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Comparative Tolerability Profile of Hypertensive Crisis Treatments

Ehud Grossman,[1] *Avi N. Ironi*[1] and *Franz H. Messerli*[2]

1 Internal Medicine D, The Chaim Sheba Medical Center, Tel-Hashomer, Israel

2 Department of Internal Medicine, Section on Hypertensive Diseases, Ochsner Clinic and Alton Ochsner Medical Foundation, New Orleans, Louisiana, USA

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Abstract

Hypertensive crisis is defined as a severe elevation in BP and is classified as either urgency or emergency. In hypertensive urgency there is no end-organ injury and no evidence that acute BP lowering is beneficial. Indeed, rapid uncontrolled pressure reduction may be harmful. Therefore, in hypertensive urgencies BP should be lowered gradually over 24 to 48 hours using oral antihypertensives.

When the cause of transient BP elevations is easily identified, appropriate treatment should be given. When the cause is unknown, an oral antihypertensive should be given. The efficacy of available treatments appear similar; however, the underlying pathophysiological and clinical findings, mechanism of action and potential for adverse effects should guide choice. Captopril should be avoided in patients with bilateral renal artery stenosis or unilateral renal artery stenosis in patients with a solitary kidney. Nifedipine and other dihydropyridines increase heart rate whereas clonidine, β-blockers and labetalol tend to decrease it. This is particularly important in patients with ischaemic heart disease. Labetalol and β-blockers are contraindicated in patients with bronchospasm and bradycardia or heart blocks. Clonidine should be avoided if mental acuity is desired.

In hypertensive emergency there is an immediate threat to the integrity of the cardiovascular system. BP should be immediately reduced to avoid further end organ damage. Sodium nitroprusside is the most popular agent. Nitroglycerin (glyceryl trinitrate) is preferred when there is acute coronary insufficiency. A β-blocker may be added in some patients. Loop diuretics, nitroglycerin and sodium nitroprusside are effective in patients with concomitant pulmonary oedema. Enalaprilat is also theoretically helpful, especially when the renin system might be activated. Initial treatment of aortic dissection involves rapid, controlled titration of arterial pressure to normal levels using intravenous sodium nitroprusside and a β-blocker. If β-blockers are contraindicated, urapidil or trimetaphan camsilate are alternatives. Hydralazine is the drug of choice for patients with eclampsia. Labetalol, urapidil or calcium antagonists are possible alternatives if hydralazine fails or is contraindicated. For patients with catecholamine-induced crises, an α-blocker such as phentolamine should be given; labetalol or sodium nitroprusside with β-blockers are alternatives.

There are few, if any, comparative or randomised trials providing definitive conclusions about the efficacy and safety of comparative agents. Some investigators recommend decreasing the diastolic BP to no less than 100 to 110mm Hg. A reasonable approach for most patients with hypertensive emergencies is to lower the mean arterial pressure by 25% over the initial 2 to 4 hours with the most specific antihypertensive regimen.

1. Definition of Hypertensive Crisis

Hypertensive crisis, defined as a severe elevation in blood pressure (BP), such as a diastolic BP above 120 to 130mm Hg,[1] can be subclassified as either emergency or urgency in nature.[2]

Hypertensive emergency is relatively rare and defined as such only when there is an immediate threat to the integrity of the cardiovascular system (table I). Patients with a hypertensive emergency require an immediate reduction in BP, generally effected by means of intravenous therapy in an intensive care setting, to avoid serious end organ damage.

Unlike hypertensive emergency, patients with severe elevation in BP who have no evidence of progressive end-organ injury are classified as having an urgent hypertensive crisis and require only a gradual reduction in BP over a period of 24 to 48 hours.

According to a recent study the prevalence of hypertensive crisis in an emergency room is 3% of total patients in 1 year, but is 27% of all medical urgencies-emergencies.[3]

Before it was possible to treat accelerated-malignant hypertension, survival was 20% and 1%, for 1 and 5 years respectively.[4] During the last 2 decades survival has improved, with a 10 year survival rate of 67% and mean survival of 18 years being reported.[4]

Therapy has dramatically reduced immediate deaths from hypertensive encephalopathy, acute renal failure, haemorrhagic strokes and congestive heart failure.

Table I. Definition of a hypertensive emergency

Moderate to severe elevation of arterial pressure associated with:
Malignant hypertension[a]
Intracranial hemorrhage
Atherothrombotic cerebral infarction
Acute congestive heart failure
Acute coronary insufficiency
Acute renal insufficiency
Acute aortic dissection
Adrenergic crisis (phaeochromocytoma crisis, clonidine withdrawal, food and drug interactions with monoamine oxidase inhibitors, amphetamine overdose)
Eclampsia

a Malignant hypertension is a syndrome characterised by elevated blood pressure accompanied by encephalopathy or nephropathy or by papilloedema and/or microangiopathic haemolytic anaemia.

2. General Treatment Guidelines

The initial goal of antihypertensive therapy is not to rapidly normalise BP but rather to prevent damage to target organs. This can be done by gradually decreasing mean arterial pressure, while minimising the risk of organ hypoperfusion.[5] Before discussing drug therapy for patients with hypertensive crises we would like to emphasise that outcome data attesting to benefits of acutely lowering BP are not available. Thus, most interventions currently used to treat hypertensive crises have never been vigorously scrutinized. Much of the therapy, therefore, is entirely empirical and based on an attempt to best match pathophysiological findings with pharmacological properties of antihypertensive agents.

A number of pharmacological agents are available in the management of hypertensive crisis.[6] Those agents can be divided by mechanism of action and route of administration (parenteral *vs* oral or sublingual)(table II).

Drug selection should be based on the severity of the crisis and on the specific hypertensive case. Emergency situations should be aggressively treated, typically using intravenous medication in units with monitoring facilities.[7]

3. Parenteral Agents for Hypertensive Emergencies

Several parenteral agents are available for the treatment of hypertensive emergencies (table III).

3.1 Sodium Nitroprusside

Sodium nitroprusside is the most popular agent used in the treatment of patients with hypertensive emergency. It is a short acting direct vasodilator, requiring a constant intravenous infusion, that can decrease BP in all patients irrespective of the severity of the BP increase. The drug is light sensitive

Table II. Drugs for treatment of hypertensive crisis

Drug	Mechanism of action	Route of administration
Sodium nitroprusside	Vasodilator	IV
Diazoxide	Vasodilator	IV
Hydralazine	Vasodilator	IV
Nitroglycerin (glyceryl trinitrate)	Vasodilator	IV, SL
Nifedipine	Calcium antagonist	PO
Nitrendipine	Calcium antagonist	PO
Nicardipine	Calcium antagonist	IV
Nimodipine	Calcium antagonist	IV
Isradipine	Calcium antagonist	IV, PO
Trimetaphan camsilate	Ganglionic blocker	IV
Phentolamine	α-Blocker	IV
Urapidil	α-Blocker with central serotonin (5-hydroxytryptamine; 5-HT) antagonist activity	IV
Esmolol	β-Blocker	IV
Labetalol	α- and β-Blocker	IV, PO
Captopril	ACE inhibitor	PO
Enalaprilat	ACE inhibitor	IV
Fenoldopam	Dopamine agonist	IV
Clonidine	α_2-Agonist	PO
Furosemide (frusemide)	Loop diuretic	IV, PO

IV = intravenous; **SL =** sublingual; **PO =** oral.

and should be shielded from light to prevent degradation. The initial recommended infusion rate is 0.25 μg/kg/min and may be increased by 0.25 μg/kg/min every 5 to 10 minutes. Sodium nitroprusside dilates both the arteriolar resistance and the venous capacitance vessels, thereby decreasing peripheral resistance without causing an increase in venous return.[8] The drug does not have any direct negative inotropic or chronotropic effects on the heart. By reducing preload and afterload, sodium nitroprusside improves left ventricular function in patients with congestive heart failure and low cardiac output and reduces myocardial oxygen demand in patients with ischaemic heart disease.

