REVIEW - New Drugs in Hypertension

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Hypertension has become a major problem of public health in this country affecting a large population. Although hypertension has been recognised as a disease over a century *(Mahomed 1874),* the major advance in therapy have occured in the past two and half decades Statistics acquired from life insurance data clearly indicated that higher the systolic or diastolic pressure, the greater the mortality from cardiovascular diseases. It now appears that hypertension underlies a whole variety of cardiovascular diseases including sudden death, angina pectoris, acute myocardial infarction (with or without complication), aortic aneurysm, atherosclerotic obstruction of aorta, strokes and Renal failure *(Roberts 1975).*

It is now clear that antihypertensive therapy reduces incidences of hypertensive complications and improve survival. The value of therapy is more apparent in persons with diastolic pressures greater than 104mm or mercury and in persons between 90–104mm of mercury it is also beneficial. The risk of cardiovascular diseases increase when there is persistent increase of the arbitrary norm of 140/90mm of mercury, irrespective of age.

All the data are consistent with the concept that vascular-vascular damage is a consequence of hypertension and that at least partial reversal is accomplished by control of blood pressure. There is no reason to believe that women will be qualitatively different from men. Black women have as many complications as do white or black men. Only white women seems to have less risk of hign blood pressure. Principal advance in antihypertensive therapy during the last twelve years has been in the individualisation of therapy.

The new drugs that are being develooped are to large extent *Tailor made* based on the pathogenesis of the disease.

A brief review of the physiology and pathophysiology of blood pressure regulation would be helpful in understanding the pharmacology of the antihypertensive drugs.

Physiological control of Arterial pressure

Normally the arterial pressure is under tight control so that constancy is assumed even during stress. Since the arterial pressure is equal to the product of cardiac output and peripheral resistance, the reflex mechanisms responsible for control of blood pressure operate by altering one or both the variables.

In hypertensives, where the arterial pressure is controlled at *too high a level,* the drug therapy is aimed at modifying control mechanisms to allow pressure to reduce to normal. The *control of peripheral resistance* occurs at the arterioles whereas the control of cardiac output is on *interplay of cardiac function* and the *extracardiac determinants of venous return* i.e., *venous capacitance and blood volume.* Thus there are four anatomic sites where arterial pressure can be influenced.

All antihypertensives must work at these sites either directly (vasodilators, propranolol, angiotensin antagonists) or directly through the reflex control mechanisms (sympatholytics).

The principal determinants of blood pressure are the Autonomic Nervous system and the Renin/Angio/aldosterone system. In the face of wide range of stresses, these systems can maintain blood pressure within normal range.

Autonomic nervous system

Stimulation of sympathetic nervous system results in acceleration of heart rate, constriction of arterial resistance vessels and venous capacitance vessels and release of renin. Such stimulation occurs in a wide variety of circumstances in normal man; it can for example be brought about by startle, by pain, by anxiety, by mental arithmetic, by upright posture and by physical exertion. The acceleration in heart rate serves to increase cardiac output. Constriction of arterioles cause increased resistance. Constriction of venous capacitance vessels causes increased return of the blood to the right side of the heart which inturn contributes to the increased cardiac output. Since the blood pressure is directly proportional to the cardiac output and peripheral resistance, all these effects of sympathetic stimulation serve to elevate the parameter. It is clear that not all the stimuli mentioned above affect the pulse and the blood pressure in exactly the same way. This is because a number of cardiovascular reflexes may be brought into play by sympathetic activation. Since the activity of almost all the sympathetic nervous system depends on the events at the neuronal level pharmacological agents which interefere with any steps in the sequence may alter the sympathetic activity and hence blood pressure.

Step I. Tyrosine → DOPA (Dihydroxy phenyl alanine)

(Tyrosin hydroxylase)
Iron
petridine cofactor)

(Rate limiting step. Inhibited by Alpha methyl para tyrosine)

Step II. Dopa → Dopamine

(dopa decarboxylase
Pyridoxal phosphate as cofactor)

(Inhibited by Alpha methyl dopa)

Step III. Dopamine → Norepinephrine

(Dopamine beta hydroxylase,
Cu ** and Oxygen)

(Inhibited by disulfiram)

Step IV. (occurs in the adrenal medulla)
Norepinephrine → Epinephrine

(N-methyl transferase)

Renin/angiotensin/aldosterone system is the second major system for blood pressure regulation

Renin, a proteolytic enzyme produced in the renal cortex by specialised cells of the afferent arterioles of the glomerulus act on leucyl-leucyl bond in a plasma alpha 2 globulin to release angiotensin I, a decapetide that is then rapidly hydrolysed to octapeptide angiotenisn II by a coverting enzyme

peptidyl dipetide hydrolases. In the adrenal cortex angiotensin II is coverted to angiotensin III (Heptapetide) by aspartyl aminopeptidases, and this angiotensin III is a potent stimulator of aldosterone release (Meyer 1976).

Renin release occurs by the activation of various receptors like baroceptors, chemoreceptors and adrenergic receptors and by ? prostaglandins.

(a) stretch or baroceptors of renal afferent arterioles sensitive to intravascular pressure and volume changes (Blein et al 1971).

(b) Changes in intraluminal concentration of sodium in the macula densa of the juxtaglomerulus apparatus (chemoreceptors) (Operil et al 1974).

