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Review

Antihypertensive drugs

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ABSTRACT

Successful treatment of hypertension is possible with limited side effects given the availability of multiple antihypertensive drug classes. This review describes the various pharmacological classes of antihypertensive drugs, under two major aspects: their mechanisms of action and side effects. The mechanism of action is analysed through a pharmacological approach, i.e. the molecular receptor targets, the various sites along the arterial system, and the extra-arterial sites of action, in order to better understand in which type of hypertension a given pharmacological class of antihypertensive drug is most indicated. In addition, side effects are described and explained through their pharmacological mechanisms, in order to better understand their mechanism of occurrence and in which patients drugs are contra-indicated. This review does not address the effectiveness of monotherapies in large randomized clinical trials and combination therapies, since these are the matters of other articles of the present issue. Five major pharmacological classes of antihypertensive drugs are detailed here: beta-blockers, diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, and calcium channel blockers. Four additional pharmacological classes are described in a shorter manner: renin inhibitors, alpha-adrenergic receptor blockers, centrally acting agents, and direct acting vasodilators.

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1. Introduction

Successful treatment of hypertension is possible with limited side effects given the availability of multiple antihypertensive drug classes. The translation of pharmacological research to the treatment of hypertension has been a continuous process, starting with drugs discovered 60 years ago, such as thiazide diuretics (1958) and currently finishing with the newest antihypertensive agent available on the market, the orally active direct renin-inhibitor aliskiren, discovered more than 10 years ago (2000) [1]. In between, there has been a continuous rate of discovery, including spironolactone (1957), beta-blockers (propranolol, 1973), centrally acting alpha-2 adrenergic receptor agonists (clonidine, 1970s), alpha1-adrenergic receptor blocker (prazosin, 1975), angiotensin converting enzyme inhibitors (captopril, 1977), calcium channel blockers (verapamil, 1977), and angiotensin II receptor blockers (losartan, 1993) [1].

The aim of this review is to describe the various pharmacological classes of antihypertensive drugs, under two major aspects: their mechanisms of action and side effects. The mechanism of action is analysed through a pharmacological approach, i.e. the molecular receptor targets, the various sites along the arterial system, and the extra-arterial sites of action, in order to better understand in which type of hypertension a given pharmacological class of antihypertensive drug is most indicated (see other articles of this issue). In addition, side effects are described and explained through their pharmacological mechanisms, in order to better understand their mechanism of occurrence and in which patients drugs are contra-indicated. This review does not address the effectiveness of monotherapies in large randomized clinical trials and combination therapies, since these are the matters of other articles of the present issue.

Five major pharmacological classes of antihypertensive drugs are detailed here: beta-blockers, diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, and calcium channel blockers (Table 1). Four additional pharmacological classes are described in a shorter manner: renin inhibitors, alpha-adrenergic receptor blockers, centrally acting agents, and direct acting vasodilators.

2. Beta-blockers

Beta-blockers are a heterogeneous pharmacological class, and their pharmacodynamic properties depend on their cardiac-selectivity, partial agonist activity and associated vasodilating properties (Fig. 1 and Table 1). They all lower BP to the same extent, although using various amounts of reduction in cardiac output and vasodilatation, according to their pharmacological properties [2].

2.1. Mechanism of action

Various mechanisms of action have been suggested in order to explain the antihypertensive action of beta-blockers: the reduction in cardiac output, in response to bradycardia, is one of the most important factors for lowering mean BP. Since any BP lowering activates the baroreflex system, the associated increase in total peripheral resistance is not surprising. However, this increase in dampened by the resetting of the baroreceptors. A reduction in sympathetic activity of central origin is also likely, leading to a reduction in vasomotor tone, and is associated with, or independent of, the reduction in renin secretion [3]. An effect on pre-junctional beta-receptors has also been suggested, leading to a reduction in norepinephrine release.

The above mechanisms of action are associated to various extents, depending of the characteristics of the beta-blocker [2]. BP lowering after beta1 selective blockers (atenolol, bisoprolol), acting preferentially on the cardiac beta1-adrenergic receptor, may also benefit from non-opposed beta2 arteriolar vasodilatation. BP lowering after vasodilating beta-blockers is accompanied by less reduction in heart rate and less increase in total peripheral resistance than after non-vasodilating beta-blockers (atenolol, metoprolol). Vasodilating beta-blockers have often a partial agonist activity at the beta2-adrenergic receptor sites (celiprolol, nebivolol), an antagonist activity at the alpha1-adrenergic receptor sites (carvedilol, labetalol), or a NO potentiating activity (nebivolol). Their vasodilating effect on small arteries is associated with a reduction in arterial stiffness, which is not fully explained by the sole reduction in BP (less distension of the stiff components of the large artery wall), and with less increase in central BP than with non-vasodilating beta-blockers. Thus, vasodilating beta-blockers are effective on the various components of central and peripheral hemodynamics: reduction in heart rate and cardiac output, relaxation of large arteries, and vasodilatation of small arteries.

