Review of Salt Restriction and the Response to Antihypertensive Drugs

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SUMMARY We evaluated the response to salt restriction in hypertensive patients receiving drugs. By restricting their salt intake to less than 80 mmol of sodium per day for 3 months, 50% of patients reaching goal compliance were able to discontinue diuretics. The literature also reveals responses to a low salt diet. Salt restriction augmented the hypotensive effect of chlorthalidone in two investigations, but not in another, and the hypotensive effect of β-blockers in three trials. Sodium intake of 10 mmol/day caused a much greater decrease in blood pressure in response to a single dose of captopril than did a sodium diet of 200 mmol/day. In patients receiving various fixed regimens for 2 months, salt restriction decreased blood pressure in all but those receiving calcium blockers. A single dose of nifedipine lowered blood pressure more in patients receiving 350 mmol of sodium per day than in the same patients given 150 or 10 mmol/day. Verapamil for 3 days was more effective in patients receiving 212 mmol of sodium per day than in the same subjects receiving 9 mmol/day. Nifedipine caused a greater decrease in diastolic blood pressure in patients who did not reduce salt intake compared to those who did. Salt restriction appears useful in salt-sensitive patients who receive β-blockers, diuretics, converting enzyme inhibitors, or centrally acting drugs. Calcium channel blockers may not require salt restriction to maximize their effect. (Hypertension 11 [Suppl I]: I-229-I-232, 1988)

KEY WORDS salt • sodium • drug treatment • drug efficacy • dietary interventions

HIGH salt intake may predispose to the development of essential hypertension, although the mechanisms by which this effect occurs are not clear. Salt consumption may trigger an increase in the level of a sodium transport inhibitor that restores sodium balance while increasing the concentration of intracellular sodium in arteriolar smooth muscle. Such an effect would promote an increase in cytosolic calcium, thereby promoting smooth muscle reactivity as well as the inhibition of norepinephrine reuptake by nerves. Reduced salt intake has been advocated to reverse this putative state of affairs; however, a subset of patients exists in whom blood pressure either does not change or actually increases with reduced salt intake. Salt sensitivity and salt resistance of blood pressure in humans may be genetically mediated, as they are in the rat.

Salt reduction has also been advocated as an adjunct to pharmacological treatment. Such a strategy appears particularly wise when drugs are used that promote salt retention. Drugs that augment distal sodium delivery, secondary aldosteronism, and urinary potassium losses might be less likely to have these effects when salt intake is reduced. A review of the literature and our own experience suggests that salt reduction augments some, but not all, pharmacological regimens.

Diuretics and β-Blockers

A comprehensive study of salt restriction used in the management of mild hypertension as sole therapy or in conjunction with diuretics, β-blockers, or both was conducted by Erwteman et al. Ninety-four patients with mild hypertension were allocated at random to restrict dietary salt to 70 mmol of sodium per day (n = 44) or continue their regular sodium intake of 130 to 140 mmol/day (n = 50). Compliance with the diet was assured by examining 24-hour urine specimens weekly. The subjects in both groups received in random order chlorthalidone (25 mg/day), metoprolol (200 mg/day), and a fixed combination of these two drugs at the same dose. Each drug regimen was given for 4 weeks and alternated with 4 weeks of placebo. Screening and treatment blood pressures were different at both levels of salt intake with all of the interventions. To deal
with regression to the mean, the investigators examined mean differences in fall in blood pressure between normal and low salt intake. (Source of data: Erwteman et al.)

Carney et al. studied 24 patients receiving medication for moderate to severe hypertension during 6 weeks of a normal diet and after 6 weeks of a low salt diet. Urinary sodium excretion was reduced from a mean of 169 to 92 mmol/day. The intervention caused a significant reduction (5 mm Hg) only in standing systolic blood pressure in the entire population. When the patients were subdivided to receive thiazide diuretics or drug regimens not containing thiazide diuretics, a reduction in mean supine systolic and diastolic blood pressures, as well as systolic blood pressure while standing, was observed in the thiazide-treated group (Figure 2).

