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Medical Bulletin

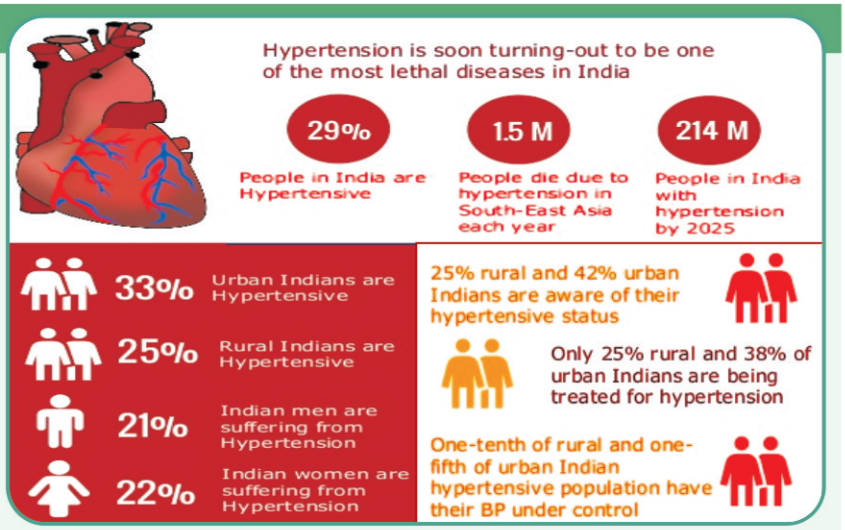
EXCEL Division of Blue Cross Laboratories

CALCIUM CHANNEL BLOCKERS

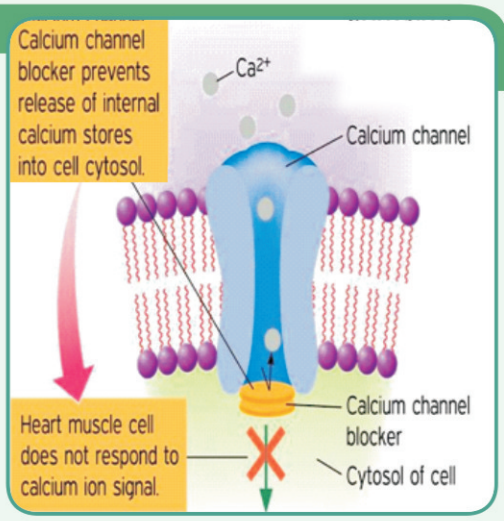
INTRODUCTION

Hypertension is the most important noncommunicable disease risk factor in India with an estimated burden of 200 million persons. High blood pressure can lead to many serious health problems, such as heart attack, heart failure, stroke, & kidney disease. Treating high blood pressure early is important in preventing these problems.

Antihypertensive agents are of various types like diuretics, beta-blockers, ACE inhibitors, ARBs & calcium channel blockers (CCBs), It is important to evaluate the best suited antihypertensive agent based on various underlying factors such as age, sex, comorbidities etc.



Prevalence of Hypertension in India



Mechanism of action of CCBs

WHAT ARE CALCIUM CHANNEL BLOCKERS (CCBs)?

CCBs are a class of antihypertensive drugs that act by blocking the influx of calcium ions into vascular smooth muscle and cardiac muscle cells during *membrane depolarization*. Because muscle contraction is largely dependent upon influx of calcium, its inhibition causes relaxation, particularly in arterial beds. Thus, the major effects of the calcium channel blockers are relaxation of vascular smooth muscle cells resulting in arterial vasodilation. While all affect the *L type voltage gated calcium channel*, CCBs like Cilnidipine additionally act on *N-type voltage gated calcium* channels, giving it a few advantages over other CCBs.

WHEN TO CHOOSE A CCB?

In choosing the optimum antihypertensive agent for an individual patient, various factors like demographic characteristics (e.g., age, gender, race) , the circadian pattern of blood pressure elevation, concomitant therapy for coexisting medical disorders may influence the response to therapy. CCBs, can be used in any age group, & are useful in patients with certain concurrent conditions (e.g., coronary artery disease, migraine, or gastrointestinal motility disorders).

