Hypertension

Definition

Hypertension is defined as sustained systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg (Table 19.1). In the UK, the prevalence of hypertension is ~32%. Of these, only 22% have controlled BP (<140/90 mmHg). Essential (primary) hypertension accounts for 80–90% of cases. Secondary causes of hypertension include endocrine and renal disorders and drug-induced hypertension (Box 19.1).

Treatment of uncomplicated essential hypertension

First-line therapy

Young non-black individuals tend to have higher activity of the renin–angiotensin–aldosterone system (RAAS), as evidenced by higher plasma renin activity. They respond well to angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), whereas those with a low plasma renin activity, i.e. the elderly and Afro-Caribbean individuals, respond better to either calcium channel blockers (CCBs) or diuretics (Figure 19.1).

Drug combinations

BP control on monotherapy is rarely achieved. The most effective way to control BP is to combine two or more antihypertensive agents that lower BP by different mechanisms. ACE inhibitors or ARBs (A) combine well with CCB (C) and diuretics (D). This gives rise to the A/CD rule for combining drugs, in which a drug from the A group is added to another from either the C or D groups (Figure 19.1). The next step is to add a drug from each group: A + C + D. If the BP is not controlled on this combination, then patients are diagnosed with resistant hypertension. The recent PATHWAY 2 study has shown that the addition of spironolactone may be effective in controlling BP in patients with resistant hypertension.

Management of hypertension in different patient groups

The elderly

Low-dose thiazide diuretics are the preferred first-line treatment. Dihydropyridine CCBs are suitable alternatives when thiazides are contraindicated or not tolerated.

The very elderly

No firm evidence exists to guide treatment for patients above the age of 80 years. If antihypertensive treatment has been started before the age of 80, they should be continued.

Diabetes mellitus

Type 2 diabetes

ACE inhibitors and ARBs have an antiproteinuric effect and delay progression from microalbuminuria to overt nephropathy. Combined use of ACE inhibitors and ARBs is not advised any more as serious side-effects, including hyperkalaemia and acute kidney injury, are a potential risk.

Type 1 diabetes

ACE inhibitors have a specific renoprotective action independent of the BP-lowering effect. ACE inhibitor therapy should be titrated to the maximum tolerated recommended dose.

Ethnic groups

Afro-Caribbean hypertensive subjects are more responsive to diuretics and CCBs. ACE inhibitors and ARBs in

Box 19.1 Causes of secondary hypertension

- Endocrine
  - Adrenal cortex
    - Conn's syndrome (primary hyperaldosteronism)
    - Cushing's syndrome
    - Congenital adrenal hyperplasia
    - Dexamethasone-responsive aldosteronism
  - Adrenal medulla
    - Phaeochromocytoma
  - Hyperparathyroidism
  - Acromegaly
- Renal
  - Renovascular disease
    - Atherosclerotic renal artery stenosis
    - Fibromuscular dysplasia
  - Renal parenchymal disease
    - Acute and chronic glomerulonephritis
    - Polycystic disease
    - Diabetic nephropathy
    - Collagen vascular disease
  - Renal transplantation
- Coarctation of aorta
- Drug-induced
  - Oral contraceptives
  - Cyclosporin
  - Steroids
  - Carbenoxolone and liquorice
  - Tyramine and monoamine oxidase inhibitors
  - Erythropoietin
  - Non-steroidal anti-inflammatory drugs
- Antiangiogenic drugs (e.g. bevacizumab)
- Pregnancy-induced hypertension

monotherapy may be less effective in blacks because the RAAS is frequently suppressed, but when these drugs are combined with a diuretic or a CCB they are quite effective.