However, non-vasodilating beta-blockers, such as atenolol, can exert deleterious effects on the arterial system, or at least have neutral effects via several mechanisms [4]. For instance, total peripheral resistance and sympathetic drive are not decreased by atenolol, despite less deleterious effects of catecholamines on the heart after beta-blocker. Atenolol decreases target organ damage to a lesser extent than renin-angiotensin system blockers in hypertensive patients, thus a certain amount of vasoconstriction and increased media-to-lumen ratio remains after beta-blockers [5] as well as left ventricular hypertrophy and carotid intima-media thickness. Compared to vasodilators, the reduction in aortic stiffness and central blood pressure is limited [6] even when atenolol is associated with a calcium-channel blocker [7]. Nonvasodilating beta-blockers can even stiffen large arteries through a direct "pro-fibrotic" effect, when the lowering of blood pressure is not large enough to unload the stiff components of the arterial wall [8]. This deleterious effect of beta-blockers can be due to several mechanisms: cross-linking of collagen and elastin fibers and increased TGF-β production. The later occurs when beta2- or alpha-adrenergic receptors are stimulated. The stimulation of lysyl-oxidase is an additional mechanism. Finally, insulin-resistance and

Table 1
Pharmacological classes and sub-classes of antihypertensive drugs.

Pharmacological classes	Sub-classes	Molecules
Major classes		
Beta-blockers	Non-vasodilating with β1-selectivity	acebutolol, atenolol, betaxolol, bisoprolol
	Non-vasodilating without β1-selectivity	carteolol, esmolol, metoprolol, nadolol, oxprenolol, penbutolol, propranolol, timolol
	Vasodilating	celiprolol, carvedilol, labetalol, nebivolol, pindolol
Diuretics	Loop diuretics	furosemide, bumetanide, torsemide
	Thiazides diuretics	bendroflumethiazide, chlorothiazide, chlortalidone, hydrochlorothiazide, indapamide, polythiazide, trichlormethiazide
	Potassium sparing diuretics	amiloride, eplerenone, spironolactone, triamterene
Angiotensin-converting enzyme inhibitors		benazepril, captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril, zofenopril
Angiotensin II receptor blockers		candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Calcium-channel blockers	Non-dihydropyridines	diltiazem, verapamil
	Dihydropyridines	amlodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nitrendipine
Other classes		
Renin inhibitors		aliskiren
Alpha-adrenergic receptor antagonists		doxazosin, prazosin, terazosin
Centrally acting agents		clonidine, methyl-dopa, rilmenidine
Direct acting vasodilators		hydralazine, minoxidine

Molecules are listed in alphabetical order.

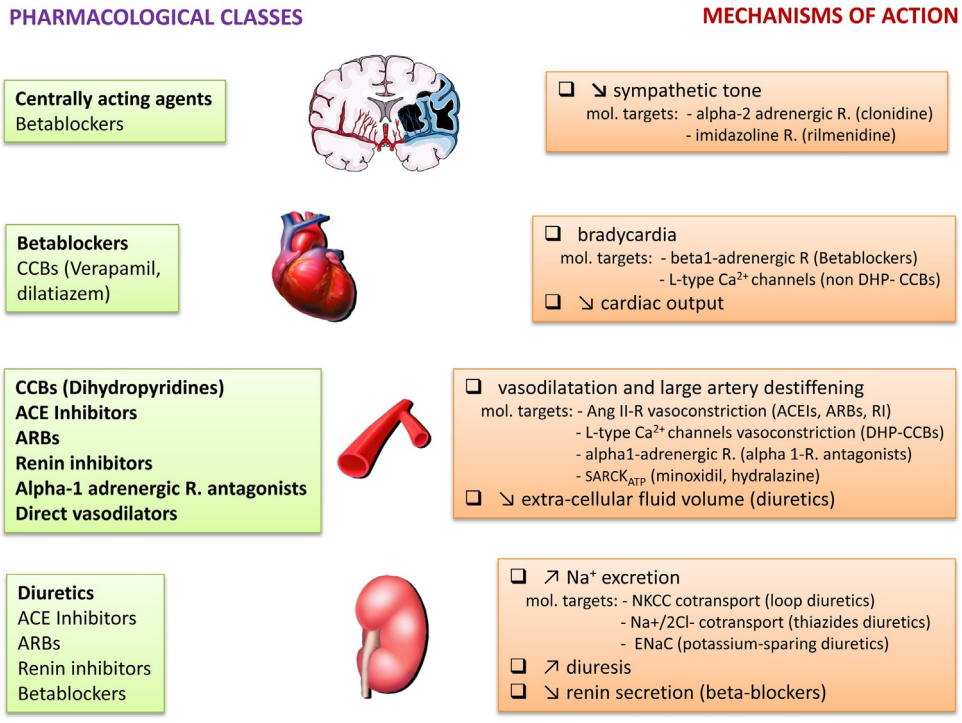

Fig. 1. Pharmacological classes and corresponding mechanisms of action of the antihypertensive effect.
Actions at the level of the brain, heart, vessels and kidney are given for the various pharmacological classes. Bold names mean that this is the main mechanism of action. Molecular targets are given for each mechanism of action. ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; DHP, dihydropyridine; R., receptor; $SARCK_{ATP}$, sarcolemnal adenosine triphosphate-dependent potassium channels.

increased risk of incident diabetes, observed after beta-blockers, can exaggerate arterial damage [9].

2.2. Side effects

Beta-blockers should not be used in patients with moderate to severe asthma (since adrenergic bronchodilatation requires intact beta-2 receptors), unstable heart failure resulting from systolic dysfunction, second- or third-degree atrioventricular block, or the sick sinus syndrome (without a pace-maker). Beta-blocker may worsen glucose intolerance and mask hypoglycemic symptoms [10] (Table 2).

