The Antimicrobial Effects of Antihypertensive Agents: A Review of Their Pharmacological Properties

1Rohan K. Patel, 2Shruti P. Shah, 3Aparna R. Mehta, 2Tushar S. Parmar

1Department of Pharmacology, Smt. Kashibai Navale Medical College and General Hospital, Pune, Maharashtra, India; 2Department of Public Health Dentistry, Maharashtra University of Health Sciences, Nashik, Maharashtra, India; 3Section of Oral Pathology, Institute of Dental and Craniofacial Sciences, Mumbai, Maharashtra, India; 4Department of Obstetrics and Gynecology, Lokmanya Tilak Medical College and Hospital, Mumbai, Maharashtra, India

ABSTRACT

The increased incidence of hypertension and diabetes mellitus worldwide puts the human health under peril. Susceptibility of these patients for various infections endangers their life. Alarmingly increasing antibacterial resistance is a cause of major concern. By the year 2015 chances of people dying due to drug resistant bacterial infections will be more than that from cancer. Hence there is a need for the development of potent newer antimicrobials or to test and confirm the antibacterial properties of non-antibacterial drugs used to treat various conditions. Hypertension is one area where the antihypertensive drugs used to treat the condition have proved their potential activity against various infections. The antihypertensive drugs which were observed to have antimicrobial action are calcium channel blockers like verapamil, amlodipine, nifedipine and lacidipine, central sympatholytic drug alpha methyl dopa and beta blocker like propranolol. Verapamil which is an ion channel blocker has shown potential against mycobacterium tuberculosis when used along with approved anti tubercular drugs and helped in prevention of drug resistance. Similarly, alpha methyl dopa showed significant in vitro activity against atypical mycobacteria. Propranolol exhibited anti fungal and antitoxoplasmal activity. Verapamil helped to reverse chloroquine resitance developed by plasmodium falcifarum malaria parasite. This suggests that properties of these antihypertensive in treating various bacterial and nonbacterial infections should be studied extensively by many clinical studies to authenticate their use.

Keywords: antimicrobial, antihypertensive, bacterial, nonbacterial.

INTRODUCTION

Incidence of hypertension as a disease complex is rising alarmingly worldwide due to increased longevity and as a result of faulty and stressful life style. Diabetes mellitus is one of the predisposing cause for the onset of hypertension which is known to enhance the susceptibilty of patients to various infections. This requires the need for selection of proper antimicrobial drugs. Some studies have reported that by year 2050,more and more individuals will die of drug resistant bacterial infections than that from cancer[1,2]. Recently various organisms have developed resistance against existing antimicrobial drugs which warrants the need to discover newer antimicrobial drugs or to explore the possible antimicrobial action of available non-antimicrobial drugs[3,4]. Co-existence of hypertension and diabetes and increased chances of infection in these class of patients necessitates the need to know whether any of the drugs used for this condition possess any antimicrobial action. Certain antihypertensive drugs were found to have antimicrobial actions. These are some of the calcium channel blockers, central sympatholytic like alpha methyl dopa and beta blocker like propranolol[5-10].

Calcium channel blockers

Verapamil- Verapamil is a calcium channel blocker of voltage dependent L- type calcium channels. It is an ion channel blocker. Recently ion channel blockers including verapamil have been tried for their activity against mycobacterium tuberculosis [M.tubercuosis] bacilli.

M. tuberculosis bacillus due to its impenetrable cell wall, its intracellular survival in host cell and its long duplication time makes it difficult to control pathogen and hence it can become resistant to antitubercular drugs. This requires long term chemotherapy to eradicate this infection, which can create an obstacle to the drug adherance and for the patient's compliance. Prolonged drug therapy also exposes the patient for drug toxicity. This necessitates the need for better and time efficient drugs or the use of adjuvant drugs which will potentiate the effectiveness of existing drugs. Ion channel blocker verapamil was tested against drug resistant M.tuberculosis strain both in human infected macrophages and in vitro .This drug being an ion channel blocker is also an efflux inhibitor. In vitro studies, it exhibited synergistic inhibitory activity against tubercular organisms when it was combined with antiTB drugs like Isoniazide and Rifampicin[5,11,12].

It is observed that M.tuberculosis efflux genes get overexpressed when they are exposed to antibiotics in vitro and also within the macrophages. This efflux pump activity contributes to drug resistance by making the intracellular drug concentration sub inhibitory[13-16]. This also exposes the organism to develop drug resistant mutants[15-18]. Verapamil showed rapid and high killing activity against M.tuberculosis which correlates with decreased intracellular ATP levels suggesting the interference in the energy metabolism. Inhibition of respiratory chain complex, and decreased ATP production which provides energy for bacterial efflux pump mechanism which forms the major cause for drug resistance, gets inhibited by

verapamil resulting in to the reduction of antiTB drug resistance. Thus, verapamil contributes to bacteriocidal effect[19-21].

