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SALT, THE KIDNEYS, AND ARTERIAL HYPERTENSION

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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.

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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.

Table 1: Important dates for the sodium and hypertension story

Dietary and drug manipulation
- Chloride deprivation could lower the BP (1904) (2)
- Rice-fruit diet with salt restriction successful in malignant HTN (1940s) (3)

Experimental procedures in rats
- Development of salt-sensitive and salt-resistant rats (1960s, 1980s) (4, 5)

Epidemiological observations
- Prevalence of HTN in different populations related to the amount of salt intake (1961) (6)
- Positive correlation between 24h urinary sodium excretion and BP in cross population analyses and at individual level (1988) (7)

Pathophysiologic mechanisms of salt-induced HTN
- Pressure-natriuresis (1969) (9)
- Humoral factor-inducing HTN after high salt intake (1976) (10)
- Plasma Na-K pump inhibitor with natriuretic and vasoconstrictive properties (1980) (11)

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 systolic BP in cross population analyses and also at the individual level in the 10,000 adults of this study (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-

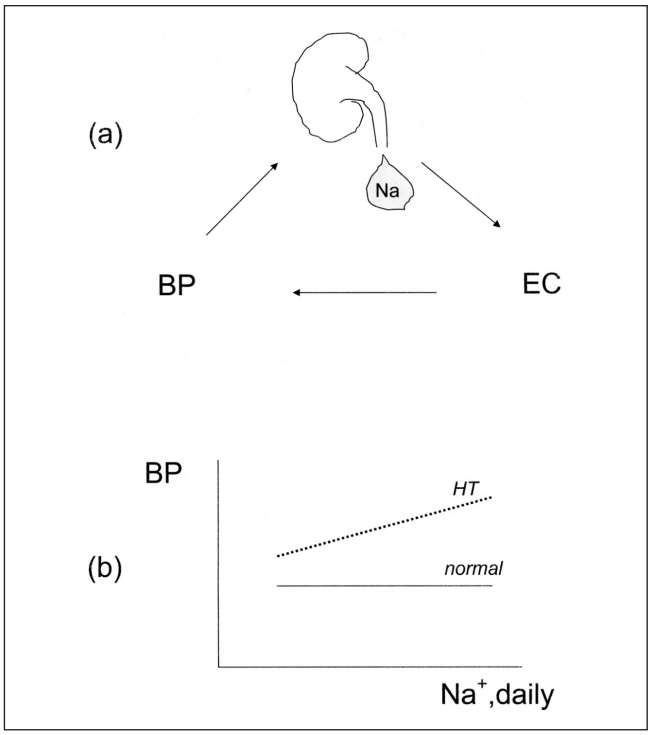

Figure 1: *The phenomenon of pressure-natriuresis is shown as panel (a). A rise in BP leads to enhanced salt and water excretion by the kidneys, which tends to lower the BP, in a classical negative feedback fashion. The normal relationship of BP to daily urine sodium, a good measure of dietary intake, is one of infinite gain, with the BP being regulated to normal for a wide range of sodium intakes, shown on panel (b). In hypertension, experimental or clinical, this relationship no longer holds, and the BP rises with increased sodium intake (HT: hypertensive condition; EC: extracellular volume).*

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 arteriolopathy, 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-

Table 2 : Factors causing salt sensitivity

Primary
- Monogenic (see table 3)
- Polygenic : race

Secondary
- Renal disease
- Insulin resistance
- Endocrine disorders : adrenal (Cushing, primary aldosteronism)
  acromegaly
  hyperparathyroidism
- Age
- Drugs : licorice, mineralo- or glucocorticoids

Table 3: Mutations and polymorphisms associated with salt-sensitive hypertension in humans

Potential action	Abnormality and Description
Along the renal tubule	- α adducin gene: cytoskeletal protein increasing sodium reabsorption (37).
At the proximal tubule	- Polymorphisms of angiotensinogen gene AGT (M 235 T), angiotensin converting enzyme (I/D), angiotensin AT_1 receptor A 1166 C (39)
At the thick ascending limb of Henle	- Activating mutation of the Chloride Channel CClKb : elevated plasma sodium, decreased GFR (32)