Vivid dreams, insomnia, hallucinations, and depression may occur during beta-blocker therapy, more often with the highly lipid-soluble beta-blockers (propranolol, metoprolol, pindolol) which may penetrate the central nervous system better. Impotence is a side effect common to many beta-blockers, although it may occur less frequently with vasodilating beta-blockers.

Table 2
Compelling and possible contra-indications of antihypertensive drugs.

Pharmacological classes	Compelling	Possible
Major classes		
Beta-blockers	Asthma	Metabolic syndrome
	AV block (grade 2 or 3)	Glucose intolerance
		Athletes and physically active patients
		Chronic obstructive pulmonary disease (except for vasodilator bate-blockers)
Diuretics	Gout	Metabolic syndrome
		Glucose intolerance
		Pregnancy
		Hypercalcemia (except loop diuretics)
		Hypokalemia
Mineralocorticoïd receptor antagonists	Acute or severe renal failure (eGFR < 30 mL/min)	
Angiotensin-converting enzyme inhibitors	Pregnancy	Women with child bearing potential
	Angioneurotic edema	
	Hyperkalemia	
	Bilateral renal artery stenosis	
Angiotensin II receptor blockers	Pregnancy	Women with child bearing potential
	Hyperkalemia	
	Bilateral renal artery stenosis	
Non-dihydropyridines calcium-channel blockers (diltiazem, verapamil)	A-V block (grade 2 or 3, trifascicular block)	
	Severe LV dysfunction	
	Heart failure	
Other classes		
Renin inhibitors	Pregnancy	Women with child bearing potential
	Angioneurotic edema	
	Hyperkalemia	
	Bilateral renal artery stenosis	
Centrally acting agents	Severe depression	

Adapted from the 2013 ESH-ESC Guidelines for the Management of Hypertension, with permission (ref [69]).

3. Diuretics

Thiazide diuretics and loop diuretics increase natriuresis and diuresis [11]. Both can be considered as one major therapeutic class of antihypertensive drugs, although they represent two distinct pharmacological classes. Their major mechanisms of action and side effects are described separately. Potassium sparing diuretics represent another therapeutic class (Fig. 1 and Table 1).

3.1. Loop diuretics

Furosemide and bumetanide belong to the most frequently used loop diuretics.

3.1.1. Mechanisms of action

Loop diuretics exert their effects in the nephron at the apical membrane in the thick ascending limb of the loop of Henle. They inhibit Na^+ and chloride (Cl^-) reabsorption at the $Na^+/K^+/2Cl^-$ cotransporter (NKCC), by competing with Cl^-. The normal dose-response relationship, i.e. the relationship between Na^+ excretion and loop diuretic excretion rate, is that of a sigmoidal curve. It can be shifted downward and to the right in presence of NSAIDs and subsequent inhibition of prostaglandin synthesis [12]. Na^+ excretion is associated with hypokalemia and mild metabolic alkalosis, due to increased K^+ and H^+ excretion in the collecting tubule in response to the higher Na^+ concentration at this level, and significant secondary hyperaldosteronism in response to hypovolemia [11]. Other major effects of loop diuretics include a decrease in free water excretion during water loading, and reabsorption during dehydration, because of reduced osmotic gradient in the medulla. An increased Ca^{2+} excretion is also observed in response to the inhibition of the paracellular Ca^{2+} transport across renal epithelia [2].

Loop diuretics lower BP through a reduction in extra-cellular fluid volume. The decrease in plasma volume that occurs in response to an increased Na^+ excretion, reduces venous return and lowers cardiac output. These changes in plasma volume can stimulate the sympathetic nervous system and the renin angiotensin aldosterone system.

The onset of diuresis with furosemide is rapid, within 1 h, peaking at 3–6 h, with a smaller effect after 12 h [13].

3.1.2. Side effects

Side effects of loop diuretics are dose-dependent, and include hyponatremia (Na^+ depletion and dilution), hypokalemia, metabolic alkalosis, hypovolemia, hypotension, and to a lesser extent hyperuricemia, hypocalcemia, hypomagnesemia, hyperglycemia, hyperlipidemia, urinary urgency, and impotence [12]. Loop diuretics are contra-indicated in patients with gout (Table 2).

3.2. Thiazides

Hydrochlorothiazide, chlortalidone and indapamide belong to the most frequently used thiazide diuretics (Fig. 1 and Table 1).

3.2.1. Mechanisms of action

Thiazide diuretics exert their effects in the nephron at the apical membrane in the early convoluted distal tubule, where they inhibit the coupled reabsorption of Na^+ and Cl^-. The natriuretic effect of thiazide is smaller than that of loop diuretics because a smaller fraction of filtered load of Na^+ is reabsorbed at the distal tubular site of action of thiazides, compared to the more proximal site of action of loop diuretics (ascending limb of the loop of Henle) [12]. Na^+ excretion is associated with hypokalemia and mild metabolic alkalosis, due both to an increased K^+ and H^+ excretion in the collecting tubule in response to the higher Na^+ concentration at this level, and a significant secondary hyperaldosteronism in response to hypovolemia. Thiazide diuretics impair the urinary diluting capacity. By contrast to loop diuretics, thiazide diuretics preserve urinary concentrating mechanisms [11].

