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Pharmacotherapy of Hypertension

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ABSTRACT

Hypertension is responsible for considerable morbidity and mortality all over the world affecting black population more than the Caucasian population. Hypertension is the leading non-communicable disease in Nigeria with a prevalence rate of 11% amongst adults aged 15 years and above. Most cases of hypertension are classified as idiopathic or primary hypertension for lack known aetiology and generally respond to pharmacotherapy. This article reviews the available drugs used in the control of hypertension emphasis been on pharmacologic classification, mechanism of action as well as adverse drug reactions associated with their use. Physicians are reminded of the central role of thiazides in lowering blood pressure and encouraged to watch out for adverse drug reactions as a possible cause of treatment failure.

INTRODUCTION

Hypertension is defined as sustained elevation of blood pressure 140/90 mmHg, a level that has been associated with significant cardiovascular risk [1]. Transient elevation of blood pressure may occur as a result of increased activity, emotion or illness. Blood pressure also varies at different times of the day. Hypertension may be described as primary or benign (essential) when there is no obvious disorder causing it. This type of hypertension is different from secondary hypertension where there is a primary disorder known to be responsible for the sustained elevation of blood pressure. Blood pressure is the product of cardiac output (CO) and the peripheral resistance (PR) and the basis of control of hypertension using various anti-hypertensive drugs revolves around this equation. Thus, drugs with capacity to reduce one or both variables of cardiac output and peripheral resistance could serve as a remedy for hypertension [2].

Hypertension is commoner amongst black population than Caucasian population [3]. Hypertension is responsible for considerable morbidity and mortality being one of the leading causes of deaths all over the world. In Nigeria, Hypertension is the leading non-communicable disease and is found in more than 11% of 15 years or older adults [4].

Treatment of hypertension involves pharmacotherapy as well as non-pharmacologic means including lifestyle modification. This article is intended to discuss anti-hypertensive drugs with particular reference to class mechanism of action, adverse effects and clinically important drug interactions.

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Pharmacology of Anti-hypertensive Drugs

Classes of antihypertensive:

Drugs for the treatment of hypertension have been conventionally grouped on the basis of mechanism and/or site of action and further differentiated using their chemical classes. Below are the main classes of drugs used in the treatment of hypertension.

- Thiazide and thiazide-like diuretics
- Centrally acting sympatholytic drugs
- Ganglion blockers
- Adrenergic neurone blocker
- Adrenergic receptor blockers
    - Beta adrenergic receptor blockers
    - Apha adrenergic receptor blockers
    - Mixed α and β adrenergic receptor blockers
- Calcium channel blockers
- Vasodilators
- Angiotensin Converting Enzyme inhibitors (ACEI)
- Angiotensin II Receptor Blockers (ARB)
- Renin inhibitors

Thiazide and Thiazide-like Diuretics

Thiazide and thiazide-like diuretics are the most commonly used antihypertensive all over the world [5, 6]. Diuretics alter Na^+ balance and have generally been used as mono-therapy for treatment of hypertension and have also served in enhancing antihypertensive effects of most other drugs particularly vasodilators. Thiazides interact with Na^+ - Cl^- symporter in the kidneys leading to increased salt and water excretion and therefore reduced cardiac output. However, the initial contraction of extracellular volume returns to normal even with the continued use of thiazides and it has therefore been hypothesized that thiazides maintain reduction of blood pressure by reducing tone of vascular smooth muscle thus leading to reduction of peripheral resistance [7]. The group includes: chlorothiazide, hydrochlorothiazide, chlorthiazide, bendroflumethiazide, hydroflumethiazide, chlothalidone, indapamide, metolazone.

Thiazides exhibit variable rate and extent of absorption though generally good. Oral bioavailability may be almost 100% as in the case of bendroflumethiazide to hydroflumethiazide and chlorthalidone with 50-65% to as low as less than 20% in the case of chlorothiazide [8]. Elimination half lives are also variable and may be as short as 1.5 hours for chlorothiazide and as long as about 2 days for chlorthalidone. Renal excretion occurs mostly but biliary excretion of about 10% has been documented in chlorthalidone and metolazone.