Interaction of sodium nitroprusside with sulphydryl groups in erythrocytes and tissues generates cyanide ions that are converted to thiocyanate by rhodanese in the liver and then excreted by the kidney. However, with prolonged administration of sodium nitroprusside or administration to patients with hepatic impairment or renal insufficiency, free cyanide may accumulate and interfere with aerobic metabolism, resulting in metabolic acidosis. Cyanide also interferes with the vasodilator action of sodium nitroprusside and may eventually lead to tachyphylaxis. Therefore, thiocyanate concentrations should be monitored periodically and maintained below 100 mg/L in patients with hepatic impairment, renal insufficiency and in those receiving high dosages of sodium nitroprusside (3 μg/kg/min) or a prolonged infusion (>24 to 48 hours). It should be noted that the development of thiocyanate accumulation cannot be predicted and even a dose that is considered unlikely to cause adverse effects may be toxic.[9-11] Patel et al.[12] reported a high rate of sodium nitroprusside toxicity when it was given to patients with unstable post coronary artery bypass grafts. Symptoms of thiocyanate toxicity include fatigue, nausea, headache, disorientation, psychotic behaviour, skin rashes, anorexia, seizures, unexplained cardiopulmonary arrest, coma, diffuse encephalopathy and even death.[13] When cyanide toxicity is diagnosed it can be treated by the administration of amyl nitrate, sodium nitrate and a sulphydryl compound such as sodium thiosulfate.[14] Sodium thiosulfate can be used to prevent thio-

cyanate toxicity [14] In case of failure to respond to such therapy, hyperbaric oxygen therapy, haemodialysis or charcoal haemoperfusion may prove beneficial, although there is limited experience with these modes of therapy.[15]

The advantages of sodium nitroprusside in controlling hypertensive crisis in cardiac patients have been studied extensively. Kaplan and Jones[16] compared the effects of sodium nitroprusside and intravenous nitroglycerin (glyceryl trinitrate) in 20 patients during elective coronary artery surgery. Both regimens were effective in reducing intraoperative BP. However, nitroglycerin improved electrocardiographic ST segment depression in 8 of 10 patients, whereas sodium nitroprusside made the ST segment depression more pronounced in 3 of 10 patients. Decreased coronary perfusion pressure and intracoronary steal syndrome may be involved in the worsening of ischaemia seen in patients receiving sodium nitroprusside. Flaherty et al.[17] found that sodium nitroprusside increased intrapulmonary shunting whereas nitroglycerin decreased it, thus making nitroglycerin more useful for managing patients with large intrapulmonary shunt or pulmonary hypertension.

Fremes et al.[18] found that nitroglycerin caused a greater reduction in myocardial oxygen demand and consumption than sodium nitroprusside in hypertensive patients after elective coronary bypass surgery. Therefore, if perioperative myocardial ischaemia is suspected in the setting of postoperative hypertension, nitroglycerin may be a better antihypertensive agent.

The efficacy of sodium nitroprusside was compared with fenolodopam[19,20] with diazoxide and hydralazine[21] and with urapidil [22,23] in hypertensive crises, and was found to be effective in almost 100% of the cases.

In spite of the fact that sodium nitroprusside can increase intracranial pressure,[24] the fall in systemic pressure seems to block the rise in cerebral blood flow. It is therefore still recommended for

Table III. Parenteral agents for treatment of hypertensive emergencies

Drug	Dosage	Onset of action	Duration of action	Adverse effects
Sodium nitroprusside	0.25-10 μg/kg/min	Immediate	1-2 min after infusion stopped	Nausea, hypotension, thiocyanate and cyanide toxicity, methaemoglobinaemia (rare)
Nitroglycerin (glyceryl trinitrate)	5-100 μg/kg/min	1-5 min	3-5 min	Headache, nausea, tachycardia, vomiting, tolerance with prolonged use
Diazoxide	50-150mg over 5 min or 75-150mg every 5 min or 10-30 mg/min for 15-30 min	1-5 min	4-12h	Increased cardiac output and heart rate, precipitate ischaemia, sodium retention, hyperglycaemia, postural hypotension
Hydralazine	10-20mg IV, or 10-50mg IM, repeat every 4-6h	5-30 min	3-9h	Increased cardiac output and heart rate, headache, angina
Nicardipine	5-15 mg/h	5-15 min	30-40 min	Hypotension, tachycardia, nausea, vomiting, flushing
Trimetaphan camsilate	1-15 mg/min	1-10 min	3-10 min after infusion stopped	Hypotension, tachyphylaxis, orthostatic effect, sympathetic blockade, respiratory arrest
Labetalol	20-80mg every 10-15 min or 2-4 mg/min	5-10 min	3-6h	Nausea, scalp-tingling, dizziness, bronchospasm, bradycardia, heart block
Urapidil	12.5-25mg bolus followed by infusion of 5-40 mg/h	3-5 min	4-6h	Hypotension, headache, dizziness
Phentolamine	5-10mg bolus	1-2 min	3-5 min	Tachycardia, flushing, headache, angina
Esmolol	0.5-1 mg/kg followed by 50-300 μg/kg/min	1-2 min	10-20 min	Hypotension, nausea
Enalaprilat	0.625-1.25mg	15 min	4-12h	Hypotension, renal failure
Fenlodopam	0.1-1.6 μg/kg/min	5-40 min	60 min	Headache, flushing, hypotension

IM = intramuscular; **IV** = intravenous.

management of some patients with encephalopathy and cerebrovascular accidents.[1,25] Despite its effectiveness as antihypertensive agent, sodium nitroprusside has not been used widely in pregnancy because of negative outcomes in animal experiments.[26]

3.2 Nitroglycerin (Glyceryl Trinitrate)

Nitroglycerin is an antianginal as well as antihypertensive agent that dilates peripheral capacitance and resistance vessels. By diminishing preload, nitroglycerin decreases left ventricular end diastolic volume and pressure and myocardial wall tension, thus reducing myocardial oxygen consumption. These changes favour redistribution of coronary blood flow to the subendocardium, which is more vulnerable to ischaemia. Nitroglycerin may dilate epicardial coronary vessels and their collaterals and increase blood supply to ischaemic regions. At higher doses nitroglycerin dilates arteriolar smooth muscle, thereby reducing peripheral resistance and afterload. Continuous intravenous nitroglycerin is effective in decreasing the incidence of myocardial ischaemia in patients with coronary artery disease undergoing cardiac and noncardiac surgery.[27] Nitroglycerin is a better vasodilator of coronary conductance arteries than sodium nitroprusside and for that reason is preferred in the management of hypertensive crisis associated with acute coronary insufficiency.[25] Intravenously, nitroglycerin infusion also has been used in controlling hypertensive crisis during pregnancy. Snyder et al.[28] reported the successful use of intravenous nitroglycerin in controlling hypertension during anaesthesia for caesarean section, without neonatal respiratory depression or hypotension. The usual initial dose is 5 to 15 μg/min and can be titrated upward to a desired therapeutic endpoint. A dose as high as 200 to 300 μg/min may be required to achieve an adequate response.[29] Onset of action is almost immediate with a very short duration of action of approximately 3 to 5 minutes.[30] Prolonged use of nitroglycerin is not associated with toxicity, but tolerance to its haemodynamic effects has been reported.[31] The main adverse effects are headache and hypotension. The drug can also be used sublingually in selected patients.

3.3 Diazoxide

Diazoxide is a direct rapid-acting vasodilator that decreases total peripheral resistance with a reflex increase in heart rate and cardiac output. The compensatory increase in cardiac output and heart rate can be blocked by concomitant β-blocker therapy. Since it does not cross the blood brain barrier, diazoxide has no direct effects on cerebral circulation, but of course cerebral blood flow will fall if systemic pressure is reduced below the lower limit of autoregulation.[32] In the past diazoxide was initially given as a rapid bolus of 300mg. However, the standard rapid intravenous bolus administration may cause profound hypotension with subsequent myocardial ischaemia and cerebrovascular insufficiency.[33] The safer course is to give the drug either by slow infusion of 15 to 30 mg/min over 15 to 30 minutes or by smaller bolus doses of 75 to 100mg intravenously, every 5 to 10 minutes. These methods are equally effective and are associated with fewer adverse effects.[34] The adverse effects of diazoxide include fluid retention, nausea, flushing, dizziness and hyperglycaemia.[8] When using diazoxide, significant adverse effects such as postural hypotension, maternal and fetal hyperglycaemia and cessation of gestational labour that results from relaxation of the uterine smooth muscle, must be borne in mind. Diazoxide is contraindicated in patients with severe angina, acute myocardial infarction, dissecting aneurysm and congestive heart failure.

