Treatment of High Blood Pressure in Patients with Chronic Renal Disease

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The treatment of HTA plays a central part in the management of Chronic Kidney Disease (CKD) in all its stages, especially in patients following a substitute treatment of renal functions. HBP can be both the cause and the consequence of CKD. The HBP control in CKD patients represents one of the most important concerns of clinicians. HBP treatment is non pharmacological as well as pharmacological.

Keywords: HBP treatment, HBP control, CKD patients, pharmacological treatment, non pharmacological treatment

Non pharmacological treatment of HTA involves mainly changes in the life style, such as : giving up smoking, diet, moderate physical activity, weight loss, and, especially, restricted salt intake. The intake of sodium should be restricted to 1.5-2.3 g/day. A further decrease of alimentary sodium does not trigger a supplimentary benefit since it can cause the activation of the renin-angiotensin-aldosterone system (RAAS) [1].

It is of utmost importance to reach and maintain a suitable ,*dry weight* in dialysis patients. Dry weight is defined as the post-dialysis weight the patient tolerates without hypotension or other clinical manifestations (intra- or interdialytic). The decrease of *dry* weight can determine normal BP values to the same extent medication therapy can. The DRIP (Dry Weight Reduction in Hemodialysis Patients) Study showed that the reduction of dry weight by 0.9 kg led to the decrease of interdialysis BP by 6.9/3.1 mmHg, without requiring the increase of doses of antihypertensive drugs [2].

Taking into account the expertise of Tassin Dialysis Center, the normal blood pressure values define normovolemia, whereas the HBP presence equals hypervolemia [3].

In most cases, the non pharmaceutical methods are not sufficient to control HBP in CKD patients. Because of treatment resistance, about 60% of the CKD patients require three or more antihypertensive drugs associated [4]. The therapeutic targets vary according to the risk group the patients belong to. Thus, for the low risk ones, without associated organ affectation, the therapeutic target is 140/90 mmHg. In case of diabetic patients or patients with additional high or very high risk, the therapeutic target for arterial pressure is 130/80 mmHg [5].

Associated diseases, contraindications, adverse effects, the patient's compliance to treatment, drug bioavailability have to be taken into account when choosing the antihypertensive agent; in case of dialysis patients, the degree of drug elimination during dialysis must be considered.

When hemodialysis patients are concerned, HBP onset greatly depends on: inter dialysis hypervolemia, arterial calcifications associated to atherosclerosis, the treatment with erythropoietine and chronic inflammation [6,7].

Experimental part

The meta-analysis of randomized trials shows that decreasing BP values by using antihypertensive drugs reduces cardio-vascular morbidity and mortality, dialysis patients included [2].

Results and discussions

All classes of antihypertensive drugs can be used, except for diuretics, which are generally inefficient in patients with low rate of glomerular filtration (RGF) [8].

Inhibitors of angiotensin converting enzyme (IACE) and angiotensin II receptor blockers (ARB)

KDOQI (Kidney Disease Outcomes Quality Initiative) recommends blood pressure values to be maintained under 130/80 mmHg in patients with diabetic nephropathy. Many epidemiological studies shop that over 50% of diabetic patients have increased BP levels [9]. In CKD patients undergoing early ACE inhibitors treatment, the relative risk of developing renal failure has been reduced by 30%, compared with patients treatated with antihypertensive drugs in other classes [10].

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ACE inhibitors and ARB are the first-line therapy in diabetic patients with albuminuria. These classes of drugs have antihypertensive, renoprotective effects and lower proteinuria by 20% [4]. Taking into consideration the fact that the main mechanism of action is the vasoconstriction of the efferent arteriole, these drugs may precipitate the onset of acute renal failure in the presence of hypovolemia [9].

Angiotensin II receptor blockers (ARB, sartans) by directly acting on the receptors, have an added nephroprotective effect compared to ACE inhibitors, and the further advantage of fewer adverse reactions. Clinical studies have demonstrated that irbesartan reduces the CKD progression by 18-30% in diabetic patients, with a more obvious effect when higher doses are administered (300 mg/day compared to 150 mg/day).

The Irbesartan Diabetic Nephropathy Trial (IDTN) compared the effects of irbesartan and amlodipine in 1715 hypertensive patients with Type II diabetes and CKD. Although BP in the contol groups was similar, in the irbesartan-administered group the risk of nephropathy progression and mortality were by 23% lower compared to the amlodipine – administered group.

The association of drugs in the two classes - ACE inhibitors and ARB – is not recommended in CKD patients because of the risk of hyperkalemia. The kinetiks of various drugs differs in dialysis patients; fosinopril, which is not affected by dialysis and does not require supplimentary post dialysis doses, is the exception [2].

