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Anti-Hypertensive and It's Pharmacology: A Review

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ABSTRACT

One of the major modifiable risk factors of cardiovascular/cerebrovascular/renal morbidity is hypertension. Pharmacological therapy for hypertension targets the major physiological influences of blood pressure, which include vascular tone, sympathetic activity and circulating volume. The provided literature covers a wide range of types of anti-hypertensive drugs, such as diuretics, beta-adrenoceptor blockers, alpha 1-adrenoceptor blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium-channel blockers, centrally acting alpha 2-agonists and direct vasodilators. Their pharmacological mechanisms, related pharmacokinetic aspects, adverse effects, drug interactions and some of their clinical uses are summarized here. Adrenergic pharmacology is given special mention since van Zwieten discusses the distribution and blockade of α- and β-adrenoceptor and its effects on vascular resistance, cardiac function and sympathetic activity. Pepper adds an action-oriented section on choosing the right drug, side effects, interactions, and treatment for the individual. The articles together show that it is important to match the mechanism and safety of an antihypertensive to the clinical features and co-morbidities of the patient in order to achieve rational antihypertensive therapy.

KEY WORDS: hypertension; antihypertensive drugs; pharmacology; α-adrenoceptors; β-adrenoceptors; diuretics; ACE inhibitors; calcium-channel blockers

1. INTRODUCTION

It is common for hypertension to have no symptoms at all; however, it is very closely linked to coronary artery disease, left ventricular hypertrophy/heart failure, stroke, renal failure and visual impairment. [1] Pepper stresses the need to take into account evidence of long-term benefit, as well as age, race, co-morbidities and lifestyle when choosing an antihypertensive. The main drugs employed in treatment include diuretics, β-adrenergic blockers, α-adrenergic blockers, ACE inhibitors and calcium-channel blockers and are used for the primary care of the patient, while ARBs, central-acting drugs and direct vasodilators are used for supplementary or special indication purposes. [2] Three major physiological control systems need to be considered in the pharmacology of these drugs. Diuretics affect sodium and water handling in the kidneys; adrenergic drugs affect the sympathetic regulation of the heart and blood vessels; and renin–angiotensin-system inhibitors affect the kidneys' ability to retain sodium and hold water. CCBs decrease calcium-induced contraction of the cardiovascular system and blood vessels.[3] This mechanism-based approach can be used to understand the therapeutic benefits and the predictable side effects.

2. DIURETICS

Thiazide and related diuretics, loop diuretics and potassium-sparing diuretics inhibit sodium reabsorption at various locations in the nephron. Thiazides work in the distal convoluted tubule while the loop diuretics are the most potent diuretics in natriuringic. [4] The thiazides work in the distal convoluted tubule and the loop diuretics have the highest natriuresis. Diuretics that spare potassium work in the collecting duct which can be used in conjunction with thiazides to reduce potassium excretion. The fall in blood pressure that occurs with the onset of diuresis has been correlated with a decrease in circulating volume, while the prolonged antihypertensive response was correlated with the decrease in sodium content of the wall of the arterioles. [5] Thiazides are said to be highly effective as a first line treatment in uncomplicated essential hypertension, especially in isolated systolic hypertension in elderly patients. They also may enhance the activity of other antihypertensive agents. Loop diuretics are better for use when sodium

retention is severe, or there is a significant renal impairment. The use of potassium-sparing agents alone has relatively little antihypertensive activity on their own, but they are beneficial in combination therapy. Side effects of thiazide and loop diuretics: hyponatremia, hypokalemia, metabolic alkalosis, dehydration, hyperuricemia and metabolic alterations of glucose and lipids. Hypokalemia should be particularly considered in patients who are at risk of arrhythmia. The big problem with potassium-sparing medications is hyperkalemia (high blood potassium levels), which can happen when the medication is taken with ACE inhibitors or with potassium supplements. NSAIDs can decrease the antihypertensive effects of diuretics, and diuretics can increase levels of lithium in the blood. [6,7]