3.4 Hydralazine

Hydralazine is a direct arteriolar vasodilator, with little effect on venous capacitance vessels, that produces a rapid BP decrease with diastolic pressure reduced more than systolic.[13] Its administration results in activation of baroreceptor reflexes leading to increases in heart rate, myocardial contractility and cardiac output and an augmentation of renal blood flow. Hydralazine can be given

intravenously or intramuscularly in initial doses of 10 to 50mg. The drug should not be diluted with solutions containing dextrose or other sugars, because of its ability to form potentially toxic hydrazones.[13] The drug reduces systemic vascular resistance and BP in severe hypertension in pregnancy[35] without a significant change in uteroplacental blood flow.[36]

Although hydralazine easily crosses the placenta, its relative safety and efficacy combined with the extensive clinical experience have made it the most widely used antihypertensive agent in hypertension associated with pregnancy.[13] The major drawbacks of hydralazine are adverse effects that include reflex tachycardia, salt and water retention, intense flushing, headache, nausea, vomiting, myocardial ischaemia and increased intracranial pressure. Therefore, the use of intravenous hydralazine is limited to patients with pre-eclampsia or eclampsia.

3.5 Calcium Antagonists

3.5.1 Nicardipine

Nicardipine is a dihydropyridine calcium antagonist which can be administered intravenously.[37] It is an effective antihypertensive agent that decreases afterload by reducing total peripheral resistance without reducing cardiac output. Nicardipine improves left ventricular ejection fraction and pumping activity, both in normal and failing hearts.[38] The drug dilates the coronary arteries more selectively than the remainder of the arterial tree, without changing the heart rate.[39] It may preserve tissue perfusion, and therefore may be advantageous in patients with ischaemic disorders, such as coronary, cerebrovascular and peripheral vascular disease. The drug is given as a continuous infusion at a starting dose of 5 mg/h followed by increments of 2.5 mg/h every 5 minutes until either a maximal dose of 15 mg/h is reached or the desired reduction in BP is achieved. Nicardipine has been used for the treatment of postoperative hypertension.[40-46] Floyd et al.[41] used intravenous nicardipine in the treatment of acute hypertension in 11 patients undergoing coronary artery bypass grafting. Administration of 10 to 15 mg/h of nicardipine decreased BP by more than 15% within 25 minutes, without a significant change in heart rate or cardiac index. In a double blind study intravenous nicardipine was compared with placebo in 123 patients with a BP of over 213/126mm Hg.[40] Of 73 patients who were treated with nicardipine, the therapeutic goal was achieved in 67 patients. Several adverse effects were reported; 30 patients had headache, 7 patients had hypotension and 7 patients experienced nausea. The pharmacodynamics of nicardipine are comparable to sodium nitroprusside in terms of onset, duration and offset of action. Halpern et al.[44] and David et al.[46] found that nicardipine was as effective as sodium nitroprusside in patients with severe postoperative hypertension. Patients receiving intravenous nicardipine can then be easily switched to oral medication.

3.5.2 Nimodipine

Nimodipine is a potent cerebral vasodilator that has been approved for use in relieving the vasospasm accompanying subarachnoid haemorrhage. Nimodipine has improved the outcome of patients with aneurysmal subarachnoid haemorrhage.[47,48] Its beneficial effect in aneurysmal subarachnoid haemorrhage seems to be unrelated to its antihypertensive effect or to its cerebral vasodilator properties and is perhaps related to preserving functioning neurons by preventing calcium influx to the ischaemic cells.[48]

3.5.3 Isradipine

Isradipine is useful in the treatment of hypertensive crisis and in intraoperative and perioperative hypertension.[49] In 10 symptomatic patients with hypertensive crisis, intravenous administration of isradipine at a dose of 7.2 μg/kg/h for 3 hours reduced mean arterial pressure significantly without major adverse effects.[50] Thus, parenteral isradipine may be used in patients with hypertensive crises.

3.5.4 Verapamil and Diltiazem

There is limited published experience with intravenous verapamil and diltiazem in the treatment

of hypertensive crisis. These drugs therefore have little if any role in the treatment of this condition.

3.6 Trimetaphan Camsilate

Trimetaphan camsilate is a ganglionic blocker agent that inhibits both sympathetic and parasympathetic autonomic activity. It has a rapid onset and brief duration of action and must be administered by continuous intravenous infusion with constant monitoring of BP. The usual starting dose is 0.5 to 1 mg/min titrated to obtain the desired BP level. One needs to titrate the drug carefully, and to elevate the head of patient's bed during the infusion to avoid severe postural hypotension. Trimetaphan camsilate is particularly useful in aortic dissection because it can be titrated carefully to permit smooth control of BP and because it decreases cardiac output and left ventricular ejection rate. Tachyphylaxis develops frequently after 24 to 48 hours because of intravascular volume expansion, and this may be attenuated by the use of diuretics. Adverse effects include blurred vision, exacerbation of glaucoma, dry mouth, respiratory depression, nausea, constipation, fetal meconium ileus, paralytic ileus, impairment of renal blood flow with azotaemia and urinary retention. Because of the frequency and severity of the adverse effects associated with this drug and the availability of more effective agents, it is now used only in patients with life threatening disorders such as dissecting aortic aneurysm.[25]

3.7 Labetalol

Labetalol produces selective antagonism at postsynaptic α-adrenoceptors and nonselective antagonism at β-adrenoceptors. The drug can be given intravenously either by repeated bolus of 0.25 to 0.5 mg/kg every 10 to 15 minutes or by a continuous infusion of 2 to 4 mg/min. Alternatively, the drug can be given in a bolus injection of 100mg followed by an infusion of 2 to 4 mg/min. The average effective total dose is 200mg. The response rate in patients with hypertensive crisis is about 80 to 93%.[51-58] The drug was found to be effective and well tolerated in patients with myocardial infarction,[55] in patients with acute postoperative hypertension after aortocoronary bypass surgery[56] or surgery requiring general anaesthesia,[57] in neurovascular surgical patients, in children with hypertensive crises and in hypertensive crisis complicating pregnancy.[13,58] The drug is contraindicated in patients with acute left ventricular failure, second or third degree atrioventricular block and chronic obstructive pulmonary disease. Caution is needed to avoid postural hypotension if patients allowed out of bed. Nausea, itching, tingling of the skin and β-blockade adverse effects may be noted. Transition to oral therapy with the same drug is not difficult.

3.8 Urapidil

Urapidil is a selective post-synaptic α_1-adrenoceptor antagonist with strong vasodilating properties. The fact that it also antagonises the pre-synaptic serotonin $5HT_{1A}$ receptors explains the lack of reflex tachycardia in response to peripheral vasodilatation. Urapidil has a rapid onset of action, with a response rate of 81 to 100% in hypertensive emergencies.[59-61] Urapidil is given as an intravenous bolus at a dose of 12.5 to 25mg followed by a continuous infusion at a rate of 5 to 40 mg/h. It has no effect on coronary sinus blood flow, myocardial oxygen consumption and myocardial lactate extraction, and it does not increase intracranial pressure. Adverse effects occur in 2% of all patients and include hypotension, headache, dizziness. Urapidil is well tolerated and efficient in intra-operative hypertensive crises. In a recent study, the drug was given to 42 patients with intra-operative hypertensive crises. A significant reduction in BP was observed within 10 minutes in 81% of the patients.[62] In 2 recent studies [22,23] the safety and efficacy of urapidil were compared with sodium nitroprusside. In 1 study,[22] 81 patients with hypertensive emergency received either sodium nitroprusside or urapidil. Response to treatment (BP reduction to below 180/95mm Hg within 90 minutes) was similar in both treatment groups (89% for urapidil and 97% for sodium nitroprusside). However, during the follow-up period, 24% of the patients in

the sodium nitroprusside group and only 2% of the patients in the urapidil group exhibited BP re-elevation. Moreover, major adverse effects were more common in the sodium nitroprusside group. Since urapidil is equally effective compared with sodium nitroprusside with less adverse effects, urapidil is a reasonable alternative to sodium nitroprusside in the treatment of hypertensive emergency, especially in intra-operative hypertensive crisis.

