Learning objectives:

- To understand regulation of blood pressure and significance of hypertension
- To familiarise oneself with blood pressure monitoring
- To identify drugs used in hypertension and appreciate their characteristics
- To review current guidelines for the management of hypertension
- To understand management goals
- To appreciate use of drug therapy, patient monitoring and follow-up required
- To identify principles of drug therapy in hypertensive emergency.

Background

Hypertension is a chronic condition characterised by a sustained diastolic reading greater than or equal to 80 mmHg and a systolic reading greater than or equal to 120 mmHg (120/80 mmHg). Occurrence can damage blood vessels and increase probability of development of atheromatous disease. Treatment is aimed to decrease morbidity and mortality.

Factors implicated in primary hypertension include:

- age
- genetics
- environment
- weight
- race.

Causes of secondary hypertension include:

- renal disease
- pregnancy
- hormonal factors
- drug-induced factors (e.g. oral contraceptives, corticosteroids).

Regulation of blood pressure

- Peripheral vascular resistance (depends on arteriolar volume)
- Cardiac output (depends on heart rate, contractility, filling pressure, blood volume)
- Blood pressure = cardiac output × peripheral vascular resistance.

Sympathetic nervous system

Baroreceptors present in the aorta and carotid sinus:

- increase cardiac output
- increase peripheral resistance.

The renin–angiotensin–aldosterone system is shown in Figure 20.1.
**Risk factors**

- Family history
- Age
- Obesity
- Smoking
- Lifestyle: stress, sedentary, diet
- Diabetes mellitus
- Hyperlipidaemia.

**Target organ damage due to hypertension**

- Cardiovascular: constriction of arterioles and insufficient blood flow to coronary vasculature leads to angina, myocardial infarction; left ventricular hypertrophy may occur due to increased cardiac output leading to heart failure.
- Renal: arteriolar nephrosclerosis leads to polyuria, nocturia, protein and red blood cells in urine, elevated serum creatinine, renal insufficiency.
- Cerebral: decreased blood flow and decreased oxygen supply lead to transient ischaemic attacks, cerebral thromboses, haemorrhage.
- Retinal: damage to arterioles of retina leads to haemorrhage, visual disturbances.

**Blood pressure measurement**

**Using a sphygmomanometer (see also Chapter 11)**

- Patient should be relaxed, sitting down with arm at about the level of the heart; check pressure in both arms.
- Three consecutive elevated readings taken on three separate occasions should be documented before the diagnosis of ‘hypertension’ is applied to a patient.
- Interpretation of results: systolic reading is more important than diastolic reading; patient history and family history are taken into consideration when deciding on line of action.

Occurrence of hypertension may exacerbate:

- atherosclerosis
- coronary artery disease
- congestive heart failure
- diabetes mellitus
- insulin resistance
- stroke
- renal disease
- retinal disease.

**Figure 20.1 Renin–angiotensin–aldosterone system.**
Management goals

- European Guidelines for the management of hypertension were issued in June 2007 by the European Society of Hypertension jointly with the European Society of Cardiology.
- Overall goal to achieve blood pressure (BP) of 140/90 mmHg.
- Goal takes into consideration comorbidities (e.g. in diabetes the goal is to achieve 130/80 mmHg).
- Pharmacotherapy should consider the five important drug classes: ACE inhibitors, angiotensin receptor antagonists, beta-blockers, calcium channel blockers and diuretics.
- Choice of drug therapy should depend on:
  - comorbidities (e.g. diabetes mellitus – ACE inhibitors or angiotensin receptor antagonists; metabolic syndrome – angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, calcium antagonists)
  - history of clinical events (e.g. myocardial infarction – beta-blockers, ACE inhibitors, angiotensin receptor antagonists; angina pectoris – beta-blockers, calcium channel blockers (avoiding short-acting dihydropyridines); heart failure – diuretics, beta-blockers (particularly carvedilol), ACE inhibitors, angiotensin receptor antagonists)
  - organ damage (e.g. renal dysfunction – ACE inhibitors, angiotensin receptor antagonists; left ventricular hypertrophy – ACE inhibitors, angiotensin receptor antagonists, calcium channel blockers).
- Regardless of which drug therapy is used, monotherapy achieves blood pressure goal in only a limited number of patients. Majority of patients require multiple drug therapy.
- Lifestyle measures are relevant for all patients: smoking cessation, weight reduction and maintenance, reduction of excessive alcohol intake, physical exercise, reduction of salt intake, increased fruit and vegetable intake, decreased saturated and total fat intake.