ISOLATED SYSTOLIC HYPERTENSION (ISH):

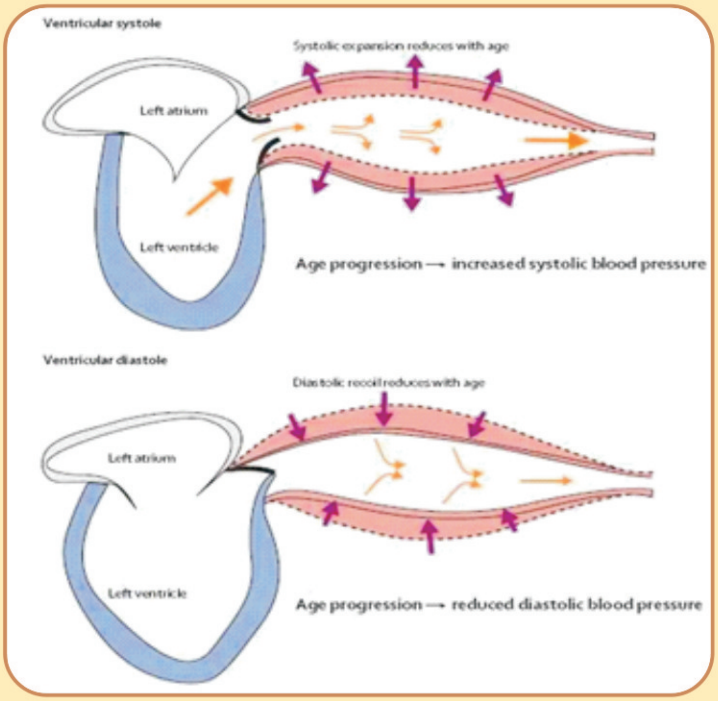
Elderly patients are more prone to having isolated systolic hypertension (ISH) systolic BP ≥140 mm Hg; diastolic BP <90 mm Hg which is likely a result of an increase in arterial stiffness from arteriosclerosis or impairment of nitric oxide mediated vasodilation. More than 65% of hypertensive patients aged ≥60 years and more than 90% of those aged >70 years have ISH and this is associated with a 2- to 4-fold increase in the risk for stroke, myocardial infarction (MI), or cardiovascular (CV) mortality. CCBs as well as thiazide like diuretics can be used as first-line treatment in ISH patients, as they substantially reduce the risk of stroke.

DIABETICS

Studies have shown that CCB treatment was positively associated with β-cell function in hypertensive T2DM patients, implying that CCBs could be considered to treat hypertensive T2DM patients with reduced β-cell function.

RENAL PROTECTION

Prevention of renal damage by strict BP control is very important aim of antihypertensive therapy. Studies have shown that CCB could be particularly positive for the long-term maintenance of GFR levels when compared with a diuretic and with an ACE inhibitor. In the absence of albuminuria and with a preserved GFR (>60 ml/min), a CCB can be contemplated as first-step therapy & seems to preserve GFR in an adequate manner.

