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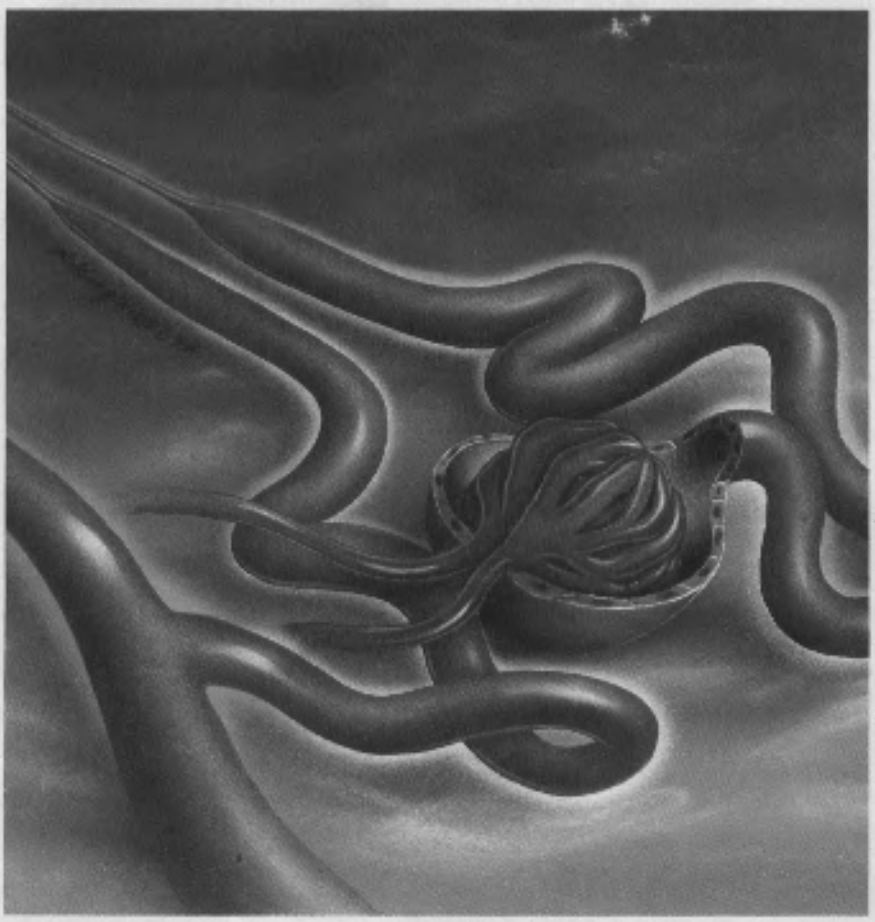
Diuretic Combinations in the Treatment of Edema: Rationale and Recommendations

Some edematous patients who are diuretic-resistant must be treated with two different classes of diuretics to obtain control.

David H. Ellison, MD

Most patients with edematous disorders such as congestive heart failure, nephrotic syndrome, and cirrhotic ascites can be treated successfully with dietary NaCl restriction and a single class of diuretic drug. For resistant patients, it may be necessary to combine two different classes of diuretic drug to control symptoms. Recent experimental work has shown that specific renal adaptations contribute to diuretic resistance by increasing the capacity of the kidney to reabsorb NaCl. Combination diuretic therapy can be used to overcome these processes, but its indiscriminate use can also lead to serious complications. A rational approach to diuretic-resistant patients is based on understanding how adaptive renal responses can be treated and prevented using targeted diuretic therapy. Such an approach provides the most effective diuresis without undue complications.



Combination diuretic therapy is one of the best examples of drug synergism: the effect of the combination exceeds the sum of the effects of each agent alone. Patients completely resistant to even a potent loop diuretic often produce massive amounts of urine when a drug with only modest potency, such as a thiazide, is added to the regimen. Such therapy, while potent, is potentially hazardous, and a thorough understanding of renal NaCl homeostasis and mechanisms of diuretic action is needed to achieve therapeutic success without toxicity. In this review, we will discuss causes of diuretic resistance and mechanisms of diuretic interaction to generate a rational approach to diuretic therapy of refractory edema.

