Drug interactions and consequences of sodium restriction\textsuperscript{1,2}

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ABSTRACT Dietary sodium restriction has several clinical benefits, particularly that of enhancing the antihypertensive action of diuretics and other blood-pressure-lowering drugs. In individuals who form hypercalciuric stones, sodium restriction along with thiazide diuretics helps to reduce urinary calcium. However, there are adverse consequences of sodium restriction, particularly in elderly patients with impaired sodium conservation mechanisms. Ischemic and nephrototoxic injuries are induced more readily in sodium-depleted animals and patients because of impaired renal hemodynamics and activation of the renin-angiotensin system. Acute renal failure can be precipitated by sodium restriction and concomitant angiotensin-converting enzyme inhibitors, nonsteroidal antiinflammatory drugs, and immunosuppressive drugs. Dietary sodium restriction in animals enhances the chronic nephrotoxicity of cyclosporine and tacrolimus, whereas similar doses of these drugs do not produce structural damage in salt-replete animals. Maneuvers that block angiotensin II protect against renal scarring and drug-induced arteriolopathy in this model. Sodium restriction can enhance the renal tubular reabsorption of drugs such as lithium, leading to toxic blood concentrations. Calcium antagonists may have better efficacy when prescribed to salt-replete hypertensive persons. Finally, there is evidence that activation of the renin-angiotensin system by sodium depletion will enhance the growth of cysts in animal models of cystic renal disease. In individual patients, the effects of sodium restriction by diet should balance anticipated benefits against any possible adverse consequences. Am J Clin Nutr 1997;65(suppl):678S–81S.

KEY WORDS Drug interactions, sodium restriction, nephrotoxicity, nonsteroidal antiinflammatory drugs, NSAIDs, angiotensin-converting enzyme inhibitors

INTRODUCTION

Sodium, as the major cation of the extracellular space, is tightly regulated by the body to preserve a relatively constant concentration in body fluids as well as an adequate total body content. The latter is particularly important inasmuch as the maintenance of extracellular volume is important in circulatory hemostasis and blood pressure control. Dietary sodium restriction may lead to increased physiologic signals to activate sodium-saving mechanisms such as the renin-angiotensin system, sympathetic nervous system, and vasoconstrictor prostanoids, which tend to moderate decreases in extracellular and intravascular volume at the expense of systemic blood pressure.

POTENTIATION OF DRUG EFFECTS AND BENEFICIAL INTERACTIONS

Dietary sodium restriction potentiates the blood pressure effects of antihypertensive drugs (1). There is little doubt that this is an effective way of maximizing the hypotension produced by a wide variety of therapeutic agents, including diuretics, \( \beta \)-blockers, \( \alpha \)-blockers, vasodilators, and angiotensin-converting enzyme (ACE) inhibitors (2). With calcium antagonists, however, which are a popular class of antihypertensive drugs, there is a somewhat different response to sodium restriction. These drugs have a blunted effect when a patient or animal is rigidly sodium restricted (3, 4). In fact, the efficacy of the calcium antagonists, as well as the effect of calcium supplementation on blood pressure lowering, is enhanced when sodium intake is normal. This interesting phenomenon is now undergoing testing in clinical trials of the blood pressure effects of dihydropyridine calcium antagonists in subjects with various sodium intakes (DA McCarron, unpublished observations, 1994). Although the pathophysiology of this observation is unclear, adequate calcium nutrition is essential for maximizing the response to dietary or pharmacologic maneuvers to lower blood pressure by restricting sodium intake.

Thus, although sodium restriction may reduce blood pressure in a subset of individuals and augment responses to a wide variety of different antihypertensive drugs in others, this dietary intervention can activate counterregulatory systems that may modify the beneficial effects of normotension by changes in sympathetic nervous tone and increases in the activity of the renin-angiotensin system. There seems to be no simple way to clinically assess individual patient response before restricting sodium. In addition, the mechanism of antihypertensive action of the thiazide diuretics could be by increased tubular reabsorption of calcium rather than by sodium depletion, because long-term diuretic-treated hypertensive patients restore intravascular volume within weeks while maintaining a long-term blood pressure-lowering effect. Similarly, a person who adheres faithfully to a low-salt diet may have increased calcium reabsorption by the kidney. Because salt loading and essential hypertension are associated with increased urinary losses of divalent cations, it appears to be prudent to maintain calcium
nutrition, as is now recommended by the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (5).

