Treatment of Arterial Hypertension With Nifedipine In Patients With Chronic Renal Insufficiency

Thesis

Submitted in Partial Fulfilment of

Master Degree in

General Medicine

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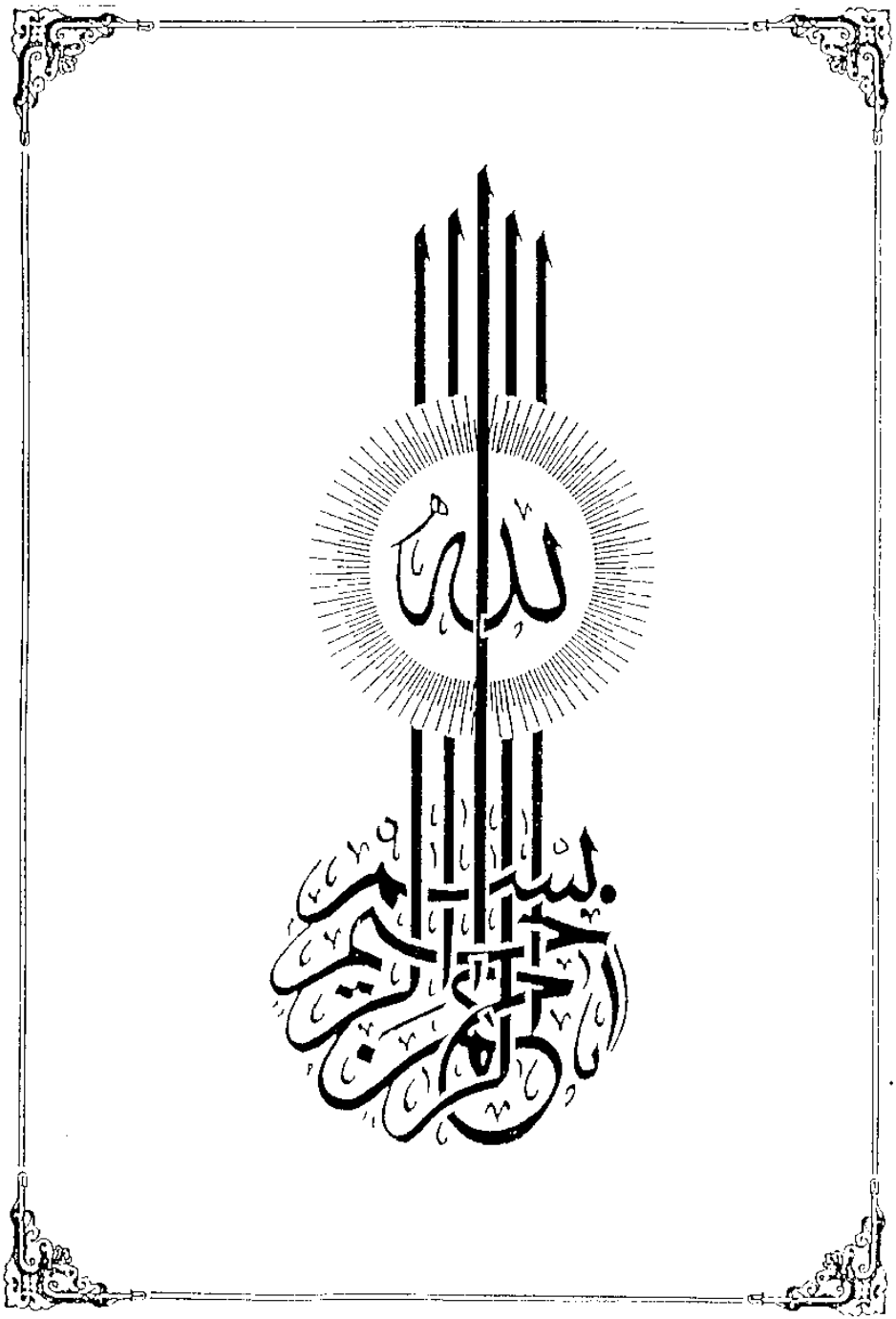
1987

ACKNOWLEDGEMENT

I would like to express my sincere gratitude and heartful thanks to Professor Dr. Wahid Mohamed El Said, Professor of General Medicine and Nephrology, Ain-Shams University, for his valuable guidance, expert assistance and fruitful criticism.

I wish to thank Professor Dr. Hussein El Damasy, Professor of General Medicine and Endocrinology, Ain-Shams University, for his generous supervision and sincere support.

Iam also indebted to Dr. Mahmoud Abdel Fattah, Lecturer of Medicine and Nephrology, Ain-Shams University for his indispensable advice and continuous encouragement. He spent a lot of time guiding and directing me.



