Treatment of Hypertension

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INTRODUCTION

- hypertension is the most common risk factor for heart attack, stroke, and heart failure and second only to diabetes for renal failure.

- With a longer life span and increasing obesity, the incidence of hypertension will continue to increase, particularly in developing societies .

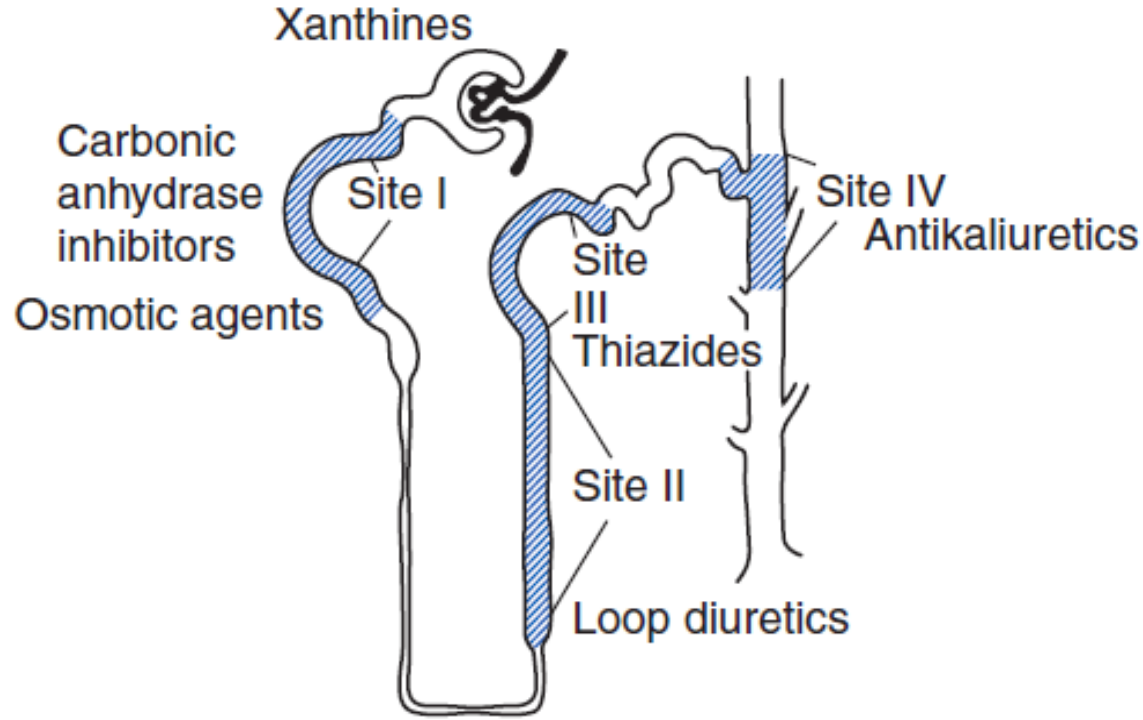
- Therefore, the use of drugs for the treatment of hypertension will continue to grow.

- currently available antihypertensive drugs, preferably in concert with appropriate lifestyle changes and self monitoring, can control the BP in most hypertensive patients.