Thiazide diuretics lower BP through a reduction in extra-cellular fluid volume, in a similar way as loop diuretics [14].The early response to thiazide diuretics, in the setting of no-salt-added diet, results in a net Na^+ loss of 100–300 mmol in a few days, which translates into a 1–2 L reduction in extra-cellular fluid volume. Plasma Na^+ concentration are unchanged in the process. The decrease in plasma volume that occurs in response to an increased Na^+ excretion, reduces venous return and lowers cardiac output. These changes in plasma volume can stimulate the sympathetic nervous system and the renin angiotensin aldosterone system.

The onset of diuresis with hydrochlorothiazide is rapid, within 2 h, peaking at 3–6 h, with a smaller effect after 12 h. Chlortalidone is a longer-acting thiazide, which can be useful when a lengthier period of natriuresis is desired [14].

3.2.2. Side effects

Side effects of thiazide diuretics are dose-dependent, and include hyponatremia (Na^+ depletion and dilution), hypokalemia, metabolic alkalosis, hypovolemia, hypotension, and to a lesser extent hyperuricemia, hypomagnesemia, hyperglycemia, hyperlipidemia and impotence. They resemble those of loop diuretic [12]. The only exception is hypercalcemia which occurs after thiazide diuretics, instead of hypocalcemia after loop diuretics. Indeed, there is an increase in Ca^{2+} reabsorption at the level of the distal tubule after thiazide diuretics [15]. The mechanism involves the lowering of Na^+ concentration at the tubule epithelial cells level. Indeed, thiazides indirectly augment the basolateral Na^+/Ca^{2+} antiporter activity, which in turn decreases the intracellular Ca^{2+} concentration, and thus increases the driving force for reabsorption from the lumen.

Thiazide diuretics are contra-indicated in patients with gout (Table 2).

3.3. Potassium-sparing diuretics

This sub-class includes competitive antagonists of aldosterone, such as spironolactone, eplerenone, and drugs which act independently of aldosterone, such as amiloride and triamterene (Fig. 1 and Table 1).

3.3.1. Mechanisms of action

These drugs inhibit active Na^+ reabsorption at the level of late distal tubule and collecting duct. Particularly, spironolactone acts as a competitive antagonist of mineralocorticoid receptors, present in the cytoplasm of tubular cells in the late distal tubule and the collecting duct. Spironolactone blocks the binding of its ligand aldosterone, thus its translocation to the cell nucleus, homodimerization and binding to hormone response elements present in the promoter of some genes. This blockade results in the reduction of proteins regulating ionic and water transports, mainly the epithelial sodium channel (ENaC), the Na^+/K^+ pump, and the glucocorticoid induced kinase (SGK1), leading to the inactivation of Na^+ reabsorption. By contrast, amiloride and triamterene block ENaC in the luminal membrane of the collecting duct, independently of aldosterone [16].

Only a modest natriuretic effect can be expected, since a smaller fraction of filtered load of Na^+ is reabsorbed at this distal site of action, compared to the more proximal site of action of loop diuretics and thiazide diuretics.

3.3.2. Side effects

Hyperkalemia is a common side effect, particularly in patients with chronic renal disease and heart failure or diabetes, receiving potassium-sparing diuretics or potassium supplements, or taking an ACEI, an ARB, or an NSAID. Hyperkalemia is associated with metabolic acidosis. Impotence, decreased libido, bilateral gynecomastia and mastodynia are frequent complications of spironolactone therapy. They are related to the sexual side effects of spironolactone, since spironolactone inhibits the binding of dihydrotestosterone to androgen receptors, which results in an increased clearance of testosterone. Treatments with eplerenone, which is a more selective aldosterone antagonist, or with amiloride and triamterene, are much less complicated by these sexual side effects [16].

Potassium sparing diuretics, particularly mineralocorticoid receptor antagonists, are contra-indicated in patients with acute or severe renal failure (eGFR < 30 mL/min) (Table 2).

4. Angiotensin converting enzyme inhibitors

The first ACEI available for hypertension treatment was captopril in the early 1980s, rapidly followed by enalapril, perindopril, lisinopril, ramipril, quinapril, benazepril, cilazapril, trandolapril, fosinopril, moexipril, imidapril and zofenopril (Fig. 1 and Table 1).

4.1. Mechanisms of action

Angiotensin converting enzyme inhibitors (ACEIs) target a pluripotent zinc metalloproteinase which catalyses the conversion of angiotensin I to angiotensin II, so called angiotensin converting enzyme (ACE) [17]. ACE is located in the endothelial cells of large and small vessels, capillaries and venules, and in pulmonary endothelial cells. Importantly, ACE may modulate the amount of angiotensin II entering the systemic arterial circulation because of its strategic position within the lungs and the strategic position of the lungs in the general circulation.

An important feature of ACEIs is their binding affinity for tissue ACE, that depends on their tissue binding affinity, potency, lipophilicity and tissue retention. Although tissue retention is not needed when ACEI concentrations are high, for instance during the first half of the 24 h, both inhibitor binding affinity and tissue retention can help to prolong the inhibition of ACE. ACEIs are potent vasodilators [12]. Because angiotensin II is a potent vasoconstrictor peptide, the blockade of its production leads to vasodilation of small resistance arteries, reduction in total peripheral resistance and BP lowering. Cardiac output remains unchanged. Despite BP lowering, heart rate remains unchanged, and there is no postural hypotension, likely because ACEIs reset baroreceptor function [17].