At the distal tubule	- With hyperkalaemia and hypercalciuria:
	  - Pseudohypoaldosteronism type 2 (Gordon's syndrome) : activation of the thiazide-sensitive cotransport by mutation of WNK_1 and WNK_4 genes (33)
	  - Activating mutation of the NaCl cotransport (45)

At the collecting tubule	With hypokalaemia : - Glucocorticoid remediable aldosteronism: chimeric gene of aldosterone synthase (CYP_{11} B_2) and 11 ß OHase (CYP_{11} B_1) (47) - Aldosterone synthase (CYP_{11} B_2) (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) - Liddle syndrome : autosomal dominant, increased activity of ENac (36)

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 where homozygous for the wild-type allele. Moreover, this mutation in the adducin 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 antihypertensive 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,

53, 54). The ouabain-like hormone may be found in approximatively 40% of patients with essential hypertension.

Other mechanisms could be implicated in the relation between salt intake and hypertension, such as activation of intrarenal angiotensin II production, oxidative stress, and renal inflammation responsible for subtle renal injury, with subsequent limitation of sodium excretion. High salt intake may enhance renal oxidative stress by several mechanisms, one of which is an increase of angiotensin II at the proximal tubular level (55).

Johnson has proposed a two-phase development of essential hypertension (56). The first phase is initiated by renal vasoconstriction induced by either a hyperactive sympathetic nervous system, activation of the renin-angiotensin system or genetic or acquired hyperuricaemia. During this phase, hypertension is salt-resistant and rennin-dependent. The kidney is anatomically normal. Over time, preglomerular vascular disease develops, associated with renal ischaemia and tubulointerstitial inflammation, both stimulated by angiotensin II. This shifts the hypertension to a salt-sensitive, volume-dependent pathway. This can also explain the decrease in dipping phenomenon seen for the 24h BP pattern of chronic kidney disease **(**CKD) patients, associated with an elevated nocturnal natriuresis that is proportional to the decrease of glomerular filtration rate (57). At this moment, the aforementioned ouabain-like substances could come into play, being produced in response to extracellular volume expansion. They would inhibit the sodium pump, which in the kidney would facilitate natriuresis, but in the vasculature would facilitate vasoconstriction. The elevated BP would then be the sequential consequence of the dietary sodium intake, an impaired natriuresis, an increased extracellular volume, and the reactive increase in peripheral arterial resistance.

IMPACT OF SALT RESTRICTION IN HYPERTENSIVE POPULATIONS

The effect of dietary sodium on volume expansion and high BP is mainly acknowledged in CKD patients, a population characterized by a high prevalence of hypertension. Non-pharmacological approaches to treat HTN are recommended in these subjects to assist in lowering their BP. These recommendations are especially important because CKD itself is associated with an increased risk of cardiovascular morbidity and mortality.