Management of hypertension

- Confirm diagnosis through repeated blood pressure measurement
- Patient assessment for underlying cause(s) and comorbidities
- Assess occurrence of target organ damage
- Review treatment options
- Establish treatment goals
- Identify and manage other risk factors (e.g. hyperlipidaemia)
- Patient follow-up.

Reviewing treatment options

- Pharmacotherapy or non-pharmacological measures only?
- Which drug(s)?

Diagnosis and management of hypertension are shown in Figure 20.2.

Cardiovascular risk assessment

- Urine test for proteinuria and albuminuria
- Blood tests: glucose, electrolytes, creatinine, serum total cholesterol and high-density lipoprotein (HDL) cholesterol
- ECG.

Lifestyle changes

- Weight reduction
- Exercise
• Diet (low-salt diet)
• Smoking cessation
• Alcohol restriction.

Factors influencing choice of drug
• Contraindications to drug
• Presence of target organ damage, renal disease, diabetes or cardiovascular disease
• Other coexisting disorders
• Interactions with drugs used for other conditions by the patient
• Age
• Occupation
• Lifestyle.

Use of antihypertensive drugs
• Initiate drug therapy at a low dose
• Consider multiple drug therapy
• Change to different class of drugs if drug is not producing effect on blood pressure levels or if side-effects are a significant problem
• Use formulations that provide a 24-hour control: better adherence and ensure control of blood pressure in early morning when there is surge of blood pressure. (Note use of ambulatory blood pressure monitors to detect variation of blood pressure control.)

See Figure 20.3 for decision-making in management of hypertension.

Potential indications for the use of ambulatory blood pressure monitor
• Unusual blood pressure variability
• White coat hypertension
• Evaluation of nocturnal or drug-resistant hypertension
• Determining efficacy of treatment over 24 hours
• Diagnoses and treatment of hypertension in pregnancy.

Drug therapy
• Diuretics: reduce blood volume
• Sympatholytics: reduce ability of sympathetic system to raise blood pressure
Calcium channel blockers: reduce peripheral resistance
ACE inhibitors, angiotensin II antagonists: reduce peripheral resistance

Diuretics

- Create a negative sodium balance resulting in a reduction of blood volume
- Thiazides (e.g. bendroflumethiazide, indapamide)
- Loop diuretics (e.g. furosemide) are used mainly in pulmonary oedema due to ventricular failure, chronic heart failure (see also Chapter 22).
- Potassium-sparing diuretics (e.g. amiloride (+ hydrochlorothiazide), spironolactone)
- Caution: hypokalaemia.

Thiazide diuretics

- Reduce sodium and water retention in the distal convoluted tubule in the kidney resulting in a reduction of the peripheral resistance
- Cause loss of potassium and magnesium salts
- Potassium supplementation should be considered
- Maximal hypotensive effect is reached at relatively low doses.

Bendroflumethiazide and indapamide are compared in Table 20.1 and their chemical structures shown in Figure 20.4.

Potassium-sparing diuretics

- Retain potassium and therefore no need to consider potassium supplementation
- Act in the distal convoluted tubule
- Are weak diuretics and in fact may be found in combination products with thiazides.
Side-effects of diuretics

The side-effects of diuretics are listed in Table 20.2. Hypercalcaemia and impotence may also be reported as side-effects.

For potassium-sparing diuretics, hyperkalaemia rather than hypokalaemia may occur. Key monitoring parameters to identify occurrence of hyperkalaemia include gastrointestinal hyperactivity, muscle weakness and cramps.

### Table 20.2 Side-effects of diuretics

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Key monitoring parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalaemia</td>
<td>Fatigue, weakness, bilateral calf pain, palpitations, gastrointestinal upset</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Tachycardia, dizziness upon standing up, thirst, postural hypotension, decreased skin turgor</td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>Feeling of fullness in arch of foot, occasionally painful joint – development of gout (usually big toe), high serum uric acid</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>High serum cholesterol and triglycerides</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>High serum glucose</td>
</tr>
</tbody>
</table>

### Cautions and contraindications of diuretics

- Gout
- Renal disease
- Diabetes
- Electrolyte imbalance.

### Drug interactions

- Potassium-sparing diuretics: ACE inhibitors since ACE inhibitors may cause hyperkalaemia
- With NSAIDs: hypotensive effect is inhibited.

