Congress Papers

SALT, THE KIDNEYS, AND ARTERIAL HYPERTENSION

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Key words: salt, sodium, hypertension, pressure-natriuresis, cardiovascular risk

ABSTRACT

The kidneys play a major role in the regulation of the salt balance and thereby, regulate blood pressure. Salt sensitivity is acquired or genetically-induced and is noted in about 50% of patients with essential hypertension. This property leads to a high cardiovascular risk. In this situation, the benefit of salt restriction is significant, and this dietary change should be associated with a high potassium intake. In patients treated by antihypertensive drugs, salt restriction improves the blood pressure control, which can permit a reduction of the number of drugs required to achieve a normal blood pressure. The recommended maximal salt intake should not exceed 6 grams/day (NaCl). Because most dietary salt comes from processed foods, the help of the food industry is crucial for a long-term compliance with a reduced salt intake, which could yield an additional important benefit in the reduction of cardiovascular risk.

INTRODUCTION

Salt (sodium chloride, NaCl) is essential for life. Many mechanisms work in concert in the body to tightly regulate the body’s sodium content and concentrations. These are essential for the maintenance of circulatory volume and cell membrane potential.

Sodium chloride is a primary determinant of extracellular fluid volume and thereby has an important role in blood pressure (BP) regulation. Kidney function determines the blood and plasma volume, and these affect the heart function, such as stroke volume. This, and the peripheral arterial resistance, determine the blood pressure.

Dynamic regulation of renal sodium excretion is needed to respond to variations in dietary sodium intake. Of the physiological mechanisms invoked to maintain sodium balance, pressure-natriuresis is pre-eminent.

Although essential hypertension (HTN) is a complex disease with polygenic and environmental contributions, a large body of evidence exists for the notion that increased salt intake contributes to the development of essential HTN (1).

SODIUM AND HYPERTENSION

The understanding of the role of sodium in human HTN can be divided into four parts, which are chronologically overlapping: dietary and drug manipulations, experimental HTN, epidemiological studies, and suggested pathophysiological mechanisms (Table 1).

The first part began with Ambard and Beaujard in 1904 (2) who reported that chloride deprivation may be associated with a decline in the blood pressure (BP) of hypertensive patients. As reported in the 1940s, the rice-fruit diet of Kempner (3) was successful in reversing malignant HTN in 2/3 of the patients studied.
The second part is characterized by experimental work in rats showing the importance of salt in the regulation of blood volume and BP. For instance, by selective breeding, Dahl et al. (4) developed a unique strain of rats in which hypertension routinely developed after they were fed a high salt diet. In contrast, salt resistant rats were also developed which did not develop HTN in spite of the presence of sodium in their diet (5).

The third part is based on epidemiological observations showing that the prevalence of hypertension in different populations is linked to the amount of sodium regularly consumed (6). More recently, the Intersalt study showed a highly significant positive relation between 24 hour urinary sodium excretion and BP in cross population analyses and at individual level (1988) (7). Essential hypertension is seen primarily in societies with average sodium intakes above 100 mmoles/day, but is rare in populations with average sodium intakes of less than 50 mmoles/day. This suggests that the development of salt-induced hypertension requires a threshold of salt intake, independent of other risk factors for hypertension, such as obesity (8).

The fourth part deals with the mechanisms leading to high BP. In 1969, Guyton and Coleman emphasized abnormal extracellular fluid volume regulation in the pathogenesis of hypertension (9). In 1976, Haddy and Overbeck (10) proposed that hypertension due to salt was humorally mediated, a theory which was extended from Dahl’s work done in rats. This concept of a humoral substance as the link between salt intake and high BP was elegantly summarized by de Wardener and MacGregor in 1980, who proposed a role for an Na-K pump inhibitor with natriuretic properties as the vasoconstrictor substance leading to high blood pressure, a substance which is secreted in response to a renal defect of salt excretion (11).

However, despite much work over the past century, the precise mechanisms linking salt to high BP remain only partially understood.

