Drugs for systemic hypertension and angina

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Abstract

Drugs used for the treatment of hypertension and for management of angina are discussed. Their major mechanisms of action, key pharmacokinetic principles essential for their safe use, and important adverse effects are explained. Each class of drug is also given context for effective clinical use.

Keywords Alpha-blockers; angina pectoris; beta-blockers; calcium channel blockers; hypertension; nitrates; sinus node inhibitor; vasodilators

What's new?

- Aliskiren, a direct renin inhibitor, is not recommended for use in combination with an ACE inhibitor or angiotensin II receptor antagonist due to a potential for deterioration in renal function and hyperkalaemia
- Ivabradine is a specific sinus node inhibitor that slows heart rate without negative inotropic actions. It is an alternative to a β-blocker or a heart rate-limiting calcium channel blocker. It has an additive anti-anginal action when given with a β-blocker, but should be avoided with non-dihydropyridine calcium channel blockers
- Ranolazine is a late sodium current inhibitor that relaxes the myocardium in diastole and reduces myocardial oxygen demand, while increasing intramyocardial coronary blood flow. It does not have negative inotropic actions

Drugs for systemic hypertension

Drugs used for the management of hypertension manipulate three systems that control systemic blood pressure: the autonomic nervous system, the renin-angiotensin-aldosterone system and locally acting vascular mediators (Figure 1).

Calcium channel blockers

Mechanisms: calcium channel blockers reduce blood pressure largely by arterial vasodilatation, achieved by blocking the influx of calcium via transmembrane L-type channels in the smooth muscle cells of resistance vessels. These channels are also present in the myocardium and blockade here causes a reduction in heart rate and contractility, which contributes to the reduction of systemic blood pressure.

Calcium channel blockers can be subdivided into the dihydropyridine group (such as nifedipine and amlodipine) and the non-dihydropyridines (Table 1), which bind to different sites on L-type calcium channels. The different sub-unit structures of these channels in vascular and cardiac tissue explain drug selectivity; the dihydropyridines act mainly on vascular smooth muscle, whereas verapamil and, to a lesser extent, diltiazem also have important actions on the myocardium.[1]

Pharmacokinetics: most calcium channel blockers have short half-lives and modified-release formulations are necessary for a prolonged action. Amlodipine has a longer half-life of 1–2 days.

Adverse effects: dihydropyridines produce vasodilator effects, such as flushing, headache, ankle oedema and reflex tachycardia. Many of these (other than oedema) can be reduced by using a modified-release formulation. By contrast, diltiazem and verapamil produce less vasodilatation but can cause bradycardia and heart block, which is a greater risk when they are taken with a β-blocker. Verapamil and diltiazem can exacerbate heart failure owing to their negative inotropic effects, but many dihydropyridines can also reduce myocardial contractility when left ventricular function is impaired.

β-adrenoceptor antagonists (β-blockers)

Mechanism: β-adrenoceptor antagonists are competitive antagonists; they reduce blood pressure by decreasing cardiac output and, indirectly, by reducing renin release, which results in vasodilatation and decreased plasma volume.[2] There are many different β-blockers with differing pharmacological effects (Table 2).

- β_1-adrenoceptor selective (cardioselective) drugs (e.g. atenolol, bisoprolol and metoprolol) show selectivity for β_1-adrenoceptors, although this decreases at higher doses.
- Non-selective drugs (e.g. propranolol) are antagonists at both β_1- and β_2-adrenoceptors. Both non-selective and β_1-selective drugs have the same effect on blood pressure.
- Partial agonist activity at β-adrenoceptors (e.g. pindolol) results in less resting bradycardia and some peripheral vasodilation.
- Vasodilator activity may also be produced by drugs with antagonist action at α-adrenoceptors (e.g. labetalol and carvedilol), or by those promoting endothelial nitric oxide production (e.g. nebivolol). Vasodilatation may be advantageous when treating hypertension.[3]

Pharmacokinetics: lipophilic drugs, such as propranolol and metoprolol, have good gut absorption and extensive liver metabolism which varies greatly among individuals, so individualized dosing is more important to maximize benefit. Their half-lives are generally short, and modified-release formulations are usually preferred.

Hydrophilic drugs, such as atenolol, are less well absorbed orally, but are excreted unchanged in the urine. They usually give more predictable plasma concentrations and generally have longer half-lives.

