Drugs acting on the heart: antihypertensive drugs

Matthew Charlton

Jonathan P Thompson

Abstract

Antihypertensive drugs are used commonly in anaesthesia and intensive care medicine. Patients might require antihypertensive drugs before surgery for the treatment of essential hypertension, pre-eclampsia or, occasionally, for conditions such as phaeochromocytoma; during surgery as part of a deliberate hypotensive anaesthetic technique; or to reduce postoperative cardiovascular complications. Here, we discuss the physiology of blood pressure control, the pharmacology of antihypertensive drugs, current guidelines, and practical applications of antihypertensive therapy.

Keywords Antihypertensive agents; autonomic nervous system; blood pressure; hypertension; renin—angiotensin system; vasomotor system

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Learning objectives

After reading this article, you should be able to:

- categorize antihypertensive treatments according to their mechanisms of action
- name the important potential adverse effects associated with specific antihypertensive drugs
- decide when hypertension should be treated, according to recent guidelines

Introduction

Arterial pressure is modulated by the interaction among vessel tone, blood volume, and cardiac function, which are regulated by local and nervous mechanisms. Local mechanisms include metabolites that influence vascular tone and blood flow within tissues. Nervous mechanisms control the distribution of blood throughout the body, as well as coordination of cardiac output, heart rate, and contractility. The autonomic nervous system (ANS) is controlled by centres in the spinal cord, brainstem and hypothalamus, which are influenced by higher centres. The renin—angiotensin system (RAS) affects vascular tone and excretion of sodium and water in response to changes in circulating volume and arterial pressure. Blood pressure can be manipulated by drugs acting at several of these sites (Figure 1).

Autonomic nervous system

Centrally acting agents

Clonidine: a central α_2-agonist that decreases sympathetic tone and is occasionally used for the treatment of hypertension. Premedication (3—5 μg/kg orally or 1—2 μg/kg intravenously) attenuates perioperative sympathetic responses. Clonidine reduces the minimum alveolar concentration (MAC) of anaesthetic agents and has analgesic effects when administered epidurally, being synergistic with opioids. Adverse effects include sedation, bradycardia and rebound hypertension after acute withdrawal of chronic therapy.

Methyldopa: a DOPA analogue that is metabolized to α-methylnorepinephrine, which acts as a potent central α_2-agonist. Methyldopa is mostly used in the treatment of pregnancy-associated hypertension; the initial dose is 250 mg two or three times daily. Adverse effects include oedema, hepatotoxicity, positive direct Coombs' test (10—20%), and bone marrow suppression.

Moxonidine: an imidazoline I_1-receptor agonist and a structural analogue of clonidine that acts as a central sympatholytic agent. Moxonidine is used when systemic vascular resistance is high but heart rate and stroke volume are normal. It also can be used in the management of hypertension associated with end-stage renal failure. The main adverse effect is bradycardia.

General anaesthetic agents: also cause hypotension, mainly by decreasing central sympathetic tone and lowering the peripheral vascular resistance by causing dose-related vasodilatation.

Sympathetic outflow

Epidural and spinal: local anaesthetics and opioids inhibit the sympathetic outflow leaving the spinal cord from T1—L2, causing vasodilation and hypotension.

α-Blockers

α-Blockers inhibit the action of catecholamines at peripheral α-adrenergic receptors.

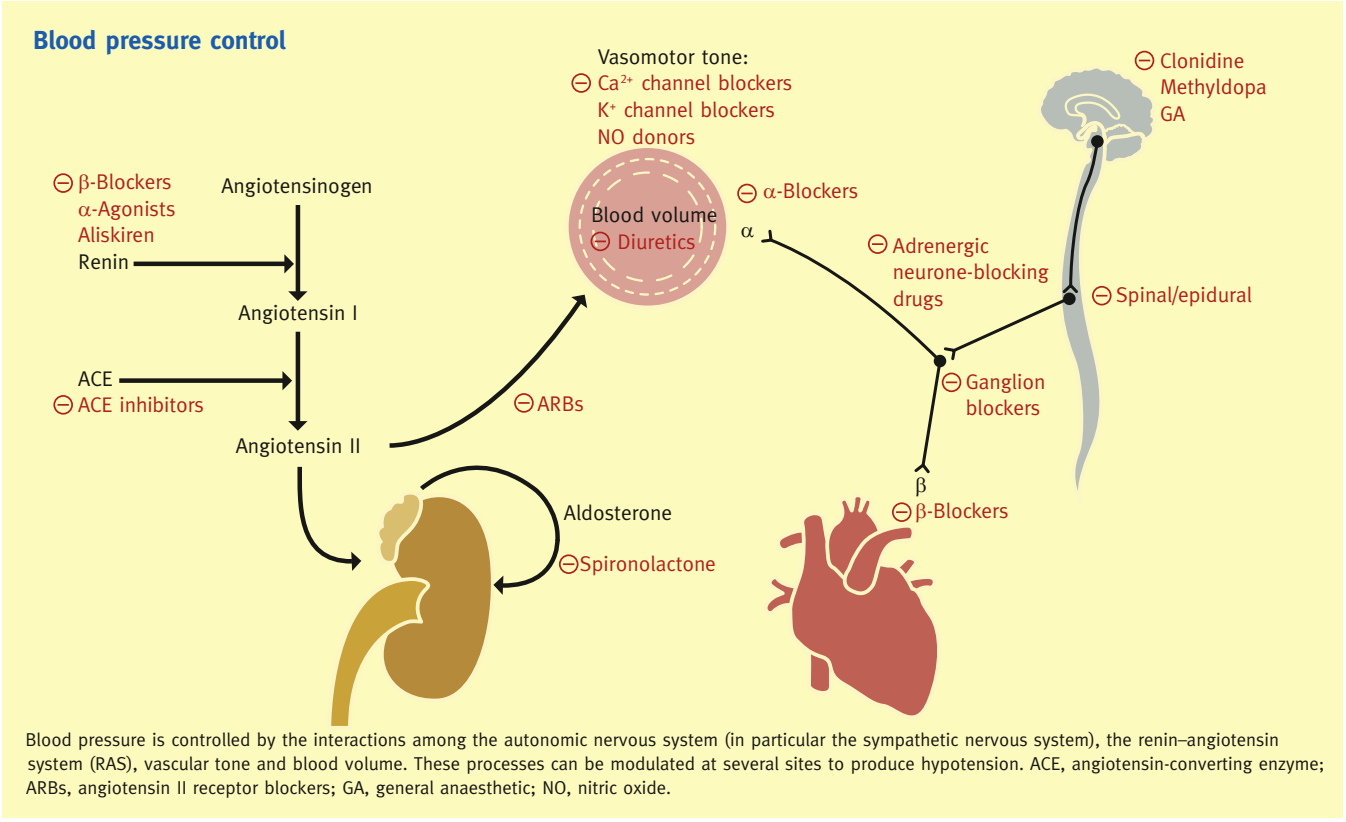
Phentolamine: a competitive non-selective, short-acting α-blocker used in the treatment of hypertensive crises seen with phaeochromocytoma or cocaine intoxication. An intravenous dose of 1—5 mg causes a rapid reduction in blood pressure for 5—20 minutes.