### Beta-blockers

- Competitively block beta receptors of the sympathetic system resulting in slowing of the heart, reduction in the force of contractions and lengthening of diastole.
- Side-effects: bradycardia, heart failure, hypotension, bronchospasm, peripheral vasoconstriction, fatigue, depression, vivid dreams.
- Cautions/contraindications: asthma, COPD, peripheral vascular disease, Raynaud’s phenomenon, heart block, diabetes mellitus (they may mask symptoms of hypoglycaemic attacks).

Various beta-blockers are compared in Table 20.3 (see also Chapter 21) and their chemical structures are shown in Figure 20.5.

Propranolol has a high octanol-buffer partition coefficient indicating a high lipophilicity. It enters the central nervous system better than other beta-blockers. Its primary clearance route is through the liver while more hydrophilic agents such as atenolol are cleared primarily through the kidneys. This should be kept in mind when selecting a drug in patients with renal or liver disease.

### Intrinsic sympathomimetic activity

Beta-blockers act by stimulating beta receptors when background sympathetic activity is low and blocking them when activity is high.

- Less resting bradycardia and possibly less cold extremities
- Extrapolation in practice: limited.

### Side-effects

The side-effects of beta-blockers are summarised in Table 20.4.
Angiotensin-converting enzyme inhibitors

ACE inhibitors decrease formation of angiotensin II, resulting in decreased vasoconstriction and decrease in aldosterone production, which in turn results in decreased fluid retention.

- Rapid onset of action
- Side-effects: hypotension (especially first dose), hyperkalaemia, cough, renal impairment
- Cautions: patients receiving diuretics, peripheral vascular disease, renovascular disease, severe or symptomatic aortic stenosis, hypertrophic cardiomyopathy
- Check renal function prior to initiating therapy
- Monitor renal function during therapy
- Care in elderly patients since they are at risk of renal side-effects
- Avoid concomitant NSAID use in patients at risk of renal side-effects since concomitant use increases risk and antagonises hypotensive effect of ACE inhibitors.

Some ACE inhibitors are compared in Table 20.5.

Captopril (see Figure 20.6) contains a sulphhydryl group which serves as the zinc-binding group.
that is required for ACE inhibitory effects. The presence of the sulphhydryl group is associated with a higher incidence of skin rashes and taste disturbances. Also the sulphhydryl component may form a disulphide which results in a short half-life for the product.

Enalapril, lisinopril, perindopril and ramipril (see Figure 20.7) are dicarboxylate-containing ACE inhibitors that do not feature a sulphhydryl group. The presence of large hydrophobic heterocyclic rings in the N-ring of perindopril, ramipril, moexipril, quinapril and trandolapril result in increased potency and longer half-life when compared with enalapril and lisinopril. This feature also results in enalapril and lisinopril lacking lipid solubility. Perindopril shows the highest oral bioavailability, followed by trandolapril.

**Side-effects**
The side-effects of ACE inhibitors are summarised in Table 20.6.

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**Angiotensin II receptor antagonists (ARBs)**

These are specific angiotensin II receptor antagonists, which thus block the vasoconstrictor and aldosterone-secreting effects of angiotensin II.
• Do not inhibit breakdown of bradykinin, so less likely to cause cough as a side-effect
• Used as an alternative therapy to ACE inhibitors
• Side-effects: hypotension, dizziness, hyperkalaemia
• Caution: renal artery stenosis.

ARB half-lives and starting dosages are listed in Table 20.7 and their chemical structures in Figure 20.8.

**Calcium channel blockers**

• Examples: dihydropyridines: nifedipine, amlodipine
• Interfere with the opening/closing of calcium channels in cardiac, vascular and smooth muscle cells
• The dihydropyridines (e.g. nifedipine, amlodipine) cause peripheral vasodilatation and have little direct effect on heart compared with verapamil and diltiazem (which are other types of calcium channel blockers)
• Rapid onset of action
• Should be avoided in heart failure
• Upon withdrawal may exacerbate angina

**Rilmenidine**

This drug selectively binds to $I_1$-imidazoline receptors in the brainstem. The receptors influence adrenergic vasomotor tone involved in blood pressure regulation. $I_1$-imidazoline receptors are also available in the kidneys.
Rilmenidine is an antihypertensive agent with a central action on the brainstem and a peripheral activity in the kidney. Its characteristic is that it is selective for the $I_1$-imidazoline receptors rather than also interacting with cerebral alpha-2-adrenergic receptors.

- Available as tablets 1 mg, dosage regimen: one tablet per day
- Contraindications: severe depression, renal insufficiency (creatinine clearance <15 mL/min)
- Side-effects: rare; asthenia, palpitations, insomnia.