(c) Neurogenic–involving dense sympathetic innervation of Juxta glomerulan (JG) cells in afft. arterioles–renin release is increased by activation of Beta receptors (blocked by beta blockers and is independent of vascular effects (Weinberger et al 1975) and

(d) Prostaglandins (PGs) especially PGI_2 increase renin secretion and Indomethacin, a Prostaglandin synthetase inhibitor reduces plasma renin (Craig C.R. et al, Modern Pharmacology, Little Brown, Pub. 1982). Captopril induced fall of blood pressure increases PGE_2 exretion in urine and indomethacin reduced the urinary PGE_2 and the hypotensive effect of captopril indicating that captopril induced its hypotensive effect is through production of Prostaglandins.

Renin release is controlled by 3 negative feedback loops.

(a) *Short loop* Direct suppression of renin by angiotensin,

(b) *Medium loop* Feedback resulting from vasoconstriction produced by angiotensin II which increases renal perfusion pressure and

(d) *Long loop* acts in concert with medium loop through release of aldosterone, with subsequent sodium and water retention resulting in increased effective blood volume and renal perfusion.

Pathophysiology of hypertension

A relatively small number of patients develop hypertension as a manifestation of treatable underlying causes. A vast majority of patients with hypertension have no discernible underlying causative factor. These patients are said to have essential hypertension (term introduced by Ludwig Traube 1856) on the belief that increase in blood pressure in these individuals was *essential* to maintain adequate perfusion of vital organs). Hypertension can be classifed on the basis of the degree of disease–Malignant or non malignant.

The essential hypertensive patients are themselves now known to be heterogenous on the basis of several hemodymanic and humoral characteristics. Perhaps the most useful is categorisation on the basis of renin status and this categorisation has been alleged to have *etiologic*, *prognostic* and *therapeutic* significance.

CATEGORISATION OF ESSENTIAL HYPERTENSION BY RENIN STATUS

CHARACTERISTIC	2LREH	[1]NREH/ HREH[3]
Plasma renin activity	low	higher
Age	older	younger
Frequent in caucasians	20 per cent	55 per cent
Frequent in Afro-Americans	40 per cent	
BP reduction with aminoglutethimide	***	
BP reduction with spironolactone	***	*
BP response to saralasin	may be pressor.	may be depressor
Diurectic response	***	*
Propranolol response	*	***
Phenoxybenzamine response	*	***

1. NREH – Normal renin essential hypertension
2. LREH – Low renin essential hypertension
3. HREH – High renin essential hypertension

The LREH patients differ from normal and HREH in that they are somewhat older and one can postulate that LREH is in fact end stage process, presumably as a result of some long-term effect of hypertension on the kidneys (Brown et al 1974).

Since plasma renin activity (PRA) is low in primary hyperaldosteronism, it has been suggested that LREH patients have an excess of an unidentified "cryptic" mineralocorticoids. Aminoglutethimide (an alpha methyl glutarimide inhibits the conversion of cholesterol to 20 alpha hydroxy cholesterol viz., the first reaction steroidogenesis from cholesterol which interrupts production of both cortisol and aldosterone) reduces blood pressure in low renin but not in normal/high renin patients. Spironolactone, antagonist of mineralocortcoid activity, is a more effective antihypertensive in patients with low renin than with high or normal renin hypertensives. Other diuretics are also effective in low renin patients.

Reduced plasma renin activity by indomethacin in certain clinical situations suggest that Prostaglandins may play an important role in blood pressure homeostasis.

It is also possible that low PRA in LREH patients could have a neurologic basis. It is known that untreated parkinson's disease, renin levels are subnormal (Michelakis & Robertson 1970). Parkinsonian patients, many of whom reduced blood pressure, might be expected to have had a compensatory elevation in Plasma renin activity. Their failure to do so and the limited response of their plasma renin activity levels to postural stimulation suggest a neurologic basis for their low PRA.

Angiotensin antagonist saralasin was expected to identify renin dependents from renin nondependents varieties. It reduces blood pressure in HREH/NREH patients and also in LREH patients provided the patients are sodium depleted. Since saralasine has weak agonist properties, some patients with LREH will actually manifest and increase in blood pressure during infusion.

LREH is characterised by its volume dependent nature and initial therapy is well accomplished by diuretics. (Sennet, 1974).

Role of sympathetic N system

Pheochromocytoma had long been recognised as a catecholamine dependent cause of hypertension. Increased sympathetic activity has been observed in 80 per cent of borderline cases of hypertension. Plasma noradrenaline levels are increased in many cases of essential hypertension. Many patients with early hypertension have features suggesting a greater increase in beta adrenergic activity (cardiac stimulation and renin release). Urinary cyclic adenosine monophosphate excretion is normal in supine posture and abnormal in upright posture (Hamet et al 1973). The five fold increase in plasma cyc AMP induced in normal subjects by insulin hypoglycemia is decreased in LREH and increased in HREH (Lowder, Hamet and Liddle 1976). An imbalance in vascu-

lar tissue levels of cyclic guanosyl monophosphate and cyc. GMP has been proposed as a mechanism of hypertension (Amer 1975).

Patients with highest plasma PRA do appear to respond most readily to propranolol (Hollifield et al 1976) and patients with low renin activities tend to respond to higher doses of propranolol. Another line of evidence that HREH may be a hyper-adrenergic state is the relatively greater response of Blood Pressure to Phenoxybenzamine and phentolaminein this sub-group than in low renin hypertensives (Hollified et al 1977).