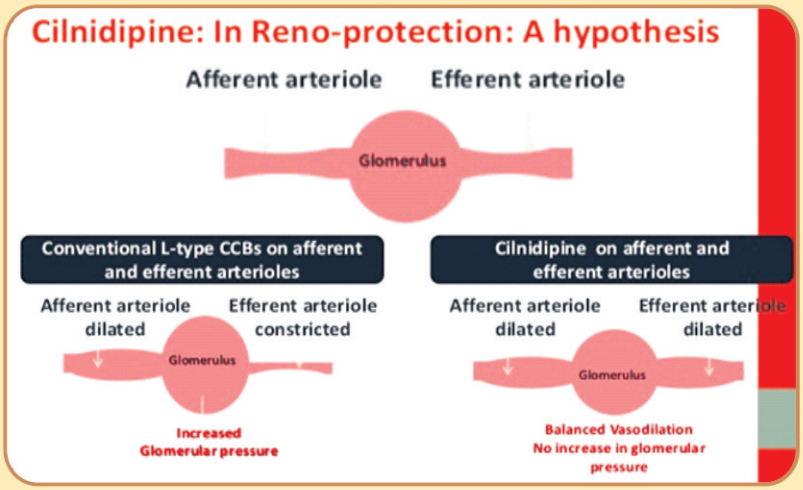


Role of aortic compliance on BP & effect of ageing

Amongst the CCBs, evidence of the renoprotective effect with cilnidipine, are more consistent as compared to amlodipine. Cilnidipine has been reported to have a more beneficial effect on proteinuria progression than amlodipine. The N-type calcium channel blockade that inhibits renal sympathetic nerve activity might reduce glomerular hypertension by facilitating vasodilation of the efferent arterioles. This is known to significantly reduce glomerular pressure offering effective podocyte (acts as a permeability barrier restricting the passage of large molecules like albumin) protection, which further results in significant anti-proteinuric effect.

Also, the Renin-angiotensin-aldosterone system (RAAS) can be suppressed through the sympatholytic actions of N-type CCBs & thereby prevent impaired kidney function.

Mechanism of reno-protection of Cilnidipine



REFLEX TACHYCARDIA

Reflex tachycardia is a common side effect associated with many dihydropyridine CCBs which act through L-type calcium channel only. Replacing these drugs with cilnidipine, a dual L- and N-type CCB may reduce the heart rate.

PEDAL OEDEMA

Despite similar blood pressure reduction, the frequency of pedal oedema varies between CCBs. CCBs with an N-type channel blocking effect may dilate the venules through sympathetic nerves distributed to these vessels. Hence have a lesser incidence of pedal oedema compared with the other CCBs which act only on L-type calcium channels. Thus, cilnidipine being N-type and L-type CCB, has been associated with a lower incidence of pedal oedema compared to only L-type channel blocker like amlodipine.

Hence, it can be concluded that CCBs are a preferred choice of antihypertensive agents, especially among the elderly as well as among patients with co-morbid conditions like diabetes and renal problems. Among the CCBs, cilnidipine due to its unique feature of being both N-type and L-type CCB, presents better renal protection as well as fewer side effects like reflex tachycardia and pedal oedema.

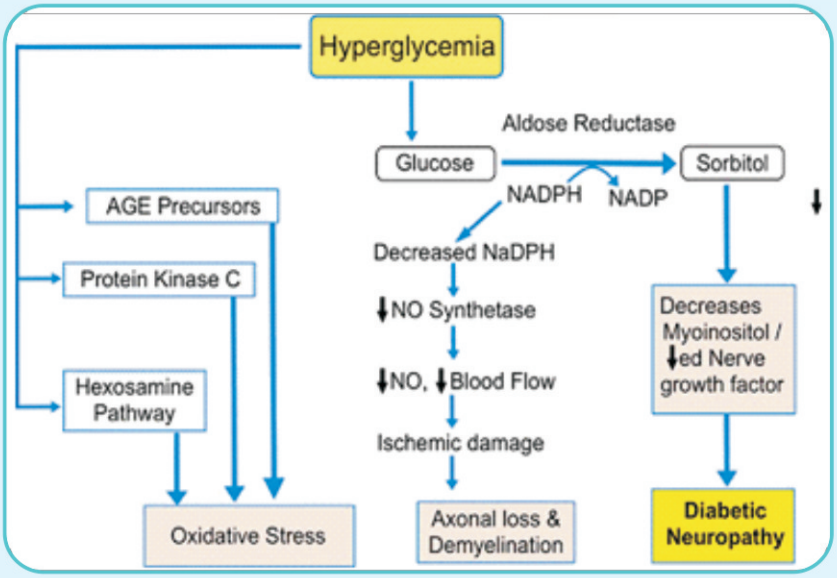
Source:
Curr Opin Cardiol 2019; 34(4): 331-341; J of Clin Hypertension 2019; 21 (5): 638-647;; Nat Inst of Diab & Dige and Kidney Diseases; 2012-. Calcium Channel Blockers. (Updated 2017); Am J of Medicine 2016; 129(12): 1251-1258; Cardiol Res 2016; 7(5): 167-172.; J Adv Pharm Technol Res 2015; 6(2): 81-85; Am Health Drug Benefits 2012; 5(3): 146-153; Hypertension Research 2012; 35: 1058-1062; J of Am Soc of Nephrology 2005; 16(3): S64-S66.