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-

dium intake by approximately 75 mmoles/day, with a fall in systolic BP of 5 mmHg among hypertensives. This lowering of BP was correlated with the change in 24-hour urinary 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 fall 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 mmoles/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 mmoles. 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 soit innée (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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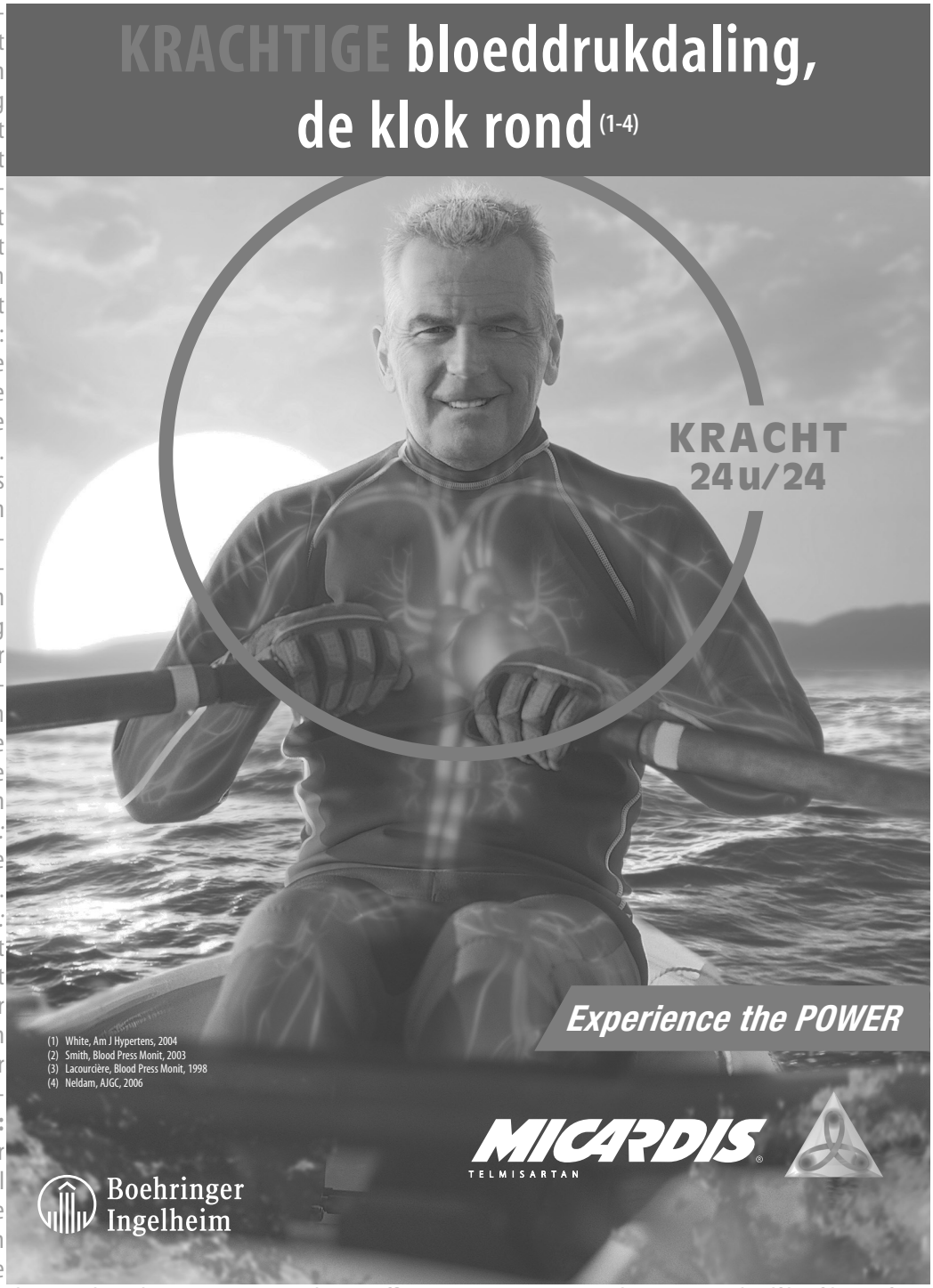
Micardis 40 mg tabletten – Micardis 80 mg tabletten. Samenstelling en verpakkingen: Tablet: telmisartan 40 mg – doos met 28 tabletten en klin. verp. met monodosissen. Tablet: telmisartan 80 mg – dozen met 28, 56 en 98 tabletten en klin. verp. met monodosissen. Het kan voorkomen dat niet alle verpakkingsgroottes in de handel worden gebracht. **Therapeutische indicaties:** Behandeling van essentiële hypertensie. **Dosering en wijze van toediening:** *Volwassenen:* De doorgaans effectieve dosering bedraagt 40 mg éénmaal daags. Sommige patiënten hebben al voldoende baat bij een dagelijkse dosering van 20 mg. In gevallen waar de gewenste bloeddruk niet wordt bereikt, kan de dosis telmisartan worden verhoogd tot een maximum van 80 mg. Als alternatief kan telmisartan worden gebruikt in combinatie met thiazide-type diuretica zoals hydrochloorthiazide, waarvan is aangetoond dat het een aanvullend bloeddrukverlagend effect heeft met telmisartan. Wanneer een verhoging van de dosering overwogen wordt, dient gerealiseerd te worden dat het maximale antihypertensieve effect over het algemeen vier – acht weken na de aanvang van de behandeling wordt bereikt. Nierinsufficiëntie: Voor patiënten met milde totmatigenierinsufficiëntie is aanpassing van de dosering niet noodzakelijk. Beperkte ervaring is opgedaan met patiënten met ernstige nierinsufficiëntie en met hemodialysepatiënten. Een lagere startdosis van 20 mg wordt aangeraden voor deze patiënten. Leverinsufficiëntie: Bij patiënten met lichte tot matige leverinsufficiëntie mag de dosering niet hoger dan 40 mg zijn. *Ouderen:* Aanpassing van de dosering is niet nodig. *Kinderen en jongeren:* Micardis wordt niet aanbevolen voor het gebruik bij kinderen jonger dan 18 jaar vanwege een gebrek aan gegevens over veiligheid en werkzaamheid. **Contra-indicaties:** • Overgevoeligheid voor het werkzame bestanddeel of voor één van de hulpstoffen. • Tweede en derde trimester van de zwangerschap en borstvoeding. • Galwegobstructies. • Ernstige leverinsufficiëntie. **Bijwerkingen:** De totale incidentie van bijwerkingen gemeld voor telmisartan (41,4%) was gewoonlijk vergelijkbaar met placebo (43,9%) in de placebogecontroleerde studies. De