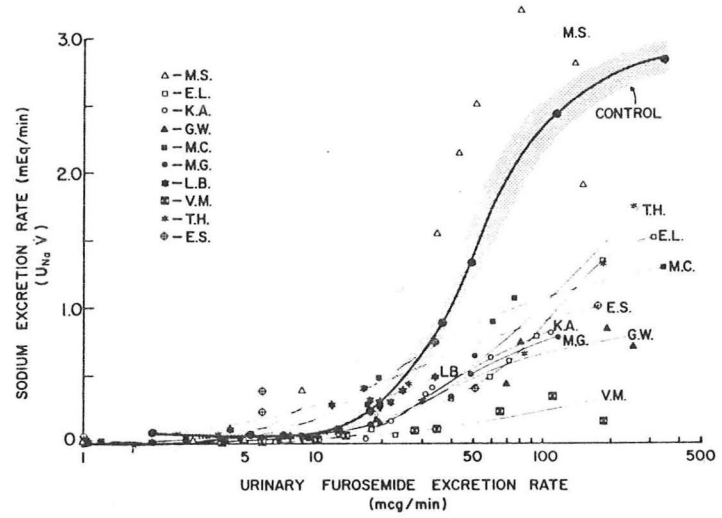


Fig 20: Relationship between urinary furosemide excretion and response in normal controls and in individual patients with congestive heart failure. (From Brater et al, 1980).

Interestingly, however, it appears that the time course of drug absorption is affected by CHF and that the magnitude of the effect is dependent upon the severity of the patient's disease. In patients with stable, compensated CHF, absorption is delayed so that the time at which peak amounts of either bumetanide or furosemide appear in the urine is prolonged two-fold and the peak excretion rates of diuretic attained are approximately half those of normal subjects (Brater et al., 1984) (Table VII). Moreover, if the time course of absorption of furosemide is assessed in the same patient while both decompensated and again when

compensated, the abnormalities noted above are more pronounced when the patient is in florid CHF (Vasko et al., 1985) (Table VIII) (Fig 21). The delay in absorption and concomitant decreased peak concentrations of diuretic attained, albeit with normal total absorption of drug, could contribute to the diuretic resistance that occurs with oral dosing in patients with CHF. Whether quantitatively this component is as important as the changed pharmacodynamics of response is unknown at this time and worthy of further study.

TABLE VII. TIME COURSE OF APPEARANCE OF BUMETANIDE AND FUROSEMIDE IN URINE AFTER ORAL DOSING (MEAN ± SEM)

(From Brater et al., 1984)

BUMETANIDE

	1 mg		2 mg	
	CHF	Normal	CHF	Normal
Time to peak (min)	180±19	72±7	137±17	88±9
Peak excretion rate (μg/min)	0.9±0.2	1.9±0.2	1.9±0.4	4.8±0.7

FUROSEMIDE

	40 mg		80 mg	
	CHF	Normal	CHF	Normal
Time to peak (min)	180±30	108±20	197±26	90±13
Peak excretion rate (μg/min)	19±5	59±17	35±14	68±16

TABLE VIII. TIME COURSE OF FUROSEMIDE ABSORPTION IN DECOMPENSATED VS. COMPENSATED CHF

(MEAN ± SEM)

(From Vasko et al., 1985)

	Decompensated	Compensated
Time to peak (min)	242±25	177±21
Peak serum concentration (μg/ml)	1.11±0.24	1.57±0.36

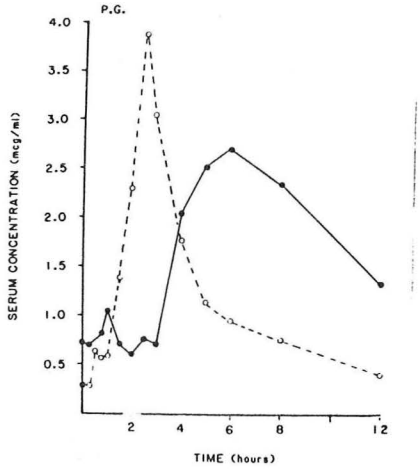


Fig 21: Representative time course of urinary furosemide excretion in a patient with congestive heart failure after oral dosing when in the decompensated state (closed symbols) and again when compensated (open symbols). From Vasko et al, 1985).