VITAMIN B12 AND DIABETIC NEUROPATHY

Diabetic neuropathy is nerve damage due to high blood glucose levels and high levels of fats, such as triglycerides causing damage to the nerves over time. Diabetic peripheral neuropathy (DPN) affects approximately 44% of older diabetics with some patients presenting extremely painful symptoms.

Diabetic neuropathy can be of different types depending on the type of nerves affected.

- **Peripheral Neuropathy:** About half of diabetics with neuropathy have peripheral neuropathy, which affects the nerves of feet & legs & sometimes arms and hands.
- **Autonomic Neuropathy:** Damage nerves that control internal organs, leading to problems with heart rate, blood pressure, digestive system, sex organs, sweat glands, & eyes.
- **Focal Neuropathies:** This condition typically causes damage to single nerves, most often in hand, head, torso, or leg. The most common types of focal neuropathy are entrapment syndromes, such as carpal tunnel syndrome.
- **Proximal Neuropathies:** Rare and disabling type of nerve damage to the hip, buttock, or thigh. The damage typically affects one side of the body & may rarely spread to other side.



Pathogenesis of diabetic neuropathy

PATHOGENESIS OF DIABETIC NEUROPATHY

Many hypotheses for the pathogenesis of diabetic neuropathy are known. The chronic, more insidious neuropathy is predominantly due to persistent hyperglycaemia while the acute, usually self-limiting neuropathy may be due to vascular causes.

Hyperglycaemia results in accumulation of *advanced glycosylated end products* (AGE products) and activation of other pathways ultimately leading to oxidative stress, axonal loss, and demyelination, resulting in nerve dysfunction.

Excess glucose also gets converted into sorbitol & decreases levels of myoinositol, a nerve growth factor which leads to diabetic neuropathy. Optimal glucose control is, therefore, the primary preventive measure.

ROLE OF B_{12} IN DIABETIC NEUROPATHY

Dietary deficiency of vitamin B_{12} can result from poor diets or amongst strict vegetarians. Lack of stomach acid in elderly patients & among people taking proton pump inhibitors, leads to poor absorption of the vitamin from animal products.

Vitamin B_{12} deficiency has been associated with significant neurological pathology, especially peripheral neuropathy including diabetic neuropathy. Vitamin B_{12} supplements are typically derived from two sources: cyanocobalamin or methylcobalamin. Cyanocobalamin is converted to methylcobalamin in the liver, which is the active form of vitamin B_{12}. Methylcobalamin helps in production of *myelin & Lecithin*, which cover & protect the nerve fibres.

Apart from methycobalamin, pyridoxine and folic acid are also neurotropic vitamins. Pyridoxine functions as a conenzyme in pathways responsible for synthesis of neurotransmitters as well as a cofactor in sphingolipid synthesis which are important for myelin formation. Folic acid promotes nerve injury repair by affecting the Schwann cell function & improving the axon quantity.

THERAPEUTIC USE OF METHYCOBALAMIN

Methylcobalamin is used in the treatment of diabetic neuropathy as it facilitates myelinogenesis and nerve regeneration, & can be used as a prophylactic measure as well as an adjunct treatment option for the progression & treatment of diabetic neuropathy. Studies have suggested oral methylcobalamin at a dose of 500 mcg three times daily significantly improved the somatic and autonomic symptoms with regression of the diabetic neuropathy signs.

Currently, the agents used to reduce symptoms of pain in diabetic peripheral neuropathy include analgesics, tricyclic antidepressants and anticonvulsants. Unfortunately, there is no evidence that any of these agents modify the underlying pathophysiology of peripheral neuropathy.
It has been shown that high doses of methylcobalamin improves nerve conduction in neuropathy, & was associated with a significant increase in the rate of motor nerve fibre regeneration.

Source:
CNS Neuroscience & Therapeutics 2020; 26(1): 50-13; Neural Regen Res 2019; 14(1): 132-139; Integrative Medicine (4th Ed) 2018; e8: 120-132; Curr Med Issues 2017; 15(3): 189-199; Singapore Med J 2016; 57(2): 5559;Austin J of Pharmacology & Therapeutics 2015; 3(3): 1076; Medical J of Babylon 2014; 2(3); Acta Neurol Taiwan 2005; 14(2): 48-54.