### ROLE OF THE KIDNEYS IN THE RELATION BETWEEN SALT AND HYPERTENSION

Sodium and chloride are freely filtered at the glomeruli and then reabsorbed along the tubules: 65% at the proximal level, 25% at the loop of Henle, 5% at the distal tubule and 2%-4% at the collecting tubule where the final and precise regulation is achieved along with the well-known influence of aldosterone. All of these features of the normal physiology of renal sodium handling are relevant to the pathophysiology of hypertension.

As emphasized by Guyton et al. (12), the kidney is important in the regulation of BP, through the central role of the pressure-natriuresis phenomenon. An increase in effective circulating volume leads to a rise in perfusion pressure of the kidneys, and a natriuresis that tends to restore the effective circulating volume to normal (Fig 1a). This pressure-natriuresis servo-mechanism prevents the incremental increases in BP that could arise from transient circulatory expansion. This mechanism may explain why many remain normotensive despite dietary sodium intakes of 100 mmoles/day or more. It is likely that in healthy subjects, a sufficient pressure-natriuresis enables maintenance of a normal BP (Fig 1b).

However, if there is a resetting of the pressure-sodium excretion curve, it would prevent the return of BP to normal. Indeed, impaired sodium excretion is the hallmark of virtually every form of HTN, and particularly in CKD.

Other mechanisms, beyond mere dietary sodium excess, must thus participate in the relation of salt intake to hypertension.

In most hypertensives, but already at the prehypertensive stages, renal vascular resistance is indeed elevated in parallel to a decrease in renal blood flow. This could result from increased sympathetic activity or vascular sensitivity to the sympathetic tone and abnor-
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Mal renal modulation of angiotensin II in relation to salt intake. Age, drugs and also genetic abnormalities of the sodium transport throughout the renal tubules are additional culprits in the impaired natriuresis that may be found in hypertension.

IMPORTANCE OF CHLORIDE IN SALT INTAKE

Almost 80 years ago, Berghoff and Geraci noted that the BP rose in hypertensive individuals on a high sodium chloride intake, but not on a high sodium bicarbonate intake (13). This was confirmed many decades later (14). An increase in sodium chloride intake can lead to volume expansion and a rise in BP, a consequence which is much less evident if sodium is given with another ion such as citrate or bicarbonate (15, 16). This phenomenon suggests that the anion ingested with sodium affects the distribution of sodium between the intracellular and extracellular compartments. In fact, sodium bicarbonate may increase the sodium content of skeletal muscle, but without expanding the extracellular fluid volume (17).

SALT SENSITIVITY

The acute BP responsiveness to variations in salt intake is known as salt sensitivity. This characteristic varies considerably from individual to individual (18). The definition of salt sensitivity is generally related to changes in BP after a few days of large changes in salt intake and does not usually apply to the potential long-term effects of dietary salt restriction.

Salt sensitivity was found to have a lasting influence by an Italian group. They reported that the incidence of hypertension was higher in a group of salt-sensitive people in comparison to those with low salt sensitivity who had been studied 15 years earlier for this BP sensitivity. This effect persisted after adjustment for age, intercurrent changes in body mass index and baseline BP on low salt diet (19).

The prevalence of this property increases with age. Thus, older age is associated with glomerular afferent arteriopathy, glomerulosclerosis, and tubulointerstitial fibrosis, each of which could impair natriuresis. Salt sensitivity is also more marked in African-Americans, obese people, those with potassium-deficient diets, diabetic patients, and those with acquired renal dysfunction (20). The majority of these situations are characterized by low-renin concentration.

Prediction of salt sensitivity has attracted recent attention. For instance, Melander et al. showed that low-renin and atrial natriuretic peptide concentrations in the plasma may predict the BP response to changes in the dietary sodium (21). The baseline plasma renin level correlated inversely, and that of atrial natriuretic peptide correlated directly with salt sensitivity. These salt-sensitive patients may have microalbuminuria and an absence of nocturnal decrease in BP. Salt sensitivity of BP is characterized by a reversal in the diurnal rhythm of sodium output (22). In healthy patients, the BP is normally lowest at night, as is sodium excretion. However, if sodium has been retained during the day, the BP may rise to a higher level needed to eliminate it. Then, persistent nocturnal elevation of the BP occurs, so-called “non dipping”, probably to enhance nocturnal natriuresis.