MECHANISMS OF ACTION

All diuretic drugs act by inhibiting Na reabsorption by epithelial cells along the nephron. These drugs are classified according to the sites and mechanisms of their actions (Table 1). Along each segment (Figure 1), Na reabsorption across the epithelium is mediated by two pathways, one in the luminal membrane that moves Na from the lumen into the cell and the other, at the basolateral membrane, that moves Na from the cell back into the blood. The ouabain-sensitive

Drugs Discussed in This Article:

Acetazolamide (Diamox, Dazamide)
Albumin
Amiloride (Midamor)
Bumetanide (Bumex)
Chlorothiazide (Diuril, Diurigen, Sodium Diuril)
Chlorthalidone (Hygroton, Thalitone)
Dopamine (Dopastat, Intropin)
Ethacrynic acid (Edecrin)
Furosemide (Lasix)
Hydrochlorothiazide
Indapamide (Lozol)
Metolazone (Mykrox, Zaroxolyn)
Spironolactone (Aldactone)
Theophylline
Triamterene (Dyrenium)

Na/K adenosine triphosphatase (ATPase) is present along the basolateral membrane of cells throughout the nephron. This pathway uses the metabolic energy from adenosine triphosphate (ATP) to move Na from cell to blood. Lumen-to-cell pathways are unique to each segment, however; such pathways are the targets of specific diuretic drugs and form the cellular basis of diuretic action.

Diuretics that act primarily along the proximal tubule include the carbonic anhydrase inhibitor acetazolamide (Diamox, Dazamide) (Figure 1), which acts indirectly to inhibit exchange of Na for H by cells of the proximal tubule. (Carbonic anhydrase catalyzes production of protons and bicarbonate inside the cell and disposal of carbonic acid in the lumen.) Carbonic anhydrase inhibitors are not commonly used for the treatment of edema because they are not potent during chronic use, but they may be useful for acute therapy of selected patients (see below). Diuretics that act along the loop of Henle, such as furosemide (Lasix) and bumetanide (Bumex), on the other hand, are very potent. These loop diuretics can increase renal NaCl excretion to 20% or more of the filtered Na load. Loop diuretics are protein-bound anions that act from the lumen of kidney tubules to inhibit a pathway that carries 1Na, 1K and 2Cl into cells. Absorbed rapidly following oral administration, these drugs have very short half-lives, which has certain clinical implications (see below).

The class known as distal convoluted tubule (DCT) diuretics, which include thiazides and thiazide-like drugs, are also protein-bound organic anions. These drugs are secreted into the lumen by proximal tubule cells but act along the DCT (Figure 1) to inhibit a pathway that couples Na and Cl movement. Compared with loop diuretics, DCT diuretics do not increase renal NaCl excretion as much (maximum up to 5% of the filtered Na load) but generally have longer half-lives. Diuretics that act along the collecting duct (Figure 1) are quite weak natriuretic agents. Collecting duct (CD) diuretics inhibit Na reabsorption either directly, as with triamterene (Dyrenium) and amiloride (Midamor) (which are sodium channel blockers), or indirectly, as with spironolactone (Aldactone) (an aldosterone antagonist). CD diuretics do not tend to increase renal K excretion; often called "potassium-sparing diuretics," they are used in combination therapy to minimize hypokalemia.

MECHANISMS OF RESISTANCE

Edematous states, such as congestive heart failure and cirrhosis of the liver, can often be treated effectively by restricting dietary NaCl intake. When edema is resistant or severe, drugs are often employed. In this setting, the goal of diuretic therapy is not so much to increase renal NaCl and water excretion as to reduce the extracellular fluid

