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 here. Their major mechanisms of action, key pharmacokinetic principles essential for safe use and important adverse effects are explained. Each class of drug is also given context for effective clinical use.

Keywords α-Adrenoceptor blockers; β-adrenoceptor blockers; angina pectoris; calcium channel blockers; hypertension; MRCP; nitrates; sinus node inhibitor; vasodilators

Key points

- Antihypertensive medications target three main mechanisms to lower blood pressure: the renin–angiotensin system, the autonomic nervous system and locally active mediators
- Anti-anginal medications primarily aim to reduce myocardial oxygen demand or improve oxygen supply to the myocardium
- Oxygen demand to the myocardium is typically reduced by direct action on the heart reducing heart rate and contractility, by reducing preload by dilatation of the venous system, or by reducing afterload by decreasing arterial resistance

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 (e.g. nifedipine, amlodipine) and non-dihydropyridines (Table 1), which bind to different sites on L-type calcium channels. The different subunit structures of these channels in vascular and cardiac tissue explain drug selectivity; dihydropyridines act mainly on vascular smooth muscle, whereas verapamil and, to a lesser extent, diltiazem also have important actions on the myocardium.

Pharmacokinetics: most calcium channel blockers have short half-lives, so 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-adrenoceptor blocker. Verapamil and diltiazem can worsen heart failure owing to their negative inotropic effects, but many dihydropyridines 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. There are many different β-blockers with differing pharmacological effects (Table 2):

- β_1-adrenoceptor selective (cardioselective) drugs (e.g. atenolol, bisoprolol, 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 vasodilatation.
- Vasodilator activity can also be produced by drugs with antagonist action at α-adrenoceptors (e.g. labetalol, carvedilol), or by those promoting endothelial nitric oxide production (e.g. nebivolol). Vasodilatation may be advantageous when treating hypertension.

Pharmacokinetics: lipophilic drugs, such as propranolol and metoprolol, have good gut absorption and extensive liver metabolism that 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.

Adverse effects: β_1-adrenoceptor antagonists can cause acute left ventricular failure when given in large doses to people with

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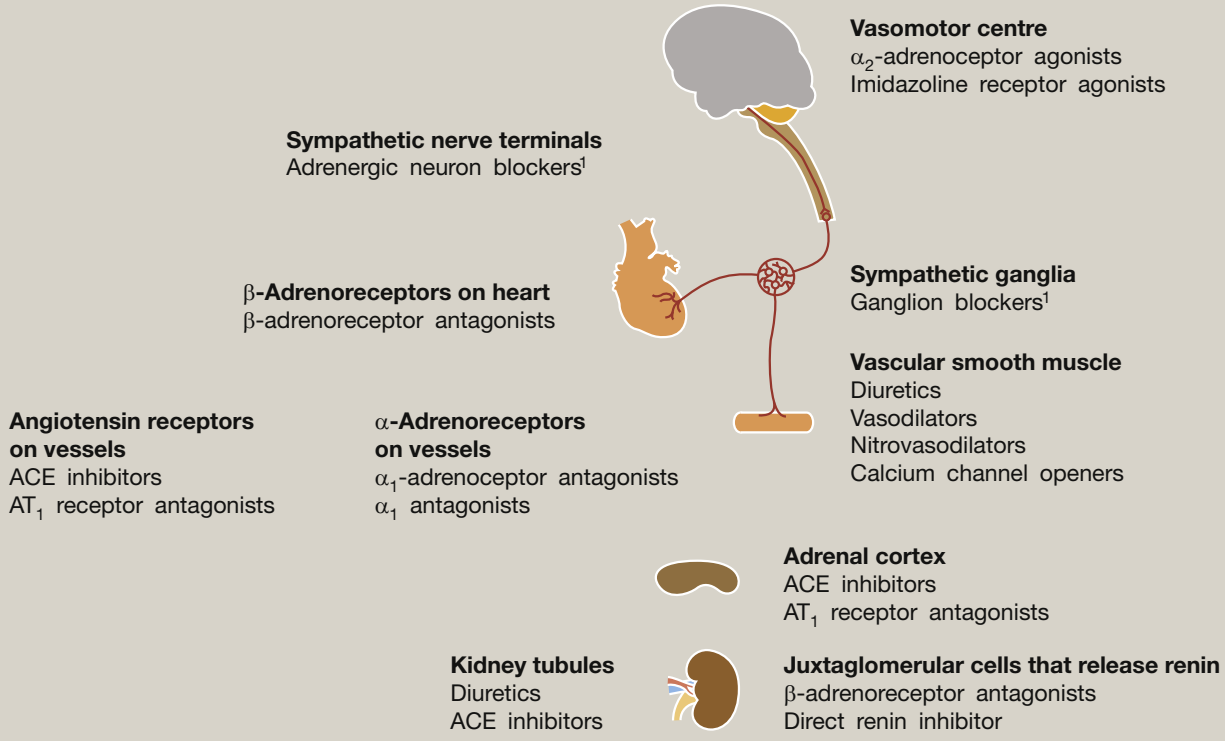
Sites of action of drugs for the treatment of hypertension



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

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

Figure 1 AT1 receptor: Angiotensin II receptor type 1.

Calcium channel blockers

Drug	$t_{½}$ (hours)	Modified-release	Negative inotropic effect	Vasodilator	Bradycardia	Dose reduction	Pregnancy	Breastfeeding
Dihydropyridines								
Amlodipine	30–60	No	No	+++	No	L	?A (3)	A
Felodipine	12–25	Yes	No	+++	No	L	A	
Isradipine	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)	
Non-dihydropyridines								
Diltiazem	2–5	Yes	++	++	Yes	L, R	A	?A
Verapamil	2–5	Yes	+++	+	Yes	L	A	

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 trimester (3) as can inhibit labour.
Breastfeeding: manufacturer advises avoid (A) as no information is available, or avoid (?A) unless no suitable alternative.
$t_{½}$, plasma half-life.

Table 1

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