RENOVASCULAR HYPERTENSION:

5 per cent of patients with hypertensive diseases have renovascular hypertension. Recent experiments utilising the Angiotensin blocker, saralasin, indicate that the early renovascular hypertension probably is largely due to circulating angiotensin II. However, Chronic renovascular hypertension is additjvely related to other factors, such as an expanded extracellular fluid volume. In patients with renovascular hypertension the acute effects of blockade of angiotensin II do not result in decrease of blood presssure if the subject is not salt depleted. The hypertension resulting from renal arterial stenosis is a consequence of both increased cardiac output and peripheral vasc. resistance as might be expected from excessive angiotensin II generation (Tarazi et al 1973). However, plasma renin activity is not consistently elevated during chronic renovascular hypertension and there are other diseases (e.g. cirrhosis) where high PRA, angiotensin II and aldosterone con . in plasma are not associated with hypertension. Thus our understanding of the pathogenesis of the syndrome of hypertension is incomplete Peart 1975).

DRUGS IN HYPERTENSION

Sympatholytic: Drugs altering central sympathetic outflow:

Alpha methyl DOPA (Aldomet)

The search for mechanism of action progressed much slowly than its clinical application. The data now available indicate that the major antihypertensive effect is not due to inhibition of decarboxylase. Anthypertensive action of methyl dopa is on the central nervous system as evidence by the antagonism by decarboxylase inhibitors penetrating central nervous system and the action is due to the metabolic product of methyl dopa viz., alpha methyl nor epinephrine. Alpha methyl nor epinephrine potentially stimulates alpha adrenergic receptors viz., preferentially presynaptic alpha 2 receptor that inhibits sympathetic out flow from central nervous system. Central site of action is confirmed by the fact that hypotensive effect of I.V or centrally administered methyl dopa can be blocked by central administration of alpha adrenergic blocker (Talazoline).

Its peripheral action also do contribute to antihypertensive effect viz, reduction in renal vascular resistance, direct peripheral vasodilatation and reduction in plasma renin activity (insignificant). Reduction of blood pressure in 4-6 hrs and the duration of upto 24hrs, cardic output and renal blood flow is maintained. On prolonged administration reduction in Cardiac output and bradycardia persisted. Functional competence of symp. N. system is maintained, unaccompanied by orthostatic hypotension and exercise induced hypertension. The drug does not produce miosis or ptosis etc.

Other effects include sedation, lighter sleep, increased rapid eye movement (REM) sleep and can prevent rise in body temperature by bacterial and leucocyte pyrogens. Large doses cause hypothermia (Mirt and Duin 1972). Increased secretion of prolactin has been reported.

Absorption appears to be 25 per cent and renal excretion amounts to 2/3 clearance of the drug. Although some accumulation of methyl dopa occurs in patients with impaired renal or hepatic disease, dosage regimen need not be substantially adjusted.

Interference: Interference with test for catecholamines. False positive test for pheochromocytoma is possible.

Toxicity: Occasional postural hypotension, edema, hepatic dysfunction, positive direct coomb's test, hemolytic anemia, and very rarely rebound hypertension.

Clonidine

Centrally acting antihypertensive agent whose effect can be achieved by microgram quantities. It,

(a) inhibits sympathetic outflow from CNS and
(b) increases the depressor effects of baroceptor stimulalation, while the acute peripheral effects of the drug are vasoconstrictor. The antihypertensive action of clonidine is a result of the direct action of the unchanged drug unlike alpha methyl dopa.

The site of action is medullary alpha adrenergic receptors, the stimulation of which leads to inhibition of peripheral sympathetic activity. It is more potent as alpha 2 agonist. (By its potent alpha 2 agonistic activity it inhibits release of non adrenaline. The hypotensive effect of clonidine can be blocked by alpha adrenergic blockers and tricyclics. When given I.V. peripherally mediated alpha vascoconstrictor action predominates actually leading to incease in Blood Pressure. Reduction of sympathetic activity leads to fall in Blood Pressure, heart rate and urinary catecholamine levels. Plasma renin activity is diminished and cardiac output is lowered through a slight reduction peripheral vascular resistance. Reduction in renal vascular resistance maintains adequate renal blood flow (RBF). Exercise induced changes in Blood Pressure, Cardiac Output Heart rate, Stroke Volume, and peripheral resistance are qualitatively normal. The hypotension produced after acute administration of clonidine is associated with a clear reduction of the discharge rate of preganglionic adrenergic nerves, as well as bradycardia. The latter is due to both a reduction in sympathetic and an increase in vagal tone. The increase in vagal discharge involves an increase sensitivity of baroceptor reflexes. Other central actions are similar to Chlorpromazine which include marked sedation, reduce body temperature and antipsychotic properties and inhibition of centrally mediated salivation (accounts for dry mouth).

Intra venous clonidine produces initial rise which is not seen with oral administration. Pulmonary arterial pressure and cardiopulmorary blood volume decreases, which indicates relaxation of capacitance vessels. Clonidine causes and acute increase in cerebro vascular resistance with a decrease in cerebral blood flow (probably used in migraine) in man. Postural hypotension is less. Even after 1 year treatment clonidine alone exhibits constant effects viz., increase in cardiac index, heart rate and BP during exercise, less degree of postural hypotension, and unaffected reflex control of capacitance vessels. Clonidine cause a decrease in plasma renin by its central action. But the possibility of direct action on the kidney cannot be ruled out.

Pharmacokinetics: Mean plasma half life is 12 hours. (range 6-24 hours) and the duration 4-24 hours peak plasma levels are

attained in 2-4 hours and the Bioavailability is 75 per cent. Tolerance is rare if concomitant diuretic therapy is given.