Table 1

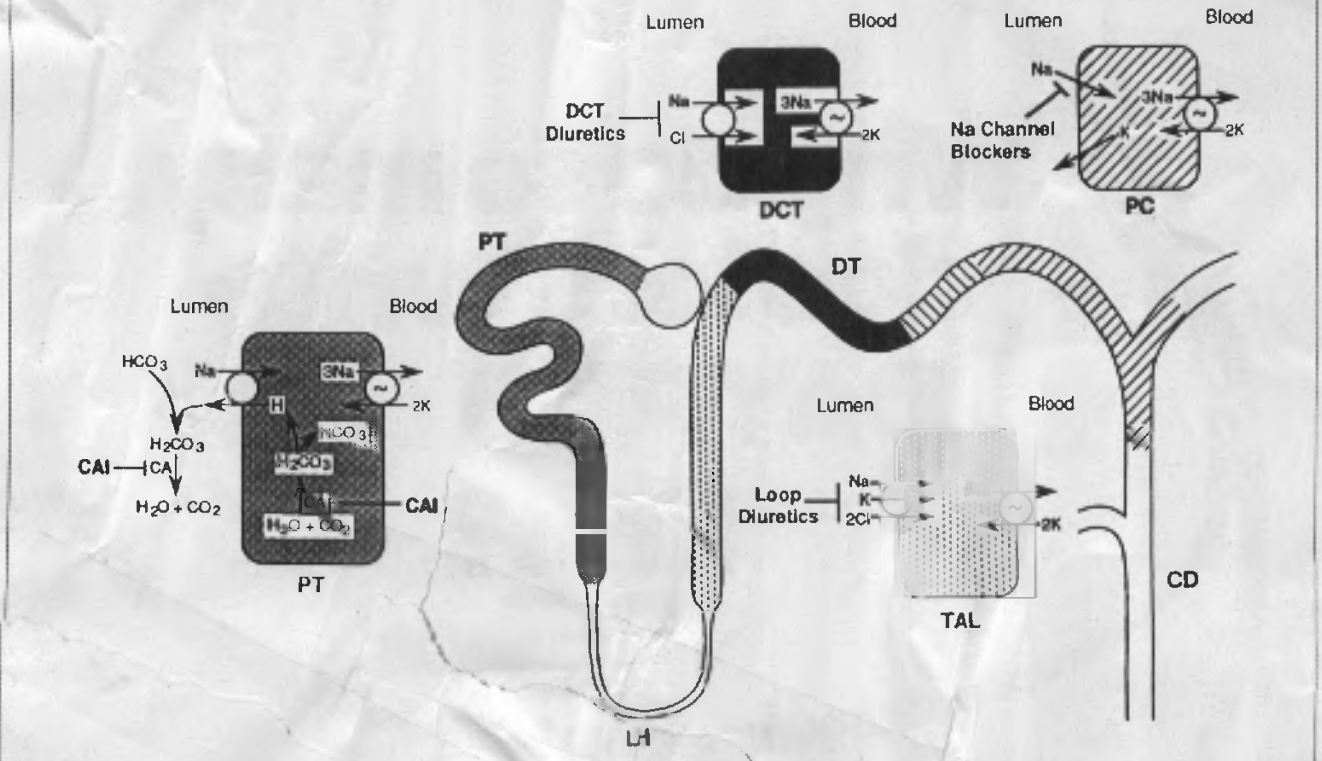
Physiological Classification of Diuretic Drugs

Proximal Diuretics	Loop Diuretics	DCT Diuretics	CD Diuretics
Carbonic Anhydrase Inhibitors	Na-K-2Cl Inhibitors	Na-Cl Inhibitors	Na Channel Blockers
Acetazolamide	Furosemide	Hydrochlorothiazide	Amiloride
Phosphodiesterase Inhibitors*	Bumetanide	Metolazone	Triamterene
Theophylline	Ethacrynic Acid (Edecrin)	Chlorthalidone (Hygroton, Thalitone)	Aldosterone Antagonists
Others		Indapamide (Lozol)	Spironolactone
		Many others	

*The mechanism by which phosphodiesterase inhibitors increase NaCl excretion is not known with certainty and may involve hemodynamic and tubular effects (perhaps mediated by cyclic adenosine monophosphate).

Figure 1

Sites and mechanisms of action of important diuretic drugs



Predominant sites and mechanisms of action of clinically important diuretic drugs. Patterns identify sites of action along the nephron and corresponding cell types; ■PT, proximal tubule; LH, loop of Henle; ▩TAL, thick ascending limb cell; DT, distal tubule; ■DCT, distal convoluted tubule cell; CD, collecting duct; ▨PC, principal cell; CA, carbonic anhydrase; CAI, carbonic anhydrase inhibitors. Carbonic anhydrase catalyzes the conversion of water and CO_2 to carbonic acid and the dissociation of carbonic acid to water and CO_2. This enzyme prevents secreted protons from accumulating in the tubule lumen by allowing carbonic acid to dissociate and acts inside the cell to provide H ions for secretion. Both intracellular and luminal actions of carbonic anhydrase inhibitors are important in their ability to reduce Na reabsorption by the renal proximal tubule. Note that Na channel blockers probably act along the connecting tubule ▧ as well as the collecting duct ▨. Spironolactone (not shown) is a competitive aldosterone antagonist and acts primarily in the cortical collecting tubule. Reproduced with permission from *Annals of Internal Medicine.* 1991;114:886–894. In Ellison, DH. Epithelial cell hypertrophy: a physiological cause of diuretic resistance.