POST ANTIBIOTIC EFFECT

INTRODUCTION

Antimicrobial resistance (AMR) has emerged as a major threat to public health estimating 10 million deaths annually by 2050 & hence become necessary to draw attention to the escalating global crisis of AMR fuelled by the irresponsible and irrational use of antibiotics. India carries one of the largest burdens of drug-resistant pathogens worldwide and is one of the largest consumers of antibiotics worldwide.

In general, there are two strategies to combat the rapid rise of antimicrobial resistance: novel antibiotic development or more effective use of existing drugs. Given the prohibitive time and financial costs of the former, the latter strategy is becoming increasingly critical. In doing so, it is important to move beyond steady-state measures of efficacy and emphasize the importance of temporal dynamics in drug response, post-antibiotic effect (PAE) being one such response.

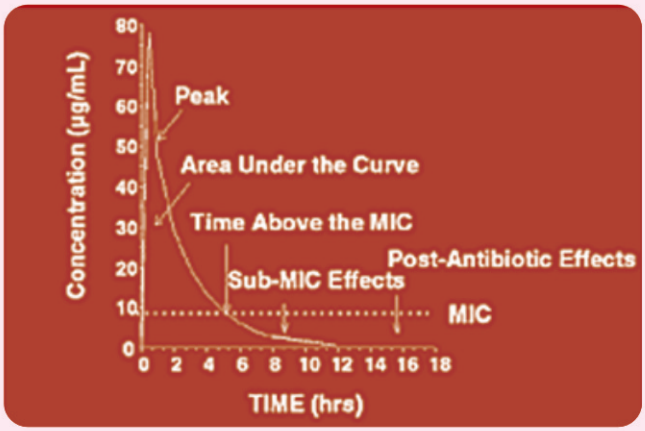
WHAT IS PAE?

Post-antibiotic effect (PAE) is defined as the persistent suppression of bacterial growth after a brief antimicrobial agent exposure.

Moreover, during the PAE period, bacterial growth would be further suppressed because of the sub-inhibitory concentrations of drug, which is defined as post-antibiotic subminimum inhibitory concentration effect (PAE-SME).

The clinical significance of this is, drug that produce a long PAE and PAE-SME may be important pharmacodynamic parameters for designing longer dosing intervals, reducing adverse effects, and lowering costs.

PAEs can vary by drugs and micro-organism. For example, prolonged PAEs have been reported after aminoglycoside or fluoroquinolone exposure of Gram-negative L. bacilli, whereas most β-lactam antibiotics exhibit shorter PAEs.



MECHANISM OF PAE

Mechanisms by which PAE occurs include both nonlethal damages induced by the antimicrobial agent and a limited persistence of the antimicrobial agent at the bacterial binding site.

To explain the mechanism of action of PAE, it has been suggested that an alteration of DNA function is possibly responsible for this effect, since most inhibitors of protein and nucleic acid synthesis (aminoglycosides, fluoroquinolones, tetracyclines, clindamycin, certain newer macrolides/ketolides, rifampicin and rifabutin) induce long-term PAE against susceptible bacteria.

To provide further credence to this theory, cell wall active agents (betalactams and vancomycin) either have no or very short PAEs.

Hence, extending the dosing interval of an antimicrobial agent that has a PAE has several potential advantages, among them reduced cost, less toxicity, and better compliance among outpatients receiving antimicrobial therapy.

Source:
Indian J of Community Medicine 2019; 44(1): 4-8; Infect Drug Resist 2018; 11: 2107-2115;Adv.Exp Med Biol 2018; 1052:51-61; Mol Syst Biol 2017; 13(10): 948; Infectious Diseases 2010; 2: 1275-1287;Indian Journal of Pharmacology 2002; 34: 390-396;. Antimicrobial Agents & Chemotherapy 1999: 1324-1328.Clin Pharm 1992; 11(10): 865-875.

