



REVIEW ON RECENT ADVANCES IN A MODERN DAY TREATMENT: DIURETIC THERAPY

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ABSTRACT

The choice of drugs to initiate therapy for the management of hypertension remains contentious and diuretics are central to this controversy. Because most of the major trials involve complex treatment algorithms and allow diverse background treatments, one of the greatest challenges lies in separating out true class specific effects – for example, separating true class-specific effects of diuretics from those of beta blockers. Thiazide diuretics were the first tolerated efficient antihypertensive drugs that significantly reduced cardiovascular morbidity and mortality in placebo-controlled clinical studies. Although these drugs today still are considered a fundamental therapeutic tool for the treatment of hypertensive patients, a description of successful use of diuretics in specific edematous states, such as congestive heart failure, chronic renal failure, nephrotic syndrome, and liver disease, is followed by a brief discussion of the management of resistant edema and the use of diuretics in non edematous states, including essential hypertension and other conditions. The elements required to successfully achieve adequate natriuresis under such conditions are analyzed. Because achieving diuresis may result in significant hypokalemia, hyponatremia, metabolic alkalosis, and worsening prerenal azotemia, the prevention and management of these complications of diuretic therapy are also reviewed.

Key words Diuretics, congestive heart failure, edema, cirrhosis, body building, autism, toxemia, poisoning (forced diuresis).

INTRODUCTION

One of the most contentious issues in the management of hypertension over the past two decades has been the choice of drugs to initiate therapy. This is particularly true for the patient with uncomplicated hypertension, without compelling indicators for any particular drug class. Central to this controversy has been the role of diuretics, which have at various times, and by various authorities, been preferred, avoided or regarded as an equivalent option, compared with other drug classes¹⁻¹⁴. Although thiazide and thiazide-like diuretics are indispensable drugs in the treatment of hypertension, their role as first-line or even second-line drugs is a provoking debate. The European Society of Cardiology/ European Society of Hypertension (ESC/ESH) guidelines recommend that thiazide diuretics should be considered as suitable as b-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers for the initiation and maintenance of antihypertensive treatment⁽¹⁵⁾. The Seventh Report of the Joint National Committee (JNC VII) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends that thiazide diuretics should be preferred drugs in “most” hypertensive patients, either alone or combined with drugs from other classes⁽¹⁶⁾. Lowering blood pressure (BP) has been shown to reduce the risk of cardiovascular (CV) morbidity and mortality. The main benefit of lowering BP is due to the reduction in the risk of stroke and heart failure (HF). In many trials in which a reduction in CV events was documented, antihypertensive therapy was diuretic-based⁽¹⁷⁻²²⁾. The choice of drugs to initiate therapy for the management of hypertension remains contentious and diuretics are central to this controversy. Because most of the major trials involve complex treatment algorithms and allow diverse background treatments, one of the greatest challenges lies in separating out true class specific effects – for example, separating true class-specific effects of diuretics from those of beta blockers. Despite these difficulties, the evidence confirms that diuretics are at least as effective as the newer first line groups in preventing cardiovascular events. The main area of doubt lies in relation

to the risk of renal outcomes and of metabolic outcomes, such as new onset diabetes – where the evidence suggests that drugs that inhibit the renin-angiotensin system may be more protective than all other drug classes. These issues are reflected in the most recent international guidelines, all of which include diuretics among the first-line drugs for the treatment of hypertension, although they do differ on the role of diuretics in the initiation of therapy²³.

Era where diuretics are being used therapeutically as Antihypertensive Drug

When diuretics were introduced in the 1960s they were mainly used as adjunct therapy to more powerful drugs such as the adrenergic agents or hydralazine, used in the treatment of moderate or severe hypertension.²⁴ By the seventies, beta blockers had been accepted and therapy extended to milder grades of hypertension, using ‘step therapy’, a regimen in which treatment was initiated with a diuretic, with the addition if necessary, of a beta blocker and then of a vasodilator, usually hydralazine. The availability of new classes of blood pressure-lowering drugs – the ACEI, the CCB and the alpha blockers – coincided with the publications of the landmark meta-analysis by Collins *et al*²⁵ which revealed that the expected reductions in stroke were realized but that the reduction in myocardial infarction was disappointing, being much less than predicted by the major observational studies²⁶. Many thought that the diuretics, with their well known metabolic side-effects such as hypokalaemia, dyslipidaemia and glucose intolerance might be responsible. Therefore, newer agents gained favour during the eighties, step therapy was discarded and the age of monotherapy was ushered in, with widespread belief that single drug therapy would suffice, with attractive simplicity and efficacy.⁽²⁴⁾ Three major trials in more elderly subjects published in 1991 and 1992 confirmed that despite their metabolic side effects, diuretics were very effective in preventing both stroke and coronary heart diseases.²⁷ These studies, coupled with the lack of trials demonstrating that ACEI or CCB could prevent these hard end-points, led to a