(ECF) volume: increases in renal NaCl excretion are usually necessary, but not in themselves sufficient, to attain this goal. In fact, if dietary NaCl is high, a single daily dose of loop diuretic has little or no effect on ECF volume because of "postdiuretic Na retention," in which the kidney can compensate fully for the effects of the drug during the 18 hours after it has worn off.[1]

Although loop diuretics such as bumetanide and furosemide can increase renal NaCl excretion up to 20% of the filtered NaCl load, these drugs may not always be the most effective options. DCT diuretics (thiazides, for example), given once daily to persons with normal renal function, produce greater 24-hour NaCl losses than do loop diuretics.[2] This difference reflects differences in half-life, loop diuretics being relatively shorter-acting (duration of action <6 hours) than most thiazides.[3] The effect of half-life is most prominent when excessive dietary NaCl intake, together with postdiuretic Na retention, induces a period of positive NaCl balance. This is not to suggest that DCT diuretics are uniformly more potent than loop diuretics: the underlying potency of loop diuret-

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*Usual adult dosage is 1200 mg (two 600-mg caplets) once a day. For osteoarthritis patients of low body weight or with milder disease, an initial dosage of one 600-mg caplet once a day may be appropriate.

Contraindicated in patients with hypersensitivity to DAYPRO or in individuals with nasal polyps, angioedema, or bronchospastic reactivity to aspirin or other NSAIDs.† Severe and occasionally fatal asthmatic and anaphylactic reactions to NSAIDs have been reported; there have been rare reports of anaphylaxis with DAYPRO. As with other NSAIDs, the most frequently reported adverse reactions were related to the GI tract. In patients treated chronically with NSAID therapy, serious GI toxicity such as bleeding, ulceration, and perforation can occur. Severe renal and hepatic reactions have been reported. There may be a risk of fatal hepatitis with oxaprozin, such as has been seen with other NSAIDs.

† Nonsteroidal anti-inflammatory drug.

SEARLE

Table 2

Causes of Diuretic Resistance

- Patient Noncompliance
  - Not taking drug
  - High NaCl intake
- Impaired Bioavailability
  - Congestive heart failure
  - Nephrotic syndrome
  - Cirrhotic ascites
- Impaired Diuretic Secretion by Proximal Tubule
  - Renal failure
  - Old age
  - Renal transplantation
  - Congestive heart failure
  - Drugs
    - NSAIDs (loop and DCT diuretics)
    - Cimetidine (amiloride and triamterene)
- Protein Binding in Tubule Lumen
  - Nephrotic syndrome
- Hemodynamic
  - Vasodilators (ACE inhibitors and others)
  - Nonsteroidal anti-inflammatory drugs
  - Hypoxemia
- Enhanced NaCl Reabsorption
  - NSAIDs
  - Adaptation to chronic diuretic therapy

NSAIDS = nonsteroidal anti-inflammatory drugs; ACE = angiotensin-converting enzyme.

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ics may be unmasked by dietary NaCl restriction. Further, DCT diuretics are relatively ineffective when Na avidity is strong or in renal failure. The overall therapeutic efficacy of diuretics depends on their intrinsic ability to inhibit Na reabsorption, on their duration of action, and on a variety of potentially confounding variables, such as the level of renal function.

An edematous patient is often considered resistant to diuretics when treatment with a potent diuretic drug (usually a loop diuretic) in moderate doses fails to reduce ECF volume to the desired level. Causes of diuretic resistance have been reviewed[4-6] and are summarized in Table 2. A simple approach to the diuretic-resistant patient is summarized in Table 3. Patients apparently resistant to diuretics may be ingesting too much NaCl; in such patients, net NaCl balance is neutral during loop diuretic administration. If an individual at steady state (ie, stable weight) excretes more than 100 mmol (2.3 g) Na over 24 hours, then the patient is ingesting too much NaCl and the diuretic is working effectively; Na losses of more than 100 mmol per day should be sufficient to permit control of edema. In such cases, the best treatment is to restrict NaCl intake further; increasing the dose of the loop diuretic may not be successful.