### Contraindications and cautions

The contraindications and cautions to use of drug therapy are summarised in Tables 20.9 and 20.10.

### Drug interactions

Some of the common drug interactions with antihypertensive drugs are listed in Table 20.11.

### Potential problems with non-prescription medicines in hypertension

- Antacids (high sodium content)
- Cold preparations for systemic use containing sympathomimetics
- NSAIDs
- Potassium-containing preparations (e.g. salt substitutes, potassium citrate indicated for cystitis).

### Pharmacist patient review

- To monitor blood pressure
- To provide patient support with drug therapy and lifestyle modifications
Drug therapy in the elderly

- Calcium channel blockers indicated as first-line agents
- Diuretics less effective when there is compromised renal function
- Beta-blockers less potent in the elderly
- Effect of ACE inhibitors may be decreased due to lower renin levels.

Hypertension in pregnancy

Two conditions associated with hypertension in pregnancy are *pre-eclampsia* – pregnancy-induced hypertension, 140/90 mmHg developing during pregnancy in a woman whose blood pressure was previously normal – and *eclampsia* – occurrence of convulsions caused by hypertension.

- Methyldopa is the drug of choice.
- Calcium channel blockers (amlodipine and nifedipine): manufacturer advises avoidance but risk of uncontrolled maternal hypertension should be balanced against risk of use of drug.
- Beta-blockers tend to cause birth of smaller babies.
- ACE inhibitors and angiotensin II receptor blockers cannot be used – they may damage the fetus and cause problems in the neonate.
- Diuretics avoided because of decreased intravascular volume.

Phaeochromocytoma

Phaeochromocytoma is a tumour of chromaffin tissue of the adrenal medulla or sympathetic paraganglia.

- Leads to uncontrolled and irregular secretion of adrenaline and noradrenaline
- Causes raised blood pressure, increased heart rate, palpitations, headache
- Use phenoxybenzamine, alpha-blockers or beta-blockers.

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**Table 20.11 Common drug interactions with antihypertensive drugs**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Interacting drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretics</td>
<td>NSAIDs</td>
<td>Decreased hypotensive effect</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>Digoxin toxicity if hypokalaemia occurs</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Antiarrhythmics</td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Sympathomimetics</td>
<td>Severe hypertension</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</td>
<td>Decreased hypotensive effect</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>NSAIDs</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td>ACE inhibitors and angiotensin II receptor blockers</td>
<td>K⁺ supplementation, K⁺-sparing diuretics</td>
<td>Hyperkalaemia</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; NSAIDs, non-steroidal anti-inflammatory drugs.
Hypertensive emergency

This is a severe elevation in blood pressure with a diastolic above 120–130 mmHg and the presence of acute or on-going end-organ damage, with cerebral infarction and pulmonary oedema being the most common occurrences of end-organ damage.

- This may be a medical emergency and requires prompt reduction of blood pressure within minutes to 1 hour
- Conditions that predispose to hypertensive emergency include phaeochromocytoma, renal vascular disease, head injury, severe burns, eclampsia
- Goal of treatment: diastolic pressure 100–119 mmHg.

Major complications that occur in a hypertensive emergency include:

- angina
- myocardial infarction
- congestive heart failure
- cerebral infarction
- intracranial haemorrhage.

Management of hypertensive crisis

- Very rapid fall in blood pressure can cause reduced cerebral perfusion leading to: cerebral infarction, blindness, renal function deterioration, myocardial ischaemia
- Oral antihypertensive drugs are used to decrease blood pressure slowly
- Parenteral treatment: rarely adopted; drug of choice is nitroprusside.

Nitroprusside

- Direct-acting arterial and venous vasodilator that is available for parenteral administration
- Immediate onset of action
- Antihypertensive effect disappears within 2–5 minutes after discontinuation
- Starting dose: 0.5–10 micrograms/kg per min via continuous infusion
- Caution: hypothyroidism, hyponatraemia, ischaemic heart disease, impaired cerebral circulation, elderly, hypothermia
- Side-effects: hypotension, nausea and vomiting; if treatment is for more than 24–28 hours, thiocyanate toxicity (it reacts with sulphhydryl groups in blood and tissue producing thiocyanate).