Urinary calcium excretion is directly correlated with sodium intake and protein intake (6). Patients with isolated hypercalciuria may develop hematuria or calcium-containing nephrolithiasis in adolescence and young adulthood. When such patients have been studied, they have high sodium and protein intakes relative to calcium intake. In fact, calcium intake per se is not a strong predictor of urinary calcium excretion, which is much better correlated with the dietary ingestion of sodium and protein. In patients who form calcium stones and in other patients with idiopathic hypercalciuria, sodium restriction is a proven therapeutic maneuver that minimizes calcium excretion and thus minimizes the risk of stone formation (7).

ADVERSE DRUG-SODIUM INTERACTIONS

Dietary sodium restriction can increase the tubular reabsorption of therapeutic agents as can diuretic-induced depletion of extracellular fluid volume. For example, lithium carbonate, which is the mainstay of therapy for serious bipolar disorders, can be markedly influenced by these processes. Toxic lithium plasma concentrations leading to acute and chronic central nervous system and renal side effects can be precipitated by sodium depletion (8). When a patient being treated with lithium is placed on a low-salt diet or given a diuretic, careful dose adjustment is required to prevent this common drug-nutrient interaction.

EFFECT OF SODIUM RESTRICTION ON DRUG-INDUCED ALTERATIONS OF RENAL HEMODYNAMICS

Drugs that precipitate acute renal failure often manifest this complication during sodium depletion. The commonly used nonsteroidal antiinflammatory drugs (NSAIDs) do not alter renal hemodynamics under normal circumstances (9). However, in the setting of sodium depletion, cyclooxygenase inhibitors block vasodilator prostaglandin synthesis, which augments the unopposed activation of the renin-angiotensin and sympathetic nervous systems and produces renal vasoconstriction, acute renal dysfunction, and ultimately acute renal failure (10). This hemodynamic complication can be reversed rapidly when recognized; unfortunately, many patients do not realize that these readily available over-the-counter drugs have any potential interactions. Older patients with impaired sodium conservation, patients with atherosclerotic renal disease, and hypertensive patients treated with diuretics are particularly vulnerable (11). Although warnings about these potential risk factors are on the package insert for prescription NSAIDs, over-the-counter NSAIDs carry no such warning. In the setting of extracellular fluid volume depletion induced by intercurrent gastrointestinal illness or insensible losses, patients adhering to a sodium-restricted diet are more vulnerable and should be instructed to liberalize their sodium intake, particularly if they are taking concurrent salicylates or NSAIDs. Sodium depletion by diet can produce major declines in renal function even in normal subjects taking therapeutic doses of these drugs (12).

Chronic renal failure due to prolonged use of analgesic compounds or NSAIDs can also be accelerated by sodium depletion. In these patients, because the renal injury first appears in the medullary and papillary structures of the kidney, concentrating, diluting, and sodium conservation mechanisms are frequently impaired even without decreases in the glomerular filtration rate. Thus, intercurrent sodium restriction, volume losses from gastrointestinal illness, and insensible losses in hot, humid environments may worsen renal function and hasten the events leading to chronic renal failure (13). This was documented recently in countries with an equatorial climate in patients using prescribed NSAIDs (14).

ACE inhibitors are valuable therapeutic agents for hypertension, left ventricular failure, and prevention of the progression of chronic renal disease. In settings where maintenance of renal glomerular filtration pressure is dependent on an activated renin-angiotensin system, angiotensin II causes preferential vasoconstriction on the efferent arteriole of the glomerulus. This helps to maintain intracapillary glomerular pressure and thus to maintain glomerular filtration. When the renin-angiotensin system is blocked by ACE inhibitors, efferent resistance drops, with resultant falls in intraglomerular pressure and glomerular filtration (15). This is the basis for the captopril test for diagnosis of renovascular hypertension. In patients with atherosclerotic disease of the renal arteries or when renal perfusion is markedly diminished, such as in congestive heart failure or even in salt-restricted persons or those taking diuretics, ACE inhibition can cause the glomerular filtration rate to decrease. Nearly all the patients who have suffered acute renal failure in the context of ACE inhibition were consuming salt-restricted diets or receiving diuretic therapy. In clinical practice, older individuals should be monitored carefully for intercurrent volume depletion when they are taking ACE inhibitors. It is good practice to have a blood chemistry profile taken shortly after institution of such therapy in patients consuming salt-restricted diets or taking diuretics for maintenance of blood pressure control.