WHAT'S trending

COVID-19 Vs SEASONAL FLU Vs COMMON COLD

As fears over novel coronavirus infection, or Covid-19 grow, there is the chance of one pressing the panic button at the slightest hint of feeling unwell. But the truth is that it could be COVID-19 or just a common flu, the key being able to distinguish between them.

There are various distinguishing features that help to understand whether to advise for testing.

Signs /Symptoms	Covid-19	Flu	Cold
Incubation Period	1-14 days	1-4 days	1-3 days
Onset of Symptoms	Gradual	Abrupt	Gradual
Fever	Often & High Fever	Often	Rare, Mild if present
Cough	Dry Cough, Often Severe	Dry Cough	Mild
Runny Nose	Infrequent	Sometimes	Common
Sneezing	infrequent	Sometimes	Common
Watery Eyes	Infrequent	Common	Common
Diarrhea	Sometimes	Sometimes	Rare
Body Aches	Sometimes	Common	Slight
Sore throat	Sometimes	Sometimes	Common
Headache	Sometimes	Common	Rare
Loss of Appetite	Sometimes	Common	Sometimes
Shortness of breath	Common	Rare	No
Difficulty in breathing	Common	Sometimes	No

Not every person suffering from fever, cold and cough are suffering from COVID-19, and is mainly seen among individuals with a history of travel from infected countries or contacts with positive cases. Many asymptomatic carriers are found to be positive and therefore it is important to be vigilant and be alert while screening the patients and at the same time not cause unnecessary panic as well…

DIABETIC DRUGS FOR HEART FAILURE WITH PRESERVED EJECTION FRACTION

For patients with heart failure with preserved ejection fraction (HFpEF), current treatments address only accompanying conditions & symptoms. Therapy commonly involves treating high blood pressure & coronary artery disease, along with life style modifications.

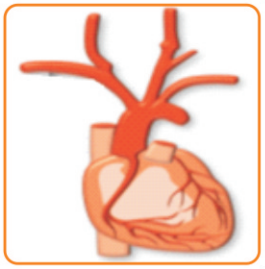
No treatment is yet available for HFpEF, however, sodium glucose co-transporter 2 (SGLT2) inhibitors currently used to lower blood glucose for the treatment of type 2 diabetes are now being investigated for HFpEF.

Using SGLT2 inhibitors for this purpose became of interest when researchers reported that these drugs reduced the risk of cardiovascular death and heart failure hospitalization in a cohort of patients with type 2 diabetes. Individuals with HFpEF without diabetes on SGLT2 inhibitors also showed similar results.

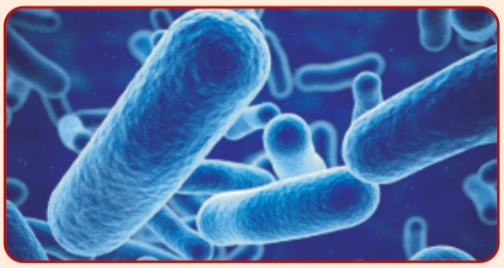
Cleveland clinic noted that "With an FDA decision anticipated in 2020, these drugs, among others, are introducing potential new treatment options for patients with this heart failure subtype."

Potential Mechanisms:

- Blood pressure
- Body weight
- Arterial stiffness
- Cardiac oxygen demand
- Oxidative stress
- ▼ Lack of sympathetic nerve activation
- ▲ Cardiac Function
- Glucagon secretion



ANTIBIOTIC FOR DRUG RESISTANT SUPERBUGS



US researchers have used ***Artificial intelligence (AI)*** to identify a powerful new antibiotic capable of killing several drug-resistant bacteria or superbugs.

The scientists at MIT and Harvard trained a machine learning algorithm to analyze chemical compounds capable of fighting infections using different mechanisms. The team trained the model on about 2500 molecules, identifying a compound the called ***"Halicin"***. It killed many bacteria that are resistant to treatment including Clostridium difficile, Acinetobacter baumannii and Mycobacterium tuberculosis.

This development raises hope for the future of antibiotics and comes at a critical time, as it is predicted that without immediate action to discover and develop new drugs, deaths attributable to resistant infections will reach 10 million a year by 2050.

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