incidentie van de bijwerkingen was niet gerelateerd aan de dosis en liet geen correlatie zien met geslacht, leeftijd of ras van de patiënten. De bijwerkingen hieronder weergegeven zijn verzameld uit alle klinische studies waarin 5788 hypertensieve patiënten werden behandeld met telmisartan. De bijwerkingen zijn geclassificeerd met de frequentie-aanduidingen aan de hand van de volgende indeling: zeer vaak (≥1/10); vaak (≥1/100, <1/10); soms (≥1/1.000, <1/100); zelden (≥1/10.000, <1/1.000); zeer zelden (<1/10.000). Binnen de onderstaande frequentiegroepen worden bijwerkingen in afnemende mate van ernst genoemd. – Infecties en parasitaire aandoeningen: Vaak: symptomen van infectie (bv. urineweginfecties inclusief cystitis), bovenste luchtweginfecties inclusief faryngitis en sinusitus. – Psychische stoornissen: Soms: angst. – Oogaandoeningen: Soms: visusstoornissen. – Evenwichtsorgaan:- en ooraandoeningen Soms: vertigo. – Maagd armstelselaandoeningen: Vaak: buikpijn, diarree, dyspepsie,. Soms: droge mond, flatulentie. Zelden maagklachten. – Huid en onderhuidaandoeningen: Vaak: eczeem. Soms: hyperhidrosis. – Skeletspierstelsel- en bindweefselaandoeningen: Vaak: artralgie, rugpijn (bv. sciatica), spierkrampen of pijn in de extremiteiten, myalgie. Soms: tendinitis. – Algemene aandoeningen en toedieningsplaatsstoornissen : Vaak: pijn op de borst, griepachtige verschijnselen. Daarnaast zijn sinds de introductie van telmisartan gevallen van erytheem, pruritis, syncope, insomnia, depressie, braken, hypotensie (inclusief orthostatische hypotensie), bradycardie, tachycardie, afwijkende leverfunctie, leveraandoening, nierinsufficiëntie inclusief acuut nierfalen, hyperkaliëmie, dyspnoe, anemie, eosinofilie, trombocytopenie, asthenia en gebrek aan werkzaamheid gemeld. De frequentie van deze bijwerkingen is niet bekend. Zoals bij andere angiotensine II antagonisten zijn incidentele gevallen van angio-oedeem, urticaria en aanverwante reacties gemeld. Laboratoriumgegevens: Zelden is een hemoglobine-afname of een urinezuurtoename in het bloed waargenomen, welke vaker voorkwamen tijdens de behandeling met telmisartan dan met placebo. Toename van creatinine of leverenzymen is waargenomen tijdens behandeling met telmisartan, maar deze veranderingen in laboratorium gegevens kwamen met dezelfde of lagere frequentie voor vergeleken met placebo. Bovendien zijn er, sinds de introductie van telmisartan, gevallen gemeld van verhoogde waarden van creatine fosfokinase (CPK) in het bloed. **Aflevering:** Op doktersvoorschrift. **Registratienummers:** Micardis 40 mg: 28 tabl.: EU/1/98/090/002; 28 x 1 tabl.: EU/1/98/090/013; Micardis 80 mg: 28 tabl.: EU/1/98/090/006 ; 56 tabl.: EU/1/98/090/007; 98 tabl.: EU/1/98/090/008; 28 x 1 tabl.: EU/1/98/090/014. **Datum laatste aanpassing van de bijsluiter:** 03/2007.