NEPHROTOXIC ACUTE RENAL FAILURE AND SODIUM RESTRICTION

The kidney is predisposed to nephrotic injury by many commonly used therapeutic agents because of its high blood flow rates, extensive surface area for filtration and reabsorption, and innate renal mechanisms for concentrating drugs and chemicals in tubular fluid. In addition, there is relatively low oxygen tension in the medullary areas of the kidney that are critical for concentration and acidification of the urine (16). Kidneys exposed to extracellular fluid volume contraction and salt depletion increase proximal tubular reabsorption of filtrate because of the sodium-avid state. This often exacerbates tissue damage by increasing the amount of toxin transiting the cells of the proximal tubular nephron segment. This has been aptly shown in most experimental models of nephrotic injury, including those of injury due to mercuric chloride, uranyl nitrate, and the clinically used amphotericin B, radiocontrast media, aminoglycoside antibiotics, cyclosporine, and tacrolimus (FK506) (17).

Amphotericin B

Amphotericin B is still the treatment of choice for systemic fungal infections, which have become more prominent lately.
because of the advent of human immunodeficiency virus infection, cancer chemotherapy, and organ transplantation. Nephrotoxicity manifested by azotemia, impaired renal concentrating ability, renal tubular acidosis, and magnesium wasting complicate many adequate therapeutic courses (18). The major risk factor for this type of toxicity is salt depletion, both experimentally and clinically (19). Salt loading has gradually been adopted by many clinicians as a means of ameliorating the nephrotoxicity of amphotericin B. Well-controlled randomized trials confirmed the protective role of sodium chloride supplementation (20). The mechanism of this protective effect of sodium chloride is unknown, however.

Radiocontrast media

Routine diagnostic medical practice in seriously ill patients includes many radiographic procedures requiring contrast media. These include angiograms, urography, and computerized axial tomography scanning procedures. There is a significant incidence of acute renal failure in high-risk groups, which mainly include patients with preexisting renal disease and patients with diabetic nephropathy. One of the major risk factors for contrast nephropathy is volume depletion. The only therapeutic maneuver that is clinically useful is maintenance of adequate extracellular fluid volume by saline infusions or formal hydration protocols (21). The exact mechanism of this protective effect is unclear but it is commonly accepted in clinical practice that sodium restriction should be discontinued electively before contrast studies, inasmuch as activation of the renin-angiotensin system is one of the postulated mechanisms facilitating the adverse hemodynamic effects of contrast dyes.

Aminoglycoside antibiotics and cisplatin

Despite close therapeutic monitoring of aminoglycoside therapy by pharmacokinetic methods, nephrotoxicity complicates 10–15% of all courses of therapy. Although risk factors have been shown for aminoglycoside toxicity, there are solid experimental studies clearly showing that sodium loading minimizes whereas salt depletion enhances aminoglycoside-induced nonoliguric acute renal failure. Drug reabsorption by tubular cells is enhanced by sodium depletion and extracellular fluid volume contraction (22).

Similarly, cisplatin-induced nephrotoxicity can be minimized by sodium chloride loading (11). All patients receiving cancer chemotherapy should discontinue salt-restricted diets and have their extracellular fluid volume maximized before undergoing chemotherapy. Obviously, the volume deficit can be made worse by chemotherapy-induced nausea and vomiting.

Cyclosporine and FK506

New immunosuppressive agents have revolutionized organ transplantation, allowing superior 1- and 2-y patient and graft survival for heart, kidney, liver, kidney-pancreas, and lung transplants. One major adverse side effect of these new drugs is dose-related acute renal failure. Experimentally, sodium depletion enhances the tendency for renal vasoconstriction produced by these agents. A major form of toxicity due to these drugs is afferent arteriolar vasoconstriction, which can be minimized by various pharmacologic maneuvers, including blockade of the renin-angiotensin system. Much more important clinically is a progressive chronic renal nephrotic insult that is characterized by striped tubulointerstitial fibrosis and afferent arteriolopathy (23).