Hypertensive crises

A hypertensive crisis is defined as severe hypertension with ongoing or impending target organ damage. The rate of the rise in BP in relation to the previous levels of BP is more important than the absolute BP level. A *hypertensive emergency* is defined as a situation that requires immediate BP lowering (not necessarily to normal values) to prevent or limit target organ damage. *Hypertensive urgency* is a situation in which severely elevated BP is not accompanied by any evidence from the history, physical examination, or laboratory investigations of acute target organ damage. Individuals under this category could be:

1. Known hypertensive patients who are not compliant with their medication; prior therapy should be restarted (if there are no side-effects).
2. For patients taking their medications regularly, therapy should be increased (either by increasing the dose(s) of drugs or by adding new drugs).
3. For patients on no treatment, hypertension therapy should be started with oral agents (e.g. nifedipine sustained [SR] or modified release [MR]) and a follow-up appointment arranged urgently with a hypertension clinic.

Individuals with untreated severe or accelerated hypertension have a dreadful long-term prognosis if their high BP is not treated properly. The most common causes of death are renal failure, stroke, and myocardial infarction (MI).

Management of hypertensive emergencies

The key to a successful outcome is the prompt recognition and initiation of treatment. Full medical history and physical examination, including palpation of all peripheral pulses and a fundoscopic examination, is mandatory. Specific points in the patient's past medical history include the patient's BP prior to presentation and drug history (including prescription, over-the-counter, and recreational drugs).

Initial investigations should include full blood count (FBC), electrolytes, urea, creatinine, urine dipstick, chest X-ray (CXR), and electrocardiograph (ECG). These tests should be performed simultaneously with the initiation of the antihypertensive therapy.

The approach in treating hypertensive emergency is initially to reduce BP by ~20–25%, with further reductions accomplished more gradually. The initial reduction should be achieved over a period of 2–4 h, with less rapid reduction over the next 24 h.

Pathophysiology

A sudden increase in peripheral vascular resistance (PVR) (e.g. secondary to non-compliance) triggers an increase in circulating levels of vasoconstrictor substances such as angiotensin II and noradrenaline.

Aortic dissection

Aortic dissection must be excluded in any patient presenting with severe hypertension and chest pain, back pain, or abdominal pain. The condition is life-threatening, with very poor prognosis if not adequately treated (mortality is 1%/h). Aortic dissection is classified as type A if it involves the ascending aorta or type B if it does not. Surgical treatment is usually required for type A dissection, whereas type B responds more favourably to medical treatment. Severe refractory hypertension is nearly omnipresent, especially in the acute phase even in patients without history of hypertension.

Propagation of the dissection is dependent not only on the elevation of the BP itself, but also on the velocity of left ventricular (LV) ejection and the rate of increase of the aortic pulse wave. Therefore, the immediate reduction of BP and shear stress is of paramount importance to prevent the extension, haemorrhage, and rupture of the dissection. BP should be reduced quickly (within 15–30 min) to the lowest tolerated level that preserves adequate organ perfusion. The initial treatment of choice is a combination of intravenous (IV) β-blocker (e.g. esmolol or metoprolol) or a combined α–β-blocker (e.g. labetalol) and a vasodilator (e.g. sodium nitroprusside

[SNP] or dihydropyridine CCB). The recent CAFÉ trial, a substudy of the ASCOT trial, has shown that a combination of a dihydropyridine CCB and an ACE inhibitor was more effective in reducing central aortic pressure than a combination of a β-blocker and a diuretic. Therefore, the combination of a CCB and an ACE inhibitor should be considered in the treatment.

Acute pulmonary oedema

More than 90% of patients with heart failure (HF) have a history of hypertension. The clinical syndrome of HF is usually characterized by signs and symptoms of intravascular and interstitial volume overload. IV glyceryl trinitrate (GTN) is the drug of choice in the initial treatment, together with an IV loop diuretic (e.g. furosemide) and diamorphine. GTN reduces both preload and afterload while improving coronary bloodflow. There is very little clinical experience with the use of ACE inhibitors in patients with acute LV failure, but a short-acting ACE inhibitor (e.g. captopril) may be added if necessary.

It is important to stress here that patients with malignant hypertension who present with acute (flash) pulmonary oedema may not have volume overload. In fact, they may have volume depletion secondary to pressure natriuresis. Therefore, IV diuresis may exacerbate the hypertension and cause further clinical deterioration. The use of diuretics should be reserved for patients who are clinically fluid-overloaded and should not be prescribed routinely.