In studies on the role of dietary sodium and BP, we...
found that urinary 24h sodium excretion was not different between normotensives (168 mmoles/24h) compared to hypertensives (164 mmoles/24h). In these studies, the salt-sensitive hypertensive, but also normotensive populations, tended to show increased extracellular volume (23, 24), which could only occur if they had an increment in sodium retention that leads to a new equilibrium, albeit at the price of ongoing hypertension.

About 50% of hypertensive patients are salt-sensitive, whereas normotensive people have this characteristic 40% of the time (24, 25). Moreover, salt-sensitive patients also display a higher serum level of LDL cholesterol and a lower level of HDL cholesterol than salt-resistant ones, with greater urinary albumin excretion, perhaps related to a greater glomerular capillary pressure (26). These modifications explain to some extent the higher cardiovascular risk and renal disease risk of these patients (27), especially if high salt intake is associated with overweight (28).

**MECHANISM(S) OF SALT SENSITIVITY**

The mechanism of a salt-induced elevation of BP has received much attention, but with no simple explanation. This is probably due to a multiplicity of mechanisms (Table 2).

One mechanism could be related to renal arteriolopathy impairing blood flow and leading to sodium retention. The subsequent rise in BP might restore natriuresis but at the price of a persistent arterial hypertension. A generalized microvascular defect could be the link between salt sensitivity, insulin resistance and hypertension. Thus, obesity, insulin resistance, and microalbuminuria are situations characterized by salt sensitivity and frequently associated with hypertension. Verhave et al. (29) noted that sodium intake was related to urinary albumin excretion especially in high body mass index patients.

A Dutch group (30) observed that the human capillary recruitment in skin examined during postocclusive reactive ischaemia was inversely correlated with salt sensitivity and insulin resistance. This could link a microcirculatory insufficiency to an impaired natriuresis and subsequent hypertension.

Beyond the microvasculature, there is very good evidence for enhanced renal tubular sodium reabsorption as a clear-cut mechanism of sodium sensitivity. The transporters in question include the proximal tubular Na–H exchanger (31), the chloride channel of the loop of Henle (32), the distal tubular NaCl cotransporter (33, 34), and the collecting tubule amiloride-sensitive epithelial Na channel (ENaC) (35).

Another specific transport-related mechanism for inherited salt sensitivity could be a defect in the gene for alpha-adducin, a cytoskeletal protein that in-

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**Table 2: Factors causing salt sensitivity**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>Primary</td>
<td>Monogenic (see table 3)</td>
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<tr>
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<td>Polygenic : race</td>
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<td>Secondary</td>
<td>Renal disease</td>
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<td>- Insulin resistance</td>
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<td>- Endocrine disorders : adrenal (Cushing, primary aldosteronism)</td>
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<td>hyperparathyroidism</td>
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<td></td>
<td>- Age</td>
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<td></td>
<td>- Drugs : licorice, mineralo- or glucocorticoids</td>
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</tbody>
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**Table 3: Mutations and polymorphisms associated with salt-sensitive hypertension in humans**

<table>
<thead>
<tr>
<th>Potential action</th>
<th>Abnormality and Description</th>
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<tbody>
<tr>
<td>Along the renal tubule</td>
<td>α adducin gene: cytoskeletal protein increasing sodium reabsorption (37).</td>
</tr>
<tr>
<td>At the proximal tubule</td>
<td>Polymorphisms of angiotensinogen gene AGT (M 235 T), angiotensin converting enzyme (I/D), angiotensin AT1 receptor A 1166 C (38)</td>
</tr>
<tr>
<td>At the thick ascending limb of Henle</td>
<td>Activating mutation of the Chloride Channel CCiKb : elevated plasma sodium, decreased GFR (32)</td>
</tr>
</tbody>
</table>
| At the distal tubule | - With hyperkalaemia and hypercalciuria:  
|                      |   - Pseudohypoaldosteronism type 2 (Gordon’s syndrome) : activation of the thiazide-sensitive cotransport by mutation of WNK, and WNK, genes (33)  
|                      |   - Activating mutation of the NaCl cotransport (45) |
| At the collecting tubule | With hypokalaemia :  
|                         |   - Glucocorticoid remediable aldosteronism:  
|                         |     - chimeric gene of aldosterone synthase (CYP, B.) and 11β OHase (CYP, B.) (47)  
|                         |     - Aldosterone synthase (CYP, B.) (49)  
|                         |   - Mineralocorticoid receptor [R] : autosomal dominant (Geller’s syndrome) HTN aggravated by pregnancy activated by progesterone (48)  
|                         |   - Apparent mineralocorticoid excess (AME), Autosomal recessive. Mutation of the gene 11ß OH steroid deshydrogenase 2 (50)  
|                         |   - Aldosterone synthase (CYP 11 B2) (49)  
|                         |   - Mineralocorticoid receptor [R] : autosomal dominant, increased activity of ENaC (36)  