3.9 Phentolamine

Phentolamine is a parenteral nonspecific α-adrenergic blocking agent with rapid onset and short-lasting antihypertensive effect. It is given intravenously in a boluses of 5 to 10mg and repeated administration may be necessary. Adverse effects include tachycardia, vomiting and headache. In patients with coronary artery disease phentolamine may induce angina pectoris or myocardial infarction. It is specifically useful in treatment of catecholamine mediated hypertensive crises.[34] However, it is not consistently effective in other types of hypertensive emergencies.

3.10 Esmolol

Esmolol is an ultra-short acting β_1-selective adrenergic blocker. The duration of action is extremely short, about 30 minutes, because of its rapid metabolism by a specific plasma esterase. This characteristic provides a significant advantage over similar agents such as propranolol because it is possible to titrate esmolol easily to the desired effect.[6] The drug can be administered either as a bolus injection or as a continuous intravenous infusion. The recommended loading dose is 0.5 to 1 mg/kg followed by an infusion of 50 to 300 μg/kg/min. Esmolol is frequently combined with direct vasodilators to provide a more desirable haemodynamic profile. The negative chronotropic effect produced by esmolol may be beneficial in patients with ischaemic heart disease. Recently esmolol has been used successfully with sodium nitroprusside in a few cases of hypertensive crises.[63-66] Further prospective studies are required before esmolol can be recommended for routine use in the treatment of hypertensive crisis.

3.11 Enalaprilat

Enalaprilat is the only available ACE inhibitor that can be administered intravenously, although in 1 report captopril was given intravenously to treat hypertensive crises.[67] Enalaprilat rapidly lowers BP within minutes in patients with severe hypertension, without causing excessive hypotension or adverse reactions. The initial recommended dose for enalaprilat is 0.625 to 1.25mg administered over 5 minutes. The maximal single dose should not exceed 5mg for patients receiving diuretics and 1.25mg for patients with renal impairment.[68] The initial dose can be repeated after 1 hour if clinical response is inadequate. The total daily dose should not exceed 20mg. In patients with severe renal insufficiency the dose should be decreased because the compound is excreted primarily by the kidney.

Enalaprilat is more effective in patients with high-renin forms of hypertension, and may induce a dramatic fall in BP in patients who are volume depleted by prior dietary sodium restriction or diuretic use.[69] African-Americans seem to respond poorly to enalprilat, possibly because of their low renin levels.[70] Because enalprilat may induce severe hypotension in volume depleted patients, it should be used with caution in patients who are at risk for cerebral hypotensive episode. In patients with hypertensive emergency the response rate is about 65%. Hirschl et al.[71] evaluated prospectively the efficacy and safety of various doses of parenteral enalaprilat in patients with hypertensive crises. 65 consecutive patients with hypertensive crises (urgency or emergency) were randomly allocated to receive different doses of enalaprilat (0.625, 1.25, 2.5 and 5mg). In 41 (63%) of 65 patients the treatment goal was achieved, with a similar response rate for all enalaprilat doses. Thus, 0.625mg may be adequate as initial dose in the treatment of hypertensive crisis. In another study enalaprilat was compared with intravenous urapidil and sublingual nifedipine in the management of hypertensive crisis.[72] Only 70% of the patients

in the enalaprilat group achieved goal BP (less than 180/95mm Hg within 45 minutes after start of treatment) versus 96 and 71% in the urapidil and nifedipine groups respectively.

Enalaprilat may be an alternative treatment for hypertensive crisis in patients with congestive heart failure. The most common adverse effect is hypotension. The risk for hypotension increases in patients with evidence of renal hypertension, volume depleted patients and patients with prior use of diuretics. Enalaprilat is contraindicated in patients with evidence of bilateral renal artery stenosis or in patients with unilateral stenosis of a single kidney.[34] Thus, enalaprilat is an effective antihypertensive agent in acute situations,[73] and can be easily replaced by oral enalapril for long term maintenance therapy.

3.12 Fenoldopam

Fenoldopam is a selective post-synaptic dopaminergic (DA_1) receptor agonist with weak α_2-antagonistic properties.[19] Fenoldopam is a natriuretic agent that has a potent vasodilative action affecting, primarily, the renal vasculature.[19,74] Several clinical trials recently showed the effectiveness of intravenous fenoldopam in the treatment of severe hypertension and hypertensive crisis.[19,20,74,75] Bodmann et al.[75] studied the haemodynamic effects of intravenous fenoldopam in 12 patients with hypertensive crises. At a dose of 0.2 to 0.5 μg/kg/min, fenoldopam decreased BP to desired levels within 5 to 40 minutes in all patients. Haemodynamically the drug induced a decrease in total peripheral resistance and in pulmonary vascular resistance with a slight elevation in heart rate. No adverse events were reported and in none of the patients did rebound hypertension occur upon termination of the drug. In another open, controlled, randomised, parallel trial, intravenous fenoldopam was compared with sodium nitroprusside in 18 patients with severe hypertension and mild renal failure.[19] Both antihypertensive medications were infused at a maximal dose increment of 0.2 μg/kg/min (fenoldopam) and 1 μg/kg/min (sodium nitroprusside) with a maximal infusion rate of 1.5 μg/kg/min for fenoldopam or 8 μg/kg/min for sodium nitroprusside. Both antihypertensive agents successfully controlled BP in all patients. The rate of adverse effects was similar in both groups of patients. However, in 2 patients treated with sodium nitroprusside toxic concentrations of thiocyanate were detected. Thus, fenoldopam may be superior to sodium nitroprusside for the control of hypertensive crisis in patients with decreased renal function. Gretler et al.[20] compared the ECG changes in 21 patients with hypertensive emergencies treated with either fenoldopam or sodium nitroprusside. Both drugs reduced BP significantly in all patients. New T-wave inversion occurred in 2 patients treated with fenoldopam and in 4 patients treated with sodium nitroprusside. It seems that fenoldopam is comparable to sodium nitroprusside and can be used in hypertensive emergency.

3.13 Diuretics and Other Agents

In addition to an antihypertensive agent, a potent diuretic, usually furosemide, can be given intravenously. However, the use of diuretics is somewhat controversial since most patients with hypertensive crisis are characterised by a contracted plasma volume. However, even if not given initially, a diuretic will likely be needed after other antihypertensives are used, since reactive renal sodium retention usually accompanies a fall in pressure and may blunt the efficacy of nondiuretic agents. Of note, if the patient is volume-depleted additional diuresis could be harmful.[8]

A number of other agents were tried in hypertensive crises including methyldopa, propranolol, reserpine and guanethidine. However, those drugs have largely been replaced by newer agents and probably have no role in the current treatment of hypertensive crises.

4. Treatment of Specific Hypertensive Emergencies

A multiplicity of disorders or diseases accompany the elevated BP that constitutes a hypertensive crisis and there is a broad spectrum of pharma-

cological agents that may be selected for treatment of these conditions. Some agents that are useful for 1 hypertensive emergency may actually be contraindicated for another.[76] The recommended therapeutic approach for specific conditions is summarised in table IV.

4.1 Hypertensive Encephalopathy

When mean arterial pressure reaches a critical level (around 180mm Hg) the previously constricted vessels are unable to withstand the pressure, counterregulation fails and generalised vasodilatation ensues. Such a breakthrough of cerebral blood flow (CBF) leads to hyperperfusion of the brain under high pressure and results in cerebral oedema and the clinical syndrome of hypertensive encephalopathy.[8] This scenario occurs at a much higher BP in patients with chronic hypertension than in previously normotensive persons. If untreated, the clinical picture progressively worsens, culminating in coma and death. Hypertensive encephalopathy is often indistinguishable from other acute neurological complications of hypertension, i.e. cerebral infarction, subarachnoidal bleeding or intracerebral haemorrhage. The only definite criterion to confirm a diagnosis of hypertensive encephalopathy is a prompt improvement in the patient's condition in response to antihypertensive therapy.[77] First choice drugs for this condition include intravenous sodium nitroprusside, labetalol, urapidil or nicardipine.