ST-elevation myocardial infarction and acute coronary syndrome

Hypertension is very common in patients presenting with acute coronary syndrome (ACS). The overall prevalence of hypertension in US patients presenting with non-ST-elevation myocardial infarction (NSTEMI) is ~50%, while in Europe the prevalence is ~34%.

IV GTN is the drug of choice for ACS and ST-elevation myocardial infarction (STEMI) as it reduces PVR while improving coronary perfusion. β-Blockers attenuate the activity of the adrenergic system and the RAAS, and improve survival in post-MI patients. In ACS, IV β-blockers should be started then switched to oral when the patient is stable. When β-blockers are contraindicated, a non-dihydropyridine CCB (diltiazem or verapamil) can be used if the patient does not have severe LV dysfunction. Short-acting dihydropyridine CCB should not be used in the treatment of a hypertensive crisis when associated with ACS or acute STEMI. ACE inhibitors could be added if hypertension persists, as they significantly improve survival during STEMI. SNP, unlike GTN, increases heart rate and provokes ST-segment elevation, and should not be used alone.

Cocaine overdose

Cocaine overdose is often associated with uncontrolled severe hypertension and coronary artery vasoconstriction, leading to angina, MI, or sudden death. These effects are mediated through α-adrenergic receptors and therefore β-blockers alone (i.e. without α-blockers) may exacerbate the hypertension and the clinical condition, and are therefore contraindicated. A non-dihydropyridine CCB (e.g. diltiazem or verapamil) or a combined α–β-blocker, e.g. labetalol, may be used.

Severe pre-eclampsia and eclampsia

Pre-eclampsia is defined as hypertension (BP ≥140/90 mmHg) in the second half of pregnancy (i.e. after 20 weeks of gestation) associated with proteinuria and oedema. Eclampsia is the occurrence of seizures in a patient with pre-eclampsia. Treatment with antihypertensive drugs is not usually indicated in pregnancy for BP <160/100 mmHg. ACE inhibitors and ARBs are contraindicated in pregnancy because of the increase in foetal and neonatal morbidity and mortality. Methyldopa remains the mainstay of treatment for patients with moderate gestational hypertension because of its foetal and neonatal safety. The drug, however, has many adverse side-effects. Labetalol and nifedipine may be considered if methyldopa is contraindicated or not tolerated.

For pre-eclamptic patients with severe hypertension, IV hydralazine or labetalol could be given. SNP can cause profound reflex paradoxical bradycardia and hypotension, and should be avoided.

Malignant hypertension

Malignant (accelerated) hypertension is a syndrome characterized by severely elevated BP accompanied by retinopathy (including exudates, haemorrhages, or papilloedema), nephropathy, encephalopathy, and microangiopathic haemolytic anaemia. Pathologically it is characterized by fibrinoid necrosis in arterioles, myointimal proliferation in small arteries, platelet and fibrin deposition, and breakdown of normal vascular autoregulation function. The resulting vasoconstriction induces severe elevation in BP and widespread endothelial damage. The resulting renal ischaemia prompts massive release of renin and angiotensin II, triggering a vicious cycle. The rapid increase in BP enhances pressure natriuresis, which further stimulates the RAAS, resulting in secondary hyperaldosteronism, hypokalaemia, and metabolic alkalosis.

Malignant hypertension rarely occurs de novo, and is usually a consequence of untreated essential or secondary hypertension such as renal artery stenosis, phaeochromocytoma, or scleroderma. The incidence of malignant hypertension remains stable across the UK and Europe, with ~1–2 cases per 100 000 per year. Malignant hypertension has a very poor prognosis if untreated, with a mortality rate >90% within 1 year, but, with proper treatment, 5-year survival is 60–75%. Most patients who present with malignant hypertension have volume depletion secondary to pressure natriuresis. Therefore, further diuresis may exacerbate the hypertension and cause further deterioration in kidney function.