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fluences sodium reabsorption at the renal proximal tubule. Its mutation could lead to enhanced sodium reabsorption, in part via increased Na-H exchange (36). When this gene was tested for polymorphisms, the hypertensive patients with a heterozygous mutation for the mutant allele had greater BP reduction with salt restriction than did those who were homozygous for the wild-type allele. Moreover, this mutation in the aducin gene was related to cardiovascular events in hypertensive people (37).

Besides monogenic hypertension, a combination of renin-angiotensin system polymorphisms could exist and be associated with altered renal sodium handling and hypertension (38), especially at the renal proximal tubular sites (39). Insulin can also increase the sodium reabsorption by renal proximal tubules (40).

There are dopaminergic effects on proximal tubular sodium reabsorption. We have noted that young normotensive patients with a family history of hypertension had a lower urinary dopamine excretion in response to salt loading, as compared to matched subjects without such a family history (41).

At the thick ascending limb of Henle, an increase in the activity of the Chloride channel CLC-Kb can lead to hypertension and also a reduced glomerular filtration rate, perhaps due to activation of the tubulo-glomerulo feedback. Those with this genetic mutation (32) have higher BPs and also a significantly higher plasma sodium concentration resulting from renal sodium retention (42). For de Wardener and Macgregor (43), this small rise in plasma sodium (1 to 3 mmol/L) is responsible for the tendency for an increase in extracellular volume (due to a transfer of fluid from the cells and a stimulation of the thirst centre). Recently, this group noted that such an increase in plasma sodium concentration may stiffen vascular endothelium and reduce its nitric oxide release (Oberleithner et al.) (44). This could enhance peripheral arterial resistance and thereby, blood pressure.

At the distal tubule, an increase in sodium and chloride reabsorption could be genetically stimulated either by a mutation in WNK kinases (33, 34) but also directly by mutation in the thiazide-sensitive sodium-chloride cotransporter (45).

At the collecting tubule the ENaC transporter is associated with the rare, but well-described autosomal dominant genetic form of hypokalaemic hypertension called Liddle syndrome (35). In this syndrome, there is a gain-of-function mutation in the ENaC with enhanced sodium reabsorption in the distal nephron. Correlatively, inhibitors of ENaC are useful adjunctive anti-hypertensive agents (46). At the level of aldosterone and its effect on the distal nephron, there are a number of specific hypertensive syndromes. These include the excessive formation of aldosterone in glucocorticoid-remediable hypertension (47), activation of the mineralocorticoid receptor mutation exacerbating hypertension during pregnancy (48), polymorphisms of the aldosterone synthase (CYP11B2) (49) or mutation of the 11 beta hydroxysteroid dehydrogenase type 2 gene (syndrome of apparent mineralocorticoid excess (50). All of these contribute to rare forms of salt-sensitive and frequently hypokalaemic hypertension.

A more common occurrence is apparent hyperaldosteronism with normokalaemia, that is found in hypertensives with a high serum aldosterone-to-renin ratio (AAR), but without adrenal adenoma. These may be found in 10% or more of resistant hypertensive subjects (51).

The complexity of HTN is particularly illustrated in this topic of genetics and salt. As pointed out a few years ago by the 2007 Nobel Laureate Oliver Smithies (52), in HTN, many genetic differences (what he called “many little things”) could be associated with different environmental factors, the sodium aspect being only one, leading to a multitude of different forms of elevated BP.