Dose: (100mcg–200mcg tabs.) 200 mcg to 2mg per day. Side effects: dry mouth and sedation. Sodium and water retention (diuretic therapy is advocated).

Withdrawal rebound hypertension (in 8-12 hours) (reinstitution of clonidine or administration of alpha & beta blockers) (When compared with equipotent doses of methyldopa, clonidine produces more side effects) During elective surgery other drugs should be substituted well in advance.

Status ability of clonidine to lower pressure without paralysis of peripheral autonomic homeostasis control mechanism is highly desirable but side effects are such that treatment must be individualised with constant medical surveillance and this drug cannot be used in hypertensive emergencies, An added use of this drug is in the treatment of migraine (Shegaz et al 1972).

Drugs blocking autonomic ganglion like trimetaphan, pentolinium are used rarely only during hypertensive emergencies. But their use is also not without danger since sudden reduction of blood pressure has led to irreversible blindness in a few cases.

Adrenergic neurone blockers Guanethidine (insmelin). Because of its basic guanidine group entry into the CNS is very much restricted. Prolonged administration depletes stores of noradnenalins. Single dose administration interferes with excitation deploraisation mechanism. Guanethidine must enter adrenergic neurone for it to act. Drugs like tricyclics phenothiazine prevents entry into nerve endings. Amphetamine reverses the guanethidine effect by

(a) preventing its uptake and

(b) by releasing guanethidine. Chronic therapy with guanethidine reduces blood pressure in all patients. Blocks sympathetic reflexes, reduces venous tone allowing increased venous capacitance. Heart rate decreases and cardiac output decreases. Reduction of GFR and RBF with increase in plasma PRA activity. (patients with LREH may be misclassified if they are tested while taking guanethidine).

Once sympathetic reflexes are inhibited, blood pressure becomes a function of blood volume and posture. The volume expansion that occurs with chronic guanethidine therapy may result in tolerance to its antihypertensive effect. Thus in patients on chronic therapy with guanethidine, a failure in control could be due to inadequate drug reaching its site for action in the neuronal terminal or to tolerance due to volume expansion (former might result from poor compliance or suboptimal dosage while the latter might be due to inadequate diuretic therapy).

When inadequate clinical response occurs physicians may have difficulty in deciding whether guanethidine therapy is to be increased or more diuresis effected.

A useful test is the venous reflex. If venous reflex is attenuated, the diuretics are increased and failure of venous reflex attenuation necessitates increase of guanethidine dose. The long half life of guanethidine late phase pool approaches the half life of digitoxin, hence the loading regimen with guanethidine therapy. The normal leading dose is 75mg orally. Subsequently 30 per cent of all the previous dose administered after a 6 hour interval.

Side effects: Postural hypotension, exercise hypotension, diarrhoea, decreased libido, nasal stuffiness.

Status: A potent antihypertensive with relatively no CNS side effects mainly for chronic therapy in severe form of hypertension.

Bethanidine

Derivative of guanethidine claimed to have less side effect viz., especially on libido and the incidence of diarrhoea is said to be less. It has a half life of 7–11 hours and must be given several times a day.

Rawolfia alkaloids

They have both central and peripheral actions. They exhibit modest antihypertensive action. Reserpine which is the principal alkaloid of rauwolfia serpintina, produces bradycardia, reduction of peripheral resistance and reduction in cardiac output. Venous capacitance is increased and peripheral pooling of blood occurs. It causes activation of parasympathetic system which is seen by increase weight, increased gastric secretion, depression and suicidal tendencies often seen with this drug which the dose is increased more than 0.2mg tds. The drug still finds its usefulness in the treatment of mild hypertensives. Major machanism of action to this drug is by causing slow depletion of catecholamine stores.

Monoamine Oxidase Inhibitors (MAO-I)

The nonhydrazine derivatives of MAO inhibitors like pargyline are used in certain forms of hypertension. They act at the level of the adrenergic neurone and they favour the formation of false neurotranismitter viz., octopamine which is less potent than nor-epinephrine and which dilutes NE. These drugs cause serious drug interactions with drug and foods containing indirectly acting sympathomimetic amines like tyramine (in cheese, wines etc.). These indirectly acting sympathomimetic amines in the presence of MAO inhibitors release increased amounts of NE stored in greatly accumulated quantities and precipate hypertensive crisis. It appears that MAO exists in at least in two forms with dissimilar substrate preferences and differential sensitivity to selective inhibitors (clorgyline vs MAO-A and deprenyl vs MAO-B). Recently clorgyline, closely related structurally to pargyline has been introduced in the treatment of hypertension. A chemically similar compound, deprenyle, was found to be selectively effective against MAO-B. MAO-A preferentially deaminates physiological substrates such as 5HT, NE,E, metanephrine, and normetanephrine. It also deaminates other beta hydroxylated phenylethylamines such as octapamine. Preferential substrates for MAO-B include benzylamine, tryptamine, 5-0-methyltryptamine and phenylethylamine. Tyramine, dopamine and 3-0-methyltyramine are metabolised by both isoenzymes to similar degrees. (Houslay and Tipton 1976). Of particular interest is the observation that human platelets and striatum contain MAO-B. Thus administration of deprenyl 10mg/day inhibits MAO-B in brain greater than 90 per cent and appears to have beneficial effect in patients with Parkinson's disease. This agent is purported not to produce the beer, cheese and win tupe of reactions, since MAO-A which is present in liver and GIT, is not inhibited. Tyramine which is absorbed from GIT can still be effectively metabolised in individuals treated with deprenyl.

Clorgyline, still under investigation, can be claimed to induce less number of reactions. The status of MAO-I is still controversial.

