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Medical Bulletin

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CILNIDIPINE IS MORE EFFECTIVE IN REDUCING THE SYMPATHETIC OVERACTIVITY AND OFFERING RENO-PROTECTION IN HYPERTENSION

Essential hypertension is a chronic disease affecting more than one billion population globally & it requires long-term medical attention. Sympathetic overactivity is considered to be a hallmark of hypertensive cardiovascular disease morbidity and mortality because chronic activation of the sympathetic nervous system has been shown to produce adverse effects on the myocardium and the peripheral circulation. Additionally, hypertension is a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD).

Management of high blood pressure is not only crucial for cardiovascular outcomes but also for preserving renal function. The kidneys play a pivotal role in blood pressure regulation, and sustained hypertension leads to progressive nephron damage. Therapeutic strategies aimed at lowering blood pressure while protecting renal function are essential.

Calcium antagonists are now widely used for the treatment of various types of hypertension due to their ability to lower the high blood pressure effectively. Both sympathetic and plasma renin activity are known to increase in response to a rapid decrease in blood pressure after administration of dihydropyridine calcium antagonists. Also, calcium antagonists can increase renin activity resulting from direct action on the juxtaglomerular apparatus. The increased renin activity seems to be harmful for patients treated with calcium antagonists because increased renin activity enhances angiotensin II production, which exerts various deleterious actions. Evidence has accumulated that links high levels of plasma renin activity to metabolic imbalances in hypertension. In addition, heart failure patients with a high level of activation of the renin-angiotensin system and who show further an increase in plasma renin activity after therapy respond poorly to long-treatment with vasodilator drugs. Thus, increased plasma renin activity alone appears to be unfavorable with hypertension, in addition to causing cardiac complications. These effects are believed to contribute to cardiac and vascular structural alterations that may advance disease progression.

The desirable calcium antagonist for the treatment of hypertension should have the potential to suppress sympathetic overactivity, thus the existence of 3 types of voltage-dependent calcium channels, L-, N-, and T-type, has increased attention, which seem to have the potential to suppress norepinephrine release from the presynaptic site.

Cilnidipine, a dual L/N-type calcium channel blocker, offers a unique mechanism of action that targets both afferent and efferent arteriolar tone, thereby providing superior renoprotection. Studies have demonstrated cilnidipine could suppress cardiac sympathetic overactivity without affecting plasma renin activity, despite that cilnidipine lowers the systemic blood pressure to a degree similar to that produced by amlodipine.

Renoprotective Benefits of Cilnidipine:

1. Reduction in Proteinuria

- Cilnidipine significantly reduces urinary albumin excretion compared to amlodipine.
- Studies such as the **J-Circle study** and **AMBITION trial** reported that patients on cilnidipine showed marked reduction in albuminuria even when blood pressure control was equivalent in both groups.

2. Preservation of Glomerular Hemodynamics

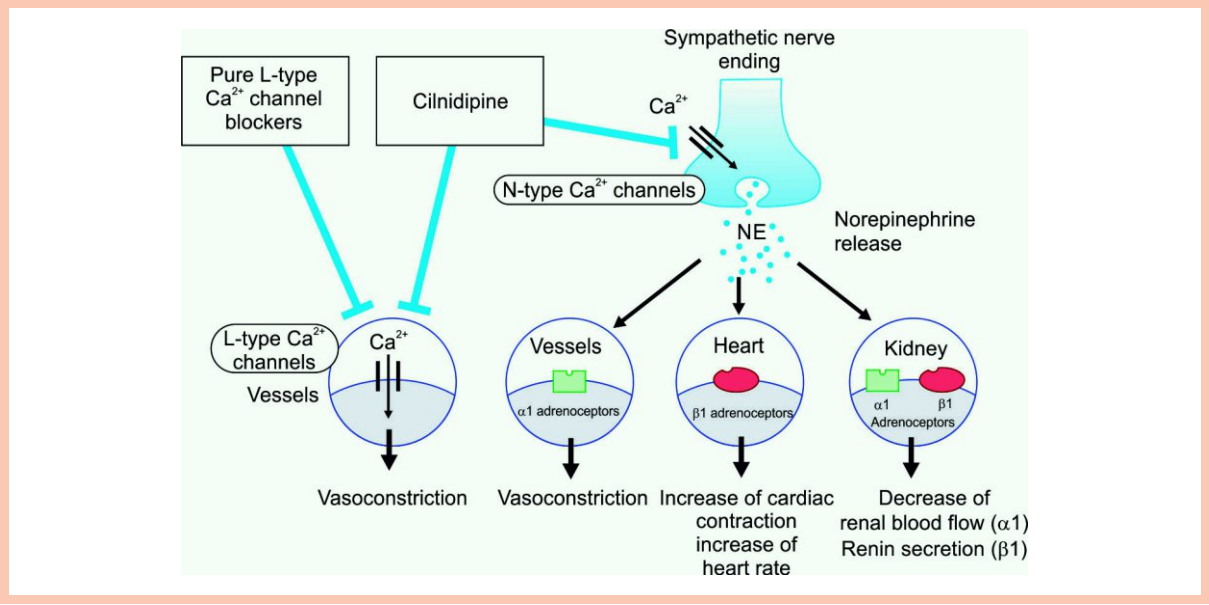
- By dilating both afferent and efferent arterioles, cilnidipine reduces intraglomerular pressure, mitigating hyper filtration injury.
- This mechanism is particularly beneficial in patients with diabetic nephropathy or pre-existing CKD.