4.2 Cerebrovascular Accidents

4.2.1 Intracerebral Haemorrhage

As a result of intracerebral haemorrhage, intracerebral pressure rises and higher intra-arterial pressure is required to perfuse the brain adequately. In this condition, hypertension may be a result of increased intracerebral pressure and may resolve spontaneously within 48 hours.[77] Rapid reduction in BP may indeed prevent further bleeding, but at the risk of cerebral hypoperfusion.[1] In a recent retrospective study, Dandapani et al.[78] compared the morbidity and mortality outcome of patients with intracerebral haemorrhage according to their initial BP and the control of BP during the first 2 to 6 hours of presentation. They demonstrated an improved outcome in those patients who had an initial mean arterial pressure lower than 145mm Hg and in those who had their mean arterial pres-

Table IV. Preferred agents for specific hypertensive emergencies

Emergency condition	Preferred agent	Comments
Hypertensive encephalopathy	Sodium nitroprusside, labetalol, nicardipine, urapidil	Avoid methyldopa and diazoxide
Cerebrovascular accident	Sodium nitroprusside, labetalol, urapidil, esmolol, nimodipine	Benefit from acute lowering of BP is uncertain
Dissecting aortic aneurysm	Sodium nitroprusside with a β-blocker (propranolol or esmolol), labetalol, trimetaphan camsilate, urapidil	Titrate BP to the lowest possible level. Avoid hydralazine, diazoxide
Acute left ventricular failure	Sodium nitroprusside, nitroglycerin (glyceryl trinitrate), enalaprilat, urapidil, furosemide (frusemide), morphine	Avoid labetalol, esmolol, diazoxide, hydralazine
Coronary insufficiency	Nitroglycerin, sodium nitroprusside, labetalol, nicardipine, esmolol	BP should be reduced gradually. Avoid hydralazine, diazoxide
Perioperative hypertension	Sodium nitroprusside, nitroglycerin, labetalol, isradipine, nicardipine	Nitroglycerin is preferred in managing postcoronary bypass hypertension
Eclampsia	Hydralazine, labetalol, urapidil	Avoid diuretics, trimetaphan camsilate, sodium nitroprusside, ACE inhibitors
Catecholamine excess	Phentolamine, labetalol	Avoid diuretics
Renal insufficiency	Hydralazine, labetalol, fenoldopam, nicardipine	Avoid β-blockers

BP = blood pressure.

sure controlled below 125mm Hg. This retrospective study may suggest that markedly elevated BP may adversely affect the prognosis in hypertensive patients with intracerebral haemorrhage. Nevertheless, there is no consensus with regard to the advisability of reducing BP in these patients.[25] In any event, the reduction should not exceed 20% of pretreatment BP level.[79] If BP is extremely elevated (diastolic pressure >140mm Hg) and lasts longer than 20 minutes, intravenous treatment is recommended.[80] Preferred drugs for this condition include intravenous sodium nitroprusside, labetalol or urapidil. Recently it was reported that nimodipine has improved the outcome of patients with aneurysmal subarachnoid haemorrhage.[47]

4.2.2 Acute Ischaemic Stroke

Cerebral infarction causes an impairment in the autoregulation of CBF; therefore, elevated BP will accentuate perfusion through the damaged tissue, leading to oedema and compression of normal brain tissue. This provides evidence for carefully reducing BP in hypertensive patients with stroke.[8] Conversely, because of local vasoconstriction, high arterial BP is required to perfuse jeopardised brain tissue around the infarcted area. This provides evidence against reducing BP in acute ischaemic stroke. Moreover, chronic hypertension and cerebral vascular disease move the autoregulation curve of CBF to the right so that a decrease in CBF occurs at a higher BP level than in normal individuals. Therefore, cerebral hypoperfusion may appear at levels of BP that are still above the upper limit of normal. Patients with an acute ischaemic stroke demonstrate elevated BP levels on admission to the hospital. However, a spontaneous decrease in BP is usually observed within the first 4 days after the event.[81] Moreover, no beneficial effect has been demonstrated by short term lowering of BP in patients with acute ischaemic stroke. On the contrary, Rordorf et al.[82] recently showed that a subset of patients, particularly those with multiple stenosis of cerebral arteries, may improve neurologically upon elevation of the BP.

Brott and Reed[80] recommended no antihypertensive treatment if BP is <180/105mm Hg. If BP is >230/120mm Hg and persists for more than 20 minutes, intravenous treatment is recommended. The target BP should be 160 to 170/95 to 100mm Hg for previously normotensive patients and 180 to 185/105 to 110mm Hg for previously hypertensive patients. Although Brott and Reed[80] suggested a treatment regimen in acute stroke based on level of the BP, Powers[83] pointed out that the benefits to be derived from acutely lowering BP in patients with acute stroke of any kind remain conjectural and unsupported by good clinical or experimental studies. Sodium nitroprusside and nicardipine are the agents of choice whenever the BP is to be reduced for patients with acute ischaemic stroke.[84] Nimodipine is being investigated in this condition with equivocal results so far. Gelmers et al.[85] reported improved survival for men but not women, and a better neurological outcome in patients treated with nimodipine compared with those given a placebo. Martinez-Vila et al.[86] reported no benefit on survival or neurological outcome except for those patients who had mild deficits at the onset, who did seem to achieve greater recovery in the nimodipine group.

4.3 Acute Aortic Dissection

Most patients with acute aortic dissection who do not receive treatment die within 1 year, and most of the deaths occur within 2 weeks.[77] Once diagnosis is suspected attempts should be made to decrease the shear stress to the aortic wall with suitable agents.[77] BP should be reduced within 15 to 30 minutes to the lowest tolerated level that preserves adequate organ perfusion.[25,34] It has to be kept in mind that the force and velocity of ventricular contractions and pulsatile flow determine the shear stress on the aortic wall.[34] Drugs such as diazoxide, hydralazine and nifedipine, which reflexively stimulate sympathetic activity and increase the shear stress on the aortic wall are contraindicated. Initial treatment should consist of a combination of intravenous sodium nitroprusside and an intravenous β-blocking agent, most commonly propranolol. Used alone, sodium nitroprusside increases the velocity of ventricular con-

traction so that simultaneous β-blockade is obligatory.[34]

4.4 Acute Left Ventricular Failure

Severe hypertension may precipitate acute left ventricular failure.[77] Prompt reduction of BP decreases the work load of the failing myocardium and improves cardiac function.[77] Immediate decrease of afterload with a balanced vasodilating agent such as sodium nitroprusside is indicated in this circumstance.[34] Nitroglycerin is a reasonable alternative that has less afterload reducing capability, but may increase myocardial blood flow to ischaemic areas in patients with acute myocardial ischaemia. As urapidil has no influence on heart rate and myocardial oxygen consumption, it is a potential alternative to sodium nitroprusside and nitroglycerin if BP is insufficiently reduced. Concomitant therapy with oxygen, diuretics or opioids may enhance efficacy of antihypertensive agents.[34] Although the ACE inhibitors may be useful in this situation,[68] there is a paucity of clinical experience concerning the therapeutic response to ACE inhibition in patients with acute left ventricular failure.[77] Drugs causing reflex tachycardia (diazoxide, hydralazine) or decreasing myocardial contractility (labetalol) should be avoided in this setting.[34]

4.5 Ischaemic Heart Disease

Reduction of systemic BP by intravenous nitroglycerin reduces cardiac work, wall tension, and oxygen demand and therefore has became the drug of choice for this crisis.[25] Flaherty[87] found that infarct size was limited and left ventricular ejection fraction was higher in a group of patients receiving intravenous nitroglycerin shortly after the onset of myocardial infarction than in a control group. However, there was no statistically significant difference in 3 month mortality between the groups. Intravenous vasodilators, mainly sodium nitroprusside and nitroglycerin, have been tested in 11 trials involving 2170 patients with acute myocardial infarction and have reduced mortality by 43%.[88] Cautious treatment of hypertension in patients with acute myocardial infarction is likely to be beneficial. Conversely, unnecessary reduction in BP could compromise an already unstable situation,[77] and therefore BP should be reduced gradually until symptoms subside or until the diastolic BP is approximately 100mm Hg.[1] Rapid reduction of BP with any drug may cause ECG changes.[20,89] These changes, observed during infusion of sodium nitroprusside[15] and after oral nifedipine,[89] are usually not accompanied by left ventricular wall motion abnormalities.