ADRENERGIC RECEPTOR BLOCKERS

Adrenergic alpha receptor stimulation leads to vaso-constriction of arterioles and venules whereas beta stimulation leads to dialtation of arterioles, increased rate and force of cardiac contraction, broncholilation, renin release and promotion of

glycogenolysis, lipolysis, etc. Recent studies have shown the presence of presynaptic alpha 2 receptors, stimulation of which leads to inihibition of NE release. Postsynatic receptors can be specifically blocked by drugs and the sympathetic system can be influenced by one way or the other.

Alpha receptor blockers

Phentolamine, indoramine and phenoxybenzamine are employed in circumstances where hypertension is due to overactivity of the adrenergic system or the overproduction of adrenergic neurotransmitting substances as in clonidine withdrawal, guanethidine induced acute hypertension, pheochromocytomas and tetanus.

Phentolamine has been used in hypertensive crisis to determine whether the hypertension is due to catecholamine excess.

Prazosin, a new drug, is also an alpha adrenergic blocking agent. In addition, it has direct vasodilator properties. The interesting feature with prazosin is that it blocks selectively postsynaptic alpha 1 receptors without affecting presynaptic alpha 2 receptors thereby not affecting the negative feedback effect of NE on its own release. This is discussed in detail under vasodilators.

Beta blockers

Prichard and Boaks proposed seperation of beta andrenergic blockers into 3 divisions.

1. Drugs without beta[1] selectively.
2. Cardioselective drugs.
3. Drugs with alpha adrenoreceptor blocking activity.

1. *Drugs without beta*1 selectivity include pronethalol, propranolol, alprenolol, oxoprenolol, pindolol, penbutalol, bunitrolol, bunolol, nadolol, timolol.
2. *Cardioselective drugs* include atenolol, acebutolol, metoprolol, practolol, tolamolol.
3. *With alpha adrenoreceptor blocking activity* eig. Labetolol.

Propranolol was found to be the drug of choice in many hypertensives. Renin release by kidney is partially under beta adrenergic control and propranolol therapy reduces PRA at relatively doses and particularly attenuates the elevation in renin activity that occurs with standing or during exercises (McAllister 1972). Propranolol is most successful in reducing BP in patients with NREH and HREH in doses of 80-320mg/day. Even in patients whith low renin activity at doses of 1000-2000mg it exerts anti-hypertensive activity.

Suggested mechanism of actions may be

(a) reduction in PRA (not the only mechanism)
(b) reduction in cardiac output.
(c) peripheral adrenergic neurone blockade
(d) interference with baroceptor function
(e) effect of cardiovascular control system of the medulla.

The observation that intravenous propranolol reduces PRA and cardiac output without reducing BP underscores the fact that mechanisms other than simply renin reduction are involved (Julius and Esler 1975). Propranollol has wide dosage range 10-4000mg/day with greater plasma binding and with a half life of 4 to 5 hours on chronic medication. Plasma levels of 50mg/ml reduces plasma renin activity while 100mg/ml completes beta blockade. Propranolol is ideally combined with a diuretic and/or hydrallazine (additive).

Side effects: It may cause heart failure, asthma, hypoglycemia, CNS disturbances, and in certain persons on prolonged medication it leads to interstitional pulmonary fibroisis and retroperitoneal fibrosis. Other effects like renal impairment, Raynauds phenomenon, peripheral arterial insufficiency, myasthenia gravis and CNS disturbances like lack of concentration, lethargy etc., are caused by propranolol.

The development of cardioselective beta blockers like atenolol, metoprolol etc. may provide physicians with drug capable of reducing blood pressure without danger of pulmonary complications. However, because the mechanism of anti-hypertensive action is not exactly known each beta blocker must be judged individually in clinical studies to determine its efficacy.

Labetolol

It is both an alpha and beta blocker with 3 times more blocking effect on beta than alpha blockade (3:1 ratio). A double blind trial has confirmed that dosages as low as 400mg/day significantly reduced blood pressure. Major side effect is postural hypotension in small percentage of patients. It is found to be useful in essential hypertension, pheochromacytoma and in clonidine withdrawal hypertension.

VASODILATORS

Hydrallazine

Lowers peripheral vascular resistance and reduces blood pressure with an increase in cardiac output by baroceptor reflex mechanism, (although it is a MAO-I, contribution by this mechanism is insignificant). It directly dilates arterial by relaxing the arterial smooth muscle. The baroceptor induced increase in stroke volume and hear rate together with increase in myocardial oxygen consumption requires a drug like beta blocker to reduce the heart rate. Renin stimulation effect of hydrallazine is due to reflex sympathetic discharge.

Hypotensive effect of hydrallazine is greatly enhanced by addition of a diuretic and/or propranolol. The triple combination of diuretic, propranolol and hydraallazine constitute a unique heamodynamic approach in the treatment of hypertension, since three of the chief determinants of blood pressure are affected; cardiac output (propranolol-to attenuate the reflex cardiac stimulation and hyperreninemia), plasma volume (diuretic), and peripheral vascular resistance (hydrallazine).

Its derivative dihydrallazine is claimed to have less side effects for which there is no confirmed report. Side effects like reversible lupus erythematosus has been reported which is dose dependent (seen with doses larger than 200mg/day) and not all patients are affected. Hydrallazine can cause sodium and watter retention. Preferential dilatation of arterioles minimises postural hypotension. Hydrallazine (apresoline) 10-20-mg qid upto 100-150mg/day. In a recent study with primary pulmonary hypertension this drug is well tolerated.