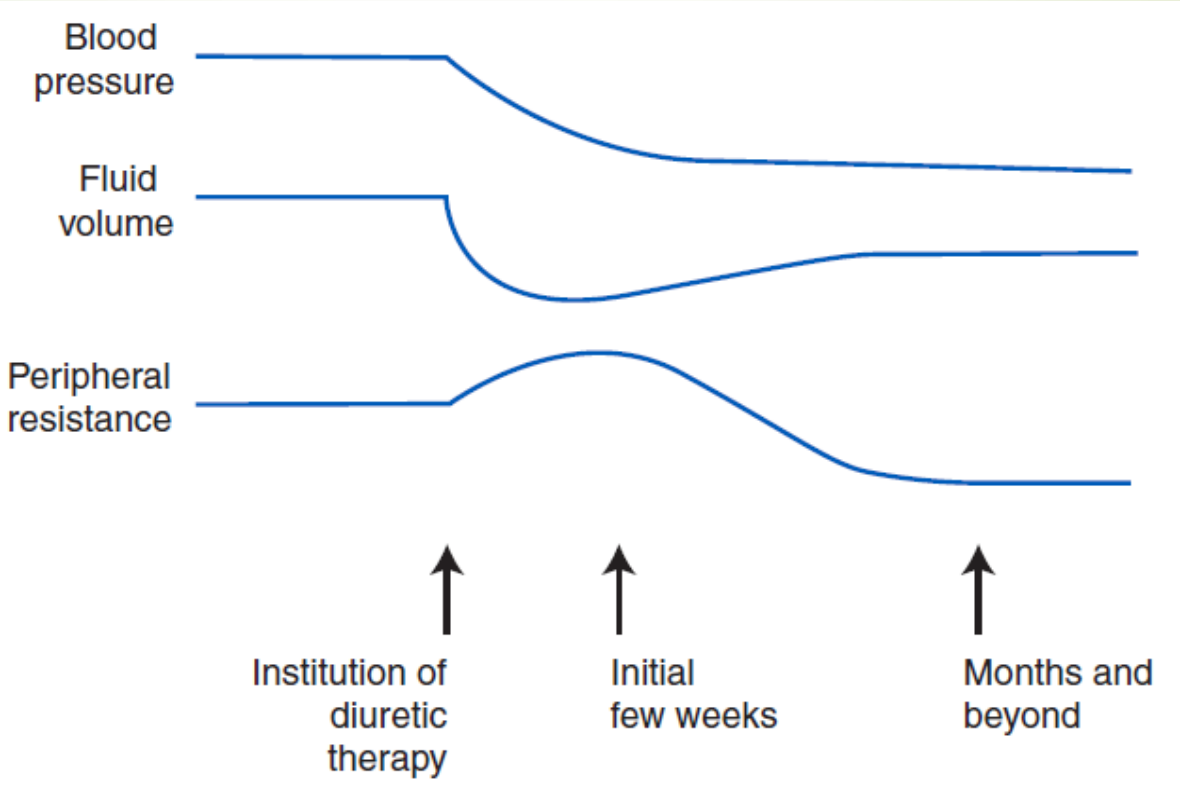
drugs using in the HTN treatment

- Diuretics
- Adrenergic-Inhibiting Drugs
- Calcium channel blockers
- Drugs acting on the renin–angiotensin system
- Direct vasodilator

1-DIURETICS


Xanthines
Carbonic anhydrase inhibitors
Site I
Site IV
Antikaliuretics
Site III
Thiazides
Osmotic agents
Site II
Loop diuretics

Thiazide Diuretics



Hydrochlorothiazide (25mg, 50 MG)

- The recommended daily dose of thiazide diuretics 12.5 mg today
- In hypertensives with good renal function, most of the antihypertensive effect will be obtained from such small doses, with less hypokalemia and other side effects
- The full antihypertensive effect of low doses of diuretic may not become apparent in 4 weeks, so patience is advised when low doses are prescribed

Indapamide (NATRILIX 1.5)/ chlorthalidone

- Used at low doses, the fall in BP is significantly larger with chlorthalidone and indapamide as compared with hydrochlorothiazide
- both chlorthalidone and indapamide have been shown to reduce cardiovascular events in randomized trials, whereas there is no evidence with low-dose hydrochlorothiazide
- longer duration of action of chlorthalidone and indapamide (24 or more hours versus 6 to 12 hours with hydrochlorothiazide)
- some experts suggest chlorthalidone (12.5 to 25 mg/day) or indapamide (1.25 to 2.5 mg/day) as the low-dose diuretic of choice