return of diuretics and beta blockers to a position of strength. Thus in the 1990s, diuretics were accepted as first-line drugs once again by all authorities,^{2, 3, 7, 8, 11, 12} with general agreement that they were especially effective in older people^{4, 9, 10, 28}.

Now, in the twenty-first century, treatment is spreading to 'normotensive' subjects at high risk of cardiovascular events, such as those with established coronary disease, cerebrovascular disease, renal disease or diabetes^{4, 9, 10, 28}. All authorities agree that now a day Diuretics reached the age of combination therapy for the majority of subjects requiring blood pressure-lowering drugs. Although all guidelines agree that diuretics are among the first-line groups of drugs and that they may be used to initiate treatment, the guidelines differ regarding their place in the pecking order. The phases of diuretic being used is summarized below,

Table: 1. Phases in the use of Diuretics²⁹

1. In 1960s
 - ADJUNCT to more potent drugs
 - Moderate and severe hypertension
2. In 1970s
 - First step in STEP THERAPY
 - Included in most major trials
3. In 1980s
 - Transition to MONOTHERAPY
 - Metabolic effects: fall from grace
4. In 1990s
 - First Line drugs
 - Vindicated by SHEP, STOP, MRC
5. 21st Century
 - More controversy: ALLHAT versus ANBP2 and ASCOT
 - Cardiovascular versus Metabolic Outcomes

ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

ANBP2: Australian National Blood Pressure Study

ASCOT: Anglo-Scandinavian Cardiac Outcomes Trial

SHEP: Systolic Hypertension in the Elderly Program

MRC: Medical Research Council

CCB: Calcium Channel Blocker

ACE: Angiotensin Convertase Enzymes

CV: Cardio Vascular

HF: Heart Failure

BP: Blood Pressure

JNC: Joint National Committee

ESC/ESH: European Society of Cardiology/ European Society of Hypertension

STOP: Swedish Trial in Old Patients with Hypertension

Specific situations and indications for diuretics⁽²³⁾

There are a number of specific situations that the major guidelines list as 'compelling indications' for diuretics as blood pressure-lowering agents.

These include:

1. Elderly subjects with systolic hypertension.
2. Black subjects, at least those of African origin.
3. Subjects with established cerebrovascular disease (in combination with ACEI).
4. Subjects with heart failure or ventricular dysfunction.
5. Avoid diuretics in patients at particular risk of new diabetes
 - Impaired Glucose Tolerance (IGT)
 - Impaired Fasting blood sugar (IFG)
 - Overweight and below 60 years of old
 - Metabolic syndrome

Uses of diuretics other than antihypertensive drugs

Diuretics use in Cirrhosis

Cirrhosis, the third-leading cause of death in the United States,⁽³⁰⁾ describes a chronic liver disease characterized by the buildup of scar tissue, according to the Merck Manual. Cirrhosis develops over several years and often doesn't produce symptoms until complications arise. Because cirrhosis cannot be cured, treatment aims to slow the progression of the disease and relieve the symptoms caused by complications. Diuretics, commonly called water pills, eliminate excess fluid, making them useful for treating several complications of cirrhosis. Blood flows from the stomach and intestines into the liver allowing the liver to hold approximately 13 percent of the total volume of blood at any one time, according to the Lucile Packard Children's Hospital at Stanford. When scar tissue builds up in the liver, blood cannot flow freely. This causes pressure to increase in the portal vein, which is the conduit that carries the blood from the digestive tract to the liver. This condition, known as portal hypertension, redirects blood into the smaller blood vessels surrounding the liver, leading to a buildup of fluid in the body. Ascites describes the accumulation of fluid within the abdominal cavity. As blood pressure in and around the liver rises, the body releases vasodilators, which are substances such as vasopressin to help relax blood vessels. Although relaxing the blood vessels helps to reduce the portal hypertension, the vasopressin, an antidiuretic, causes the body to retain more sodium and water. The additional water increases the volume of blood that actually contributes to the high portal blood pressure. The pressure causes the fluid to leak from the blood vessels and accumulate in the abdominal cavity⁽³⁰⁾. Many types of diuretics exist, each inhibiting the reabsorption of sodium in different places along the tubes within the kidneys. Doctors often choose Spirolactone, classified as a potassium sparing diuretic, to treat the complications of cirrhosis. Furosemide, a loop diuretic, can help increase the effectiveness of Spirolactone but produces few results in cirrhosis when used alone. Following a diet low in sodium increases the effectiveness of diuretics in treating cirrhosis.