When diuretic resistance persists in the face of adequate NaCl restriction, or (commonly) when dietary compliance is not optimal, other approaches should be considered. It is especially important to consider whether the patient needs and will tolerate further reductions in ECF volume. If so, drugs that may interfere with the action of diuretics, such as nonsteroidal anti-inflammatory drugs, should be discontinued, if this is clinically tolerated. If the patient is being treated with a CD or DCT diuretic, it is appropriate to change to a loop diuretic. If resistance persists, it is crucial to decide whether the problem reflects an inadequate dose of diuretic or NaCl retention between doses. Loop diuretics have steep dose-response curves; an observant patient should be able to notice an increase in urine output during 4 hours after each oral dose. If there is no such response, the diuretic dose is probably below threshold and can be doubled. This process can be repeated until a notable response is obtained or until a maximal safe dose is achieved. (Oral doses above 240 mg are usually not indicated.) If each dose induces a notable diuresis but ECF volume remains expanded, administration may be made more frequent or a second class of diuretic drug may be added.

MECHANISMS OF ADAPTATION

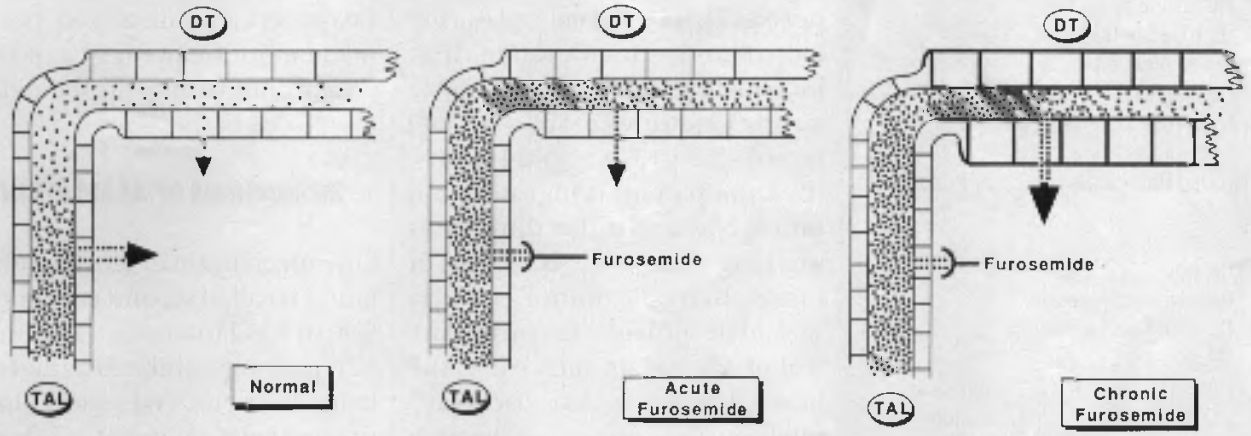
One mechanism of diuretic adaptation is called secondary stimulation of NaCl retention. The transport pathways inhibited by diuretic drugs are arranged axially along the nephron (Figure 1). When a diuretic drug is administered acutely, some of the NaCl not reabsorbed in the diuretic-sensitive nephron segment is reabsorbed along distal segments, because NaCl transport is load dependent. When a loop diuretic is administered, for example, NaCl delivery to and reabsorption at the distal tubule increase (Figure 2). The effect of a diuretic drug on urinary Na and Cl excretion thus reflects the sum of its effects in both sensitive and nonsensitive nephron segments. To inhibit secondary reabsorption, drugs such as DCT diuretics, which block NaCl reabsorption along the distal tubule, may be prescribed.

One mechanism of diuretic adaptation is called secondary stimulation of NaCl retention.