MECHANISM OF HYPERTENSION DUE TO SALT INTAKE

As noted above, in the presence of high dietary sodium intake, subtle renal abnormalities may cause a blood volume excess, then an increase of cardiac output. Subsequent autoregulatory mechanisms at the peripheral arteriolar walls may cause an elevation of non-renal peripheral vascular resistance, and thus, hypertension.

This reactive elevation in peripheral arterial resistance could occur via ouabain-like substances blocking the Na-K ATPase pump. In response to excessive salt intake, there is secretion of ouabain-like substances from the hypothalamus or adrenal glands. Their initial effect might be beneficial, by the reduction of Na-K ATPase-mediated renal sodium reabsorption. But by their inhibition of the vascular smooth muscle cell sodium pump, there is an increase in intracellular sodium concentration followed by an increase in the entrance of calcium in the cell through the Na-Ca exchange. This would lead to vasoconstriction and hypertension (23,
Among these non-drug treatment measures, a dietary sodium reduction to less than 100 mmoles/day may be effective. It has been shown recently that high salt intake may accelerate the loss of renal function by permitting the fibrogenic effect of TGF beta 1 and also by promoting higher proteinuria (58). Moreover, the anti-proteinuric benefit of renin-angiotensin blockade is enhanced when reducing salt in the diet.

In essential HTN, dietary salt restriction has long been advocated as an important component of non-pharmacologic treatment.

A multi-centre randomized feeding study, termed the DASH (Dietary Approaches to Stop Hypertension) trial, demonstrated that a diet rich in fruits, vegetables, whole grains, poultry, fish, nuts, and low-fat dairy products substantially lowered BP in hypertensive and also in normotensive people compared to a typical US diet (59). More recently, the DASH-sodium trial was published (60), comparing the DASH diet with a typical US control diet at 3 levels of salt intake: 2.9 grams/day, 5.8 grams/day and 8.7 grams/day. Reduction of salt intake resulted in an additional lowering of BP for those on the control typical diet and also for those on the DASH diet.

In older subjects, a moderate reduction in sodium intake - from 177 mmoles/24 hour to 94 mmoles/24 hour - was accompanied by a lowering of systolic BP of 7 mmHg, during a two-month study (61). A similar intervention resulted in a fall of BP of 7.6 mmHg systolic and 3.3 mmHg diastolic by replacing common salt by a low sodium, high potassium and high magnesium mineral salt in the active group as compared to a control group without such modification (62). In the intervention group, the decrease in urinary sodium excretion was 28% as compared to the baseline value. However, 25 weeks after the end of the study, the difference in BP was no longer detectable between the groups.

It may be debated as to whether weight loss or dietary sodium restriction is more effective in lowering the BP. Fifteen years ago we found that the combination of weight loss and sodium restriction did not appear to be more effective than any separate dietary measure as seen in a prospective study lasting for 3 months (63).

Sodium restriction can also shift the circadian rhythm of BP from non-dipper to dipper in essential hypertension as shown by Uzu et al. (64). This was particularly noted in salt-sensitive patients.

A recent Cochrane review of numerous studies lasting at least for 4 weeks or more confirmed the beneficial antihypertensive effect of decreasing dietary so-
sodium intake by approximately 75 mmol/day, with a fall in systolic BP of 5 mmHg among hypertensives. This lowering of BP was correlated with the change in 24-hour sodium excretion (65).

In older subjects, the compliance of large arteries is very often reduced, especially in hypertensive people. In older subjects with systolic HTN, a 60% dietary sodium reduction can improve the large artery compliance (66) with in parallel a decrease in resting systolic BP. Sodium chloride may influence arterial stiffness by altering vascular structure, and it may reduce the bioavailability of nitric oxide by increasing plasma sodium concentration (44), by increasing asymmetric dimethylarginine and by elevating levels of reactive oxygen species. Moreover, sodium chloride induces activation of angiotensin II signalling within tissues. All these modifications could be reversible after salt restriction (67). In addition, in vitro studies suggest that a high salt diet can inhibit the expression of angiotensin type 2 receptor in resistance arteries, allowing angiotensin II to have a greater effect on the vasoconstricting AT1 receptor (68).

Clinically, it is accepted that salt restriction improves the BP control of patients taking antihypertensive agents allowing a reduction in the number and/or the dose of anti-hypertensives.