Meer gedetailleerde informatie kunt u op aanvraag verkrijgen. Boehringer Ingelheim – Vesalius Science Park – Arianelaan 16 – 1200 Brussel – Tel.: 02/773.33.11.

Micardis	40 mg	28 tab	30,49 €
Micardis	80 mg	28 tab	43,21 €
Micardis	80 mg	56 tab	63,24 €
Micardis	80 mg	98 tab	94,28 €



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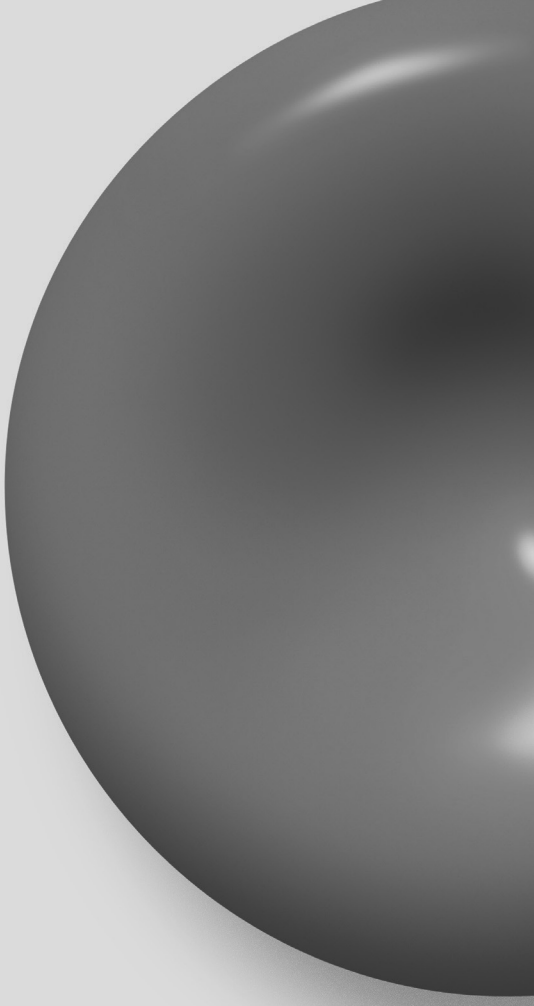