3. Sympathetic Suppression

- N-type channel blockade leads to decreased sympathetic tone.
- Chronic over activation of the sympathetic nervous system contributes to renal vasoconstriction, sodium retention, and further hypertension a vicious cycle that cilnidipine helps break.

4. Synergy with RAS Blockade

- Cilnidipine, when combined with ACE inhibitors or ARBs, offers additive renoprotection.
- Unlike amlodipine, cilnidipine does not counteract the beneficial efferent arteriole dilation induced by RAS inhibitors.



It appears that cilnidipine can be used favorably in patients with heart failure. On the other hand, amlodipine had no detrimental effect on the cardiac sympathetic system and the neurohormonal status of essential hypertension. These drugs did not affect plasma norepinephrine concentration and renin activity suggesting, cilnidipine may suppress cardiac sympathetic activity but amlodipine has little suppressive effect. Thus, the use of N-type calcium channel antagonists appears to be safe and beneficial for long-term treatment of essential hypertension. In particular, the unique character of cilnidipine may provide a new strategy for treatment of cardiovascular disease with sympathetic overactivity.

Source:*Chopra et.al;Journal of the Association of Physicians of India, Volume 72 Issue 1 (January 2024) ; Kadian et.al; Cardiovascular & Hematological Agents in Medicinal Chemistry, 22, 1, (40-50), (2024).*

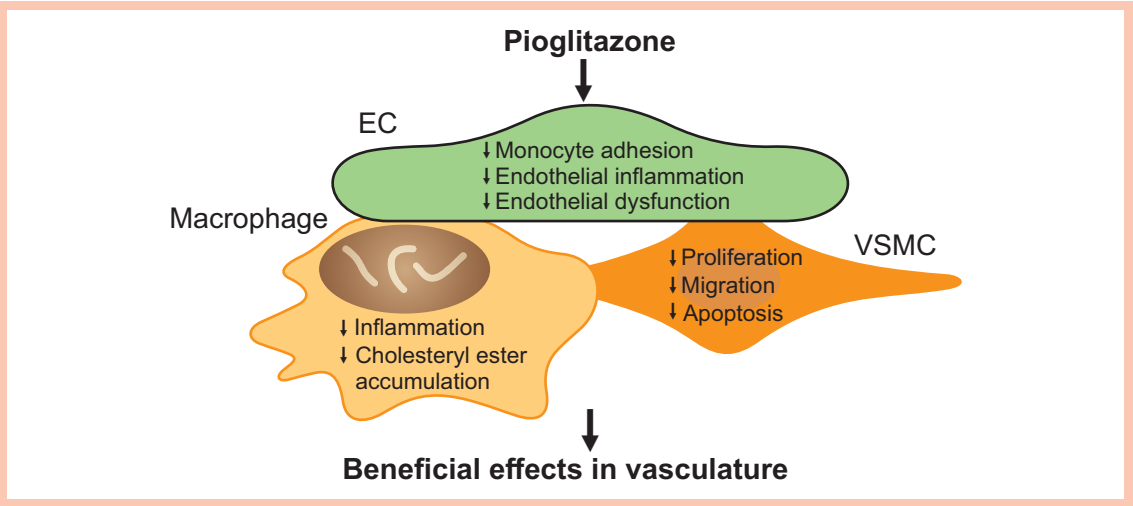
PIOGLITAZONE AND ENDOTHELIAL DYSFUNCTION : PLEIOTROPIC EFFECTS AND POSSIBLE THERAPEUTIC IMPLICATIONS

Thiazolidinediones, as an insulin-sensitizing group of drugs, have been shown to exert beneficial effects on the cardiovascular system independently of their action on glucose and insulin sensitivity. They have been demonstrated to be effective alone or in combination with a sulfonylurea, metformin, or insulin. The peroxisome proliferator activated receptor-gamma (PPARγ) agonist, pioglitazone, belongs to the insulin-sensitizing group of drugs, which is used in the treatment of type 2 diabetes mellitus (T2DM).

