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Variability in Human Drug Response
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Effect of disease on the pharmacokinetic and pharmacodynamic determinants of response to diuretics

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ABSTRACT

Loop diuretics are used in all edematous disorders, but each disease represents a different pathophysiology. As such, the mechanisms by which response to diuretics is altered in these disorders differ. In turn, these differences in mechanism translate to differences in therapeutic strategy. For example, the primary mechanism accounting for diuretic resistance in patients with renal insufficiency is pharmacokinetic wherein inadequate amounts of diuretic reach the site of action within the lumen of the nephron. The appropriate therapeutic strategy is to administer large doses of diuretics to attain effective amounts of diuretic at the site of action.

In contrast, in patients with cirrhosis or congestive heart failure, the mechanism of diuretic resistance is pharmacodynamic wherein the nephron has a submaximal response to the diuretic. Large doses of diuretic are not helpful in this circumstance; rather modest doses should be administered more frequently or combinations of diseases affect response to diuretics should be used. Understanding pharmacokinetic and pharmacodynamic mechanisms by which diseases affect response to diuretics allows more rational therapy.

Key words: diuretics, edema, renal insufficiency, cirrhosis, congestive heart failure.

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INTRODUCTION

Diuretics are used in primary disorders of the heart (congestive heart failure), kidney (renal insufficiency and nephrotic syndrome), and liver (cirrhosis). The goal of therapy is the same in each of these disorders; namely, to cause negative salt and water balance. However, since each of these edematous disorders involves a different primary organ system, the pathophysiology differs among them. In all of the edematous disorders, resistance to diuretics occurs wherein natriuretic response is less than occurs in healthy persons. The mechanism for this altered response differs in all of the conditions enumerated above. Importantly,

understanding these differences allows translation to therapeutic strategies to optimize use of diuretics.

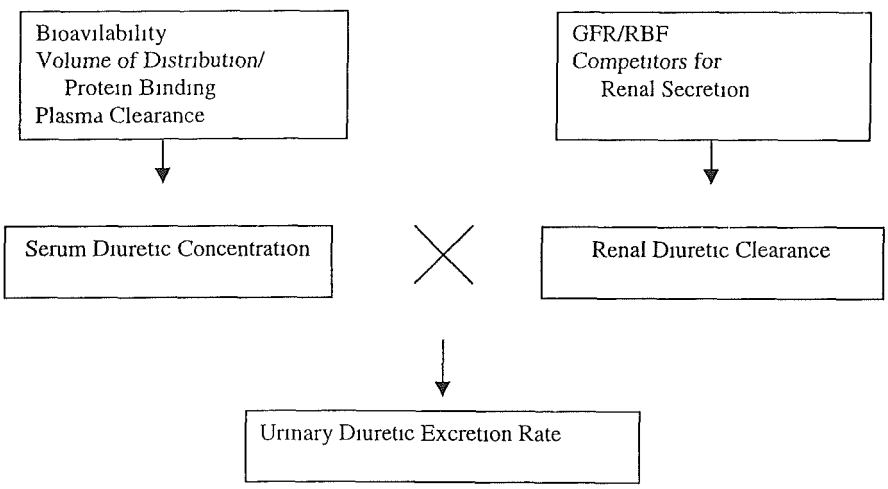
DETERMINANTS OF DIURETIC RESPONSE

All diuretics except spironolactone exert their effects from the lumen of the nephron [1-3]. As such, they must reach the urine to cause a diuresis. Routes of entry into the urine vary among diuretics. Osmotic diuretics are filtered at the glomerulus whereas other agents are actively secreted from blood into urine at the proximal tubule. Acetazolamide, loop diuretics, and thiazide diuretics are secreted by the organic acid transporter [2,4] and amiloride and triamterene gain entry via the organic base transport pathway [5,6].

Determinants of access of a diuretic into the urine can be quantified by various pharmacokinetic parameters (Table 1). Urinary diuretic excretion rate is the product of the concentration of diuretic in serum and renal clearance of the diuretic. The determinants of each of these parameters are shown in Table 1. The influence of edematous disorders on these parameters will be discussed below.

Once diuretic reaches its tubular site of action, natriuresis is a function of response of the nephron to the diuretic, so-called pharmacodynamics of response. Such response is a function of the interaction between the diuretic and the solute reabsorptive transporter it inhibits. In addition, overall response is affected by activity at other nephron sites. For example, in a patient with heart failure a loop diuretic may "normally" inhibit the Na^+-K^+-$2Cl^-$ transporter, but overall natriuresis may be subnormal because of increased solute reabsorption at other nephron sites such as the proximal and/or distal tubule. Ways in which edematous disorders can influence the pharmacodynamics of diuretic response will also be discussed below.

Table 1.
Pharmacokinetic determinants of diuretic response



DISEASE EFFECTS ON PHARMACOKINETICS OF DIURETICS

Bioavailability

Presumably the edematous condition also includes edema of the intestinal wall, which might adversely affect drug absorption. However, several studies have shown that the bioavailability of loop diuretics is the same in patients with renal insufficiency, with both compensated and decompensated heart failure and in patients with cirrhosis [7-16]. Thus, the same quantity of diuretic is absorbed in edematous patients as compared to their healthy counterparts. The rate of absorption of loop diuretics is slowed in patients with edema, and this slowing appears to be greater in decompensated patients [13]. Whether this change in rate of absorption affects diuretic response is unknown. In general, it is unlikely that changes in absorption account for disease effects on diuretic response.