Pollavini et al. studied 95 patients who received oxprenolol (160 mg/day) or chlorthalidone (25 mg/day). Subjects were instructed to decrease their daily salt intake for 4 weeks. The reductions in daily sodium excretion were significant, albeit modest (from 190-230 to 150 mmol/day). Similarly, a modestly enhanced effect of both regimens was observed (Figure 3).

Owens and Brackett studied 12 hypertensive patients whose sodium intake was reduced from 150 to 10 mmol/day (as NaCl) for 3 days. At that time hydrochlorothiazide was added, and the low sodium regimen was continued for another day. The entire protocol was repeated after the same subjects had received oral propranolol therapy (mean dose, 270 mg/day) for 4 to 14 weeks. The effect of propranolol monotherapy on blood pressure was augmented by severe sodium restriction, but no further reduction was observed with the addition of 1 day of hydrochlorothiazide.

We are currently conducting a study of dietary salt reduction in hypertensive outpatients receiving medications that include a thiazide diuretic. The 97 participants reduced their salt intake for 6 months in an effort to achieve a 24-hour urinary sodium excretion below 80 mmol/day. We recently reported the results obtained from the first 65 subjects who were studied for 3 months. Half of these subjects achieved the compliance goal, while the other half lowered sodium excretion from a mean of 150 mmol/day to a mean of 100 mmol/day. Physicians unaware of the urinary sodium excretion of each subject decreased the thiazide diuretic from the regimen of those patients whose mean sitting blood pressure decreased by more than 8 mm Hg. Of 34 compliant patients, 15 were allowed to discontinue the diuretic. The data suggest that perhaps 50% of hypertensive patients are salt-sensitive and actually respond to decreased salt intake with a decrease in blood pressure. Furthermore, a reduction sufficient to lower sodium excretion to below 80 mmol/day appears necessary to achieve this effect.

Salt restriction appears to augment the effects on blood pressure observed with β-blocking agents, which are related to different numbers of salt-sensitive and salt-resistant subjects in the various trials. Reduction of salt intake is not easily achieved, and from that standpoint the data are not encouraging. Some investigators found no additional blood pressure reduction with salt restriction in patients receiving diuretics.

**Converting Enzyme Inhibitors**

The renin-angiotensin system is ubiquitously distributed throughout the body. The kidney is the primary

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**Figure 1.** Decrease in blood pressure in 94 subjects randomized to salt-restricted or control groups and then rotated through three treatments, chlorthalidone, metoprolol, or a combination of both, alternating with placebo (diet alone). Given here are the mean differences in blood pressure fall between groups with normal and low salt intake. (Source of data: Erwteman et al.)

**Figure 2.** Blood pressure response with upright posture in 24 patients treated with hydrochlorothiazide (HCTZ) or other drugs before and after salt restriction. Only HCTZ-treated patients showed an effect. (Source of data: Carney et al.)

**Figure 3.** Blood pressure response in 95 patients treated either with chlorthalidone or oxprenolol before and after salt restriction. Modest effects on blood pressure were observed. (Source of data: Pollavini et al.)

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source of circulating renin and is also the major end-organ for the eventual products of renin, namely angiotensin II and aldosterone. The renin-angiotensin system also plays a regulatory role within the central nervous system, as well as within the walls of blood vessels and other organs in the body (see Reference 20 for review). Converting enzyme inhibitors influence the circulating and tissue renin-angiotensin system. They also impede the degradation of bradykinin, which itself has major effects on vascular tone and renal sodium homeostasis. Finally, certain converting enzyme inhibitors, if not all, influence the production of prostaglandins, including those of the E series, which also are important in renal regulation. Prostaglandins may be important in the hypotensive response induced by converting enzyme inhibitors, particularly during high salt intake. Interference with the renin-angiotensin system would be expected to produce alterations in renal sodium homeostasis and renal blood flow. Furthermore, the actions of converting enzyme inhibitors on renal function and blood pressure would likely be affected by dietary salt intake.