A second adaptive response, postdiuretic retention (discussed above), occurs because diuretics, especially loop diuretics, have relatively short half-lives and are usu-

Figure 2

Effects of furosemide on ion transport



Effects of loop diuretic (furosemide) on ion transport along the thick ascending limb (TAL) and distal tubule (DT). Dots represent NaCl. Under normal conditions, the TAL dilutes tubule fluid, and the NaCl concentration in fluid entering the DT is low. When furosemide is administered acutely, NaCl reabsorption along the TAL declines, and NaCl concentration in fluid entering the DT rises. When this process continues chronically, cells in the DT enlarge and reabsorb more NaCl. Because more NaCl is now reabsorbed by the DT, the amount of NaCl leaving the DT declines back toward control values (compare the amounts leaving the DT in the normal chronic diagrams). Reproduced with permission from Elsevier Science Publishers BV. *Diuretics IV: Chemistry, Pharmacology and Clinical Applications.* JB Puschett, Editor. 1993 (Ellison).

ally administered as boluses. When the drug concentration falls below a critical threshold and before the next dose is given, NaCl excretion may be quite low, resulting in a period of positive NaCl balance. Such retention is mediated in part by stimulation of NaCl transport along the DCT and can be blocked or modified by adding a diuretic that both inhibits transport in this segment and has a half-life longer than that of loop diuretics.

A third level of adaptation occurs only when diuretics have been administered chronically. When loop diuretics increase delivery of NaCl to the distal tubule for a long period of time, DCT cells undergo dramatic hypertrophy,[7,8] and there is an increase in the number of both Na/K ATPase pumps along the basolateral membrane and thiazide-sensitive Na-Cl cotransporters along the luminal membrane.[9-11] As a result, cells along the distal tubule can reabsorb more NaCl (Figure 2), allowing less NaCl to leave the tubule and be excreted. DCT diuretics (such as the thiazides) not only block increases in NaCl transport but may also prevent the development of cellular hypertrophy itself.[12]

TREATMENT OF RESISTANCE

Resistance to diuretic drugs rarely occurs upon the initiation of diuretic therapy but most commonly develops after loop diuretics have been employed chronically, especially in increasing doses. As seen above, adding a DCT diuretic to a regimen of loop diuretic can interfere with each of the major adaptive processes, which may be why combination diuretic therapy usually involves these two classes. This synergistic combination has proven remarkably effective. Although there is little evidence that one or another DCT diuretic is most effective, many clinicians employ metolazone because it is effective even when glomerular filtration rate is low and because its half-life is longer than that of several other DCT diuretics. This approach, however, carries a high incidence of side effects: because diuretic therapy is so effective, fluid and electrolyte depletion, sometimes massive, are common. Adverse consequences were noted in 65% of papers describing combination therapy,[13] and many clinicians have observed hypokalemia, hypotension, or prerenal azotemia.

In general, when a DCT diuretic is added, the dose of loop diuretic should not be altered (recall the steep-dose response curve, which is not affected by administration of other agents). DCT diuretics may be added in full doses [50 mg hydrochlorothiazide or 5–10 mg metolazone (Mykrox, Zaroxolyn)] when a rapid and robust response is needed, but such an approach is likely to lead to complications if follow-up is not extremely close. When the situation is less urgent and follow-up less certain, I favor using small doses of DCT diuretics (such as 2.5 mg/d metolazone) to reduce the risk. Because DCT diuretics are absorbed slightly more slowly than are loop diuretics, it may be reasonable to administer the DCT diuretic 1/2 to 1 hour before the loop diuretic. Once ECF volume has been controlled, a small dose of DCT diuretic given only three times per week is often enough to block adaptive processes and provide maintenance.

Other classes of diuretic have generally less dramatic effects when used in combination with loop diuretics. Carbonic anhydrase inhibitors have been shown to act synergistically with loop diuretics when given acutely. Chronic use is avoided, however, because their effects are limited by compensatory mechanisms. CD diuretics, such as amiloride and spironolactone, are useful in combination therapy when given to prevent hypokalemia but do not appear to enhance NaCl excretion. They are most commonly used with loop diuretics in patients with cirrhosis of the liver, in whom hypokalemia can predispose to hepatic encephalopathy.