These pathologic findings have been noted in patients treated with low doses of cyclosporine for autoimmune disease and can lead to progressive chronic renal failure. It has been difficult, however, to reproduce these pathologic findings in animal models of immunosuppressive drug nephrotoxicity. Recently, Elzinga et al (24), using dietary sodium depletion, successfully reproduced the clinical pathologic picture of chronic cyclosporine nephrotoxicity in rodents. Dietary sodium depletion also produces a similar lesion with FK506 in experimental animals (25). Sodium depletion activates the renin-angiotensin system and angiotensin II has potent effects that enhance renal scarring and arteriolar lesions caused by immunosuppressive drugs.

Recent studies with angiotensin II receptor blockers and ACE inhibitors show that tubulointerstitial fibrosis can be favorably affected even if renal hemodynamics are not improved (W Bennett, unpublished observation, 1995). This dissociation of structural and functional changes in the kidney exposed to a nephrotoxin in the setting of an activated renin-angiotensin system has profound implications for clinical therapy, because insensitive variables such as serum creatinine or even the glomerular filtration rate itself cannot be used to exclude long-term damage to the kidney in diuretic-treated patients, salt-restricted patients, or patients with activated sympathetic and renin-angiotensin systems. Impaired renal autoregulation induced by cyclosporine may add to the severity of ischemic damage noted in sodium-depleted rats. Interestingly, procollagen messenger RNA concentrations are elevated in these cyclosporine-treated rats, suggesting that angiotensin II may be important in stimulating tubulointerstitial fibrosis.

ISCHEMIC ACUTE RENAL FAILURE

Most episodes of acute renal failure in humans are thought to result from hypoxic injury to the kidney related to hemodynamic insufficiency. Renal blood flow in patients with acute renal failure is reduced by about one-third compared with that in normal healthy control subjects. Increased ATP breakdown by ischemic conditions can lead to increased adenosine formation, which may potentiate angiotensin II–mediated vasoconstriction. When oxygen supply is limited, sodium delivery to ischemic nephron segments may result in more transport work, which in turn may accelerate cellular damage. Human and animal models of acute renal failure produced by renal ischemia result in the loss of renal autoregulatory ability (16). Thus, recurrent episodes of hypotension undoubtedly exacerbate acute renal failure in terms of the extent of damage as well as the kidney’s ability to undergo repair processes. Stabilization of renal blood flow by maintenance of adequate extracellular fluid volume is therefore important. Careful attention to sodium balance in patients with an ischemic insult is critical because neither hyperfusion nor hypoperfusion is beneficial to ischemic kidneys.

MISCELLANEOUS CONDITIONS

Polycystic kidney disease is the most common renal genetic disorder, affecting ≈1 in 1000 individuals in the general population. It has an autosomal-dominant mode of inheritance with
a high degree of penetrance. Patients who inherit the gene have gradual progressive enlargement of renal cysts throughout life, culminating for many patients in chronic renal failure in the fifth or sixth decade of life. Some patients have progressive cystic enlargement but do not develop end-stage renal disease. Nonetheless, the influences on the growth of these cysts are unknown. In spontaneous and chemically induced animal models of cystic disease, sodium depletion by activation of the renin-angiotensin system can accelerate cyst growth and hasten the downhill course to renal failure (26). If this model is confirmed in humans, the common clinical problem of blood pressure elevation in association with this disease might be best managed by antihypertensive drugs that do not stimulate the renin-angiotensin system (27).

CONCLUSIONS

Sodium restriction by dietary means can provide an important adjunct to antihypertensive therapy in patients affected with essential hypertension. Sodium restriction can also reduce urinary calcium excretion in patients who form hypercalciuric renal stones. However, dietary sodium restriction can have adverse consequences such as elevating concentrations of drugs such as lithium, which are reabsorbed in the proximal tubule leading to lithium toxicity, or serving as a major risk factor for hemodynamic nephrotoxic and ischemic acute renal failure.

In any patient, the effects of sodium restriction by diet should balance anticipated benefits against possible adverse consequences. Patients should be counseled that although sodium restriction is advisable under some circumstances, there are instances in which dietary sodium should be liberalized, such as in the presence of intercurrent illnesses and interacting drugs.

REFERENCES