Clinically significant adverse effects of thiazide include erectile dysfunction and acute gout, Hypokalaemia, hyponatremia, hypochloraemia, hypomagnessemia, metabolic alkalosis and hypercalcaemia are common even when minimum effective doses of thiazides are used. When thiazides are used in combination with angiotensin converting enzyme inhibitors (ACEI) hypokalaemia may be mitigated but in most cases a potassium sparing diuretics or potassium supplement is co-administered with thiazides to prevent hypokalemia and its consequences. Hypercalcaemia results from inhibition of renal excretion of calcium and this may be explored in the treatment of osteoporosis or hypercalciuria. Other adverse effects of thiazides include: hyperglycaemia, paraesthesia, vertigo, headache, anorexia, nausea, diarrhoea, vomiting, cholecystitis, pancreatitis, photosensitivity, skin rash, blood dyscrasia [2]. Hyperglycaemia mirrors hypokalaemia and it has been observed that hyperglycaemia is reduced when potassium supplement is given as the same time [9]. Total cholesterol and LDL cholesterol as well as triglycerides are increased with chronic use of thiazide diuretics. Thiazide diuretics are to be avoided in individuals who are hypersensitive to sulphonamides. Thiazides may diminish the effects of anticoagulants and uricosuric agents and increase adverse effects of digitalis, Lithium and vitamin D. Their antihypertensive effect may be blunted by non-steroidal anti-inflammatory drugs (NSAIDs).

In most instances thiazide and thiazide-like diuretics have often been combined with potassium sparing diuretics particularly Amiloride and Triamterene to protect against loss of potassium. Potassium sparing diuretics block re-absorption of sodium at the late distal convoluted tubules as well

as the collecting ducts thus preventing the normal exchange of potassium and Hydrogen ions for sodium thus reducing potassium loss. They have variable absorption in the gastrointestinal, tract triamterene is relatively well absorbed whereas amiloride is poorly absorbed.

Centrally Acting Sympatholytic Drugs

The centrally acting sympatholytic drugs are α-methyldopa, guanabenz, guanfacine and clonidine, they stimulate pre-synaptic α-2 receptor in vasomotor centre on the brain stem to decrease sympathetic out-flow with reduction in peripheral vascular resistance as well as cardiac output with consequent lowering of blood pressure. Methyldopa requires conversion to α-methyl-norepinephrine and is therefore a pro-drug [10].

Methyldopa is useful in the treatment of mild to moderate hypertension as it lowers blood pressure by reducing peripheral vascular resistance with variable reduction in cardiac output. On chronic use methyldopa tends to cause fluid and salt retention which may blunt its antihypertensive action and diuretics may be needed to remedy it. Renal blood flow is maintained and renal function is unaltered with prolonged treatment. Patients with renal insufficiency are more sensitive to antihypertensive effect of methyldopa but it is unknown if the reason is reduced excretion or increased CNS uptake. Maximal antihypertensive effect occurs between 6-8 hours after oral or intravenous administration and effect may last for 24 hours. It has especial application in the management of hypertension in pregnancy as a result of its established safety profile. Concentration of methyldopa in the blood has minimal relevance to its antihypertensive effect since it is a pro-drug that is metabolised to the active drug in the brain. Methyldopa is absorbed in the gastrointestinal tract by an active amino acid transporter and uptake into the brain is also by active transport. The elimination half life is about 2 hours both the sulphate conjugate and other metabolites are excreted via the kidneys. Adverse effects include drowsiness, depression, dry mouth, Parkinsonian-like features, reduced libido, hyper-prolactinemia, haemolytic anaemia, fever, hepatitis [2]. Discontinuation of the drug is usually sufficient in case of hepatitis and the drug is better avoided in patients with hepatic disease. Other rare adverse effects are leukopenia, thrombocytopenia, myocarditis, pancreatitis and diarrhoea [2].