Salt restriction in subjects taking thiazide diuretics offers the possibility of greater falls in BP in subjects, with the added benefit of diminishing the degree of potassium depletion.

There are additional potential benefits of salt restriction, independent of BP. These occur:

1. Via its effect to attenuate left ventricular hypertrophy,
2. Via its effect to lower the urinary calcium excretion, which may be useful in calcium stone formers and those with osteoporosis,
3. Via its effect to enhance the antiproteinuric effect of renin-angiotensin blockers.

Such advantages justify the recent Task Force statement that advises a reduction in salt intake to 6 g/day sodium chloride or less (69). We also advise an increase in potassium intake as recently emphasized elsewhere (70).

UTILITY OF REDUCING SALT INTAKE IN NORMOTENSIVE POPULATIONS

Reducing sodium chloride intake from 170 to 100 mmol/day lowers the mean BP in normotensive adults by approximately 2 mmHg (71), but over the course of 30 years, the fall in BP could be greater, as salt restriction could minimize the normal rise in BP with aging (8). This may be associated with a 10% to 25% decline in the risk of cardiovascular diseases (72). Salt restriction may be beneficial to younger people, as well. He and MacGregor have realized a meta-analysis of the trials studying the impact of reducing salt in the diet of children 18 years old or younger for at least 2 weeks. They observed a reduction of 2.5 mmHg in systolic BP when salt intake was reduced by 54% (73).

In a fascinating long-term study, Hofman et al. assigned newborn children to a low or normal salt diet for the first six months of life (74). Those assigned to the low salt diet had a 2.1 mmHg lower systolic BP at the six month time point, compared to those on the normal diet. Fifteen years later, 167 children of the cohort were re-examined. Those assigned initially to the low salt diet had a systolic BP 3.6 mmHg lower than those originally assigned to the normal diet (75).

Hooper et al. (76) showed in a meta-analysis of studies of dietary salt reduction in adults that systolic and diastolic BP were only slightly reduced (systolic by 1.1 mmHg and diastolic by 0.6 mmHg). Overall, the urinary 24-hour sodium excretion was reduced by 35.5 mmol. Thus, modest reductions in sodium intake might yield only modest reductions in BP.

Other studies are more optimistic. In the DASH study (60), lowering sodium intake reduced BP levels, an effect observed also in normotensives of different races and gender. In the TOHP trial, dietary salt reduction appeared to reduce the risk of cardiovascular events with 10 to 15 years (77). Overall, the risk of cardiovascular events was significantly lower in the low-salt diet group (relative risk 0.70; p=0.02), after controlling for demographics, age, baseline weight and sodium excretion.

POTENTIAL SIDE EFFECTS OF SALT RESTRICTION

Ingestion of severe low salt diet could induce fatigue, due to mild reduction in plasma volume. Very low salt intake (less than 1 g/day) causes a 10% elevation in total and LDL cholesterol levels, perhaps due to haemoconcentration.

Some reports from the USA (NHANES I and II) pointed out the risk of mortality induced by excessive salt reduction in the diet (78, 79). An inverse association between sodium to cardiovascular mortality was noted. This contradicted the observations of Tuomiletho et al.
in Finland (80) who noted that a linear relationship of high sodium intake to mortality and risk of coronary heart disease. It is possible that the former analysis is evidence of reverse epidemiology, as more salt restriction may be prescribed for patients already suffering from cardiovascular disease. A subsequent analysis of the NHANES I data that excluded patients with a prior history of cardiovascular disease, did not reveal a deleterious effect of low salt intake on cardiovascular mortality (81). Nonetheless, Alderman (82) affirms that the relationship between salt intake and cardiovascular outcomes is "J" shaped and he does not advise dietary salt reduction in those who already have only a moderate daily salt intake. In the USA, recommendations for the general population are to consume no more than 100 mmoles of sodium a day (2.3 g of sodium, equivalent of 5.8 g of salt). In subjects with CKD, or HTN, lesser amounts of dietary sodium are advised, being only 65 mmoles a day. On a practical basis, this would mean elimination of processed and restaurant foods.

CONCLUSIONS

Hypertension is frequent and requires skilful management to achieve a good control of BP level and to reduce the associated cardiovascular risk.