Minoxidil (Loniten) has a vasodilator effective in patients whose blood pressure could not be controlled by other oral regimen. Mechanism of action is similar to that hydrallazine but more potent and having a plasma H.L. of 4 hrs. It is also preferentially a arteriolar dilator without effect on veins or capacitance vessles. Minoxidil reduces peripheral vascular resistance with associated reflex cardiac stimulation and sodium retention. Pulmonary hypertension has been reported in some minoxidil treated patients with high output, right sided failure and gross overload (not yet confirmed as drug induced pul-

monary hypertension). Following 1-2 weeks oral therapy, a small increase in RBF has been found. Marked sodium retention has been observed in patients who had no renal impairment. Sodium retnetion can be controlled by diuretics. Potent serious adverse effect is pericardial effusion in renal failure patients. Hypertrichosis is very common side effect. This drug is useful in patients with advanced renal disease complicated by hypertension.

Loniten: 2.5 and 10mg tab. 5mg/day increased upto 40mg; maximum recommended dose is 100mg/day.

Diazoxide Nondiuretic thiazide with powerful direct effect on vascular smooth muscles and nonvascular smooth muscles (uterus–can prolong labour). It promotes retention of sodium and water. Relaxing effect on vascular smooth muscle may be brought competitive antagonism of Ca**. Responses to vascular smooth muscles by angiotensin and NE are inhibited. The drug has high protein binding ability to an extent of 90 per cent and hence administered in the form of I.V. bolus. Since there is now evidence that tissue binding of diazoxide is actually reversible and that the degree of antihypertensive effect observed is proportional to the achieved plasma diazoxide level, the rapid bolus regimen appears to be less critical to blood pressure control than formerly assumed (Power et al 1971), (Boerth et al 1977). The H.L. of the drug is approximately 24 hours. Duration is 2-24 hours. Dosage: 75mg IV as bolus and then 150mg at 5 minute intervals until control is achieved. Reduction in glomerular filtration and renal blood flow is observed with increase in plasma renin activity. Cardiac output is increased with increased oxygen consumption (not to be used in patients with ishemic heart diseases). Diazoxide preferentially relaxes the arterioles without any effect on venous capacitance vessles. Diazoxide like thiazide diuretics can induce hyperglycemia and hyperuricemia in susceptible individuals. Diazoxide (hyperstat) Available as 20ml ampuls of 300mg. 50mg and 100mg caps.

PRAZOSIN

Although it is an alpha adrenergic blocking agent, it is discussed under vasodilators since this agent has many additional pharmacological properties. It specifically blocks post-synaptic alpha*1 receptors without effecting presynaptic alpha*
alpha^1 receptors without effecting presynaptic alpha^2 receptors. It is both *arteriolar* and *venular dilator.* It also inhibits phosphodiesterase enzyme thereby prolonging the cyc AMP half life. Prazosin has relatively little effect on presynaptic alpha^2 receptors allowing NE to exert its own feed back inhibition of release. Prazosin reduces peripheral vascular resistance without secondary reflex tachycardia or increase in renin activity as with hydrallazine, diazoxide and minoxidil.

As would be predicted from its action on capacitance vessels, it has greater effect when the patient is upright. Fluid retention occurs on chronic therapy. 99 per cent of the drug is metabolised and the half life is of 3 hours.

Side effect is mild as the drug is well tolerated. 1/3 patients may develop antinuclear factors (Marshall et al 1979). Postural hypotension and syncope occurs on first dose and in salt depleted persons. This is called the *first dose phenomenon* is probably due to inadequate return to the right side of the heart. Therefore the first dose should not be more than 1mg and preferably administered at bed time. Prazosin (Minipress) is available in 1,2 or 3 mg tabs.

Data are available that prazosin is often more effective with a diuretic and/or a beta blocker. This drug is being tried for the therapy of severe chronic congestive failure to reduce afterload.

Status. It is very promising that this drug might become the mainstay in the treatment of hypertension since this comes very close to the ideal drug. The drug is well tolerated by many patients of all types of hypertension for both short term and long term treatment. (Minizide: an open trial on the treatment of hypertension; C.U. Abengowe, Dept. of Medicine, ABUT, Kaduna, Nigeria.).

Nitroprusside

Most potent, predictable parenteral antihypertensive of any etiology. The antihypertensive effect is due to Nitroso (-NO) group which dilates arterioles and veins. Unlike arteriolar dilators hydrallazine, minoxidil and diazoxide, this drug increases venous capacitance and therefore reduce preload as well as after load and without blocking autonomic transmission (unlike trimetaphan).

Left vertricular and diastolic pressure is reduced and an improvement in left ventricular function occur in patients with heart failure. Because of rapid action and short duration minute to minute control of BP is possible in hypertensive emergencies. Renal blood flow and glomerular filtration rate are maintained and the angina is improved. The drug is given as 2V infusion and the bottle containing the drug should be covered from light and the solutions should be freshly prepared.

It is available as sodium nitroprusside USP (Nipride) 50mg in 5ml stoppered vials; 50-100mg in 500ml of 5 per cent dextrose and water; Therapy initiated with 0.5mcg/kg/minute; Average dose required may be 200mcg/min.