Volume of Distribution/Protein Binding

All loop diuretics are highly bound to albumin, which causes them to have small volumes of distribution, restricted in large part to the intravascular space [1-3,17,18]. In hypoalbuminemic conditions, such as nephrotic syndrome or cirrhosis, albumin binding diminishes, volume of distribution increases, and serum concentration is less [19,20]. However, it appears that the avidity of the proximal tubular secretory pathway is such that this small change in volume of distribution has negligible effect on delivery of diuretic to the active site in the lumen of the nephron. As such, patients with cirrhosis [20-23] and with nephrotic syndrome [19,24,25] deliver normal amounts of loop diuretic into the urine. Overall, then, changes in volume of distribution and protein binding are not causal of altered diuretic response in patients with edematous disorders.

Plasma Clearance

Edematous disorders affect the clearance of loop diuretics differently. Plasma clearance can be divided into that derived from the kidney and that from the liver. As will be discussed subsequently, renal dysfunction decreases access of diuretic to the site of action. Renal dysfunction, however, does not decrease overall clearance of bumetanide [26,27] and torasemide [14], because both of these loop diuretics have substantial hepatic clearance [14,26-29]. Hepatic elimination pathways compensate for declines in renal clearance. In contrast, for furosemide, renal pathways of elimination dominate so that decreases in renal clearance also result in declines in overall clearance and increases in half-life [1-3,17,18].

Conversely, in patients with cirrhosis or the congestive hepatopathy of heart failure, hepatic and total plasma clearance of bumetanide [27] and torasemide [16] decline while furosemide [20-23] is unchanged. The decreased overall clearance of bumetanide and torasemide with preserved renal clearance allows more of these two diuretics to be excreted into the urine [16,27].

Thus, diuretic resistance due to decreases in plasma clearance of a diuretic occurs when renal clearance declines.

Renal Diuretic Clearance

Renal diuretic clearance can be affected by overall declines in renal function and/or by blocking the active secretion of the diuretic into the urine. In patients with renal dysfunction, not only is GFR and RBF decreased, but the accumulated endogenous organic acids of

azotemia compete with loop diuretics for active secretion [30,31]. Thus, by two mechanisms, decreased renal function results in diminished renal clearance of loop diuretics and concomitantly decreased access of loop diuretics to their site of action.

Overall, then, in terms of pharmacokinetic determinants of diuretic response, the edematous disorder in which pharmacokinetic factors are causal is renal insufficiency. In the other disorders, if renal function is satisfactory, adequate amounts of diuretic reach the site of action. The appropriate therapeutic strategy for patients with renal insufficiency is to administer sufficiently large doses to allow effective amounts of diuretic to reach the urinary site of action. In reference to Table 1, one is compensating for a decrease in renal clearance by increasing serum diuretic concentrations. This strategy is the rationale for the dosing algorithms that have been developed for patients relative to their level of renal function [32].

DISEASE EFFECTS ON PHARMACODYNAMICS OF DIURETICS

If one relates the amount of diuretic reaching the urinary site of action to natriuretic response, a sigmoidal concentration-response curve, as illustrated in Figure 1, is defined [1-3]. Changes in this relationship in edematous disorders reflect pharmacodynamic changes in response to a diuretic. Patients with nephrotic syndrome, cirrhosis, and congestive heart failure demonstrate downward shifts in this curve, as illustrated schematically in Figure 1 [1-3]. The maximal response or efficacy of the diuretic is diminished so that such patients will never have the same response as a healthy subject no matter how large a dose is administered. In

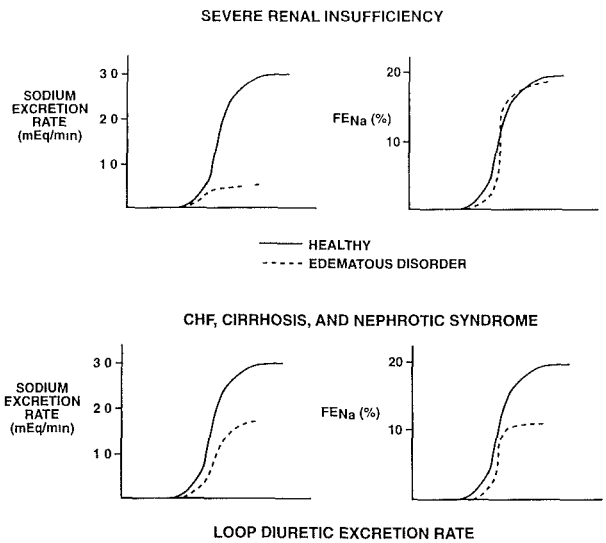


Figure 1. Illustration of the pharmacodynamics of response to loop diuretics and the change that occurs in patients with nephrotic syndrome, cirrhosis, or congestive heart failure.

fact, large doses should not be used in such patients. As discussed above, large doses are needed when there is decreased delivery of diuretic into the urine. Patients with nephrosis, cirrhosis, and heart failure do not have limitations of diuretic delivery if renal function is reasonably well preserved. Thus, large doses are superfluous. Rather frequent smaller doses should be given and/or combinations of diuretics should be used (vide infra).