Resistance to Diuretics

- Excessive dietary sodium intake
- with renal impairment (i.e., serum creatinine >1.5 mg/dL or creatinine clearance <30 mL/ minute)
- Food affects the absorption and bioavailability of different diuretics (should be taken in a uniform pattern in terms of the time of day and food ingestion)
- NSAIDs may blunt the effect of most diuretics
- Diuretics were found to be the most effective class of antihypertensive drugs to prevent heart failure

Side Effects

- *Hypokalemia* : dose dependent/ Patients on digitalis may develop toxicity
- *Hypomagnesemia:* conventional doses of diuretics rarely induce magnesium deficiency
- *Hyponatremia:* By impairing the dilution of the tubular fluid/ Rarely, severe, symptomatic hyponatremia after high doses of diuretics in thin elderly women
- *Hyperuricemia*

- *Calcium Metabolism Alterations*
- *Glucose Intolerance and Insulin Resistance(* high doses, concomitant use of β-blockers)
- *Effect on Lipids*
- Impotence may be more common with diuretics than with other drugs

Loop Diuretics(Furosemide, Bumetanide, Torsemide, Ethacrynic Acid)

- the loop diuretics are more potent and have a more rapid onset of action than do the thiazides
- they are no more effective in lowering BP or less likely to cause side effects if given in equipotent amounts
- Their major use is in patients with renal insufficiency, in whom large enough doses can be given to achieve an effective luminal concentration

- *Although it is* a commonly held belief that thiazide diuretics are not effective antihypertensive agents in patients with CKD, they appear to be as effective as loop diuretics in such patients. (study on 160 patients with advanced CKD and uncontrolled HTN- chlorthalidone)

Potassium-Sparing Agents (*Amiloride & Triamterene*)

- Since neither are potent natriuretics, they are almost exclusively used in combination with thiazides, increase their K+-sparing effect while countering the K+-wasting effect of the diuretic

- Presumably, by preventing hypokalemia, the use of K+-sparing diuretics reduced the risk of death compared to the use of non–K+-sparing diuretics

- Minimally antihypertensive effect/ are not widely used as initial therapy/ although amiloride is valuable in treating resistant HTN

Aldosterone Receptor Blockers

- They are more potent antihypertensive agents
- Spironolactone: 30% decrease in mortality in patients with severe heart failure (25 mg)/ prevent multi-organ profibrotic effect of aldosterone
- Eplerenone: in a twice higher dose has equivalence to spironolactone in blocking the mineralocorticoid receptor but a much lower blockade of androgen and progesterone receptors, explaining its fewer side effects /reduce morbidity and mortality among patients with acute MI complicated by LV dysfunction

Antihypertensive Efficacy

- Spironolactone has been used alone to treat hypertension for many years as a K+ sparer in combination with a thiazide diuretic
- it has been found to effectively control patients with refractory hypertension
- Aldosterone blockers improve diastolic function, are antiarrhythmic, reduce proteinuria in patients with diabetic nephropathy, and prevent diuretic-induced sympathetic nervous system activation and insulin resistance

Side Effects

- Spironolactone in doses of 25 to 50 mg/day induced gynecomastia in 6% of patients and biochemical abnormalities (mainly hyperkalemia) in 2% of the patients with resistant hypertension.
- Eplerenone induced gynecomastia in fewer than 1% of men. it is both safe and effective in patients with impaired renal function.

- Hyperkalemia is more common in the presence of renal insufficiency; concomitant β-blocker, ACEI, ARB, or DRI therapy; or the use of potassium supplements.

ADRENERGIC-INHIBITING DRUGS

- Of the adrenergic-inhibiting agents currently used to treat hypertension, some act centrally on a2-receptors to inhibit sympathetic nerve activity, some inhibit postganglionic sympathetic neurons, and some block the a- or β-adrenoreceptors on target organs.