Hollenberg et al. studied the effects of salt intake on the renal and blood pressure-lowering responses to captopril in normal persons and in patients with essential hypertension. Fifty-three normal subjects and 78 hypertensive patients were given diets containing either 10 or 200 mEq of sodium per day. Captopril increased renal blood flow in both groups irrespective of salt intake. The drug caused a small decrease in glomerular filtration rate in normotensive subjects but not in those with hypertension. It also induced natriuresis at both levels of salt intake. Captopril invariably decreased blood pressure; in hypertensive subjects, however, this effect was augmented by reduced salt intake.

Long-term studies incorporating dietary salt restriction and captopril treatment have not been reported. Although it appears likely that low salt intake would enhance the effects of prolonged converting enzyme inhibition, it is possible that currently unrecognized compensatory mechanisms could influence this expected result. Studies should be done to address this issue.

Calcium Blockers

Calcium plays a critical role as a modulator and initiator of many cellular functions, including striated and smooth muscle contraction, electrical activation of various excitable cells, neurotransmitter release, platelet aggregation, chemotaxis, endocrine and exocrine gland secretion, and renal function. Calcium blockers promote natriuresis in part by reducing sodium reabsorption at the distal tubule. In the rat, calcium blockers ameliorate hypertension induced by long-term infusion of angiotensin II, in part by promoting natriuresis. In three balance studies conducted in hypertensive patients, administration of these drugs resulted in a net increase in sodium excretion, resembling the effect observed with thiazide diuretics. Calcium blockers may have acted in part by interfering with the release of aldosterone. Whether the reduction in total-body sodium is important in the antihypertensive action of these drugs is currently unknown.

It is curious that the action of calcium blockers on blood pressure does not appear to be enhanced by dietary salt restriction. Morgan et al. reported on 78 patients with mild essential hypertension who were randomized to receive no treatment, thiazide diuretics, centrally acting antisynthetic drugs, β-blockers, or calcium blockers. The groups were then counseled to reduce their dietary salt intake, as verified by 24-hour urinary sodium excretion. Blood pressure remained the same in a nontreated, non-salt-restricted control group. Diuretics, centrally acting drugs, and β-blockers were all more effective with reduced dietary salt intake; salt restriction alone was also effective. In contrast, the blood pressure of patients receiving calcium blockers actually increased during salt restriction.

MacGregor et al. evaluated the effects of salt intake on the response to nifedipine both as a single dose and in a longer protocol. They found that the decrease in blood pressure in hypertensive patients after a single 5-mg dose of nifedipine was greater when the diet contained 350 mmol of sodium per day than when intake was 150 or 10 mmol/day. Initial blood pressure values were also greater at the higher two levels of salt intake. These results were corroborated in a 15-day study period.

Nicholson et al. gave eight patients low (10 mmol/day) or high (200 mmol/day) salt diets and found that the decrease in blood pressure after three doses of verapamil was greater at the higher level of salt intake than at the lower level (Figure 4). These results were corroborated in a longer-term study in which eight patients received nitrendipine for 1 month. The drug was more effective when dietary salt intake was generous (sodium excretion, 250 mmol/day) than when it was restricted (sodium excretion, 50 mmol/day).

Calcium blockers do not cause weight gain and are natriuretic. Thus, contrary to drugs that promote sodium retention, such as the direct-acting vasodilators, they may not require diuretics or salt restriction to exert a maximum effect. Furthermore, if salt-sensitive hypertension is indeed mediated by an inhibitor of sodium transport that is responsible for an increase in cytosolic calcium, calcium blockers should...

![Figure 4. Reductions in blood pressure with verapamil administered for 3 days under conditions of low and high salt intake. (Source of data: Nicholson et al.)](image-url)
be more effective under conditions in which such a circulating inhibitor is most active. A diet rich in salt would promote high levels of such a natriuretic material. Verapamil binds to α₂-receptors on platelets and in that way may compete with α₂-receptor agonists for these sites. The number of α₂-receptors has been found to increase in salt-sensitive individuals with ingestion of a high salt diet. It is possible that verapamil may impede α₂-receptor activation at higher levels of salt intake in these subjects.

The effect of salt restriction on treatment with calcium blockers is incompletely delineated, as it is for all of the antihypertensive drugs currently employed. The studies available are short-term, lacking in statistical power, and not generally directed at mechanisms. Since nonpharmacological approaches show promise, further investigations in this area are warranted.

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