Diuretics use in Edema

The high blood pressure around the body tissues affects the flow of blood throughout the body. The portal hypertension can cause the small capillaries in the legs to leak fluid. As the capillaries leak fluid, the body compensates by retaining even more salt and water in order to keep the volume of blood constant. This actually causes capillaries to leak more, allowing fluid to build up in the surrounding tissues, according to MayoClinic.com. The accumulation of fluid causes swelling in the tissues, a condition known as edema. The kidneys, filled with millions of tiny capillaries, filter blood to remove wastes while also keeping the level of water and salts in balance. Although kidneys remove salt, mainly sodium, the body reabsorbs much of it as the fluids pass through the maze of tubes in the kidneys. Diuretics inhibit the reabsorption of sodium and each molecule of sodium removed from the blood pulls a molecule of water, according to Cardiovascular Pharmacology Concepts. By removing excess water from the body, diuretics help to relieve both ascites and edema³⁰. Generalized edema can occur in a variety of disorders, including heart failure, cirrhosis (where ascites is usually most prominent), the nephrotic syndrome, and renal failure; when massive, the excess fluid accumulation is called anasarca. Edematous patients

generally respond to the combination of dietary sodium restriction and diuretic therapy, usually with a loop diuretic. Some patients, however, are resistant to this regimen. A variety of factors can account for persistent fluid retention, including inadequate diuretic dose or frequency, excess sodium intake, delayed intestinal absorption of oral diuretics, decreased diuretic excretion into the urine, and increased sodium reabsorption at sites in the nephron other than those inhibited by the diuretic³¹⁻³⁴. Nonsteroidal anti-inflammatory drugs, which reduce the synthesis of vasodilator and natriuretic prostaglandins, can impair diuretic responsiveness. Thus, these agents should be discontinued, if possible, in edematous patients³⁵.

Edematous patients are typically treated with one of the sulfonamide-based loop diuretics – furosemide, bumetanide, and torsemide. Ethacrynic acid, which is not a sulfonamide, is rarely used because it may be more ototoxic than the sulfonamide diuretics in high doses and its relative insolubility makes it complicated to administer intravenously. The primary indication for the use of ethacrynic acid is in patients who are allergic to sulfonamide-based diuretics, including thiazide diuretics. There is minimal evidence of allergic cross-reactivity between sulfonamide antimicrobials and non-antimicrobials. Thus, patients with a history of allergy to sulfonamide antimicrobial drugs would be expected to tolerate non-antimicrobial sulfonamides such as loop diuretics. Allergic reactions that do occur appear to be related to a predisposition to allergic reactions rather than sulfonamide cross-reactivity³⁶.

Diuretic in Preeclampsia, Pregnancy induced hypertension, Toxemia

Preeclampsia is defined as the combination of high blood pressure, hypertension, swelling, edema, and protein in the urine (albuminuria, proteinuria) developing after the 20th week of pregnancy³⁷. Preeclampsia ranges in severity from mild to severe; the mild form is sometimes called proteinuric pregnancy-induced hypertension or proteinuric gestational hypertension³⁸. Symptoms, which typically appear after the 20th week of pregnancy, include swelling of the face and hands, visual disturbances, headache, and High blood pressure. In severe preeclampsia, symptoms are more pronounced. Jaundice may also be present. Severe preeclampsia may lead to seizures (eclampsia) and may cause death to both mother and fetus if left untreated³⁹ Like eclampsia, severe preeclampsia is a medical emergency requiring hospitalization^{40,41}. Prescription medications to reduce high blood pressure (hypertension) are not recommended for mild preeclampsia, though they may be used when the condition becomes a serious threat to the mother's health. The prescription drugs known as diuretics are used to treat severe pregnancy-induced hypertension resulting in pulmonary edema and congestive heart failure. Agents used include the thiazide diuretics Hydrochlorothiazide (HydroDIURIL), Indapamide (Lozol), and Metolazone (Zaroxolyn); Loop Diuretics including Furosemide (Lasix), Bumetanide (Bumex), and Torsemide (Demadex); and potassium-sparing diuretics, such as Spironolactone (Aldactone), Triamteren (Dyazide, Maxzide), and Amilorides (Midamor). Diuretics may be combined with beta-blockers, such as Propanolol (Inderal), Matoprolol (Lopressor, Toprol XL), Atenolol (Tenormin), Carvedilol (Coreg), labetalol (Normodyne) and Bisoprolol (Zebeta), or ACE inhibitors, including Captopril (Capoten), Benazepril (Lotensin), Lisinopril (Zestril, Prinivil), Enalapril (Vasotec), and Quinapril