The ion channel blocker verapamil promotes vacuolar acidification by controlling the conditions in the phagosome vacuole needed for effective microbial killing and digestion through lysosomal hydrolytic enzymes[22,23]. This is controlled through the transport of cations by eukaryotic vacuolar efflux forms. This is also coupled to the energy provided by electron transport chain enzyme which are located in the membrane and proton channels[22,23]. Increased intracellular concentration of the drug enhances the transcription of the proton pump VATPase. This results in to enhanced phagosomal acidification[24] and increase in Ca2+ concentration in the lumen[25]. This activates acidification dependent lysosomal hydrolases[24] and enhances macrophage mediated killing of the mycobacteria[26,27].

Prokayotic and eukaryotic efflux pumps use the energy of either ATP [primary transporter] or PMF [secondary transporter] required for the extrusion of ions, noxious compounds or metabolites. Energy provided for this process is through oxidative phosphorylation[21,28]. The energy production in both eukaryotic and prokaryotic cells starts with NADH dehydrogenase and ends up at the respective F1 F0 ATP synthase which is the key electron transport chain enzyme and is thought to be inhibited by ion channel blocker like verapamil either directly or indirectly[21,28,29].

Enhancement of the killing activity of macrophage by ion channel blocker like verapamil was considered to be dependent upon the availability of intracellular potassium and calcium[26,27,30]. Gupta el al demonstrated that increase in calcium from intracellular calcium stores in macrophages as a result of L-type calcium channel inhibition led to reduction in mycobacterial population. M.tuberculosis modulates levels and activity of important intracellular second messengers to evade protective immune responses. Release of calcium from voltage gated calcium channels is responsible for regulation of immune responses to pathogens. Inhibition of these channels in infected macrophages induced the calcium influx, which was found to upregulate the expression of pro inflammatory genes, resulting in to the killing of intracellular mycobacteria and decreased mycobacterial population[25].

Oral verapamil is well tolerated with fewer side effects. Thus verapamil targets mycobacterium and host macrophages resulting in to - After entering in to the mycobacteria it initiates cascade of events resulting in to the inhibition of respiratory chain complexes and energy production required for the bacterial efflux activity which helps in the reduction of antibiotic resistance and potentiation of its activity. Verapamil promotes phagosome acidification and enhances transcription of hydrolases in the host cell resulting in to inhibition of bacterial growth when combined with antitubercular drugs. This combination enhances mycobacterial killing, prevents drug resistance and shortens the duration of chemotherapy.

Verapamil was found to reverse chloroquine resistance of falciparum malaria organisms by inhibiting the efflux of the drug and by enhancing intraparasitic concentration of chloroquine from subinhibitory to therapeutic one[31,32].

Amlodipine

Amlodipine was found to be effective against various bacteria in decreasing order of sensitivity against staph.aureus, vibrio cholera, vibrio parahemolyticus, shigella spp, salmonella spp, bacillus spp. Amlodipine was bacteriocidal in nature both in vitro and vivo when studied in white mice. Amlodipine was found to be more effective than felodipine, lacidipine and nifedipine and was powerful antibacterial against large number of bacteria[6]. Study done with derivatives of phenothiazines revealed their in-vitro antimicrobial activity which was found to be closely linked to the halogen groups present in the basic tricyclic ring structure of phenothiazines. In amlodipine structure one benzene ring is attached to another which may be considered as an incomplete phenothiazine ring. The presence of halogen [chlorine] moiety may be responsible for antimicrobial activity of this compound[33].

Nifedipine

Nifedipine was found to have in vitro and in vivo antibacterial activity against 331 strains of bacteria out of which 3 were of Gram positive and 12 were of Gram negative group organisms. Observed MIC of nifedipine was between 25-200mcgms/ml against almost all organisms in vitro studies. It has bacteriostatic action. Hence nifedipine has proved as an antibacterial agent which can be considered for clinical use and for further studies to confirm and evaluate its antibacterial potential[7].

Lacidipine

Lacidipine is a third-generation L type calcium channel blocker. It was screened for antibacterial activity against 389 Gram positive and negative bacterial strains.233 bacterial strains failed to grow at concentration 50200mcgm/ml of the drug. Their sensitivity pattern in descending order was as follows-staph. aureus, vibrio cholera, salmonella typhi, shigella, vibrio cholera, e.coli, bacillus spp, klebsiella and pseudomonas spp. Doses used in the animal study were non toxic and were well tolerated. Lacidipine was found to have inhibitory activity against v.cholerae 569 B in one study. It reduced the viability of the organisms and also the production of cholera toxin in animal model of rabbit ileum. Lacidipine was found to be bacteriostatic in nature[8]. Heat labile enterotoxin of e.coli is structurally and functionally similar to cholera toxin[34]. Earlier studies have shown that enterotoxin of e.coli were found to be highly sensitive for lacidipine[35]. Thus, lacidipine is both antibacterial and antitoxic also. *Centrally acting sympatholytic drug-Alpha methyl dopa*

Alpha methyl dopa has shown significant in vitro activity against atypical mycobacteria like M.avium complex, M.scrofulaceum, M.xenopi, M.marinum and M.fortuitum. Study done by N K Datta was extended to total of 53 strains of mycobacteria which also included 34 clinical isolates of drug sensitive and drug resistant strains of mycobacteria. For most of bacteria MIC was between 1025 mcgms/ml[9].