Labetalol

- Produces a reduction in peripheral vascular resistance, blood pressure and heart rate
- Rapid onset of action: 5 minutes
- Duration of effect: 6 hours or longer
- Dose: 0.5–2 mg/min continuous infusion
- Advantage: available for parenteral and oral administration and so allows easy conversion from intravenous administration to oral therapy
- Side-effects: orthostatic hypotension, nausea and vomiting, dizziness, flushing, headache
- Contraindications: asthma, congestive heart failure, bradycardia.

Diazoxide

- Causes a vasodilator effect on the arterioles resulting in decreased peripheral resistance. It also inhibits the secretion of insulin by the beta cells of the pancreas
- Available for parenteral administration
- Onset of action within 2–5 minutes with a preliminary rise in blood pressure immediately after administration
- Caution: ischaemic heart disease, renal impairment
- Side-effects: tachycardia, hypotension, hyperglycaemia, sodium and water retention
- Patient monitoring: blood pressure, blood glucose levels particularly in patients with diabetes.

Practice summary

- The regulation of blood pressure depends on the peripheral resistance and the cardiac output. These factors are affected by the sympathetic nervous system and the renin–angiotensin–aldosterone system.
• Drugs that are used as antihypertensives aim to reduce blood volume (diuretics), decrease sympathetic activity (beta-adrenoceptor blockers), reduce peripheral resistance (calcium channel blockers) and affect the renin–angiotensin–aldosterone system (ACE inhibitors, angiotensin II antagonists).
• Antihypertensives may be used in monotherapy or as combination therapy.

Questions

1 Compare atenolol and enalapril considering indications, dosage regimen, side-effects and contraindications.
2 Name two conditions when thiazide diuretics should be used with caution or are contraindicated.
3 What is the clinical implication when a patient who is receiving a thiazide diuretic is also started on naproxen?
4 Giving reasons for your answer, explain when bendroflumethiazide is indicated.
5 Describe drug therapy that should be considered as first line in a 58-year-old patient diagnosed with hypertension who has a history of diabetes mellitus. What other preventive drug therapy could be considered?

Answers

1 Atenolol and enalapril are compared in Table 20.12.
2 Gout, renal disease, diabetes, electrolyte imbalance.
3 Naproxen is a non-steroidal anti-inflammatory drug that causes salt and fluid retention, thus decreasing the hypotensive effect of thiazide diuretics.
4 Bendroflumethiazide is a thiazide diuretic that reduces sodium and water retention in the distal convoluted tubule in the kidney, creating a negative sodium balance, resulting in a reduced blood volume and a reduced peripheral resistance. It is indicated in hypertension and oedema.
5 In a 58-year-old patient diagnosed with hypertension and with a history of diabetes mellitus an angiotensin-converting enzyme (ACE) inhibitor is indicated as first-line treatment. ACE inhibitors should be used with caution in renovascular disease; however, in diabetes they have a renoprotective effect. Renal function should be checked prior to initiating therapy and monitored during therapy. ACE inhibitors may cause profound first-dose hypotension, so first doses should be given at night. Potassium levels must be monitored.

Table 20.12 Comparison between atenolol and enalapril

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Atenolol</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of action</td>
<td>Cardiodefective beta-blocker. Works by selectively blocking the beta receptors in the sympathetic nervous system</td>
<td>ACE inhibitor which decreases the production of angiotensin II, a potent vasoconstrictor, and also decreases aldosterone production and hence fluid retention. These actions lower the blood pressure.</td>
</tr>
<tr>
<td>Indications</td>
<td>Hypertension, angina, myocardial infarction, arrhythmia</td>
<td>Hypertension, heart failure</td>
</tr>
<tr>
<td>Dosage regimen</td>
<td>Once daily</td>
<td>Once daily</td>
</tr>
<tr>
<td>Side-effects</td>
<td>Bronchospasm, bradycardia, heart failure, hypotension, peripheral vasoconstriction, fatigue, depression, vivid dreams</td>
<td>Profound first-dose hypotension, persistent dry cough, renal impairment, hyperkalaemia, skin rashes</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Asthma and chronic obstructive pulmonary disease, heart block, peripheral vascular disease, diabetes</td>
<td>Pregnancy, renovascular disease, hypersensitivity</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme.
Persistent cough may be a problematic side-effect. Angiotensin II receptor antagonists do not inhibit bradykinin, have fewer side-effects than ACE inhibitors and are indicated when patients are intolerant to ACE inhibitors due to the cough side-effect. Other preventive drug therapy that can be considered to reduce cardiovascular risk includes low-dose aspirin and statin therapy.

Further reading


References


Acknowledgements

Bernard Coleiro, Consultant Physician, Department of Medicine, Mater Dei Hospital, Malta