Adrenergic Neurone Blockers

Examples include Reserpine and Guanadrel. Others are Guanethidine, Debrisoquine, Bretylium, Bethanidine. Reserpine prevents storage of catecholamines in the vesicles and therefore exposed to metabolizing enzymes leading to depletion of sympathetic neurotransmitter which is sometimes referred to as pharmacological sympathectomy. Reserpine induced depletion of biogenic amines correlates with sympathetic dysfunction and anti-hypertensive effect. Both peripheral resistance and cardiac output are reduced thus ensuring the lowering of blood pressure.

Similar to Methyldopa the concentration of Reserpine found in the systemic circulation is a poor reflection of its antihypertensive effect. Efficacy of Reserpine is enhanced by diuretics, a combination of which enjoys widespread use in developing countries. Depression is a major adverse effect of Reserpine and the drug must be discontinued at the first sign of this. Other adverse effects of adrenergic neuron blocking agents include sedation, postural hypotension, parkinsonian signs, nightmares, nasal stuffiness, fluid retention and delayed ejaculation.

Ganglion Blockers

Of all the Ganglion blockers only Trimethaphan remain relevant in the clinical management of hypertension as others have become extinct particularly in view of availability of newer drugs with better efficacy and safety profile. Trimethaphan is a quarternary ammonium compound which inhibits transmission of nerve impulses in both sympathetic and parasympathetic ganglia. It is known to produce visual disturbances. It is administered intravenously to treat hypertension and to induce controlled hypotension during surgery. Major adverse effects include marked hypotension and syncope, constipation, paralytic ileus, urinary retention and cycloplegia.

Beta–Adrenergic Receptor Antagonists

These agents competitively antagonize effects of catecholamine at beta receptors. These drugs are widely used alone or in combination for the treatment of hypertension. Atenolol and metoprolol, bisoprolol, esmolol are β-1 selective agents and theoretically spare the β-2 receptors on the respiratory tract unlike propranolol, nadolol, timolol, pindolol which lack such selectivity. They are both negatively chronotropic and ionotropic reducing both rate and force of contraction of the heart. Also β receptor antagonists prevent renin

release from the juxtaglomerular cells and reduce circulating angiotensin II, potent vasoconstrictor.

Propanolol is a non selective β-adrenergic receptor blocker effective in treatment of mild to moderate hypertension. It does not produce postural hypotension. When given orally it is well absorbed and achieves peak plasma concentration in 1-3 hours but bioavailability is low due to high first pass effects. Propranolol is well tolerated though its adverse effects include cardiac failure, gastrointestinal disturbances, bronchoconstriction, lassitude, sleep disturbances including nightmares and insomnia and erythematous rash. In addition to treatment of hypertension β-blockers are clinically used in angina pectoris, cardiac tachyarhythmias and in secondary prevention of myocardial infarction.

Alpha-Adrenergic Antagonists

Peripheral vasoconstriction is mediated by α-1 receptors in the vascular wall an effect that is antagonized by α adrenergic receptor antagonist. There are selective α-1 receptor antagonists like prazosin, terazosin, doxazosin, tamsulosin while the nonselective alpha antagonists include phentolamine, phenoxybenzamine and tolazoline.

Prazosin antagonizes α-1 receptors thus producing vasodilatation and reduction in vascular resistance. It is able to reduce blood pressure in both supine as well as standing positions. It is often administered with diuretics which mitigate its tendency to cause fluid retention.

Prazosin is extensively metabolized in the liver. Oral bioavailability is about 50% and half life is about 3 hours. The drug is highly plasma protein bound and the duration of action is about 8 – 10 hours. Adverse effects include postural hypotension, headache, dizziness, salt and water retention, nasal stuffiness.

Mixed α- and β- Antagonists

An example is Labetalol which antagonizes both α-1 and β- adrenergic receptors thus resulting reduced peripheral resistance as well as reducing cardiac output. It is of particular application in the treatment of hypertension of phaeochromocytoma. Labetalol is well absorbed orally though extensive first pass effect results in bio-availability of 20-40%. The drug undergoes oxidation and glucuronidation in the liver and it is mainly excreted in urine as the glucuronide conjugate. Elimination half life is about 8 hours. It is also available for intravenous use in hypertensive emergencies. Adverse effects include tiredness, difficulty in micturition, postural hypotension, epigastric pain. Hepatic injury has been reported in few cases [11].