In summary, after intravenous dosing to patients with CHF, resistance to loop diuretics is pharmacodynamic in nature. After oral dosing, a pharmacokinetic component of altered time course of absorption of drug may also be contributory. To circumvent the latter component, drug can be administered intravenously. However, if for some reason this were not possible, a large oral dose should eventually result in delayed attainment of amounts of drug in urine comparable to those after intravenous dosing. Since peak concentrations are approximately half normal in this circumstance and since the bioavailability of furosemide is approximately 40%, an oral dose four times higher than an effective intravenous dose would be necessary. Since bumetanide is 80% bioavailable, an oral dose twice the effective intravenous dose should suffice.

In patients resistant to intravenous doses of loop diuretics, strategies similar to those suggested for cirrhosis can be attempted. A large dose can be given to spend more time at the plateau of the "dose"-response curve. Alternatively, frequent administration of smaller, effective doses could result in an overall beneficial, cumulative effect. Theoretically, administering the dose as a continuous infusion over several hours should be more effective than giving the same dose as an intravenous bolus, and this approach could be attempted (Kaojarern et al., 1982; Lawson et al., 1978). If these strategies prove unsuccessful, other treatments of the primary disease should be instituted if they have not been already. Improving cardiovascular hemodynamics by afterload reduction has been shown to increase the response to furosemide (Nomura et al., 1981). A last maneuver that can be employed is to add diuretics such as metolazone that decrease sodium reabsorption at nephron sites proximal to the site of action of the loop diuretics. Presumably

by blocking solute reabsorption proximally, these diuretics allow delivery of sodium to the loop of Henle where the activity of the loop diuretics can then become manifest often resulting in a synergistic rather than additive response (Sigurd et al., 1975; Oster et al., 1983; Gunstone et al., 1971; Epstein et al., 1977; Ram and Reichgott, 1977; Olesen et al., 1970; Olesen, 1971; Olesen and Sigurd, 1971; Sigurd and Olesen, 1978). If one invokes this strategy, it is important to realize that the effect may not occur quickly, since metolazone in particular is absorbed very slowly. Hence, if an effect is needed quickly, one can administer acetazolamide intravenously followed by a loop diuretic and accomplish similar pharmacology (Rodicio and Hernando, 1977).

Conclusion

The different mechanisms for diuretic resistance require different therapeutic strategies. Table IX offers a summary of what is known to date, much of which has been recently learned by applying pharmacologic approaches to this often vexing clinical problem. Many potentially fruitful avenues of research remain, the results of which should allow more rational, specific, and hopefully successful therapy.

TABLE IX. SUMMARY OF MECHANISMS OF DIURETIC RESISTANCE AND POSSIBLE THERAPEUTIC STRATEGIES

Clinical Condition	Why it Happens	What to do About it
Nonsteroidal anti-inflammatory drugs	Blocks PG-mediated hemodynamic effect-dynamic	Larger Doses
Renal insufficiency (including aging)	Decreased access of diuretic to the urine-kinetic	Larger doses Combination therapy
Nephrotic syndrome	Binding of diuretic to urinary protein-dynamic ?Other dynamic causes	Larger doses Frequent small doses-IV infusion Combination therapy
Hepatic cirrhosis	Abnormal dynamics of response-mechanism unclear	Larger doses Frequent small doses Alternative treatments of primary disease; e.g. peritoneo-venous shunts Combination therapy
Congestive heart failure Oral dosing	Delayed and prolonged absorption-kinetic	IV dosing
Oral and IV dosing	Abnormal dynamics of response-mechanism unclear	Larger doses Frequent small doses-IV infusion Alternative treatments of primary disease; e.g., afterload reduction Combination therapy

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