Initial treatment of patients with angina pectoris and severe hypertension includes sublingual nitroglycerin and morphine, followed by intravenous nitroglycerin if treatment is not successful. Nifedipine should not be used in this crisis, as it causes a reflex tachycardia, increases myocardial oxygen demand and may aggravate myocardial ischaemia.[90]

4.6 Perioperative Hypertension

Most of the time, perioperative hypertension is not an emergency in the usual sense, but parenteral agents are frequently used to control BP because patients are unable to receive medications orally. Severe hypertension may occur in some patients in the postoperative period, especially after open heart and carotid artery surgery. The aetiology of this severe hypertension is multifactorial – withdrawal of antihypertensive drugs, pain, volume overload and sympathetic activation.[77] In this setting, hypertension, even of moderate severity, may jeopardise the integrity of the fresh vascular suture lines. Therapy should be individualised, and in some situations immediate lowering of the BP is warranted.[77] Hypotension is to be avoided in patients who have fresh vascular suture lines because the danger of thrombosis.[25] Sodium nitroprusside is usually the agent of choice, provided the patient is in an intensive care environment. Nitroglycerin administered intravenously may be the drug of choice for managing postcoronary bypass hypertension.[27]

4.7 Eclampsia

Pre-eclampsia occurring in pregnancy is a syndrome of hypertension, oedema and proteinuria. Some of these patients may progress to eclampsia, which is associated with seizures and end-organ damage (cerebral haemorrhage, renal failure and microangiopathic haemolytic anaemia).[91]

The important part of safe treatment is to control hypertension, keeping in mind the risk that reducing BP may further impair placental blood flow.

Hydralazine administered intravenously has been the drug of choice in recent years when diastolic BP is over 115mm Hg or when eclampsia supervenes; it is effective and does not decrease placental blood flow. Labetalol, urapidil or calcium antagonists are possible alternative therapeutic approaches if hydralazine is ineffective.[25,34,61] Diuretics, trimetaphan camsilate, sodium nitroprusside and ACE inhibitors should be avoided. If seizures are imminent or occur, magnesium sulfate should be administered parenterally.

4.8 Excessive Circulating Catecholamines

Catecholamine-induced crises are characterised by a sudden increase in predominantly α-adrenergic tone. Plasma catecholamine levels are elevated in phaeochromocytoma, in rebound hypertension following clonidine withdrawal, in hypertension associated with ingestion of sympathomimetics (cocaine hydrochloride, amphetamines, phencyclidine hydrochloride, lysergic acid diethylamide and weight-loss drugs, and in the drug interaction of monoamine oxidase inhibitors with tyramine rich-food (e.g. certain beers, cheese, wine and chicken liver).[92] When this condition is suspected, the α–adrenergic blocking drug phentolamine should be given. An alternative to phentolamine would be labetalol or sodium nitroprusside with β-blockers. A β-blocking drug may be needed if the patient has a concomitant tachycardia or ventricular ectopy. Administration of β-blocking agent should always be preceded by α-blockade to prevent unopposed α-mediated peripheral vasoconstriction.[1,77]

4.9 Renal Insufficiency

Deterioration of renal function in the face of elevated BP is considered a hypertensive emergency and requires lowering of the BP.[34] Therapy should reduce systemic vascular resistance without compromising the renal blood flow or glomerular filtration.[1] Sodium nitroprusside is effective in these cases, but because the risk of thiocyanate toxicity is increased, dose adjustment and close monitoring of thiocyanate levels are needed. Labetalol, calcium antagonists and fenoldopam are effective and well tolerated alternatives.[1] β-Blockers reduce the renal plasma flow and the glomerular filtration rate and should therefore be used with caution, if at all, in these patients.

5. Oral Agents for Hypertensive Urgency

During the last 15 years the treatment focus for hypertensive crises has moved toward the use of oral agents.

The ideal oral drug to treat a hypertensive crisis should be one that has a rapid and smooth onset of action, few adverse effects, does not cause excessive hypotension, is convenient to monitor and can be easily converted to a maintenance therapy.[93]

The fifth Joint National Committee (JNC V) recommends the use of captopril, clonidine, labetalol and nifedipine for the treatment of hypertensive urgency and emergency.[2] However, the use of oral agents should be limited to hypertensive urgency as clearly recommended by the Sixth Joint National Committee (JNC VI).[84]

5.1 Captopril

Captopril, an ACE inhibitor, was initially studied for the treatment of hypertensive crisis in a few small, uncontrolled studies using a dose of 25mg sublingually.[94-96] Sublingual captopril is well tolerated and effective in reducing BP, the onset of action occurs within 5 to 10 minutes, reaching a maximum within 30 minutes and lasting for at least 2 hours. Following oral administration of captopril on an empty stomach, maximal BP reduction is observed within 30 to 90 minutes.[93] Di Veroli and

Pastorelli[97] compared orally sublingual captopril with standard oral captopril. Patients with hypertensive emergency were given captopril 50mg either sublingually (n = 26) or orally (n = 14). In the sublingual group BP was reduced after 60 minutes from 196/112 to 154/90mm Hg with a response rate of 84%, whereas in the standard oral group BP was reduced from 197/110 to only 182/99mm Hg with a response rate of 57%.

The antihypertensive response is usually not excessive unless the patient is volume depleted. Patients with renal artery stenosis may experience sudden severe deterioration of renal function. Undesirable effects are rash and precipitous fall in BP in patients with suspected high renin levels.[34] In general, comparative trials have observed fewer adverse effects with captopril than with nifedipine administration (table V). Most studies concluded that captopril should be considered as a first line therapy in the acute management of hypertensive crisis.[97,99-102,107] However, as no outcome data are available attesting to benefits of captopril in this clinical situation.

5.2 Calcium Antagonists

5.2.1 Nifedipine

Nifedipine is a dihydropyridine calcium antagonist that lowers BP by peripheral vasodilatation with only mild negative inotropic and chronotropic effects. The advantages of nifedipine use are rapid onset of action and lack of CNS depression. Nifedipine is the most extensively studied agent for rapid control of BP and until recently was used for acute BP lowering in hospitalised patients.[72,108-146] After sublingual administration, the onset of action is within 1 to 5 minutes with a maximal effect at 20 to 30 minutes.[115,147-150] The buccal absorption of nifedipine is minimal,[151-153] and faster absorption and higher maximum concentrations were observed following the bite and swallow method when compared with other methods of administration.[151] The duration of action of a single dose of nifedipine is about 3 to 5 hours.[115] The most common adverse effect associated with nifedipine is reflex tachycardia secondary to pronounced vasodilatation. Some patients may experience symptoms of hypotension and flushing.[154] Despite its 'so called' efficacy and safety, sublingual nifedipine has not been approved by the US Food and Drug Administration for use in hypertensive emergency because lack of scientific validation of the advantageous use of the drug in hypertensive emergency.

Nifedipine also has been associated with some severe adverse affects, including retinal ischaemia, cerebral vascular accidents and myocardial ischaemia and infarction.[90,155-164] In 1 study, out of 100 patients with hypertensive crisis who were treated with sublingual nifedipine, 1 patient had pulmonary oedema, 7 patients had transient ischaemic attack and all had facial flushing.[155] Rapid uncontrolled pressure reduction may be harmful because it precipitates acute ischaemic stroke or myocardial infarction. This has been emphasised recently with regard to the short-acting nifedipine.[155] Therefore, the use of nifedipine capsules for hypertensive crisis should be abandoned.