ACEIs fail to suppress production of angiotensin II by alternative enzymatic pathways, such as chymase and other tissue-based protease [18], that can upregulate on the long term, particularly in the vasculature and the myocardium [18], and attenuate the BP lowering effect of ACEIs. Because the BP lowering effect of ACEIs is maintained for months and years, other mechanisms have been suggested, such as an increase in bradykinin (a vasodilatory peptide) concentrations in response to the inhibition of kininase II (similar to ACE), that is involved in the degradation of bradykinin into inactive peptides. In addition, ACE is responsible for the degradation of angiotensin (1–7). Thus ACEIs may increase the plasma concentration of angiotensin (1–7) which is formed in the endothelial layer of human blood vessels, and acts as vasodilator and antiproliferative agent [19].

ACEIs are able to protect target organs in hypertensive patients. Indeed, long-term administration of ACEIs is associated with a reduction of left ventricular hypertrophy (LVH), an improvement of endothelial function, a destiffening of large arteries [20,21] and a remodeling of large and small arteries [22]. Relaxation of large arteries leads to less pressure wave reflection and a slower propagation of pressure waves along the aorta, thus it is associated with a fall in central systolic and pulse pressures [6,7]. Renoprotection is observed in various setting, i.e. established type1

insulin-dependent diabetic nephropathy [23], early type2 diabetic nephropathy [24], and type1 diabetic patients without hypertension but with microalbuminuria [25]. These changes occur mostly in response to the reduction in BP, but a large number of evidences favor also a direct effect of ACEIs on the cardiac, renal and arterial tissue. For instance, several *meta*-analyses or reviews ranked ACEIs (as well as ARBs) as the most effective antihypertensive drugs to reduce LVH [26], small artery remodeling [22], and large artery stiffness [6] compared to calcium-channel blockers, diuretics and beta-blockers, although BP lowering was similar in all treatment groups. In addition, ACEIs, as well as ARB (see below), are privileged antihypertensive drugs for a BP-independent effect on arterial stiffness, mainly through long-term arterial remodeling and reduction of arterial wall fibrosis. In long-term controlled studies, the ACEIs perindopril [20] and trandolapril [21] and the angiotensin-receptor blockers (ARBs) olmesartan [27] and valsartan [28] had the capacity to reverse aortic stiffening independently of changes in BP. This ability is shared by the aldosterone antagonist spironolactone [29].

4.2. Side effects

ACEIs are generally well-tolerated drugs. However, the possibility of cough and angioedema should be kept in mind when prescribing these drugs. Cough is not uncommon (10–20%). This is a class phenomenon. It is explained by an increased in bradykinin concentrations, and possible increased concentration of other peptides such as substance P. The feature of ACEI-induced cough is that this is a dry, irritating, and non productive cough. Angioneurotic edema is a potentially life-threatening side effect. Like cough, it is explained by an increased in bradykinin concentrations, and possible increased concentration of other peptides such as substance P. This is a rare side effect that occurs in 0.55% of white patients and 1.62% of black patients according to the Octave study [30]. ACEI-related anemia is likely due to the suppression of erythropoietin production, in response to N-acety-seryl-aspartyl-lysyl-proline accumulation in plasma, a potent natural inhibitor of hematopoietic stem cell proliferation [31].

Functional renal insufficiency is more common, and may be initiated by a fall in glomerular afferent arteriolar flow, itself secondary to the vasodilatation of the glomerular efferent arteriole. Indeed, angiotensin II constricts the efferent arteriole to a greater extent than the afferent one, such that glomerular filtration rate is maintained despite low perfusion. Functional renal insufficiency occurs not only in patients with severe renal artery stenosis or solitary kidney, but also in case of dehydration, use of NSAIDs, heart failure and microvascular disease [32]. For similar reasons, ACEIs are contra-indicated during the second and third trimester of pregnancy.

Hyperkalemia is uncommon, except in patients with chronic renal disease and heart failure or diabetes, who receive potassium-sparing diuretics or potassium supplements.

ACEIs are contra-indicated in pregnancy, in patients with previous angioneurotic edema or hyperkalemia, and in patients with bilateral renal artery stenosis (Table 2).

5. Angiotensin ii receptor blockers

The first angiotensin II receptor blocker (ARB) available for hypertension treatment was losartan in the late 1990s, rapidly followed by candesartan, eprosartan, irbesartan, valsartan, telmisartan, and olmesartan (Fig. 1 and Table 1).

5.1. Mechanisms of action

ARBs antagonize the effects of angiotensin II at the level of the angiotensin II type 1 subtype receptor (AT_1). All ARBs have high affinity for the AT_1 receptor, which are found in high concentration in various tissues, particularly in smooth muscle cells, heart, kidney, aorta. ARBs used in clinical practice bind to the AT_1 receptor in a competitive manner, but with a slow dissociation, which explains why their BP lowering effect may last longer than predicted by their pharmacokinetic parameters. ARBs are also named “sartans”. AT1 receptor activation by angiotensin II is responsible for cell growth, proliferation and contraction, a phenomenon which occurs not only at the site of vascular smooth muscle cells (VSMC) of small arteries (the main effects of ARBs), but also at the site of VSMC of large arteries, cardiac myocytes and fibroblasts.

ARBs have been developed in order to fill some caveats in the mechanism of action of ACEIs. Indeed, as seen above, ACEIs fail to suppress production of angiotensin II by alternative enzymatic pathways, such as chymase and other tissue-based protease, that can upregulate on the long term and attenuated their BP lowering effect. In addition, ACEIs administration is associated with higher bradykinin plasma concentrations, increasing the risk of angioedema. Thus, targeting the blockade of angiotensin II receptors instead of angiotensin II production, appeared as an effective strategy to improve the antihypertensive efficacy and target organ protection.