Hypertensive encephalopathy

Hypertensive encephalopathy is much less common these days with the use of modern antihypertensive drugs. It is believed to be due to cerebral oedema secondary to failure of CBF autoregulation and rapid elevation of cerebral perfusion. Symptoms and signs include headache, nausea and vomiting, visual disturbances, altered level of consciousness, confusion, disorientation, focal or generalized seizures and retinopathy including papilloedema. Diagnosis may be difficult as it is one of exclusion requiring that stroke, encephalitis, vasculitis, subarachnoid haemorrhage and mass lesions need to be excluded. The definite criterion to confirm the diagnosis is a prompt improvement in the patient's clinical condition with the response to antihypertensive treatment. The goal of treatment is to reduce BP by ~25% within the first hour or to a level of 160/100 mmHg, whichever value is higher. It must be emphasized that cerebral hypoperfusion and neurological deterioration may result

if more reductions in BP are achieved quickly. In this case, BP should be allowed to increase and further reductions should be attempted more slowly.

Stroke

There is a high prevalence of apparent treatment-resistant hypertension among hypertensive individuals with history of stroke or transient ischaemic attack. Appropriate treatment of hypertension in the setting of acute stroke remains contentious. There is little scientific evidence and no clinically established benefit for rapid lowering of BP among persons with acute ischaemic stroke. Aggressive lowering of BP may cause neurological worsening and there is a need for more individualized BP monitoring and management. However, it is generally agreed that severe hypertension (BP >180/110 mmHg) may be an indication for treatment, as higher BP levels are a contraindication to IV thrombolysis. If thrombolysis is not considered, then emergency administration of antihypertensive drugs should be withheld unless the SBP is >220 mmHg and/or DBP is >120 mmHg. Treatment could be started with IV labetalol.

A reasonable goal would be to lower BP by 25% within the first day. Previously hypertensive patients with mild to moderate strokes who are not at high risk for increased intracranial pressure may have their usual prestroke antihypertensive medications restarted 24 h after their stroke.

Drugs for the treatment of hypertensive emergencies

SNP

SNP dilates arteriolar resistance and venous capacitance vessels and decreases both the afterload and preload. It is a very potent agent, with an immediate onset and short duration of action; plasma half-life is 2–3 min. Continuous arterial BP monitoring is recommended to avoid overreduction of BP. The drug is light-sensitive and should be shielded from light to prevent degradation. The usual dose is 0.3–10 μg/kg/min. Cyanide poisoning may occur with prolonged or high-dose administration, especially in individuals with renal or hepatic insufficiency. Manifestations of poisoning include central nervous system depression, seizures, and lactic acidosis.

GTN

GTN dilates arteriolar resistance and venous capacitance vessels. It reduces preload and afterload, improves LV function, and reduces myocardial oxygen demand. GTN dilates both epicardial coronary vessels with stenosis and collaterals, and increases blood supply to ischaemic areas. It is the drug of choice for reducing BP in individuals with STEMI, ACS, and acute pulmonary oedema. However, the BP-lowering effect of GTN is not as predictable as with SNP, and higher doses (up to 300 μg/min) may be required to achieve an adequate response. Onset of action is almost immediate, with a very short duration of action (half-life 3–5 min). The starting dose is 5–15 μg/min. Nitrate tolerance is a problem even within the first 24 h.

Labetalol

Labetalol is a selective α_1- and non-selective β-adrenergic receptor blocker. Its differential effects on α:β receptors are 1:3 after oral administration and 1:7 after IV administration, respectively. The drug can be given IV as a 20–80-mg minibolus injection (q 10 min) or 2–4-mg/min infusion. Labetalol produces a prompt and controlled reduction in BP in patients with hypertensive crises, with onset of action within 5 min and duration of action of 3–6 h. The drug is contraindicated in patients with acute LV failure, heart block, and chronic obstructive pulmonary disease.

Esmolol

Esmolol is an ultrashort-acting β_1-selective adrenergic blocking agent with an extremely brief half-life of <10 min. This agent is available for IV use both as a bolus and as an infusion. The recommended loading dose is 0.5–1 mg followed by an infusion of 50–200 μg/kg/min.