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Introduction

Proper blood pressure control is an essential prerequisite to longivity for patients on maintenance dialysis. Hypertension is an important predisposing factor to accelerated atherosclerosis and to high incidence of cardiovascular and cerebrovascular diseases in dialysis patients. (Linder et al., 1974, Lowrie et al., 1974, Vincenti et al., 1980).

Approximately 80% of patients with progressive renal failure approaching dialysis have hypertension, as arbitrarily defined by a diastolic pressure greater than 90 mm Hg or a systolic pressure over 150 mm Hg. (Lazarus et al., 1974).

Although the role of sodium dominates current thinking about cations and hypertension, the cellular basis of hypertension must be understood in terms of the intracellular effects of calcium. This is because the contraction of the heart muscle, the contraction of the smooth muscle in the wall of the blood vessel in response to norepinephrine and angiotensin, the acetyl choline induced release of norepinephrine, the rate of secretion of aldosterone by the adrenal glomerulosa cells, and probably the release of renin from the juxta glomerular cells, all involve calcium as an intracellular messenger, binding stimulus to response (Rasmussen, 1983).

Small changes in cellular calcium concentration bring about large changes in cell response. The regulation of calcium fluxes across the plasma membrane are very critical to proper cell function; meanwhile, excessive calcium is a cellular toxin.

Attempts were made to integrate data about the functions and properties of intracellular calcium receptor proteins with those of cellular calcium homeostasis, and relate them to the pathogenesis of hypertension. Kesteloot and Geboers (1982) reported a positive correlation between serum calcium and both systolic and diastolic blood pressures. This significant association found between calcium and blood pressure provided a strong support to the use of calcium channel blockers in the treatment of hypertension.

Nifedipine (Bay a 1040, Procardia, Adalat) is a dihydropyridine derivative that bears no structural similarity to other known vasoactive or cardioactive drugs. It is not a nitrate and its ortho NO_2 group is not essential for its pharmacologic activity. It is effective in patients with chronic hypertension (Murphy et al., 1983). Unlike verapamil, nifedipine does not cause significant electrophysiological effects (Mitchell et al., 1982), nor negative inotropic effects on the heart (Henry 1980), and may safely be combined with a beta receptor blocking agent (Harris et al., 1982). These data justify the trial to use nifedipine in treating hypertension.

REVIEW OF LITERATURE

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Hypertension In Chronic Renal Failure

Hypertension is an early and a frequent component in the uremic syndrome. The rapidity of development and the severity of hypertension vary, depending on the origin of the renal disease. In the various forms of glomerulonephritis, glomerular nephropathies, and in interstitial nephritides, hypertension develops early and is often the first clinical sign of renal involvement. It is usually not of the accelerated or malignant type but progresses with the development of uremia, and it can be controlled with regimens similar to those successful in nonrenal hypertension. Some patients with glomerulonephritis develop an accelerated phase of hypertension terminally. The exact reason is still not known, however stimulation of renin production undoubtedly plays an important role (Lazarus et al., 1974). Diseases such as obstructive uropathy, polycystic kidneys, and pyelonephritis in which there is a tendency to loose sodium with resulting volume depletion, may be associated with hypertension. If hypertension does occur in such patients, salt restriction and diuretics should be used with caution as they may induce severe volume depletion and aggravate already impaired renal function (Lazarus et al., 1974).

Patients with malignant or accelerated hypertension, and the renal lesion of malignant nephrosclerosis generally

present with hypertensive problems, whereas renal insufficiency develops secondarily (Lazarus et al., 1974).

Causes of Hypertension in Chronic Renal Failure.

The cause of increased blood pressure in early renal parenchymal disease is believed to be primarily an increase in extracellular volume (Eisenberg, 1959), although others have also found an increase in cardiac output (Fleisher 1966). Frohlich et al. (1969), described primarily an increase in total peripheral resistance in patients with renal parenchymal disease and hypertension.

As renal disease progresses and insufficiency develops, there is a less efficient excretion of fluids leading to an increase in extracellular volume that becomes primarily important as a causative factor. Hypertension in patients with advanced renal insufficiency is more directly related to expanded extracellular volume, as evidenced by the fact that most uremic patients with hypertension will respond to haemodialysis and reduction of extracellular volume (Lazarus et al., 1974).