(Accupril). Calcium channel blockers, such as Amlodipine (Norvasc), Verapamil (Calan SR, Verelan PM), Nifedipin (Adalat CC, Procardia), and Diltiazem (Cardizem CD), may also be used either alone or in combination with other drugs to treat high blood pressure. The peripheral vasodilator Hyralazine is also commonly prescribed to pregnant women with severe preeclampsia.

Diuretics use in Congestive heart failure

The principal goals of treatment of the patient in heart failure are the relief of their symptoms and improvement in their prognosis. Of all antiheart failure drugs currently available, the diuretics are therapeutically superior in their efficacy in relieving clinical symptoms and signs. Whether administered intravenously or orally, all diuretics result in a substantial reduction in the raised pulmonary vascular pressures in combination with a small reduction in cardiac output⁴⁸. Diuretics stimulate release of renin with subsequent activation of the renin-angiotensin-aldosterone system, particularly if used in large doses, although their quantitative impact on the neuroendocrine profile at different stages of heart failure remains to be defined. In patients with mild heart failure, diuretics reduce plasma catecholamine concentrations, but their sympatholytic effects in more severe cases are unknown, as are their effects on the metabolically active tissues in these patients³⁷. Diuretic resistance can be circumvented by segmental nephron blockade with a combination of low-dose diuretics that simultaneously block sodium reabsorption in the proximal tubule, the loop of Henle, the distal tubule, and the collecting duct. Diuretics improve symptoms of breathlessness and signs of peripheral edema in patients with congestive heart failure in direct relationship to the induced diuresis. These benefits are frequently associated with a substantial improvement in patients' appreciation of quality of life and economic capacity. There are few adverse reactions to chronic diuretic therapy, but the serum electrolytes should be monitored for hypokalemia and hypomagnesemia. The impact of diuretics on prognosis of patients with congestive heart failure is unknown; however, diuretics have been a major ingredient of the therapies used in all the survival trials with vasodilators, angiotensin-converting enzyme inhibitors, and beta-blocking drugs. In addition to their clinical benefits, diuretics are the most cost-effective treatment of any single drug group currently available for the treatment of patients with congestive heart failure⁴².

Diuretics use in Poisoning

Loop diuretics are used medicinally to treat high blood pressure and edema; and in cases of blood poisoning are used to flush the blood of toxins and foreign agents. It has been suggested that the infusion of mannitol intravenously might increase the rate of salicylate excretion, either by increasing urinary output or by a specific effect of Mannitol. The treatment of salicylate poisoning by forced alkaline diuresis is now well established, but the position of mannitol in the production of the diuresis is less well defined⁴³.

Diuretics use in Body building

Loop Diuretics are far and away the most commonly used diuretics in bodybuilding and the culprit in the vast majority of bodybuilding hospitalizations and deaths. Furosimide (brand name Lasix) is easily the most widely used loop diuretic and is cheap and readily available. Loop diuretics act directly on the kidneys and are another non-discriminatory

diuretic in that they remove any and all fluids coming through the kidneys. They have a profound effect on the electrolyte balance as they literally flush potassium, sodium and calcium from the body with whatever fluid enters. Side effects include a drop in blood pressure, thickening of the blood (due to lack of fluids), fainting, renal failure, extreme cramping due to electrolyte imbalances, and death (due to muscular cramping of the heart). The drug is extremely powerful and, combined with other water reduction techniques employed by bodybuilders in contest preparation; it doesn't take much Lasix to cause extremely detrimental health effects⁴⁴.