The hemodynamic effects of ARBs are similar to those of ACEIs. Because angiotensin II is a potent vasoconstrictor peptide, the blockade of its action ate AT_1 receptors leads to vasodilation of small resistance arteries, reduction in total peripheral resistance and BP lowering. Cardiac output remains unchanged. Despite BP lowering, heart rate remains unchanged, and there is no postural hypotension, likely because ARBs reset baroreceptor function.

Like ACEIs, ARBs are able to protect target organs in hypertensive patients. Indeed, long-term administration of ARBs is associated with a reduction of left ventricular hypertrophy (LVH), an improvement of endothelial function, a destiffening of large arteries [27,28] and a remodeling of large and small arteries [33]. Relaxation of large arteries leads to less pressure wave reflection and their slower propagation along the aorta, thus it is associated with a fall in central systolic and pulse pressures [6]. Renoprotection is observed in early type2 diabetic nephropathy, and proteinuria is reduced independently of BP lowering [34,35]. Whether ARBs are more effective than ACEIs for reducing proteinuria in diabetic nephropathy has not been clearly established. The first head-to-head trial of an ARB (telmisartan) versus an ACEI (enalapril) in patients with type 2 diabetes and early nephropathy [36] did not show any significant difference between drugs, for the reduction in glomerular filtration rate. In a much larger number of patients during the ONTARGET study [37], eGFR declined significantly least with ramipril compared with telmisartan, whereas the increase in urinary albumin excretion was less with telmisartan than with ramipril.

Target organ protection occurs mostly in response to the reduction in BP, but a large number of evidences favor also a direct effect of ARBs on the cardiac, renal and arterial tissues. For instance, several *meta*-analyses or review ranked ARBs (although with less date than with ACEIs) as the most effective antihypertensive drugs to reduce LVH [26], small artery remodeling [22] and large artery stiffness [6,7], compared to calcium-channel blockers, diuretics and beta-blockers, although BP lowering was similar in all treatment groups. In addition, ARBs are effective antihypertensive drugs for a BP-independent effect on arterial stiffness, mainly through long-term arterial remodeling and reduction of arterial wall fibrosis. In long-term controlled studies, the ARBs olmesartan [27] and valsartan [28] had the capacity to reverse aortic stiffening independently of changes in BP.

5.2. Side effects

ARBs are generally well-tolerated drugs. By contrast to ACEIs, cough and angioedema are much less common with ARBs since they have no effect on kininase II or other enzymes involved in the metabolisms of substance P, or other peptides

Functional renal insufficiency is as common as with ACEIs, since it has the same mechanisms. For similar reasons, ARBs, like ACEIs, are contra-indicated during the second and third trimester of pregnancy. Hyperkalemia is uncommon, except in patients with chronic renal disease and heart failure or diabetes, receiving potassium-sparing diuretics or potassium supplements.

ARBs are contra-indicated in pregnancy, in patients with previous hyperkalemia, and in patients with bilateral renal artery stenosis (Table 2).

6. Calcium-channel blockers

Calcium-channel blockers (CCBs) are a heterogeneous class of drugs, which include verapamil (a benzothiazepine), diltiazem (a phenylalkylamine), and dihydropyridines (DHPs) such as nifedipine [38] and amlodipine [39] (Fig. 1 and Table 1).

6.1. Mechanism of action

DHPs block the voltage-dependent L-type calcium channels (where "L" stands for long-lasting referring to the length of activation) [40]. Thus, DHPs block the depolarization of vascular smooth muscle cells (VSMCs), cardiac myocytes and cardiac nodal tissue (sinoatrial and atrioventricular nodes), which are primarily dependent on Ca^{2+} influx. DHP have vascular selectivity, i.e. they block the VSMC's calcium-channel preferentially to the cardiac myocyte's calcium channel, whereas verapamil and diltiazem have cardiac selectivity, i.e. they are more effective in cardiac muscle than in VSMCs [39]. The vascular selectivity of DHPs has been explained by the depolarized resting potential of VSMCs in comparison with cardiac myocytes, because it favors the "high affinity" inactivated state of the L-type calcium channel [41]. The cardiac selectivity of verapamil and diltiazem has been explained by their use-dependency, i.e. enhanced blockade of the L-type calcium channel with repeated depolarization [41].

CCBs are vasodilators of small resistance arteries. Acutely administered, they reduce total peripheral resistance and mean blood pressure, and they increase cardiac output. After chronic administration, cardiac output returned toward pretreatment levels, and mean arterial pressure and systemic vascular resistance remained low. These changes are associated with a relaxation of large arteries, thus with less arterial stiffness and wave reflection, leading to a fall in central systolic and pulse pressures [6].