3. β-ADRENOCEPTOR BLOCKERS

Norepinephrine acts competitively at β-adrenoceptors; β1 blockade in the heart results in a reduction in heart rate, myocardial contractility and atrioventricular conduction, and β1 blockade in the kidney will cause inhibition of renin release. [8] The antihypertensive action of these actions is more or less, but the full mechanism of how β-blockers reduce established hypertension has historically been incompletely understood. [9] Van Zwieten describes this mechanism within the general organization of the sympathetic nervous system, with the heart being the predominant site for the presence of β1 receptors and the bronchi and some vascular beds being the predominant site of the presence of β2 receptors. [10] Thus, there are differences in the β-blockers regarding their cardioselectivity, intrinsic sympathomimetic activity and other α1-blocking properties. Atenolol, metoprolol and bisoprolol are relatively cardioselective and labetalol and carvedilol have a combination of β blockade and α1 blockade.[11] The lipid soluble β-blockers, such as propranolol and metoprolol, are extensively metabolized by the liver by first-pass metabolism, and have a greater central nervous system effect. Dosing is not as critical for drugs that are less lipid soluble as it is for less lipid soluble drugs such as atenolol and nadolol because they rely more heavily on renal elimination. The side effects are bradycardia and conduction abnormalities, bronchospasm, fatigue, sleep disturbance and sexual dysfunction; nonselective agents can also interfere with the awareness of hypoglycemia. Abrupt withdrawal may be harmful for patients with coronary disease; therefore, abrupt withdrawal should be avoided. [12] There are important cardiovascular applications of β-blockers such as coronary artery disease and post myocardial infarction. The provided review addresses carvedilol in patients with chronic heart failure, and indicates that carvedilol might not be the optimal agent when used as a standalone treatment in elderly patients without a particular indication. [13]

4. α1-ADRENOCEPTOR BLOCKERS AND CENTRAL α2-AGONISTS

Selective α1 blockade acts by inhibiting peripheral vascular resistance through the inhibition of α1 mediated vasoconstriction. Some examples of representative drugs are prazosin, doxazosin and terazosin. Pepper mentions extensive metabolism and the variations in dosing interval; doxazosin and terazosin can be given once a day, whereas prazosin usually needs to be taken on a more frequent schedule. The main issues of concern are orthostatic hypotension and first-dose phenomenon. The receptor mechanism underlying this effect is described in more detail by Van Zwieten. [14] Postsynaptic α1 receptors in resistance vessels cause vasoconstriction and blockade causes vasodilatation of the arterioles and veins. Nonselective α blockade can lead to reflex tachycardia, increased sympathetic activity and sodium/water retention. Selective α1 blockade causes far less reflex tachycardia, which is in part due to the preservation of presynaptic α2 mediated modulation of norepinephrine release and possibly to central modulation of baroreflex activity.Selective α1 blockade causes much less reflex tachycardia, in part because of preservation of presynaptic α2 mediated modulation of norepinephrine release and possibly because of central modulation of baroreflex activity. Central acting α2 agonists like clonidine, guanfacine and methyldopa inhibit sympathetic output from the brain stem. Van Zwieten outlines central α2 receptors which are located in pontomedullary areas associated with cardiovascular autonomic regulation and which are activated by stimulation to inhibitory pathways which decrease peripheral sympathetic activity, and thereby lower blood pressure and heart rate. Sedation and dry mouth are common side effects.[15] Pepper discusses clonidine, guanabenz, guanfacine and methyldopa as central agents and mentions rebound hypertension following abrupt clonidine withdrawal. Methyldopa is mentioned as an important option in chronic hypertension during pregnancy and hydralazine is mentioned in severe peripartum hypertension. [16]