Methyldopa

- Now its use is almost exclusively for the treatment of hypertension during pregnancy
- BP is lowered maximally approximately 4 hours after an oral dose of methyldopa, and some effect persists for up to 24 hours
- Therapy should be started with 250 mg two times per day, and the daily dosage can be increased to a maximum of 3.0 g on a twice-per-day schedule
- fever and liver dysfunction, can occur with methyldopa

CLONIDINE

- BP begins to fall within 30 minutes, with the greatest effect occurring between 2 and 4 hours.
- The duration of effect is from 8 to 12 hours, so it should be given three times a day. The starting dose may be as little as 0.075 mg , with a maximum of 1.2 mg/day.
- Clonidine shares the two most common side effects, sedation and dry mouth with methyldopa but not the autoimmune hepatic and hematologic derangements.
- Depression of sinus and atrioventricular (AV) nodal function may be common, and a few cases of severe bradycardia have been reported

α-Adrenergic Receptor Blockers

- Phenoxybenzamine and phentolamine (non-selective) are used almost exclusively in the medical management of pheochromocytoma, because they are only minimally effective in primary hypertension.
- Prazosin, doxazosin, and terazosin act as a competitive antagonist of postsynaptic α1-receptors .
- These agents block the activation of postsynaptic α1-receptors and reduce peripheral resistance without major changes in cardiac output.

Antihypertensive Efficacy

- The initial dose should be 1 mg, slowly titrated upward to achieve the desired fall in BP, with a total daily dose of up to 20 mg.
- a-Blockers can be given at bedtime to provide a greater nocturnal fall in BP in and blunting of the morning surge that is involved in the increased incidence of cardiovascular events at that time .
- a-Blockers are useful as add-on therapy in patients with resistant hypertension and the preferred initial therapy for hypertensives with BPH.

Side Effects

- Postural hypotension developing in 30 to 90 minutes may be seen particularly in volume-depleted patients given the shorter-acting prazosin.

- Urinary incontinence in women may be caused by a-blockers

β-Adrenergic Receptor Blockers

- These agents are chemically similar to β-agonists and to each other .

- The competitive inhibition of β-blockers on β-adrenergic receptors produces a reduction in cardiac output, a diminution of renin release, perhaps a decrease in central sympathetic nervous outflow, and a presynaptic blockade that inhibits catecholamine release.

B1-selectivity, intrinsic sympatomimetic activity, lipid solubility

Pharmacologic Properties of Some β-Blockers

Drug	β_1-Selectivity	Intrinsic Sympathomimetic Activity	α-Blockage	Lipid Solubility	Usual Daily Dosage (Frequency)
Acebutolol	+	+	–	+	200–1,200 mg (1)
Atenolol	++	–	–	–	25–100 mg (2)
Betaxolol	++	–	–	–	5–40 mg (1)
Bisoprolol	+++	–	–	+	2.5–20 mg (1)
Bucindolol	–	–	–	+	50–200 mg
Carteolol	–	+	–	–	2.5–10 mg (1)
Carvedilol[a]	–	–	+	+++	12.5–50 mg (2,1)
Celiprolol	++	+	–	–	200–400 mg (1)
Esmolol	++	–	–	–	25–300 μg/kg/min iv
Lbetalol[a]	–	–	+	++	200–1200 mg (2)
Metoprolol	++	–	–	++	50–200 mg (2,1)
Nadolol	–	–	–	–	20–240 mg (1)
Nebivolol[a]	++	–	–	++	5–10 mg (1)
Penbutolol	–	+	–	+++	10–20 mg (1)
Pindolol	–	+++	–	++	10–60 (2)
Propranolol	–	–	–	+++	40–240 mg (2,1)
Timolol	–	–	–	++	10–40 mg (2)

Antihypertensive Efficacy

- In the usual doses prescribed ,various β-blockers have equal antihypertensive efficacy as other classes of drugs .

- However, β-blocker– based therapy has been found not to reduce strokes as well as other classes.

- Three reasons : First the less than 24 hours effect of atenolol, the most widely used β-blocker, but given only once daily in all of the trials. The second and third reasons relate to the higher central (aortic) pressure with β-blockers than with vasodilating agents.