CCBs increase coronary blood flow, thus myocardial oxygen supply, but the effects of CCBs on myocardial oxygen demand depend on their effects on heart rate. DHPs, that accelerate heart rate, are less effective for reducing myocardial oxygen consumption than verapamil and diltiazem that slower heart rate. Tachycardia is observed in response to BP lowering after DHPs, because baroreflex activation outweighs the direct effect on the sinus node. Tachycardia is less marked after chronic administration because of baroreflex resetting, and heart rate can even be normalized [42]. However, even after chronic administration, an increase in markers of sympathetic nervous system activation [43–45] has been reported with some long-acting DHPs, such as amlodipine and nifedipine GITS (Gastro-Intestinal delivery System), indicating persisting baroreflex activation. Verapamil [38] and diltiazem [46] are bradycardic agents, because of their direct inhibitory effect on the cardiac nodal tissue and lack of vascular selectivity. In parallel with their inhibitory effect on sinus node, CCBs slow conduction in the atrioventricular (AV) node. They have little if any effect on the automaticity of cardiac myocytes. Verapamil and diltiazem are negative inotropic agents, whereas DHPs have little effects, since their direct effect is partly compensated by afterload reduction and baroreflex-mediated inotropic effect. In conclusion, DHPs are more potent vasodilators, and generally have less cardiodepressant activity than representatives of other classes of calcium channel antagonists such as diltiazem and verapamil. CCBs have no direct effect on the venous system, and do not modify pre-load.

The effects of CCBs on progression of renal disease in patients with essential hypertension remain controversial. Because renal efferent arterioles do not express L-type channels, CCBs preferentially dilate the afferent arterioles, and thus may increase glomerular capillary pressure and accelerate glomerulosclerosis. However, CCBs may have renoprotective effect through additional mechanisms, including the ability to retard renal growth [47]. The newer DHPs, including manidipine [48] which inhibits both L- and T-type channels, dilate not only afferent but also efferent renal arterioles [49] and may have a beneficial effect, improving glomerular hypertension and providing renoprotection.

Ankle edema is due to fluid extravasation in response to an increase in transcapillary gradient, itself due to an imbalance between upstream arteriolar vasodilatation and downstream venoconstriction [50]. Orthostatism exaggerates the transcapillary gradient [50]. Ankle edema, that is more frequently observed with DHPs, does not mean sodium retention, but rather local hemodynamic changes.

6.2. Side effects

CCBs are generally well-tolerated drugs. High doses of DHPs often cause ankle edema, headache, flushing and tachycardia; their mechanisms have been described above, in the section on mechanisms of action [51]. High doses of verapamil can cause constipation. Gingival hypertrophy can be observed after all CCB.

Non-DHPs can induce severe bradycardia, in addition to impairment of atrioventricular conduction and depression of contractility. Therefore, CCB especially the cardiac selective, non-DHPs should not be given to patients with preexistent bradycardia, atrioventricular conduction defects, or systolic heart failure. Similarly, non-DHPs should not be administered to patients being treated with a beta-blocker, because verapamil and diltiazem exaggerate the effects of beta-blockade on cardiac electrical and mechanical activity. Verapamil and diltiazem have important drug interaction with digoxin, cyclosporine, dabigatran, atorvastatin and simvastatin, among others.

Verapamil and diltiazem are contra-indicated in patients with atrio-ventricular block, severe left ventricular dysfunction, and heart failure (Table 2).

7. Other pharmacological classes

7.1. Renin inhibitors

The only direct renin inhibitor currently available for treating hypertensive patients is aliskiren, a non-peptide and orally active drug (Fig. 1 and Table 1). Aliskiren is a highly potent and selective inhibitor of human renin [52]. The increase in plasma renin concentration, which is observed after aliskiren administration, is higher than in response to ACEIs and ARBs. However, the increase in plasma renin concentration does not translate into a paradoxical rise in BP since the reactive increase in plasma renin concentration is much smaller than the 20–100-fold rise required for overcoming the 95% of renin inhibition [53].

By contrast to each of the five major antihypertensive classes described above, no large randomized clinical trial has demonstrated a beneficial effect of aliskiren on CV or renal morbid and fatal events in hypertension. The Aliskiren Trial In Type 2 Diabetes Using Cardio-renal Endpoints (ALTITUDE), in which aliskiren was administered on top of a RAS blocker, showed no significant reduction in CV events, compared to placebo, but more adverse events, and a higher rate of hyperkalaemia, hypotension and renal complications (ESRD and renal death), [54]. Aliskiren was prescribed as monotherapy or associated with a thiazide diuretic or a calcium channel blocker in The Randomized Controlled Trial of Aliskiren in the Prevention of Major Cardiovascular Events in Elderly People (APOLLO) [55]. This study has been stopped, although no harm was evidenced in the aliskiren-treated group [55].

Renin inhibitors are contra-indicated in pregnancy, in patients with previous angioneurotic edema, hyperkalemia, and in patients with bilateral renal artery stenosis (Table 2).

7.2. Alpha-adrenergic receptor blockers

Three selective alpha1-adrenoceptor antagonists are available for the treatment of hypertension: prazosin, terazosin and doxazosin (Fig. 1 and Table 1). These agents are particularly active in BP lowering when BP is measured with the patient in the standing position, or during exercise. On the long term, the significant BP reduction is associated with little or no change in cardiac output, heart rate and cardiac index [56]. A major limitation to the use of alpha1-adrenergic receptor blockers is the first-dose phenomenon, which describes the sudden severe symptomatic orthostatic hypotension which generally occurs during the 90 min following the first dose, or when the dose is increased rapidly. Giving the pill at bedtime or using GITS (gastro-intestinal therapeutic system) which provides a true 24 h delivery, decreased the incidence of syncope [57].

7.3. Centrally acting agents

The most frequently used centrally acting antihypertensive drugs are clonidine, an alpha2-adrenergic agonist, rilmenidine, acting on nonadrenergic imidazoline receptors, and methyldopa (Fig. 1 and Table 1).