Beta blockers-propranolol

Propranolol was found to have anti fungal activity which involves inhibition of fungal hyphal growth by interefering cAMP-EFG 1 pathway[10]. Formation of hyphae plays an

important role in the fungal virulence and tissue invasion[36]. Candida albicans is an opportunistic pathogen which changes from non virulent yeast form to virulent hyphae form in response to the various environmental signals[3739]. Addition of propranolol inhibited hyphae formation of the C.albicans by inhibiting the expression of agglutinin like sequence 3[ALS 3]and ALS 8 mRNA which are regulated by cAMP-EFG 1 pathway in C.albicans. It did not affect MAP-mitogen activated protein-kinase related expression of CST 20, HST 7 or CPH 1 mRNA. Hyphae transformation is induced by activation of the MAP kinase cascade and cAMP pathway which are controlled by RAAS protein[40-42]. EFG 1 is a transcriptional factor[43,44]. Hypae specific protein such as ALS 3 and ALS 8 are cell wall proteins in C.albicans and their expressions are regulated by EFG1[45,46].

Although propranolol is used as a beta blocker in clinical medicine, the recommended blood level [50-100ng/ml][47]for the treatment greatly differs from the concentration required for the inhibition of hyphae formation. Thus propranolol might not be useful for the treatment of C.albicans infection. However it is expected that some propranolol derivative would effectively control the expression of EFG 1 and hyphae transformation of C.albicans.

Propranolol was found to inhibit C.albicans adherence on bio film formation on biotic and abiotic surfaces. C.albicans is associated with the nosocomial infection partly due to its ability to adhere to variety of biomaterial such as catheters and biofilms. These biofilms are related to the resistance to the antimicrobial agents and immune defences[48]. Hyphal formation is essential for the structural integrity of the C.albicans biofilms[49]. Propranolol probably binds to phosphatidic acid[PA], blocking diglyceral[DAG] synthesis[50]. Propranolol acts mainly in the early stages of C.albicans biofilm formation. The attachment step required for the formation of biofilm is affected by propranolol. Thus inhibition of adherence to biotic surface and inhibition of germ tube formation may explain the effect of propranolol on C.albicans bio film formation. Adhesion of fungal cells to the epithelium was significantly affected by propranolol. Thus propranolol could prevent the early stages of C.albicans colonization and bio film formation on biological and non biological surfaces.

Adherance of microorganisms to cell surfaces involves numerous factors such as cell hydrophobicity, electrostatic forces and specific adhesions[51]. Inhibitory effect of propranolol on C.albicans biofilm formation may be associated with the effect on the expression of adhesion genes like agglutinin like sequence [ALS] genes or adhesion like glycosyl phosphatidylinositol [GPI] linked cell surface proteins.

Propranolol inhibits germ tube formation by repressing the cAMP-EFG 1 pathway of C.albicans[52]. Moreover, propranolol inhibits morphogenesis by sequestering PA[50]. This suggests that the transcription factor EFG 1 can be regulated by PA and/or DAG signaling pathway. Consequently the expression of EFG 1 target genes [ALS1, ALS 3] and GPI linked cell surface protein HWP1 is also repressed by propranolol. Thus inhibition of C.albicans adherence to cell surfaces and hyphal development by propranolol results in abnormal biofilms.

Effect of propranolol on toxoplasma infection-Potential of antitoxoplasma activity of propranolol was tested in acute and chronic phases of infection. Propranolol is a membrane stabilsing agent which inhibits the entry of toxoplasma gondi trophozoite in to the cells. Efficiency of propranolol was increased against toxoplasma when combined with pyrimethamine[53].

CONCLUSION

Anti hypertensives like calcium channel blockers,central sympatholytic and beta blockers have been proved to have antimicrobial activities. Rising incidence of drug resistance in the area of various bacterial, mycobacterial, fungal and parasitic infection has raised the concern and challenged the survival of human race. The rate of discovery of newer antimicrobials is disproportionately slow as compared to the speed of development of antimicrobial drug resistance. Hence the need arises to tap the potential of non-antimicrobial drugs used to treat various conditions in which signs of infection become high due to underlying oxidative stress or due to associated conditions like hypertension. The additional antimicrobial action of antihypertensive drugs needs extensive studies both in vitro and in vivo. Minimum dose required to elicit antimicrobial action without causing any adverse effects has to be confirmed before using these drugs for associated infection in hypertensive patients.

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