Carvedilol, Bucindolol, Celiprolol and Nebivolol are third generation β adrenergic receptor blockers with significant α-1 receptor antagonistic activity like Labetalol. All of these drugs possess capability to reduce blood pressure [12-17]

Vasodilators

Clinically relevant vasodilators include sodium nitropruside, hydralazine, diazoxide and minoxidil. These drugs through different molecular mechanisms produce vascular smooth muscle relaxation and vasodilation and consequently reduce peripheral resistance and blood pressure. For example sodium nitroprusside releases nitric oxide (NO) which in turn activates Guanylyl cyclase to produce vasodilation whereas minoxidil through its metabolite minoxidil N-O sulphate activates K+ channel which leads to hyperpolarisation and smooth muscle relaxation. In chronic management of hypertension orally administered minoxidil are given in combination with diuretics, hydralazine is also used in combination with a diuretic to avoid fluid retention, a common factor with all vasodilators. Sodium nitropruside is the drug of first choice in the treatment aortic dissection. Diazoxide is an alternative. Common adverse effects of vasodilators other than fluid retention are: Increased heart rate and myocardial contractility as well as increased oxygen demand. Pericardial effusion and hypertrichosis are other adverse effects specific for those using minoxidil whereas sodium nitroprusside may cause cyanide poisoning and lactic acidosis if infused in excessive dose.

Calcium Channel Blockers

Calcium channel blockers reduce peripheral resistance by causing relaxation of vascular smooth and vasodilation [18]. Examples are: Diltiazem, Verapamil, Nimodipine, Isradipine, Nifedipine, Felodipine, Amlodipine, Bepridil, Nicardipine. Calcium channel blockers are broadly classified into: first generation which include: Diltiazem, Verapamil, Nifedipine, and second generation which include: Amlodipine, Felodipine, Nimodipine, Lacidipine. Chemical classification of Calcium Channel Blockers is as follows:

Dihydropyridines e.g. Nifedipine, Nicardipine, Amlodipine, Felodipine

Benzothiazepines e.g. Diltiazem

Phenylalkylamines e.g. Verapamil

Diarylaminopropylamine e.g. Bepridil

They are as effective in the treatment of mild to moderate hypertension but preferably in combination with diuretics [5].

All calcium antagonists are well absorbed in the gastrointestinal tract when given orally. They are extensively metabolized. Verapamil and diltiazem are available for both oral and parenteral administration. They have limited oral bioavailability due to first pass effect and are highly plasma protein bound. Amlodipine has a long elimination half life so it is given once a day whereas Nifedipine, verapamil, diltiazem have shorter elimination half life are given more frequently except in slow release formulation which permits once daily dosing.

Adverse effects include: peripheral oedema, palpitation, dizziness, transient hypotension and flushing. Others cough, wheezing, pulmonary edema, nausea, abdominal pain, constipation, rash, somnolence, worsened myocardial ischaemia has been reported in few studies.

Angiotensin Converting Enzyme Inhibitors (ACEI)

Renin converts circulating angiotensinogen to angiotensin I which in turn is converted to a potent vasoconstrictor agent angiotesin II by an enzyme known as angiotensin converting enzyme (ACE). The ACE inhibitors inhibit the conversion of agiotensin I to angiotensin II thus reducing peripheral resistance and blood pressure. Examples of ACE inhibitors are Enalapril, Quinapril, Ramipril, Benazepril, Lisinopril, Fentiapril, Pivalopril. There is increasing evidence that angiotensin converting enzyme inhibitors are better than calcium channel blocker in hypertensives who also have diabetes [19-21].