Doses greater than 10mcg/kg/min may lead to toxicity and renal failure. In the body the drug is converted to cyanide and thiocyanates. Elderly persons should be given a lower dose range. A case of methamoglobinemia has been reported with the infusion of this agent (Bower and Peterson 1975). Thiocyanate is the final product of metabolism of nitroprusside infusion. Thiocyanate accumulate during prolonged therapy. If the concentration of thiocyanate exceeds 10mg/daily, symptoms of toxemia ensues which signals cessation of therapy. Blood pressure returns to pretreatment levels within ten minutes after discontinuation of infusion of nitroprusside.

DRUGS INTERFERING WITH RENIN-ANGIOTENSIN –ALDOSTERONE SYSTEM

1. Renin inhibitors

Acid preotease inhibitor *pepstatin and analogues for tetra-*

Acid preotease inhibitor *pepstatin* and analogues for tetradecapeptides competitively inhibit the formation Angiotensin I by renin. In addition to this methyl dopa, clonidine and propranolol attenuate the release of renin and indomethacin (inhibitor of PG synthetase) inhibit renin release induced by diuretics and vasodilators.

2. Peptidyl dipeptide hydrolase inhibitors (converting enzyme inhibitors)

Various groups of peptides from the venom of snakes BOTHROPOS JARARCA, block the effects of renin angiotensin system by inhibiting the conversiton of angiotensin I to angiotensin II. These peptides are also potentiating factors for bradykinin.

A nonapeptide SQ 20.881–teprotide is not hydrolysed by

the converting enzyme. This nonapeptide, is potent competitive inhibitor of peptidyl dipeptide hydrolases when administered I.V at 0.25 to 1mg/kg. It reduces blood pressure and aldosterone in patients with renovascular hypertension. Teprotide reduces blood pressure in animals with renin dependent and is of benefit in animal models of congestive failure.

Another drug Captopril SQ 14,225 is an orally effecitve inhibitor of peptidyl dipeptide hydrolases and it blocks BP coused by I.V angiotensin II. On set of action in 15 minutes and Peak Pl. levels in 30-60 mts. H.L. is about 2 hours. Kidneys mainly inactivate captopril. Hypotensive responses to captopril is associated with reduction in palsma aldosterone, and increase in PRA.

It appears to enhance cardiac output inpatients with acute congestive heart failure by inducing a reduction in venticular afterload and perhaps preload. Treatment with captopril reduces blood pressure in patients with renovascular disease, mild essential hypertension, and in hypertension with end stage renal disease when blood pressure is not controlled by dialysis or other antihypertensives. Changes in plasma bradykinin levels are insignificant although some workers claim that its effect is partly due to potentiating bradykinin. Serious toxic effects: Proteinuria, glomerulonephritis rashes in 1 per cent of cases. Captopril: 25-100mg qds.

Angiotensin receptor blocking agents

SARALASIN: Sar-Arg-Val-His-Pro-Ala.

The amide NH_2- terminal sarcosyl substition in this analogue of Angiotensin II imparts resistance to enzymatic hydrolysis by aminopeptidases and retards the rate of saralasin's dissociation from angiotensin receptors. The alipathic aminoacid replaces the aromatic aminoacid phenylalanin at the COOH- terminal of the peptide. This modification has little or no effect on receptor affinity but markedly decreases the intrinsic activity of the compound.

Saralasin is a competitive inhibitor of angiotensin receptor. Clinical and animal studies with saralasin have recently been reviewed (Vaughan E.D. Jr. and Peach M.J. (Ed) Sarqlasin Kidney int (suppl 9) 15:s-1, 1979).

Administration by IV as bolus or by infusion at 10mcg/minute. It has a plasma H.L. 3.2 min and 1-1/2 of 8.2 mts. Being a charged peptide it does not cross the blood brain barrier. Saralasin may cause an initial increase in BP followed by fall in blood pressure. The initial pressor response may be mediated by an action on vascular angiotensin receptor. The pressor response can be minimised by pretreatment with a diuretic, except in low renin form of hypertension (LREH). Occasionally there is a rare sustained or rebound pressor response observed following termination of the saralasin infusion. This effect is both due to increase in PRA and Plasma half life of renin is much longer than saralasin. Saralasin has been shown to reduce blood pressure in patients.

1. with renovascular hypertension,
2. end stage renal disease,
3. high renin essential hypertension (HREH), and
4. malignant hypertension.

It has no antihypertensive action in patients with essential benign hypertension, except in high renin activity unless the patients are pretreated with diuretic or sodium depleted. Hemodynamic studies in human patients indicate that the depressor response is due to a reduction in the cardiac output or total peripheral resistance or both. Hypotensive response of saralasin is enhanced by direct acting vasodilators (Hydrallazine).

Major side effects

1. severe hypotension,
2. rebound hypertension (most often in patients with accelerated or malgnant hypertension)
3. Acute hypertension (most pronounced in patients with LREH).

Uses

1. As a diagnostic aid in the identification of angiotension dependent hypertension.
2. Significant value in identifying surgical candidates with renovascular hypertension and
3. Useful in the hospital management of malignant hypertension and hypertensive crisis.

EXPERIMENTAL MODELS (ANIMAL) IN HYPERTENSION

1. Models for investigation of etiology.

2. Models for investigation of therapy.

Since the early thirties of this century investigators have been capable of producing hypertension in animals which have been utilised with some success to increase our understanding of the disease process and its treatment.