Athletes preparing for bodybuilding competitions strive for the most muscular and hardest look they can possibly achieve. This involves several months or years of building muscle, followed by several weeks of a restricted diet and cardiovascular training in an effort to reduce body fat to the lowest possible level to bring out all of the definition of the muscle. Reducing water from the body in preparation for a contest can be aided in a multitude of ways. Often, most or all of these methods are employed. They include cardio training in heavy garb, elimination of sodium from the diet, excessive water intake followed by a sudden and drastic reduction of water intake, drinking mineral and electrolyte free distilled water, herbs and natural water-reduction substances and most effectively; medicinal diuretics. All can be dangerous to a degree as they strive to interfere with the body's natural homeostasis of fluid and electrolyte balance and can disrupt multiple body processes. The body, however, is a master of keeping itself in a reasonable balance. It can adjust itself in most instances to this by adjusting electrolyte balances and holding on to just enough fluids to keep functioning properly. Diuretic drugs, however, are powerful enough to override the body's defenses and create havoc in the body. Recently, herbal and natural water-loss systems have improved vastly as the result of scientific research and study. Water can now be reduced to the desirable level without putting ones health or life in danger. A cutting-edge, new for 2011 example of these products is Hydradry by Allmax Nutrition. Hydradry is a 14-Day water loss system designed specifically for pre-contest weight loss. It utilizes a three-stage water depletion system with nine separate powerful plant extracts, including two forms of taraxacum,

which is extracted from the dandelion plant. Water loss from Hydradry quick and effective; comparable to that of several other techniques combined. Further, Hydradry is fortified with a scientifically-balanced blend of B6, calcium, magnesium and potassium to keep these levels in the body stable⁴⁴. Diuretics may cause several other adverse reactions, potentially leading to discontinuation. Hypokalemia was suggested as a potential trigger of arrhythmias and sudden cardiac death³⁰, although its impact is now less than in the past because of the widespread use of low-dose thiazides, potassium-sparing diuretics, and combinations with ACE inhibitors or angiotensin receptor blockers. Muscle cramps may cause suspicion of hypokalemia. Hyponatremia is another insidious side effect of diuretics and is particularly frequent in elderly women after prolonged use of the drug. Hyperuricemia is a dose-dependent effect that may lead to acute gouty arthritis. Diuretics increase the risk of NOD (New Onset Diabetes). In a networkmeta-analysis of 22 clinical trials, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and placebo were associated with a significantly lesser risk of NOD compared with diuretics⁽⁴⁵⁾. The risk of NOD did not differ between diuretics and b-blockers.

Diuretics use in Autism

A drug normally used to increase the rate at which people urinate improves some of the symptoms of autism in children, according to a small clinical trial published today in *Translational Psychiatry*⁴⁶. Autism is a neurodevelopment disorder characterized by impaired communication and social interactions, and also by repetitive behaviors in those affected. Research has shown that signaling by a molecule called GABA, a neurotransmitter which normally dampens down neuronal activity, is altered in autism. And that this disruption of GABA is due to increased levels of chloride ions in the brain cells. Reducing these chloride ion levels might help to treat the condition, hypothesized Yehezkel Ben-Ari, a neuroscientist at the Mediterranean Institute of Neurobiology. In 2010, Ben-Ari and his co-author reported that a three-month course of bumetanide — a diuretic that lowers the concentration of chloride ions by blocking the entry of ions into the cell — decreased autistic behavior in five infants without causing side effects⁴⁷.

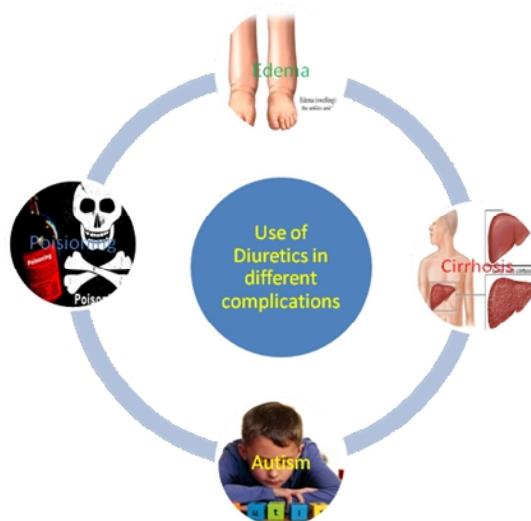


Figure 1. Uses of Diuretics in different complications of body

CONCLUSION

Diuretics continue to be a good modern day option for lowering blood pressure, edema, congestive heart failure, cirrhosis, autism, toxemia and YES! For the majority of patients diuretics can be used as first-line therapy. Rather, In case of hypertension the authors would endorse the statement by the authors of the ESH/ESC Guidelines, that 'The emphasis on first choice drugs is outdated, given the predominant role of combination therapy', and agree that the choice should be tailored in accord with the clinical situation in the individual patient.

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