Phenoxybenzamine: a long-acting, non-selective α-blocker that is mainly used in the preoperative management of phaeochromocytoma. Starting dose is 10 mg orally.

Prazosin and doxazosin: selective α_1-blockers that cause vasodilation. They are also used for benign prostatic hyperplasia (relaxation of urinary tract smooth muscle), congestive heart

Matthew Charlton *MBChB FRCA is a Specialist Registrar and Honorary Lecturer in Anaesthesia and Critical Care, University Hospitals of Leicester NHS Trust, UK. Conflicts of interest: none declared.*

Jonathan P Thompson *BSc (Hons) MD FRCA FFICM is a Senior Lecturer and Honorary Consultant in Anaesthesia and Critical Care at the University of Leicester and UHL NHS Trust, Leicester Royal Infirmary, UK. Conflicts of interest: none declared.*



Blood pressure is controlled by the interactions among the autonomic nervous system (in particular the sympathetic nervous system), the renin–angiotensin system (RAS), vascular tone and blood volume. These processes can be modulated at several sites to produce hypotension. ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; GA, general anaesthetic; NO, nitric oxide.

Figure 1

failure and Raynaud's disease. All α-blockers should be titrated carefully as first-dose hypotension can be severe. They have additional favourable metabolic effects on lipid and glucose metabolism.

β-Blockers

β-blockers cause hypotension via several mechanisms: they reduce cardiac output (decreased heart rate and contractility), central sympathetic nervous activity, plasma renin concentrations and peripheral resistance. Hence, they are useful antihypertensive agents in patients with ischaemic heart disease, obstructive cardiomyopathy, congestive heart failure (with caution), arrhythmias, anxiety and thyrotoxicosis. Adverse reactions include worsening of unstable heart failure, bronchospasm, cold extremities and impaired glucose control. β-blockers can be classified according to:

- Cardioselectivity: β_1-selective drugs (e.g. atenolol, metoprolol, bisoprolol) cause fewer adverse β_2-mediated effects, such as bronchospasm and hyperglycaemia.
- Intrinsic sympathomimetic activity (ISA): drugs with ISA (e.g. pindolol) are partial agonists that are less likely to cause bradycardia, arteriovenous conduction disturbances or cold extremities.
- Combined α- and β-blockers (e.g. labetalol, carvedilol): are non-selective β- and α_1-antagonists that cause vasodilation and have fewer adverse effects.

Atenolol is a cardioselective β-blocker with no ISA. Dose is 25–100 mg per day orally or 2.5–10 mg by slow intravenous bolus, which can be followed by an infusion.

Labetalol is a combined α_1-and β-blocker (ratio 1:7 intravenous; 1:3 oral). The oral dose is 200–800 mg daily in divided doses. An intravenous bolus of 50–200 mg can be given slowly, or an infusion of 5–150 mg/h can be titrated to effect. It reduces the systemic vascular resistance, while maintaining cerebral, renal, and coronary blood flow.

Dopaminergic agonists

Fenoldopam is an antagonist at peripheral DA_1 receptors that causes vasodilation, primarily of the coronary, renal and mesenteric vasculature. Used in hypertensive emergencies and occasionally used in low doses for renal protection from acute tubular necrosis or acute renal failure, although recent studies suggest this may not be beneficial.[1]

Renin–angiotensin system

The renin–angiotensin system (RAS) is involved in cardiovascular and fluid homeostasis. It can be manipulated at several points to cause hypotension:

- inhibition of renin release (β-blockers or central α-agonists)
- direct inhibition of renin (e.g. aliskiren)
- inhibition of angiotensin-converting enzyme (ACE) (e.g. enalapril, lisinopril) to prevent production of the potent vasoconstrictor angiotensin II
- direct blockade of angiotensin II receptors (AT1) (e.g. losartan, candesartan)
- competitive inhibition of aldosterone (e.g. spironolactone)