In CKD, dietary salt restriction is key if there is oedema and/or hypertension.

In essential HTN, dietary sodium reduction is an important aspect of the non-pharmacological approaches to treatment.

On the level of the general population, a reduction of dietary salt intake appears to be genuinely useful to decrease cardiovascular risk, even if in an individual the BP lowering is small. The salt restriction should be moderate (6 g/day) associated with a higher fruit and vegetables consumption. Repeated encouragement is needed to follow this dietary advice.

In people with salt sensitivity, the BP benefit would be substantial.

In the general population, the current expert public health advice is to decrease the salt intake. This will require public education and an ongoing dialogue with food industries.

ABSTRACT

Les reins jouent un rôle majeur dans la régulation de la balance sodée et par là contribuent à celle de la pression artérielle. La sensibilité au sel est soit acquise (génétique) et est retrouvée chez environ 50% des patients avec hypertension dite essentielle. Cette propriété expose à un risque cardio-vasculaire accru. Dans cette situation, le bénéfice de la restriction sodée est important, mais cette approche diététique doit être associée à une consommation accrue en potassium. Chez les sujets traités par médicaments antihypertenseurs, la restriction sodée améliore le contrôle tensionnel, permettant souvent de diminuer le nombre de médicaments. La quantité recommandée maximale de sel à consommer quotidiennement ne devrait pas dépasser 6 grammes, sous forme de NaCl. Vu que la majorité du sel ingéré vient d’aliments conditionnés, l’aide de l’industrie alimentaire est cruciale pour une observance au long cours de cette approche diététique, qui pourrait apporter un bénéfice significatif et additionnel à la stratégie de réduction du risque cardiovasculaire.

Mots clés : sel, sodium, hypertension artérielle, sensibilité au sel, risque cardio-vasculaire.

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Administration:
Aranesp treatment should be initiated by physicians experienced in the above mentioned indications. Aranesp is supplied ready for use in a pre-filled syringe. The injection should be given subcutaneously into the abdominal area and as an intravenous bolus injection into a large vein. The initial dose by subcutaneous or intravenous administration is 0.45 µg/kg body weight, as a single injection once every two weeks.

Intravenous Adverse Drug Reactions:
- Aranesp should be administered by the intravenous route not more frequently than once every two weeks.
- Very rare cases of convolution have been reported in patients with OBF receiving Aranesp. In isolated cases, seroconverting anti-erythropoietin antibodies mediated pure red cell aplasia (PRCA) associated with Aranesp therapy have been reported. In case PRCA is diagnosed, therapy with Aranesp must be discontinued and patients should not be switched to another recombinant erythropoietin protein. All other treatment related adverse events were observed at the 1% level or less (incidence not known and baseline). The majority were mild to moderate in severity and were consistent with the comorbidities expected in this patient population. Cancer patients in clinical studies with subcutaneously administered Aranesp, the incidence of hypertension and cardiovascular events were comparable in cancer patients receiving placebo, r-HuEPO or Aranesp. Furthermore, these adverse events were not associated with either haemoglobin concentrations (≤ 13 g/dl) or a rapid rise in haemoglobin (> 2 g/dl in four weeks). Clinical studies have shown a higher frequency of thromboembolic reactions including deep vein thrombosis and pulmonary embolism in cancer patients receiving Aranesp therapy compared to patients receiving placebo. In general, adverse events reported in clinical trials with Aranesp in cancer patients receiving recombinant chemotherapy were consistent with the underlying disease and its treatment with chemotherapy.

Contraindications:
- Patients with a history of previous thromboembolic events or those with an increased risk for thromboembolic events.
- Patients with known hypersensitivity to Aranesp.
- Patients with a history of significant cardiovascular disease.
- Patients with a history of significant peripheral vascular disease.
- Patients with a history of significant cerebrovascular disease.
- Patients with a history of significant renal disease.
- Patients with a history of significant hepatic disease.
- Patients with a history of significant pulmonary disease.
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- Patients with a history of significant pulmonary embolism.
- Patients with a history of significant deep vein thrombosis.
- Patients with a history of significant pulmonary embolism.
- Patients with a history of significant deep vein thrombosis.
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- Patients with a history of significant pulmonary embolism.