Some patients with renal insufficiency and hypertension have a component of vascular disease in addition to the increase in extracellular volume. Increased total peripheral resistance has been found in patients with chronic renal

failure (Del Greco, 1969). The influence of the renin-angiotensin axis on peripheral resistance and blood pressure in patients undergoing haemodialysis is well established (Weidman, 1971). Some of the patients with moderate hypertension and moderate elevation in plasma renin activity may respond partially to ultrafiltration, but only with the addition of other therapeutic maneuvers to reduce vasoconstriction will satisfactory control of the blood pressure be obtained. Patients with malignant nephrosclerosis or accelerated hypertension comprise another subgroup that often does not even respond to volume reduction and aggressive medical management. These patients have been shown to have extreme increases in peripheral renin levels (Weidman, 1971) that result in a rise in circulating angiotensin II and aldosterone (Laragh, 1960). Activation of the renin system creates vasoconstriction and sodium retention that may aggravate the situation by starting a vicious cycle.

Probably, there are other factors in the pathophysiology of hypertension in chronic renal failure since there is a large number of patients who have marked hypertension despite control of extracellular volume and in the absence of elevated renin levels. Possible factors include increased cardiac output; excessive hormone secretion (aldosterone and other mineralo-corticoids, and catecholamines); relative

defficiency of renomedullin (prostaglandin A_2); reset baroreceptors; increased affinity of vascular angiotensin receptors; and structural vascular changes (edema or medial hypertrophy).

Increased cardiac output in uremic patients has been documented and may be important in causing hypertension. Neff (1971) postulated that chronic anaemia in these patients might lead to increased cardiac output that subsequently causes elevation in blood pressure. He transfused blood into these patients and demonstrated a decrease in cardiac output; however there was no marked reduction in blood pressure with the maneuver.

Hormones other than renin and angiotensin may play a role in continued elevation of blood pressure. Aldosterone levels correlate well with renin levels in patients with chronic renal failure and hypertension (Weidman et al., 1973). In patients who have undergone bilateral nephrectomy, serum renin levels have been shown to be low or absent (Berman, 1972), and aldosterone levels are decreased markedly (Weidman et al., 1973). In anephric man aldosterone has been shown to respond in a direct manner to the potassium level (Weidman et al., 1973) but not to postural manipulations (Cooke, 1973). Conflicting data on the role of blood volume and ACTH in the regulation of aldosterone in anephric man have been discussed (Walker and Cooke, 1973). None of these

mechanisms are adequate to increase aldosterone levels to levels commonly found in hypertension.

Another pathophysiologic mechanism might be resetting of the baroreceptors (Kezdi and Wennemark, 1958). They suggested that in patients with hypertension, baroreceptors recognise a higher pressure level and become reset to minimize the pulse response to chronic hypertension. If the initiating cause of the elevated pressure is relieved, the baroreceptors remain at the new level and contribute rather than respond to hypertension. This mechanism was subsequently suggested to be important in the hypertensive patients with renal insufficiency (Hampers, 1969). Lazarus et al. (1974) plotted the P-R interval against changes in systolic pressure, and demonstrated a fixed or less-reactive baroreceptor mechanism in uremic patients; both normotensives and hypertensives, and thus, it was believed not to be a cause of hypertension. Pickering et al. (1972) by using the same technique, also demonstrated fixed slopes in patients undergoing long-term dialysis.

Possibly the most important factor in continued hypertension in patients with controlled extracellular volume and low renin levels is that of structural vascular abnormalities. Such changes may be due to vascular wall edema related to sodium and water retention, or perhaps due to medial hypertrophy of vessels(Conway, 1958).

Brunner (1972) demonstrated a vascular receptor for angiotensin in animals, the affinity of which varies directly with sodium intake. Changes in the affinity of these receptors could be important in determining the blood pressure when the levels of circulating angiotensin II are normal. Such a mechanism may apply to uremic patients with low or normal levels of renin and angiotensin.

The Renin Angiotensin System.

The last few years have resulted in major advances in the understanding of the physiology and pathophysiology of the renin-angiotensin-aldosterone system. This opened the way to major advances in understanding the regulation of sodium, potassium, and water balance, and the role of the renin-angiotensin-aldosterone system in the maintenance of normal and pathological blood pressure.

Renin

Biosynthesis and Chemistry.

Renin is produced by modified cells of the afferent arteriole just before it enters the glomerulus. These cells, which appear to originate from smooth muscle, are closely related to the macula densa, a group of specialised cells at the origin of the distal tubule; and together they form the juxta glomerular apparatus. The enzyme itself is stored in membrane-bound cytoplasmic granules in the juxta glomerular apparatus. Immunoflourescent methods have shown increased staining in areas of renal ischaemia. Release of renin occurs into the afferent arteriole and renal lymph. It has a molecular weight of 40,000 (Drury et al., 1984).