5. ACE INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS

ACE inhibitors inhibit the formation of angiotensin II and inhibit the breakdown of bradykinin. Their antihypertensive effect is thus the result of decreased vasoconstriction, enhanced vasodilator activity due to bradykinin, and decreased sodium and water retention due to decreased aldosterone. ARBs competitively inhibit the AT1 receptor (binding to the same site as angiotensin II), thus blocking the binding of angiotensin II to the receptor and its resulting effects on the body such as vasoconstriction and the release of aldosterone. Oral drugs are used most

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commonly; many ACE inhibitors are prodrugs and renal function can dictate dosage adjustment due to renal elimination. However, ARBs, with exception, are usually taken once a day and their main route of elimination is hepatic/biliary. Dry cough is the adverse effect that is a major characteristic of ACE inhibition and not seen with ARBs, which are thought to cause accumulation of bradykinin. Other issues are hypotension, hyperkalemia and angioedema after the initial dose. ACE inhibitors and ARBs are contraindicated during pregnancy because of fetal and neonatal toxicity. The clinical importance of ACE inhibitors is particularly highlighted in the source article in two situations: hypertension with diabetes and proteinuria, and heart failure and systolic dysfunction following myocardial infarction. May be used in combination with a diuretic, to increase antihypertensive effect. When an ACE is not well tolerated (particularly cough) ARBs are mentioned as an alternative. [16-19]

6. CALCIUM-CHANNEL BLOCKERS

Calcium channel blockers block the passage of calcium into cells of the vascular smooth muscle, myocardium and cardiac conduction system. Vascular relaxation, decreased peripheral resistance, and a decrease in myocardial contractility and conduction (which varies by drug) result from a reduction in intracellular calcium. Dihydropyridines (including nifedipine and amlodipine) are more vasodilating while verapamil and diltiazem have more effects on atrioventricular conduction and myocardial function. filecite turn0file0 Generally, these drugs are poorly bioavailable due to first pass metabolism, high plasma-protein binding and hepatic clearance. Common side effects of a vasodilator are peripheral edema, flushing, headache and hypotension. Verapamil and diltiazem may aggravate bradycardia, heart block, heart failure and may elevate the serum digoxin level. Additionally, some calcium-channel blockers interact with other drugs metabolized by the liver and grapefruit juice can enhance absorption. The provided article is about long acting dihydropyridines that have been found useful in elderly patients with isolated systolic hypertension whose thiazide therapy is poorly tolerated. It also warns against using sublingual immediate-release nifedipine in cases of hypertensive emergency due to potential for too much and too long of a drop in blood pressure and serious side effects. [20-22]