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ARANESP® 80: Each pre-filled syringe contains 80 micrograms of darbepoetin alfa in 0,4 ml (200 µg/ml). ARANESP® 100: Each pre-filled syringe contains 100 micrograms of darbepoetin alfa in 0,5 ml (200 µg/ml). ARANESP® 150: Each pre-filled syringe contains 150 micrograms of darbepoetin alfa in 0,3 ml (500 µg/ml). ARANESP® 300: Each pre-filled syringe contains 300 micrograms of darbepoetin alfa in 0,6 ml (500 µg/ml). ARANESP® 500: Each pre-filled syringe contains 500 micrograms of darbepoetin alfa in 1 ml (500 µg/ml). Darbepoetin alfa is produced by gene-technology in Chinese Hamster Ovary Cells (CHO-K1). Excipients: Sodium phosphate monobasic, Sodium phosphate dibasic, Sodium Chloride, Polysorbate 80, Water for injections. **Therapeutic indications:** Treatment of anaemia associated with chronic renal failure in adults and paediatric subjects ≥ 11 years of age. Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy. **Posology and method of 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. *Treatment of anaemia in chronic renal failure patients:* Aranesp can be administered either subcutaneously or intravenously. Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid the puncture of peripheral veins. The aim of treatment is to increase haemoglobin to greater than 11 g/dl (6.8 mmol/l). The exact target haemoglobin concentration above 11 g/dl (6.8 mmol/l) needs to be established for individual patients. A rise in haemoglobin of greater than 2 g/dl (1.25 mmol/l) over a four week period or a haemoglobin level greater than 14 g/dl (8.7 mmol/l), should be avoided. Clinical studies have shown individual patient responses to be variable. Nonetheless, the recommendations described below should be followed initially in both adults and paediatric patients and then adjusted as clinically indicated. Treatment with Aranesp is divided into two stages – correction and maintenance phase: *Correction Phase:* The initial dose by subcutaneous or intravenous administration is 0.45 µg/kg body weight, as a single injection once weekly. Alternatively, in patients not on dialysis, an initial dose of 0.75 µg/kg may be administered subcutaneously as a single injection once every two weeks. If the increase in haemoglobin is inadequate (less than 1 g/dl (0.6 mmol/l) in four weeks) increase the dose by approximately 25%. Dose increases must not be made more frequently than once every four weeks. If the rise in haemoglobin is greater than 2.5 g/dl (1.6 mmol/l) in four weeks reduce the dose by between 25 and 50%, depending on the rate of increase. If the haemoglobin exceeds 14 g/dl (8.7 mmol/l), discontinue therapy until it falls below 13 g/dl (8.1 mmol/l) and then restart the treatment at approximately 25% below the previous dose. The haemoglobin should be measured every one or two weeks until it is stable. Thereafter the haemoglobin can be measured periodically. *Maintenance Phase:* In the maintenance phase, Aranesp may continue to be administered as a single injection once weekly or once every two weeks. Dialysis patients converting from once weekly to once every other week dosing with Aranesp should initially receive a dose equivalent to twice the previous once weekly dose. In patients not on dialysis, once the target haemoglobin has been achieved with once every two week dosing, Aranesp may be administered subcutaneously once monthly using an initial dose equal to twice the previous once every two week dose. Dosing should be titrated as necessary to maintain the haemoglobin target. The exact target haemoglobin concentration above 11 g/dl (6.8 mmol/l) needs to be established for individual patients. If a dose adjustment is required to maintain haemoglobin at the desired level, it is recommended that the dose is adjusted by approximately 25%. If the rise in haemoglobin is greater than 2.0 g/dl (1.25 mmol/l) in four weeks reduce the dose by approximately 25%, depending on the rate of increase. If the haemoglobin exceeds 14 g/dl (8.7 mmol/l), discontinue therapy until it falls below 13 g/dl (8.1 mmol/l) and then restart the treatment at approximately 25% below the previous dose. After any dose or schedule adjustment the haemoglobin should be monitored every one or two weeks. Dose changes in the maintenance phase of treatment should not be made more frequently than every two weeks.When changing the route of administration the same dose must be used and the haemoglobin monitored every one or two weeks so that the appropriate dose adjustments can be made to keep the haemoglobin at the desired level. Clinical studies have demonstrated that patients receiving r-HuEPO one, two or three times weekly may be converted to once weekly or once every other week Aranesp. The initial weekly dose of Aranesp (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 200. The initial every other week dose of Aranesp (µg/every other week) can be determined by dividing the total cumulative dose of r-HuEPO administered over a two-week period by 200. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Aranesp for r-HuEPO the haemoglobin should be monitored every one or two weeks and the same route of administration should be used. *Treatment of symptomatic anaemia in cancer patients:* Aranesp should be administered by the subcutaneous route to patients with anaemia (e.g. haemoglobin concentration ≤ 11 g/dl (6.8 mmol/l). The recommended initial dose is 500 µg (6.75µg/kg) given once every three weeks. If the clinical response of the patient (fatigue, haemoglobin response) is inadequate after nine weeks, further therapy may not be effective. Alternatively, once weekly dosing can be given at 2.25 µg/kg body weight. Aranesp therapy should be discontinued approximately four weeks after the end of chemotherapy. Haemoglobin level should not exceed 13 g/dl (8.1 mmol/l). Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25 to 50% in order to maintain haemoglobin at that level. If required, further dose reduction may be instituted to ensure that haemoglobin level does not exceed 13 g/dl. If the rise in haemoglobin is greater than 2 g/dl (1.3 mmol/l) in 4 weeks, the dose should be reduced by 25 to 50%. **Contraindications:** Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients. Poorly controlled hypertension. **Undesirable effects:** The safety of Aranesp has been evaluated based on an integrated safety database of approximately 1800 chronic renal failure patients who have been dosed for up to 24 months and 1200 cancer patients who have been treated for up to four months. *General:* There have been rare reports of potentially serious allergic reactions including dyspnoea, skin rash and urticaria associated with darbepoetin alfa.. *Chronic renal failure patients:* Data presented from controlled studies included 1578 patients who received Aranesp and 591 patients who received r-HuEPO. The overall proportion of patients who discontinued treatment due to adverse events was 2% for Aranesp and 4% for r-HuEPO. Undesirable effects attributable to treatment with Aranesp include hypertension and thrombosis of the vascular access. However, in the integrated safety database, neither of these events were associated with haemoglobin level (< 12 versus > 12 g/dl) or haemoglobin rate of rise (< 1, 1 to < 2, 2 to < 3 and ≥ 3 g/dl haemoglobin per 4 week period). Injection site pain was reported as attributable to treatment in studies where Aranesp was administered via subcutaneous injection. This was seen more frequently than with r-HuEPO. The injection site discomfort was generally mild and transient in nature and occurred predominantly after the first injection. Incidence of undesirable effects considered related to treatment with Aranesp from controlled clinical studies are:

Body system	Subject Incidence	Adverse Drug Reaction
Central Nervous System/Peripheral Nervous System	Common (> 1%, ≤ 10%)	Headache
Cardiovascular	Common (> 1%, ≤ 10%)	Hypertension
Vascular disorders	Common (> 1%, ≤ 10%)	Thrombosis of vascular access
Application site	Common (> 1%, ≤ 10%)	Injection site pain

Very rare cases of convulsions have been reported in patients with CRF receiving Aranesp. In isolated cases, neutralising anti-erythropoietin antibody 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 erythropoietic protein. All other treatment related adverse events were observed at the 1% level or less (uncommon or rare), 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 concentration (< 13 versus > 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 concomitant chemotherapy were consistent with the underlying disease and its treatment with chemotherapy. Incidence of undesirable effects considered related to treatment with Aranesp from controlled clinical studies are:

Body system	Subject Incidence	Adverse Drug Reaction
Musculo-skeletal	Common (> 1%, ≤ 10%)	Arthralgia
Body/general	Common (> 1%, ≤ 10%)	Peripheral oedema
Application site	Common (> 1%, ≤ 10%)	Injection site pain
Vascular disorders	Common (> 1%, ≤ 10%)	Thromboembolic reactions

Injection site pain was the most frequently reported adverse event considered related to treatment with Aranesp (< 5%). The injection site discomfort was generally mild and transient in nature. **Marketing authorisation holder:** Amgen Europe B.V., Minervum 7061, NL-4817 ZK Breda, The Netherlands. **Marketing authorisation numbers:** EU/1/01/185/002, 004, 006, 008, 010, 012, 014, 016, 018, 020, 021 et 031. **Date of last renewal of authorisation:** 19 May 2006. **Date of revision of the text:** 02 May 2007. **Classification of the medicine**: Medicinal product subject to restricted medical prescription **More information available at**: Amgen n.v/s.a; Arianelaan, 5, Avenue Ariane, B-1200 Brussel-Bruxelles, tel: 02/775 27 11. Please refer to the full Summary of Product Characteristics before prescribing Aranesp.

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1. J.C. Egrie et al. Nephrol Dial Transplant (2001): 16; suppl 3: 3-13