ACE-Inhibitors are classified into three chemical classes or as pro-drug depending on whether the drug is immediately active or requires activation after administration. The three chemical classes are: dicarboxyl-containing group, for example, Enalapril, Quinapril, Lisinopril; sulphhydryl-containing group, for example Captopril, Pivalopril and Fentiapril; the phosphate-containing group has fosinopril as an example. Enalapril, Trandolapril, Fosinopril, Qiunapril and Ramipril are examples of pro-drugs whereas Captopril, Lisinopril, Pivalopril are immediately active on administration. ACE inhibitors are generally cleared by the kidneys thus the need for dose adjustment in renal impairment. Only Fosinopril and Spirapril are exceptions as they enjoy significant elimination by the liver. Antacids reduce absorption of ACE inhibitors and non-steroidal anti-inflammatory drugs such as aspirin antagonize their antihypertensive effects.

Captopril is rapidly absorbed following oral administration and its oral bioavailability is about 70% when taken in empty stomach. This bioavailability reduces to about 30-40% if taken with food. Captopril is distributed to most tissues in the body with notable exception of central nervous system. The half life of captopril is about 3 hours.

Adverse effects include first dose hypotension which may be observed just like in the case of prazosin and small dose is usually advised while introducing the drug. Other adverse effects include hyperkalaemia, cough, angioedema, glycosuria, neutropenia, dysgeusia, macula-papular rash. Angioedema is a potentially serious adverse effect and has been ascribed to accumulation of bradykinin and blacks are at greater risk [22]. Hyperkalemia may be worsened when co-administered with potassium-sparing diuretics like Amiloride. Alteration in sense of taste, allergic skin rashes, drug fever was observed in 10% of patients with high dose of captopril. ACE-inhibitors are contraindicated pregnancy due to fetal malformation particularly pulmonary hypoplasia. Fetal growth retardation, neonatal anuria and neonatal death may also occur.

Angiotensin II Receptor Antagonist

Drugs that competitively antagonize angiotensin II at the receptor site block the vaso-constrictive effect of angiotensin II thus reducing peripheral resistance and blood pressure. Candesartan, Eprosartan, Losartan, Valsartan, Temilsartan, Irbesartan are examples currently in use in the management of chronic hypertension.

Losartan has comparable therapeutic uses with Captopril [23, 24]. Like most angiotensin receptor blockers losartan has low oral bioavailability. It achieves peak plasma concentration within 3 hours of oral administration and has half life of about 3 hours. Losartan is about 90% plasma protein bound. Phase I metabolism involves CYP 2C9 and CYP3A4 and subsequent glucuronide conjugation in the liver. Excretion involves the kidneys as well as the liver.

Losartan and other angiotensin receptor blockers are well tolerated been known to cause angioedema in much fewer cases than ACEI [8]. Losartan may also cause hypotension and fetopathy.

It can also cause hyperkalaemia when used with potassium sparing diuretics such amiloride.

Rennin Inhibitors

Rennin inhibitors act upstream in the biosynthesis of Angiotensin II by inhibiting conversion of angiotensinogen to angiotensin I [25]. Examples include: Remikiren, Enalkiren, Aliskiren.

Remikiren is rapidly and almost completely absorbed but oral bioavailability is poor due to hepatic first pass effect. Remikiren is metabolized in the liver and excreted in the urine as well as bile with a short half life of less than 2 hours. Antihypertensive effect is enhanced by co-administration with thiazide such as hydrochlorothiazide [26, 27]. Remikiren like other inihibitors of Renin-Angiotensin-Aldosterone pathway must be used cautiously with potassium sparing diuretics in order to avoid hyperkalaemia. Other reported untoward effects are include hypersensitivity, gastrointestinal disturbances, nausea and vomiting.

CONCLUSION

In conclusion it is appropriate to note that thiazides diuretics play central role in the management of hypertension and this cuts across ethnic and racial divide [28, 29]. Thiazides are used alone or in combination with other antihypertensive drugs and in all circumstances the minimum effective dose should be preferred. Antihypertensive drugs, both the newer renin inhibitors and the relatively well established ACE inhibitors and angiotensin receptor blockers remain very useful in the management of both uncomplicated and complicated forms of hypertension. The possibility of adverse drug interaction should always be considered especially whenever medication seems to be failing the patient.

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