Models for investigation of etiology

Since kidney is the most important organ in the long term regulation of BP experimental hypertension was produced by constricting renal arteries (Goldblatt. 1934). This model and its variations are directly applicable to similar situations in man and have provided insights into the etiology of renal vascular hypertension. The initial event leading to hypertension is the prduction of renin and increased plasma renin activity. The chronic hypertension in this model or the hypertension resulting from constriction renal artery to a sole kidney (one kidney Goldblatt model) appear to be maintained by increase in extracellular volume. Renin activity is not chronically elevated nor is the hypertension in its late states reversed by inhibitors angiotensin II, unless plasma volume is diminished (Favras et al 1975). These observations can be used to explain why patients with chronic renovascular hypertension often do not have high plasma renin activity.

The one kidney Goldblatt model has also provided experimental evidence for the clinical observation that once established, correction of the original renovascular lesion does not always reverse the hypertension. Under such circumstances irreversible damage has occured in the previously normal contralateral kidney. Only if the *normal* kidney is removed will the hypertension be corrected. Even in hypertension associated coarctation of Aorta in animals, the increase in blood pressure may be associated with chemicals other than renin. Ingestion of *Salt* alone in animals can lead to hypertension especially in genetically susceptible ones. Parallels to the animals experiments are found in man. Heredity plays a strong permissive role in determining hypertensive state. Rats that *spontaneously develop hypertension* have been found (SHR). This strain develops hypertension that is influenced by, but not dependent on, salt ingestion (Louis et al 1971). The spontaneously developed hypertensive Rats (SHR) have some similarities to essential hypertension in man, but there are enough differences to suspect that study of the animals may not provide ultimate clues to the etiology of HUMAN ESSENTIAL HYPERTENSION.

Models for investigation of therapy

The SHR are a promising model of the course chronic hypertension in man. Vascular changes occur in the kidneys, cardiovascular and cerebrovascular complications develop that are similar to man. With therapy the pathological can be altered. Thus the animal model proves that the vascular lessions seen commonly in human hypertension are likely to be the result rather than the cause of hypertension. SHR experiments imply that the greatest benefit of antihypertensive therapy would result when the treatment is commenced early. The models of hypertension may have importance in drug development. Although many anti-hypertensives can lower the pressure of hypertension can increase the case of detection of the antihypertensive property of the drugs; for e.g. with aldomet it was not initially detected in animals although it was observed in man. Subsequently the hypotensive effects have been shown in the SHR, and only with prolonged infusions of aldomet in primates have the hypotensive properties been demonstrated in the normotensive animals. (Walson et al 1976).

Status of current drugs:

Considerable progress has been made during the past 30 years in the treatment of hypertension with the advent of newer drugs. Some of the newer agents have better therapeutic potential and better patient compliance than the existing drugs.

Beta blockers and thiazide diuretics or labetolol or prazosin remain as agents for monotherapy. Addition of vasodilators have shown to produce better control in cases refractory to monotherapy. Minoxidil is found to be the most active vasodilator, can be combined with betablocker and/or a diuretic. The centrally acting agents like alpha methyl dopa and clonidine given together with a diuretic appears most promising. Recently the converting enxyme inhibitor when given with frusemide appears to be most promising in refractory cases and has a better established benefit-to-risk ratio.

Majority of the patients respond much better to the existing drugs and only a small percentage of patients manifest resistance to drug therapy. Hence, it may hardly be expected that it will be possible to increase definitely the potential of reducing blood pressure, but there is still ample opportunity to improve the quality of antihypertensive drug treatment.

Future trends in antihypertensive therapy:

The search for ideal antihypertensive drugs is still continuing towards the production of effective drugs with better patient compliance. Among the vasodilators, a derivative of hydrallzine ISF 2469 (Cardralazine) is undergoing clinical trial which is based on Pro-drug concept viz., the gradual release of the active drug "IN VIVO". Based on this, converting enzyme inhibitor MK 421, an ester split enzymatically in the intestinal wall is receiving serious attention.

A novel approach is being made with drugs interfering with the transport of calcium ion across cell membranes viz., verpamil, Nifedepin or diltiazem which are being used as anti-anginal drugs. These agents have marked actions on vascular beds viz., reduction in total peripheral resistance which contributes to their antianginal effects. In addition verapamil does not cause tachycardia by its inhibitory effects on atrioventricular conductance. The major drawback is the short duration of action.

In the line of adrenoceptor agents, a selective alpha 1 antagonist *corynanthine capable of crossing blood brain barrier* gonist *corynanthine* capable of crossing blood brain barrier with short duration of action is being experimented with animals. Among the various *combined acting adrenoceptor drugs*, we have a Draco compound D2343, a drug which has alpha1 adrenergic blocking and beta 2 stimulating activity, an older drug Urapidil having alpha 1 blocking activity similar to prazosin with additional alpha 2 receptor stimulating activity and a new beta adrenoceptor blocker with additional vasodilator proerty viz., SKF 92657 (Prezidilol) all of which need detailed clinical investigation.

Among the diuretics *Indapamide* has been claimed to produce its antihypertensive effect without natriuresis or diuresis. The development of *Captopril*, a converting enzyme inhibitor is one of the important landmarks in the treatment of hypertension with entirely different approach viz., tackling the renovascular hypertension.

Another drug *Guanifacine*9(BS-100–141), chemically related to clonidine has been studied and found to produce gradual sustained reduction of blood pressure without inducing withdrawal rebound hypertension which is associated with clonidine.

During the next two decades we may expect a different approach viz., use of prostaglandins and their analogues, synthetic false renin substrates etc., Finding a completely new type of antihypertensive drugs will hardly be possible without a fundamental changes in the research approach. It is not enough to administer drugs to hypertensive rats and observe whether their blood pressure will come down. It needs more sophisticated methods and a more imaginative concept of how to interefere with pathogenic mechanisms of primary hypertension.

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