5.2.2 Nitrendipine

Nitrendipine is a dihydropyridine calcium antagonist which differs from nifedipine by having a particularly high affinity for vascular smooth muscle so that at therapeutic doses it produces marked vasodilatation with negligible negative cardiac effects. In its liquid form its efficacy is the same as nifedipine.[105] In a multicentre randomised, double-blind study sublingual nitrendipine 5mg was compared with nifedipine 10mg in 141 patients with hypertensive crisis. BP reduction was observed 10 minutes after nitrendipine administration and reached a maximum level within 45 minutes. The response rate (i.e. BP decreased to below 200/100mm Hg) was 75% within 45 minutes and 91% 4 hours after initiating treatment.[105] No severe adverse effects were observed in this study.

In another multicentre study, 114 patients with hypertensive emergency were treated with 5mg solution of nitrendipine. At 45 minutes, target arterial pressure of 160/100mm Hg or a reduction of 20/15mm Hg had been obtained in 82% of the patients. After 45 minutes, 37 patients needed a sec-

Table V. Comparative studies of oral antihypertensive agents in hypertensive crisis

Reference	Drug/route	No. pt	Age (y)	Clinical condition	Initial dose (mg)	Time to response (min)	Initial MAP (mm Hg)	Decrease in MAP (%)	Response rate (%)	No. of patients experiencing an adverse effect	Type of adverse effects
Angeli et al.[98]	Nifedipine SL	10	53	Emerg	10	50	188	22	80	3	Headache, flushing
	Captopril SL	10	61	Emerg	25	50	178	22	90	0	
Pascale et al.[99]	Nifedipine SL	60	64	Urg + Emerg	10	30	154	21	NA	12	Mainly headache
	Captopril SL	20	64	Urg + Emerg	50	30	158	21	NA	0	
	Clonidine IM	20	60	Urg + Emerg	0.15	30	160	19	NA	0	
	Furosemide (frusemide) IV	20	75	Urg + Emerg	40	30	158	17	NA	0	
Komsuoglu et al.[100]	Nifedipine SL	23	62	Urg	20	45	170	30	91	14	Flushing, headache, palpitations, drowsiness
	Captopril PO	20	62	Urg	25	60	171	30	90	2	Dry mouth, vertigo,
	Nicardipine PO	22	62	Urg	20	60	168	31	95	4	Headache
Pastorelli et al.[101]	Nifedipine SL	16	71	Emerg	10	20	135	12	80	8	Flushing, headache, hypotension
	Captopril SL	27	71	Emerg	50	20	142	14	85	0	
	Captopril PO	14	71	Emerg	50	20	140	6	NA	0	
	Ketanserin SL	15	71	Emerg	NA	20	138	6	NA	1	Headache
	Placebo PO	20	71	Emerg	NA	20	137	5	0	0	
Ceyhan et al.[102]	Nifedipine SL	24	58	Emerg	10	45	151	27	NA	6	Flushing, headache, tachycardia
	Captopril SL	28	54	Emerg	25	45	150	17	NA	0	
Just et al.[103]	Nifedipine PO	35	48	Urg	10	44	151	24	100	1	Hypotension
	Clonidine PO	32	54	Urg	0.1	77	149	21	100	NA	
Panlilio et al.[104]	Nifedipine SL	30	51	Urg	10	45	140	21	93	3	Headache
	Clonidine SL	30	51	Urg	0.3	45	147	19	83	7	Drowsiness, headache, weakness
McDonald et al.[51]	Nifedipine PO	10	48	Urg	10	30	151	20	100	1	Dizziness
	Labetalol PO	10	46	Urg	200	30	150	21	80	0	
Bussmann et al.[30]	Nifedipine SL	20	70	Urg + Emerg	10 - 20	5	149	13	95	4	Dizziness, tachycardia, headache
	Nitroglycerin (glyceryl trinitrate) SL	20	70	Urg + Emerg	1.2 - 2.4	5	145	17	85	2	Headache, nausea
Rohr et al.[105]	Nifedipine SL	73	60	Urg	10	45	150	21	78	4	Vomiting, palpitations, incontinence
	Nitrendipine SL	68	59	Urg	5	45	150	19	78	2	Flushing, incontinence
Savi et al.[106]	Nifedipine SL	12	49	Urg	10	35	145	16	NA	5	Headache, flushing
	Nicardipine SL	12	49	Urg	20	35	145	19	NA	0	

Emerg = emergency; **IM** = intramuscular; **IV** = intravenous; **MAP** = mean arterial pressure; **NA** = not available; **PO** = oral; **SL** = sublingual; **Urg** = urgency.

ond dose. 23 patients experienced adverse effects, including one with hypotension and one with ECG changes.[165] Thus, it seems that like nifedipine, sublingual nitrendipine should not be used in hypertensive emergencies.

5.2.3 Nicardipine

Nicardipine is a second generation dihydropyridine calcium antagonist that, unlike nifedipine, causes little, if any, increase in heart rate.[106,166,167] In 1 study, sublingual nicardipine was compared with nifedipine in patients with hypertensive urgencies.[106] Nicardipine appeared to be better tolerated and produced a slower and more prolonged decrease in BP than nifedipine. This difference in effect may have been because of incomplete dissolution and subsequent absorption of the nicardipine tablet. In a multicentre, randomised, double-blind, parallel, placebo-controlled trial, 53 patients with hypertensive urgency were assigned to receive orally either nicardipine 30mg or placebo. Diastolic pressure decreased by 22.2 ± 11.7mm Hg in the nicardipine group and only by 8.5 ± 10.9mm Hg in the placebo group ($p < 0.0001$). Adequate BP response was observed in 65% of the 26 patients treated with nicardipine 30mg and only in 22% of the 27 patients given placebo ($p = 0.002$). Of the 21 patients given placebo who did not have an adequate BP response, 16 (76%) had adequate BP reduction after 1 open-label dose of nicardipine 30mg. Adverse events were reported in 3 patients given nicardipine and 4 patients given placebo. Asymptomatic hypotension was noted in 3 patients, 2 in the nicardipine group and 1 in the placebo group and 1 patient treated with nicardipine reported anxiety, headache, tachycardia and chest pain.[166] During 1 week of follow-up, minor adverse events were reported in the nicardipine group. Compared with nifedipine, it seems that oral nicardipine is as effective and is safer for the initial treatment of urgent hypertension.

5.2.4 Isradipine

Isradipine, which is similar in structure to nifedipine, has been evaluated in several studies as a treatment for hypertensive crisis. In 27 ambulatory patients with hypertensive crisis, isradipine was given sublingually at a dose of 1.25 to 5mg. The onset of action occurred approximately 30 minutes after administration and reached its maximum effect within 2 hours of administration. Mean arterial pressure decreased from 153.4 ± 4.3 to 120 ± 2.3mm Hg 60 minutes after administration and to 118 ± 2.1mm Hg at 2 hours after administration. There was no difference in maximal BP reduction throughout the dosage range, although higher doses produced a more rapid fall in BP than lower doses.[168]

5.3 Clonidine

Clonidine is a central acting α_2-adrenergic receptor agonist that reduces BP by decreasing cerebral sympathetic outflow. Its onset of action is 30 to 60 minutes after administration and its maximal effect is achieved within 1 to 4 hours and lasts for 6 to 8 hours. A well accepted method of clonidine administration for hypertensive crisis is by an oral loading regimen involving an initial dose of 0.1 to 0.2mg that may be repeated as needed. However, doses higher than 0.4mg have little additional benefit in patients whose hypertension does not respond to lower doses.[169] Most studies report an average response rate of approximately 80%.[103,170,171] The drug should not be used in patients with altered mental status, because of its common adverse effect of drowsiness.[169,172,173] In addition, clonidine can cause a significant decrease in CBF.[34] One case of death from a progressive cerebral infarct following the administration of cumulative clonidine dose of 0.4mg has been reported.[173] Other complications associated with clonidine include dry mouth, occasional dizziness and the development of a hypertensive crisis upon abrupt discontinuation of therapy.[174] Because of its unpleasant adverse effects and its pharmacokinetics the popularity of this drug is declining.