7. VASODILATORS, DIRECT AND COMBINATION THERAPY

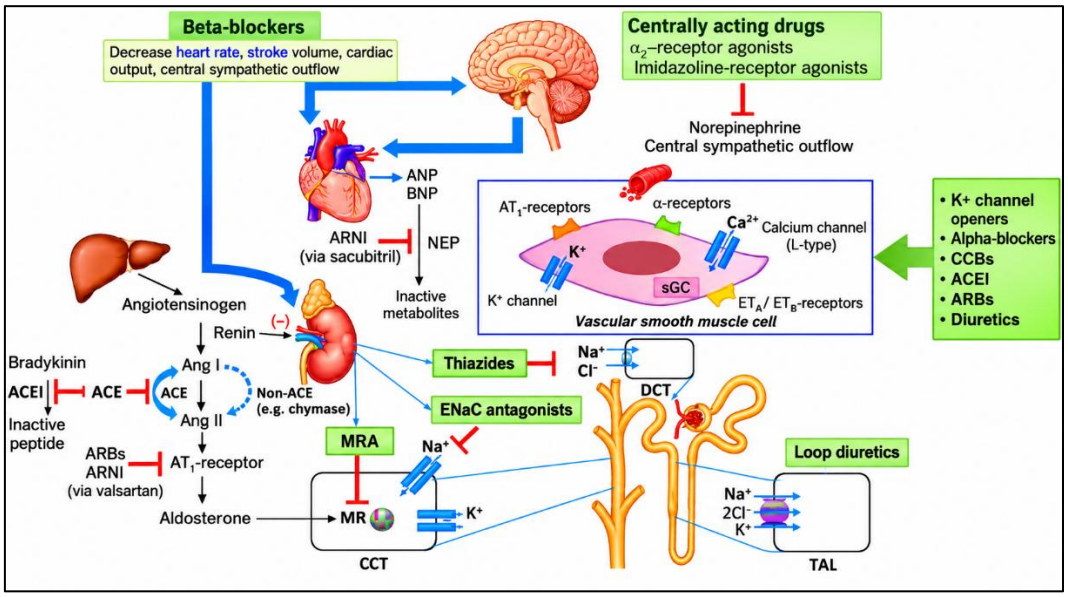
Hydralazine works directly on the smooth muscle of the arterioles to cause relaxation. It is a vasodilator that may trigger reflex tachycardia and sodium/water retention; for long-term use, it is recommended to be combined with a diuretic and a β-blocker. Hydralazine is also cited as an intravenous agent for the peripartum severe hypertension. It is well recognized that a lupus-like syndrome is an adverse effect. Filecite L10-L15 Combination treatment is considered pharmacologically sensible if complementary mechanisms augment the effects of the other agent(s) on blood pressure or if one agent has a different adverse effect which is offset by that of the other agent(s). In the provided article, examples are given of thiazide/β-blocker, ACE inhibitor/diuretic, ARB/diuretic and calcium-channel blocker/ACE-inhibitor combinations. Potassium-sparing treatment can be used to counteract the diuretic-induced loss of potassium, and the reflex responses to direct vasodilation can be controlled by using a vasodilator in combination with a β-blocker and diuretic. [20, 23-25]

8. COMPARATIVE PHARMACOLOGICAL OVERVIEW [26-28]

Class	Principal mechanism	Major adverse effects	Selected source-described uses
Diuretics	↓ renal Na+/water reabsorption	Hypokalemia, hyponatremia, hyperuricemia; hyperkalemia with K-sparing agents	Initial essential hypertension; isolated systolic hypertension; volume overload
β-blockers	β1 blockade → ↓ HR, contractility and renin	Bradycardia, bronchospasm, fatigue, hypoglycemia masking	CAD/post-MI; selected hypertension; heart failure
α1-blockers	Peripheral α1 blockade → vasodilation	Orthostatic hypotension, first-dose syncope	Mild hypertension; useful with prostatic hypertrophy
ACE inhibitors/ARBs	↓ Ang II activity; ACE inhibitors also ↑ bradykinin	Cough/angioedema with ACE inhibitors; hyperkalemia; hypotension	Diabetes with proteinuria; heart failure/systolic dysfunction

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CCBs	Block L-type Ca2+ influx	Edema, flushing; bradycardia/heart block with non-DHPs	Isolated systolic hypertension; angina/selected arrhythmias
Central α2 agonists	↓ central sympathetic outflow	Sedation, dry mouth; rebound hypertension with abrupt clonidine withdrawal	Second-/third-line therapy; methyldopa in pregnancy
Hydralazine	Direct arteriolar smooth-muscle relaxation	Reflex tachycardia, fluid retention, lupus-like syndrome	Refractory therapy; severe peripartum hypertension



9. CONCLUSION

The two articles that were supplied demonstrate that the best approach to understanding antihypertensive pharmacology is to look at the two systems that regulate vascular resistance, cardiac output, and sympathetic activity and sodium balance. Diuretics affect the handling of sodium in the kidney mainly; β-blockers affect cardiac and sympathetic mechanisms; α1 blockers decrease vascular resistance; central α2 agonists decrease sympathetic outflow; ACE inhibitors and ARBs prevent formation of angiotensin; calcium-channel blockers inhibit the calcium induced contraction; and direct vasodilators relax the vascular smooth muscle. These classes have not only blood pressure reducing properties but also pharmacokinetics, adverse effects, interactions and co-morbid conditions which must also be considered. Individual selection and monitoring will then continue to be key to rational antihypertensive treatment.

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