Aggressive therapy also is often indicated for hospitalized patients, especially those in an intensive care unit (ICU) who need urgent diuresis. Many such patients receive obligate fluid and solute loads. Some develop electrolyte complications, and many cannot take medications by mouth. Loop diuretics can be administered intravenously, and simply changing from oral to intravenous (IV) therapy may overcome resistance in patients for whom gastrointestinal (GI) drug absorption is impaired (Table 2).[14] When IV combination therapy is indicated, chlorothiazide (Diuril, Diurigen, Sodium Diuril) (500–1000 mg once or twice daily) or acetazolamide (250–375 mg once daily) can be employed. Because chlorothiazide inhibits carbonic anhydrase as well as blocking NaCl transport by the distal tubule, this drug may block compensatory processes in more than one nephron segment. Both chlorothiazide and acetazolamide act synergistically with loop diuretics when given acutely. Acetazolamide is especially useful when metabolic alkalosis and hypokalemia complicate the

Table 3

Approach to the Diuretic-Resistant Patient

1. Assess compliance with medical regimen (diet and drugs)
   - Measure daily Na excretion
   - A. If >100 mmol/day, then reduce intake.
   - B. If < 100 mmol/day, proceed as below
2. Assess status of underlying disease
   - Does patient really need further reduction of extracellular fluid volume?
   - Can treatment of underlying disease be improved?
3. Discontinue nonsteroidal anti-inflammatory drugs and consider reducing vasodilators (especially if blood pressure is low)
4. Change to a loop diuretic and increase dose until diuretic threshold or maximum safe dose is attained: once threshold is reached, then increase frequency
5. Try intravenous route (to bypass gastrointestinal tract)
6. Consider constant diuretic infusion
   - May block postdiuretic NaCl retention and be useful for hospitalized patients
   - 20 mg furosemide followed by 4-60 mg/hr IV (see text)
7. Consider diuretic combinations
   - A. Add DCT diuretic
     - *Oral*
       - metolazone 2.5 to 10 mg/day
       - hydrochlorothiazide 50 to 100 mg/day
     - *Intravenous*
       - chlorothiazide 500 to 1000 mg per day
   - B. Add distal diuretic
     - amiloride, triamterene, spironolactone
   - C. Add proximal diuretic
     - *Intravenous*
       - acetazolamide 250-375 mg/day
8. Disease-specific maneuvers
   - A. Albumin (for nephrotic syndrome, may be mixed with loop diuretic)
   - B. Theophylline (in bronchospastic disease)
   - C. Low dose dopamine (for impaired left ventricular function and acute renal failure)

treatment of edema.

In other situations, drug therapy may be targeted at the underlying disease process. Theophylline, an extremely mild diuretic that acts synergistically with loop diuretics, may be useful when bronchospasm and edema are both present. For patients with left ventricular dysfunction, low doses of dopamine (Dopastat, Intropin) clearly potentiate the action of diuretics. Low-dose dopamine infusion may also increase urine output in some patients with acute renal failure. Infusions of albumin may potentiate the effects of diuretic drugs when hypoalbuminemia complicates nephrotic syndrome. Mixing albumin and loop diuretics prior to administration has been reported to be more effective than administering each agent alone, perhaps by permitting more drug to be delivered to the kidney.[15]

For hospitalized diuretic-resistant patients, diuretics are sometimes infused continuously. This approach has several advantages over bolus administration. First, in avoiding peaks and troughs of diuretic concentration, continuous infusions prevent postdiuretic NaCl retention. Second, they are more efficient (the amount of NaCl excreted per milligram of drug administered is greater).[16] Third, some patients resistant to large bolus doses have responded to continuous infusion. Fourth, diuretic response can be titrated, allowing excellent control of NaCl and water excretion, a special advantage in the ICU, where obligate fluid administration must be balanced by fluid excretion. Finally, complications associated with high doses of loop diuretics, such as ototoxicity, appear to be less common with continuous infusions. Total daily furosemide doses exceeding 1 g have been tolerated well when administered over 24 hours.[17] One approach is to administer a loading dose of 20 mg furosemide followed by a continuous infusion at 4 to 60 mg/h. Lower dosage ranges should be sufficient for patients with preserved renal function; when renal failure is present, higher doses may be used, but patients should be monitored carefully for such side effects as ECF volume depletion and ototoxicity.

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Most patients considered resistant to diuretics respond to one of the approaches outlined above. Side effects such as prerenal azotemia and metabolic alkalosis, rather than true resistance, usually limit the ability to reduce ECF further. Controlling ECF volume without provoking complications requires a thorough understanding of physiology and a commitment to use diuretics rationally and carefully. Used in this manner, they remain among the most powerful drugs in clinical medicine today.