Insulin resistance and hyperglycemia contribute to the development and progression of atherosclerosis within a complex milieu of interrelated risk factors, which include hypertension, dyslipidemia, chronic subclinical inflammation, endothelial dysfunction (ED), and abnormalities in coagulation and fibrinolysis. Insulin resistance is typically present for some years before diagnosis, manifested as diminished stimulation of glucose transport in muscle and adipose tissue and inadequate suppression of glucose production in the liver in response to insulin. Although PPARγ activation plays an important role in glucose metabolism by enhancing insulin sensitization, the activation of quoted ligand activated transcription factor inhibits adhesion cascades and detrimental vascular inflammatory events with a distinctive role in regulating the physiology and expression of endothelial NO synthase (eNOS), thus resulting in enhanced generation of vascular (nitric oxide) NO. Knowing that NO is the most important endothelium-derived relaxing autacoid and that there is a positive correlation among insulin and the up-regulation of eNOS, the additional mechanisms related to the activation of PPARγ may be significant for cardiovascular disorders linked with diabetes mellitus, too. Accordingly, even though pioglitazone is known to exert renoprotective effects in diabetic nephropathy at doses that normalize glycemia, it has also been reported that at low doses that do not normalize glycemia, pioglitazone administration was associated with the normalization of the renal levels of connective tissue growth factor and fibronectin, tumor necrosis factor-α (TNFα), interleukin-6 (IL-6), and monocyte chemotactic protein-1, megalin, the proliferating cell nuclear antigen/caspase-3 ratio, vascular endothelial growth factor (VEGF), and the ratio between endothelial and inducible NOS. The beneficial effects of short-term, low-dosage pioglitazone on ED in regards to increasing adiponectin expression and decreasing low-grade inflammation in T2DM patients were reported as well. These and other similar findings have led to the hypothesis that pioglitazone could exert vasculoprotective effects that are independent of its metabolic action involving the activation of PPARγ.

PPARγ activation improves insulin sensitivity, decreases inflammation, plasma levels of free fatty acids, and blood pressure, so indirectly leading to the inhibition of atherogenesis, improvement of ED, and reduction of cardiovascular events. Pioglitazone is an insulin-sensitizing, anti-hyperglycemic agent which stimulates PPARγ, yet the vasculoprotective effects seem not to be directly associated to the

activation of this nuclear receptor. Nevertheless, positive correlations are currently well documented considering the improvement of different markers related to ED and pioglitazone administration.



Clinical Evidence:

- In patients with coronary artery disease (CAD) and newly detected T2DM: 12 weeks of pioglitazone (30 mg/d) improved endothelial dysfunction measured by photoplethysmographic pulse wave analysis.
- In individuals with impaired glucose tolerance: pioglitazone improved flow-mediated dilation (FMD) significantly compared with placebo.
- Compared with metformin: in a study of T2DM patients (uncontrolled on glimepiride), addition of pioglitazone improved endothelial function, insulin resistance more than metformin; though the two had similarities in some measures.

Therapeutic Implications:

- Because endothelial dysfunction is one of the earliest pathophysiologic changes in cardiovascular disease, improving it could help prevent progression of atherosclerosis, reduce cardiovascular risk.
- Pioglitazone's effects on NO, inflammation, oxidative stress suggest it could be useful even before full-blown diabetes e.g. in insulin resistance, impaired glucose tolerance.
- Possibly beneficial in microvascular complications (e.g. retina, kidney) due to its effects on microvascular endothelial health.

Pioglitazone may have value beyond glycemic control as part of cardiovascular risk reduction, especially in early insulin resistance or subclinical vascular disease.

Source: *Radenković M.et.al; Sci Pharm.18;82(4):709-21; Yu X, Chen P,et.al; Med Princ Pract.;22(2):156-60.*

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