Alpha2-adrenergic agonists, such as clonidine, stimulate alpha2-adrenoceptor in the brainstem, resulting in a reduction in sympathetic outflow from the central nervous system [58]. The decrease in plasma concentrations of norepinephrine is directly correlated with the hypotensive effect. Clonidine lowers BP by an effect on both cardiac output and total peripheral resistance. Side effects include sedation, fatigue, dryness of the mouth, reduction in libido, sleep disturbance with vivid dreams, symptomatic bradycardia, and atrioventricular blocks in predisposed patients [2].

Rilmenidine is the first example of a hypotensive drug which has more affinity for imidazolin preferring receptors than for classical alpha 2-adrenoceptors. Rilmenidine has a two to three times higher selectivity for the nonadrenergic imidazoline receptors within the nucleus reticularis lateralis, as compared to clonidine [59]. Rilmenidine dose-dependently decreases BP, acting as a vasodilator by decreasing vascular resistance through inhibition of the adrenergic nervous system, even while the BP changes due to standing and exercise [60]. Central side effects are significantly less frequent with rilmenidine than with clonidine or methyldopa. In contrast with clonidine, no sodium retention or weight gain is observed during chronic treatment with rilmenidine.

Methyldopa depletes neuronal stores of norepinephrine. Methyldopa is converted into alpha-methyl-norepinephrine which is stored in the neurosecretory vesicles of adrenergic neurons, substituting for norepinephrine itself. Methyldopa is thus released instead of norepinephrine when the adrenergic neuron discharges [2]. Side effects include sedation, fatigue, dryness of the mouth, reduction in libido, and less frequently but not rarely Parkinsonian symptoms, hyperprolactinemia, hepatotoxicity and hemolytic anemia.

Centrally acting agent are contra-indicated in patients with severe depression (Table 2).

7.4. Direct-acting vasodilators

Direct-acting vasodilators are a heterogeneous group of drugs, whose side effects are tachycardia and fluid retention. Only minoxidil and hydralazine, the most often prescribed in hypertension, will be discussed (Fig. 1 and Table 1).

7.4.1. Minoxidil

Minoxodil sulfate, the active metabolite of minoxidil [61], opens sarcolemnal adenosine triphosphate-dependent potassium channels ($SARCK_{ATP}$) on vascular smooth muscle cells (VSMCs), leading to arterial relaxation [62]. Both large and small arteries are relaxed [63]. Minoxidil acts predominantly on the arterial site of the blood vessels, without venodilation [64]. Counter-regulatory and neurohumoral changes include activation of SNS and RAAS [65] leading to fluid retention which attenuates the BP lowering effect. The extent of hypertrichosis may require discontinuation of minoxidil, but usually disappears within a few weeks [66]. Because of the severity of adverse effects, minoxidil is not indicated in any cardiovascular pathology, except, in some cases, in severe hypertension as third-line agent after a diuretic for patients unresponsive to other treatments, particularly in patients with chronic kidney disease (CKD) [67].

7.4.2. Hydralazine

Hydralazine is a direct vasodilator of resistance arterioles (Fig. 1 and Table 1). It reduces total peripheral resistances, without any effect on the venous system. As with minoxidil, counter-regulatory and neurohumoral changes occur in response to BP lowering. They include an activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. Side effects mainly include fluid retention and tachycardia that are dose-dependent and may limit the effectiveness of BP lowering [68]. Hemolytic anemia, vasculitis, glomerulonephritis, and a lupus-like syndrome have also been reported.

Hydralazine is no more indicated for the long-term treatment of hypertension [69]. However, it is indicated for gestational or chronic hypertension in pregnancy, and for urgent control of severe hypertension in pregnancy, in combination with a beta-blocker, according to the NHBPEP (Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy) [70] two conditions where there is a long experience of hydralazine with few adverse events documented [71].

8. Conclusion

In conclusion, the various mechanisms of action of the pharmacological classes of antihypertensive drugs described in this review show their complementarity for treating hypertension, well known as a mosaic of pathophysiological disturbances. Successful treatment of hypertension is possible with limited side effects. A better knowledge of the molecular receptor targets, the various sites of action along the arterial system, and the extra-arterial sites of action, allows the physician to better understand in which type of hypertension a given pharmacological class of antihypertensive drug is most indicated and in which patients drugs are contra-indicated.

An ideal drug does not exist, and research in hypertension has been a good example of such statement, given its complex pathophysiology. However, it is possible in conclusion, for research and teaching purposes, to draw the ideal characteristics of a modern antihypertensive drug. They should associate an excellent pharmacokinetic profile with high bioavailability and long half-life, an adapted pharmacodynamic profile with long duration of action and high selectivity for molecular targets (receptor, enzyme) implicated in major pathophysiological blood pressure regulation pathways, and eventually a mechanism of action which does not expose to major side effects. Thus, ideal characteristics should also include, as a consequence of the former, a high blood pressure lowering effect as monotherapy with rapid onset, a sustained efficacy over the 24 h after once-daily dose, a clear dose-response relationship allowing an easy monitoring of drug dosage, and an optimal tolerability profile.

Conflict of interest

Stéphane LAURENT has received grants, honoraria as speaker or chairman, or consultation fees for advisory board from AstraZeneca, Bayer-Schering, Boehringer-Ingelheim, Chiesi, Daichi-Sankyo, Esaote, Menarini, Negma, Novartis, Recordati, and Servier.

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