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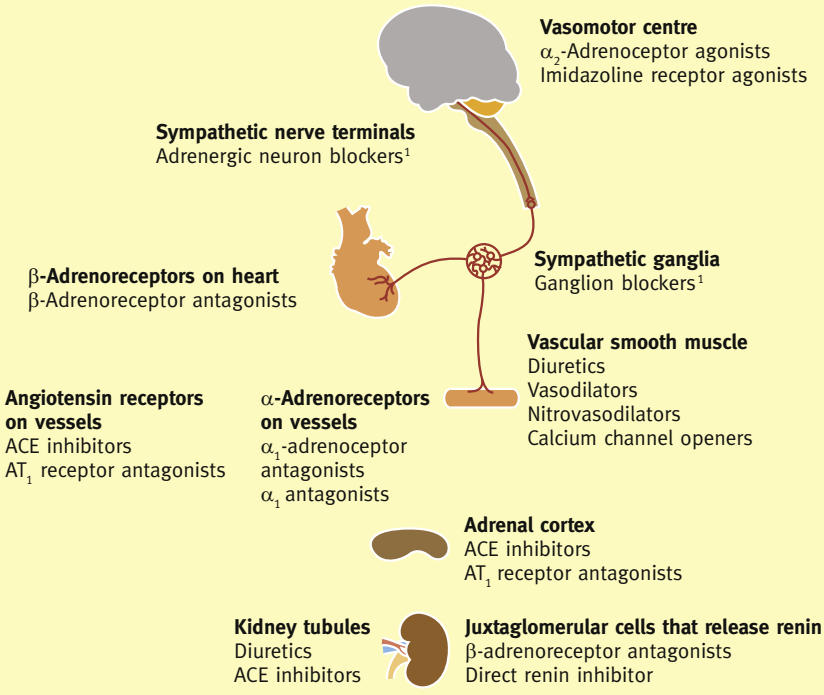
Sites of action of drugs for the treatment of hypertension



[1]Classes of drug that are rarely used now. ACE, angiotensin-converting enzyme.

Adapted from Waller DG, Renwick AG and Hillier K. *Medical Pharmacology and Therapeutics*. 3rd edition. Philadelphia: Saunders, 2010. With permission from Elsevier.

Figure 1

Adverse effects: β_1-adrenoceptor antagonists can cause acute left ventricular failure when given in large doses to people with impaired left ventricular function. They can also exacerbate intermittent claudication and Raynaud's phenomenon, and excessive bradycardia can lead to syncope.

β_2-adrenoceptor antagonism can produce bronchospasm in patients with asthma, a potential problem even with cardioselective drugs. This is rarely an issue in chronic obstructive pulmonary disease, where there is little reversibility of the airway narrowing. Gluconeogenesis in the liver is reduced,

Calcium channel blockers

Drug	T1/2 (h)	Modified release	Negative inotropic effect	Vasodilator	Bradycardia	Dose reduction	Pregnancy	Breastfeeding
Amlodipine	30–60	No	No	+++	No	L	?A,3	A
Felodipine	12–25	Yes	No	+++	No	L	A	
Isradapine	2–6	No	+	+++	No	L	?A,3	A
Lacidipine	7–8	No	+	+++	No	L	?A,3	A
Lercanidipine	3–5	No	+	+++	No	L,R	A	A
Nicardipine	1–12	Yes	+	+++	No	L,R	?A,3	A
Nifedipine	2–4	Yes	+	+++	No	L	?A,3	
Diltiazem	2–5	Yes	++	++	Yes	L,R	A	?A
Verapamil	2–5	Yes	+++	+	Yes	L	A	

T1/2, plasma half-life.
Modified-release: formulation available to prolong effect.
Negative inotropic effect: when present, avoid in heart failure.
Vasodilator: comparative degree of vasodilator action.
Bradycardia: reduces heart rate at rest and on exercise.
Dose reduction: reduce dose or avoid in liver (L) impairment, or reduce dose in renal (R) impairment.
Pregnancy: avoid (A), or avoid (?A) unless essential in third[3] trimester as may inhibit labour.
Breastfeeding: manufacturer advises avoid (A) since no information available, or avoid (?A) unless no suitable alternative.

Table 1