Other Uses

- Coronary disease
- Post MI
- Heart failure from LV systolic dysfunction
- Hypertrophic cardiomyopathy
- Severe MR
- Therapy with direct vasodilators
- Anxiety and stress

Side Effects

- Fatigue
- Diminished exercise ability
- Weight gain
- Worsening of insulin sensitivity
- New onset of diabetes
- Rise in serum triglycerides, fall in HDL cholesterol
- Possible increased risk of fetal malformations when used early in pregnancy
- Worsening of psoriasis

- If these patients become hypoglycemic, β-blockade delays the return of the blood sugar. The only symptom of hypoglycemia may be sweating, which may be enhanced by the presence of a β-blocker .

- Patients with coronary disease who discontinue chronic β-blocker therapy may experience a discontinuation syndrome of increasing angina, infarction, or sudden death .

Vasodilating β-Blockers

- Vasodilating β-blockers may be particularly effective in the treatment of elderly patients with isolated systolic hypertension.

- In addition to reducing aortic stiffness, as do other β-blockers, they also reduce the amplification of central systolic pressure by reducing the rapidity of wave reflection from the periphery ,thereby reducing cardiac work and LV wall thickness.

Labetalol

- Labetalol is a nonselective β1- and β2-receptor blocker combined with a-blocking action in a 4:1 ratio.
- It is an effective antihypertensive drug when given twice daily, maintaining good 24-hour control and blunting the early morning surges in pressure .
- The usual starting doses are 100 mg b.i.d. The maximal daily dose is 1,200 mg.
- Labetalol has been used both orally and intravenously to treat hypertensive emergencies, including postoperative hypertension and acute aortic dissection .
- It has been successfully used to treat hypertension during pregnancy .

Side Effects

- Symptomatic orthostatic hypotension is the most common side effect, seen most often during initial therapy with larger doses
- Perhaps the most serious side effect of labetalol is hepatotoxicity. Appropriate laboratory testing should be done at the first symptom or sign of liver dysfunction
- In keeping with its a-blocking effect, labetalol has less adverse effect on lipids as do β-blockers

Carvedilol

- As a nonselective β-blocker with only one-tenth as much a-blocking activity, carvedilol has been used mainly for treatment of heart failure.
- It is also approved for the treatment of hypertension.
- Beyond its slight a-blocking effect, carvedilol vasodilates by increasing generation of endogenous NO from endothelial cells .

CALCIUM CHANNEL BLOCKERS

- *Diltiazem* and *verapamil* (non-DHP): are rate slowing/ they induce vasodilation, depress cardiac contractility, and inhibit AV conduction
- *Dihydropyridines* (DHPs) are predominantly vasodilators and improve endothelial function
- CCBs are equally effective as other classes against all-cause cardiovascular mortality and major morbidity/ they have provided *less* protection against heart failure, but *more* protection against stroke than other classes

Determinants of Efficacy

- *Age*: An apparently greater antihypertensive effectiveness of CCBs in the elderly
- *Race*: blacks, the response of the BP to monotherapy with CCBs is better than to ACEIs, ARBs, or β-blockers and equal to the response to diuretics
- *Additive Effect of Diuretic or Low Sodium Intake*: sodium reduction and concomitant use of a diuretic—may not add to the efficacy of CCBs

Other Uses

- CAD
- Tachyarrhythmias (non-DHP-CCBs)
- Hypertrophic cardiomyopathy
- AR
- Vasospasm after subarachnoid hemorrhage (nimodipine)
- Peripheral vascular disease and Raynaud reaction
- Prevention of dementia and stroke

Side Effects

- Dependent edema is related to localized vasodilation and not generalized fluid retention and is not prevented or relieved by diuretics but may be relieved by addition of an ACEI
- Gingival hyperplasia may occur with DHPs
- No adverse effects on glucose, insulin, or lipids have been seen