IN CONCLUSION

In conclusion, using different classes of diuretic drug together to treat a patient who is refractory to traditional therapy is often remarkably effective. A second class of diuretic drug appears to increase renal salt excretion by blocking specific adaptive mechanisms that otherwise limit the natriuretic effect of a single agent. Unfortunately, combination therapy frequently leads to side effects including electrolyte and volume depletion, especially when used without appropriate care. Thus, combination therapy should be reserved for patients who fail to respond to a single drug, and patients who receive combination therapy should be monitored carefully for side effects.

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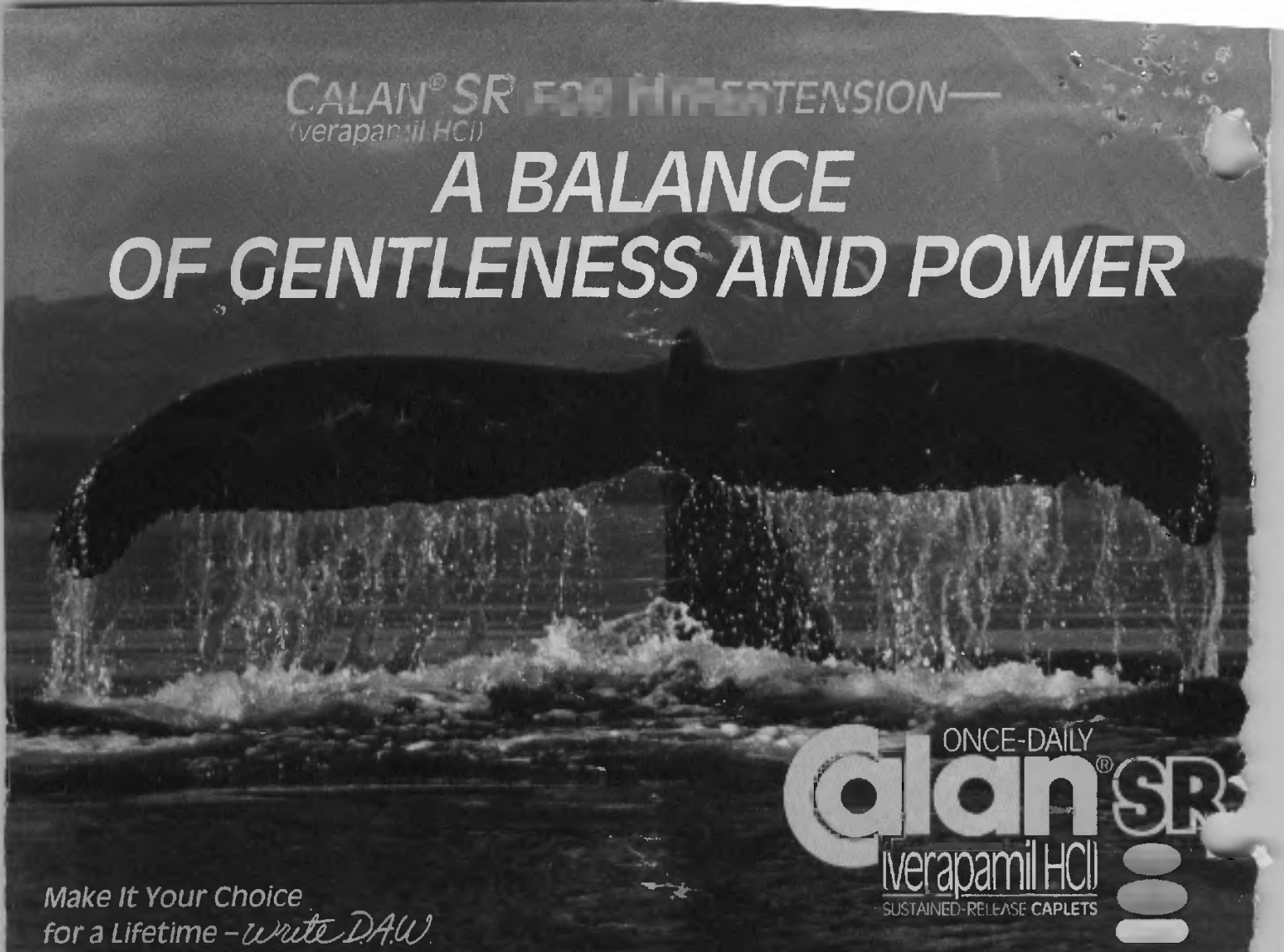

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BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

2/13/92 • P92CA7196V

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