Plasmatic renin direct inhibtors (e.g.Aliskiren) reduce arterial pressure and proteinuria, but should not be associated with ACE inhibitors or ARB because of the risk of hyperkalemia in patients with advanced chronic renal disease [11].

Beta-blockers

CKD patients, especially those undergoing dialysis, have increased vulnerability to cardiac arrhythmia because of sympathetic hyperactivity. Beta-blocker medication is a mandatory option in treating hypertension in these patients.

The cardio-protective effects of beta- blocker medication have recently been assessed in the HDPAL (Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril) trial, which compared the cardiovascular effects of beta-blockers (Atenolol) and ACE inhibitors (lisinopril) in 200 dialysis hypertensive patients, with left ventricular hypertrophy, for a period of 12 months. The incidence of myocardial infarction, hospitalization for heart failure, and the number of deaths from cardiovascular cause were 2.29 higher in the group of patients treated with lisinopril compared to those who received atenolol [2].

Calcium channels blockers (CCB) –dihydropyridines

Dihydropyridines, through their chemical structure, act specifically on the vascular wall muscles and, by decreasing the concentration of intracellular calcium, reduce muscular contractility, produce vasodilation and a decrease in arterial pressure. Calcium channels blockers with prolonged acting (felodipine, amlodipine) have effects similar to ACE inhibitors in patients with diabetic nephropathy, delaying the onset of macroalbuminuria in patients with diabetus mellitus. *Mogensen* demonstrated that the progression of microalbuminuria towards macroalbuminuria is slower in Type 2 diabetic patients compared to the ones with Type 1 diabetus treated with dihydropyridines and IACE [11].

The INVEST Study showed an approximately equal incidence of cardiovascular events in patients with ischemic heart disease who were treated with associations of drugs, calcium channels blockers and ACE inhibitors, or beta-blockers and diuretics, respectively [5].

The CCB pharmacokinetiks is not altered during dialysis [2].

Other hypotensive agents

Diuretics

Thiazide diuretics (chlorotiazide, indapamide, metholazone) reduce arterial pressure, causing natriuresis and a reduction in extracellular volume.

Guides recommend replacing thiazides with ansa diuretics when RGF (rate of glomerular filtration) decreases under 30 mL/min/1.73 sqm body surface in patients with CKD. Under these circumstances, thiazide diuretics become inefficient and their secondary effects (hyponatriemia, hypokaliemia, hyperuricemia, glucose tolerance alteration) require careful monitoring of laboratory samples [11].

Ansa diuretics can also contribute to the decrease of BP and of the symptoms of congestive heart failure, but they have limited use in patients with oligoanuria.

Aldosterone antagonists (spironolactone and eplerenone) have an effect of cardiac remodelling and reduce the glomerulosclerosis and tube-insterstitial fibrosis, but they are difficult to use in CKD patients because of the risk of hyperpotassemia [11].

Direct vasodilators (minoxidil, hidralazine) produce arteriolar and venuos vasodilation and may trigger the occurrence of edema and reflex tachicardia, which makes it neccessary to be associated with beta-blockers [2]. They are used in CKD patients as antihypertensive backup medication, because of the secondary effects and the difficulty to monitor doses.

Central alpha antagonists (e.g.clonidine) efficiently reduce BP by decreasing the central autonomic activity but, because of the adverse effects (sleepiness, dry mouth, etc), they are kept as backup medication in patients who do not respond to other classes of drugs or to be used in drug combinations.

New classes of antihypertensive drugs are currently being studied: nitric oxide donors, endopeptidase inhibitors, AT2 receptor agonists, endoteline (bosentan, darusentan) receptor antagonists [11].

Conclusions

A large number of comparative studies proved that the differences among antihypertensive drugs are small in relation to cardiovascular mortality and morbidity, emphasizing the conclusion that their benefits are firstly due to lowering the *per se* BP [5].

In many studies, medicines blocking the renin-angiotensin-aldosterone system have been proved to be more efficient in slowing down the progression of the renal disease and in reducing proteinuria. On the other hand, the ALLHAT study, made on a large number of hypertensive patients with chronic kidney disease showed that the angiotensin receptors antagonists or ACE inhibitors delay the development of the renal disease in the same way as calcium channels blockers do [5].

In pre-dialysis patients with CKD, if no special medication is recommended, IACE/ARB drugs represent the first-line medication, in agreement with AHA/ACA recommendations for CKD patients, albuminuria 300mg/

day [12]. It should also be mentioned that the target BP values have not been clearly established, especially taking into accunt the large variations in volemia among hemodialysis sessions. Antihypertensive drugs in all classes– except diuretics, but taking into consideration the drug elimination during dialysis - can be used in this group of patients [5]. The onset of intra-dialysis hypotension must be avoided in the treatment of dialysis patients, since it associates with the increase of cardiovascular morbidity and mortality [13,14].

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