5.4 Labetalol

Labetalol is a unique antihypertensive agent that competitively inhibits both α- and β-adrenergic receptors.[34] The α-blocking properties domi-

nate in the treatment of patients with hypertensive crises. Labetalol reduces systemic vascular resistance and BP without inducing reflex tachycardia or change in cardiac output. Gonzalez et al.[175] conducted a dose-response study with labetalol in 36 patients. The maximal BP lowering effect was seen at 2 hours and BP control was maintained for 4 hours. An oral dose of 200mg labetalol was found to be the most appropriate to maximise efficacy and tolerability.[175] However, several other investigators used total doses as high as 500 to 1200mg to achieve BP control.[51,176] The initial dose should be 200mg followed by hourly 200mg to a maximal total dose of 1200mg. The response rate in patients with hypertensive urgency is 80 to 94%.[51,52,176] Because of its pharmacology, labetalol should not be used in patients with chronic obstructive lung disease, congestive heart failure, atrioventricular block or bradycardia. Adverse effects include hypotension, dizziness, headache, nausea, vomiting and flushing.[51,175,177]

5.5 Prazosin

Prazosin is a peripheral α_1-adrenergic antagonist which is effective for hypertensive urgencies associated with increased circulating catecholamines. One small uncontrolled study of 8 patients with hypertensive urgency found that BP was reduced dramatically at 3 to 4 hours following a single dose of prazosin (mean 5.4 mg).[177] Patients responded less dramatically to subsequent prazosin doses. Adverse effects included syncope caused by orthostatic hypotension, palpitations, tachycardia and headache. To date, despite the lack of controlled studies that examine prazosin for treatment of hypertensive crisis, the drug is often listed as an oral antihypertensive agent for treating hypertensive urgencies.[13] However, we do not recommend its use for this indication.

5.6 Other Oral Agents

The efficacy of other oral agents including methyldopa, phenoxybenzamine, losartan potassium, valsartan and direct acting vasodilators such as minoxidil and hydralazine, in treating hypertensive urgency has not been well studied.[93] These drugs therefore have little if any role in the treatment of this condition.

6. Optimal Treatment of Hypertensive Urgency

The optimal approach in patients with hypertensive urgency is to lower the BP more gradually over 24 to 48 hours. This therapeutic approach requires a close follow-up of the patient in the first days after the acute event. When the cause of transient BP elevations is easily identified, such as pain or acute anxiety (as in panic disorders)[7,178] the appropriate therapy is analgesic or anxiolytic medication. When the cause of BP elevation is unknown, various oral antihypertensive agents are available. There are some reports attesting to the safety of intravenous drugs like labetalol or urapidil in this setting,[53,59] but this mode of treatment is not recommended. In the absence of any data comparing long term outcome with the various agents the choice of therapy should be based on efficacy and safety data.

The efficacy of the various oral antihypertensive agents seems to be similar (table V),[30,51,98-106] and it has ranged in controlled trials from between 96 to 98% for nifedipine, 79 to 100% for clonidine, 90 to 95 % for captopril, 68 to 94 % for labetalol, 65% to 91% for nicardipine, 66% to 82%% for nitrendipine and 85% for nitroglycerin. Acute lowering of BP may compromise cardiac and cerebral blood flow, especially in the elderly and therefore may be associated with serious adverse effects.[89,156-164] We have recently published a review of serious adverse effects following oral or sublingual administration of nifedipine capsule in hypertensive emergencies and pseudoemergencies.[154] Given the potential seriousness of adverse events and the lack of any clinical documentation attesting to a benefit in rapid lowering BP, nifedipine capsules and any drug that lower BP acutely to unpredictable levels should not be used in hypertensive crisis. Of note oral agents should be used only in hypertensive urgency, and not emergency, and in hypertensive urgency a slower reduc-

tion of BP over a period of hours to several days is more appropriate.[4]

It is important not to be too aggressive in lowering BP and to use the right agent for the right condition. When considering the appropriate agent, the mechanism of action and the profile of adverse effects should be taken into consideration. Nifedipine and to lesser degree captopril tend to increase heart rate and clonidine and labetalol tend to decrease it. This is particularly important in patients with ischaemic heart disease. Other limitations are the use of labetalol in patients with bronchospasm and bradycardia and second and third degree heart blocks. Clonidine should be avoided if mental acuity is desired. Captopril should not be used in patients with bilateral renal artery stenosis or unilateral renal artery stenosis of a solitary kidney. All agents should be used carefully in volume depleted patients.

7. Treatment of Specific Populations

7.1 Hypertension in Childhood

Hypertensive emergencies are rare events during childhood. Diseases most likely to result in hypertensive emergencies involve the kidney. Extremely high BP levels can be seen in patients with renal artery stenosis, acute poststreptococcal glomerulonephritis or systemic lupus erythematosus. Extremely high BP may be seen in infants with autosomal recessive polycystic kidney disease. Extrarenal causes such as phaeochromocytoma and neuroblastoma are less frequent. As in adults, the absolute BP values cannot be used as the only determinant of whether a child is experiencing a hypertensive emergency.[179] In 1 study as many as 24% of children presenting to the emergency room with hypertension required emergency management.[21] Of this group, 57 patients were treated with intravenous hydralazine or diazoxide to reduce BP within the first 12 to 24 hours. This management was associated with irreversible neurological deficits in four out of the 57 patients. In a second subgroup of 53 patients, BP was reduced more gradually over 96 hours with either intravenous labetalol or sodium nitroprusside. In this subgroup no neurological impairments were observed.[21] Unfortunately, as in adults, a precise determination of what approach is safest for achieving BP reduction has not been established. Intravenous treatment is often preferable because of greater ease in titrating BP.

In the absence of specific contraindications a continuous infusion of nicardipine or sodium nitroprusside is preferable. Intravenous labetalol as a bolus injection followed by continuous infusion, also may be used. Oral agents should be reserved for circumstances in which symptoms of end organ toxicity are mild or absent.[179] Children have a more active renin-angiotensin system than adults and a higher incidence of renal artery stenosis as a cause of severe hypertension. Therefore, ACE inhibitors should be not be used as long as the underlying cause for the hypertension is unknown.

7.2 Hypertension in the Elderly

In general, older persons have a lower blood volume, lower plasma renin activity and increased peripheral vascular resistance[180] that affect the pharmacokinetics of some antihypertensive agents. With age, the decrease in glomerular filtration rate and blunted baroreceptor reflexes increase the risk of overdose and orthostatic hypotension. If supine hypertension is treated too vigorously, older patients may experience presyncope or actual syncope. The increase in systolic BP associated with age is actually caused by an atherosclerotic-related decrease in aortic distensibility. In this setting small changes in stroke volume can result in greater changes in systolic BP. Rapid reduction of BP is especially dangerous in elderly patients and can cause transient ischaemic attacks, strokes, angina, myocardial infarction and syncope.[181] Therefore, low doses of antihypertensive agents should be used.

8. Conclusions

Hypertensive emergencies are relatively rare and are said to be present only when BP elevation confers an immediate threat to the integrity of the

cardiovascular system. In this setting immediate reduction in BP is required, usually by intravenous therapy in an intensive care unit. Unlike a hypertensive emergency, a hypertensive urgency is said to be present when severe BP elevation is not associated with end-organ injury. Outcome data attesting to benefits of acutely lowering BP in this condition are not available.

Clearly, patients with hypertensive crises are not good candidates for prospective, randomised trials. The accepted approach for patients with hypertensive urgency is to lower the BP more gradually over 24 to 48 hours with oral antihypertensive agents. Any drug that lowers BP precipitously should be avoided. The efficacy of nifedipine, captopril, clonidine, labetalol, nicardipine, nitrendipine and nitroglycerin seems to be similar. Choice of the appropriate agent should be based on the underlying pathophysiological and clinical findings, mechanism of action and the potential adverse effects.

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Correspondence and reprints: Dr *Ehud Grossman*, Internal Medicine D, The Chaim Sheba Medical Center, Tel-Hashomer, 52621, Israel.