The mechanism(s) by which changes in pharmacodynamics occur is unknown. Theoretically this could occur by a change in the interaction between the diuretic and the reabsorptive pathway it affects. Methods have not yet been developed that allow exploration of this possible mechanism. As noted previously, increased reabsorption of solute at either the proximal or distal tubule could also cause a diminished response to a loop diuretic. Though there has been no formal examination of these possible mechanisms, the fact that a synergistic response often ensues when a proximally or distally-acting diuretic is added to a loop diuretic implies that such mechanisms are indeed operative [33-38]. In turn, these observations suggest the utility of using combinations of diuretics in such patients. From a practical perspective, thiazide diuretics as distally-acting agents are the usual diuretics of choice since acetazolamide as the only currently available proximally-acting agent causes metabolic acidosis. In summary, then, in patients with pharmacodynamic causes of diuretic resistance, rather than using large doses of loop diuretics, combinations of loop and thiazide diuretics should be used.

SUMMARY

Changes in diuretic response can occur through pharmacokinetic or pharmacodynamic mechanisms. Renal insufficiency is the prototype of the former, which translates into a therapeutic strategy of administering large doses of loop diuretics. In patients with nephrotic syndrome, cirrhosis, and congestive heart failure, pharmacodynamic mechanisms dominate. The therapeutic strategy in these edematous disorders is to combine thiazide and loop diuretics. Thus, understanding the mechanisms by which disease affects response to diuretics extrapolates directly to therapeutics.

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Discussion: Effect of disease on the pharmacokinetic and pharmacodynamic determinants of response to diuretics

J. Urquhart:

If you continue with the normal subject which you began with, and you do not replace the salt and you come back and do the same thing the next day, you get a minuscule response. How come?

D.C. Brater:

There are two forms of tolerance that have been described. One occurs very quickly. If you administer a continuous intravenous infusion of a loop diuretic, within hours the response relative to the amount of diuretic reaching the site of action becomes less. Studies have shown that development of acute tolerance can be prevented simply by restoring volume losses. Presumably, this is occurring by activation of homeostatic reflexes to protect us against volume depletion. These reflexes are multiple and include activation of the renin-angiotensin system, activating the sympathetic nervous system and perhaps other pathways. All these stimuli increase proximal tubular reabsorption of sodium. There is another form of tolerance that develops with chronic therapy. It has been shown to occur in rats, and probably occurs in humans. If you block the reabsorption of solute in the thick ascending limb, sodium floods downstream, bathing distal nephrons. Over time (in the rat this takes about a week), these distal nephrons hypertrophy, and their reabsorptive capacity for sodium increases four to fivefold. Importantly from a therapeutic perspective these nephrons are where the thiazide diuretics exert their effects. As such if this pathophysiology is occurring and a thiazide diuretic is added, then patients have a substantial diuresis; not only is response restored, but a truly synergistic effect can occur with a massive diuresis.

D.A. Smith:

It was just a query on the nephrotic syndrome experiments you performed in the rat. I guess the critical point is the concentration of the albumin you use, which I think was 3.8 M, which is about half the molar concentration of the drug. I was wondering how that was chosen. And secondly, when I looked at the response curve you showed at the end of your presentation, it appeared to be superimposable before going to a lower maximum, whereas my understanding of the albumin would be that you had actually shift it to the right.

D.C. Brater:

The chosen albumin concentration was based on creating a rat model of nephrotic syndrome by administering an aminonucleoside. In these animals nephrones can be micropunctured to measure the amount of albumin that is present. We used such values to determine how much albumin to use. We performed prior *in vitro* studies to determine albumin binding to furosemide. In other words, there was substantial background work that determined selection of these different concentrations we used. We wanted them to be concentrations that reflected what one would see in that clinical condition and with using standard doses of diuretics. In terms of the response curve in the nephrotic syndrome, indeed the binding ought to shift that curve to some degree. The data I shoed are published from another group and are not our

studies, so I can not provide an explanation for that observations. In studies from the University of Michigan, a shift rightward in the relationship does occur.

L. Aarons:

I wonder whether you could comment on the use of creatinine clearance to mark active secretion, both for diuretics and, more generally, for other drugs?

D.C. Brater:

Creatinine clearance is a hybrid form of clearance, because there is a secretory component to creatinine's elimination in the urine. Its level of precision is quite low, and if you want to obtain a high-level of precision, one must use more gold standards such as inulin, GFR, or p-aminohippurate for renal blood flow. Usually GFR and RBF change in parallel. There are situations where this parallel relationship is disrupted. For example, probenecid blocks secretion of loop diuretics into the urine. In this circumstance the creatinine clearance has no relationship to the amount of drug reaching the site of action.