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HYPERTENSIVE EMERGENCIES (BM BAUMANN, SECTION EDITOR)

Control of Blood Pressure in Hypertensive Neurological Emergencies

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Abstract Neurological hypertensive emergencies cause significant morbidity and mortality. Most occur in the setting of ischaemic stroke, spontaneous intracerebral hemorrhage (ICH), or subarachnoid hemorrhage (SAH), but other causes relate to hypertensive encephalopathy and reversible cerebral vasoconstriction syndrome (RCVS). Prompt and controlled reduction of blood pressure (BP) is necessary, although there remains uncertainty as to the optimal rate of decline and ideal antihypertensive agent. There is probably no single treatment strategy that covers all neurological hypertensive emergencies. Prompt diagnosis of the underlying disorder, recognition of its severity, and appropriate targeted treatment are required. Lack of comparative-effectiveness data leaves clinicians with limited evidence-based guidance in management, although significant developments have occurred recently in the field. In this article, we review the management of specific neurological hypertensive emergencies, with particular emphasis on recent evidence.

Keywords Hypertension · Emergencies · Critical care · Neurological · Subarachnoid hemorrhage · Stroke · Intracerebral hemorrhage · Encephalopathy

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Introduction

Hypertensive emergencies are defined as large elevations in systolic and/or diastolic BP (usually >180 or >120 mmHg, respectively) in association with impending or progressive cerebral and other end organ damage [1, 2•]. Most occur in the setting of any of the major types of acute stroke, namely ischemic stroke, spontaneous ICH, or SAH, but other causes relate to hypertensive encephalopathy and a related disorder, RCVS or Call-Flemming syndrome. Prompt diagnosis of the underlying disorder, recognition of its severity, and appropriate targeted treatment are required, although not all neurological hypertensive emergencies require prompt lowering of BP, as such treatment may increase the risk of cerebral ischemia.

Of the 1 billion people affected with hypertension worldwide, it is estimated that 1 to 2 % will have a hypertensive emergency at some time in their life [2•, 3]. Of all the causes of neurological hypertensive emergencies, the majority are due to cerebral infarction (accounting for 25 % of all hypertensive emergencies), with hypertensive encephalopathy (15 %) and ICH (5 %) accounting for most of the rest [4]. The great majority of patients who present with a hypertensive emergency have prior known hypertension (80 – 90 %), often with poor adherence and/or inadequate treatment, and they are more often of non-white background, elderly and male [2•, 5, 6].

Treatment recommendations depend on the type of associated organ damage. If the patient has raised intracranial pressure (ICP) and/or neurological deterioration, they require close monitoring in an intensive care or high dependency setting to ensure careful control of BP. The lack of comparative-effectiveness data leaves clinicians with limited evidence-based guidance in their management of many hypertensive emergencies [2•, 3]. Short-acting, titratable, intravenous antihypertensive agents are generally recommended, where guideline recommendations are generally based on

experience and physiological rationale rather than hard evidence, but there have been some significant recent developments [1, 7, 8]. In this review, we review the management of specific neurological hypertensive emergencies, with particular emphasis on recent evidence. We begin with background information on the regulation of cerebral blood flow and potential implications for rapid BP lowering on the injured brain.

Cerebral Autoregulation and Implications for Treatment

An underlying hypothesis is that cerebral autoregulation is altered in the context of hypertensive neurological emergencies, which complicates the balance of potential benefits and harms of BP-lowering treatment. Under normal circumstances, cerebral autoregulation is organized to maintain a constant cerebral blood flow in the capillary bed to a mean arterial pressure (MAP) of between 60 and 150 mmHg [9]. As BP progressively increases, vasoconstriction occurs within cerebral arterioles resulting in BP exceeding the upper limit of autoregulation,. This produces breakthrough vasodilatation and increased cerebral blood flow, with disruption of the blood brain barrier and cerebral edema [10]. To complicate matters further, intracerebral pathology, for example, acute stroke, in itself may alter cerebral autoregulation (Fig. 1) [12–14]. In an altered, and increasingly pressure dependant, cerebral circulation, therapeutic reduction in BP may increase the risk of cerebral ischemia, particularly in 'at risk' penumbral areas.

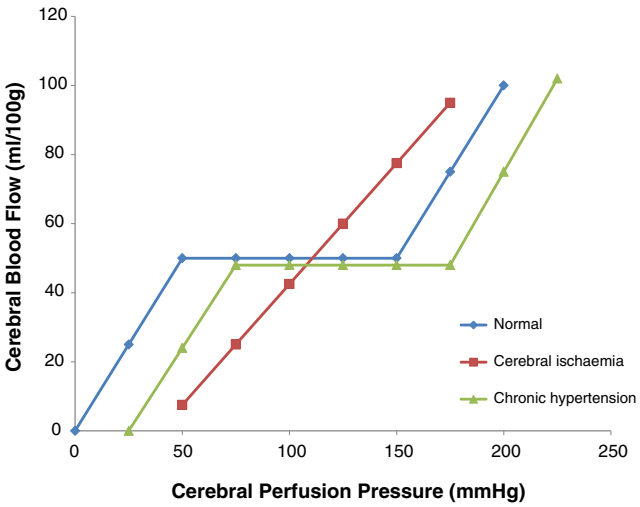

Fig. 1 The cerebral autoregulation curve in normal individuals, and in patients with chronic hypertension and cerebral ischemia. The autoregulatory curve is shifted to the right in chronic hypertension, maintaining constant CBF at higher CPP than normal. Therefore, in those with chronic hypertension, greater elevations in blood pressure than those in non-hypertensive individuals, may be required before cerebral autoregulation is overwhelmed. In the setting of cerebral ischemia, autoregulation is impaired, and CBF becomes proportional to CPP [11]

Conversely, persistently high BP may increase the risk of ongoing bleeding in SAH and ICH, promote hemorrhagic transformation of cerebral infarction in ischemic stroke, and increase the risk of cerebral edema in all neurological hypertensive emergencies [15]. Mass effect related to hemorrhage and cerebral edema in ICH, ischemic stroke, SAH and hypertensive encephalopathy, leads to elevations in ICP. In this setting cerebral perfusion pressure may be compromised by high levels of MAP [16]. Whether the monitoring of cerebral perfusion pressure in such situations improves outcomes is uncertain, but this is often used to ensure that BP is not lowered disproportionate to maintaining adequate cerebral perfusion [17, 18]. Hence, while lowering BP is essential in hypertensive neurological emergencies, it is also a complex and potentially harmful therapy that necessitates careful monitoring.

Specific Conditions

Acute Ischemic Stroke

Stroke is the second leading cause of death and the leading cause of long-term disability worldwide, with acute ischemic stroke accounting for approximately 70 % of all strokes [19]. Elevated BP is common in those presenting with acute stroke, where approximately 75 % have a BP >140/90 mmHg, and 50 % and 15 % have systolic BP (SBP) >160 mmHg and >184 mmHg, respectively [20, 21]. The natural history is for BP to decline spontaneously over the subsequent several days after the event. Elevated BP is associated with poor short- and long-term outcomes [22–25]. Data from the first International Stroke Trial suggested a U-shaped relationship between baseline SBP (within 48 h of stroke) and short-term mortality and long-term death and dependency; the lowest risk of a poor outcome was in patients with a SBP of 150 mmHg, with very high and very low BP associated with worse outcome [26]. However, other studies have found a more linear relationship between elevated in-hospital BP and poor outcomes [27–30]. Among patients receiving thrombolysis treatment, elevated BP is associated with a near linear increase in the risk of symptomatic ICH, with a U-shaped trend in the risk of death and dependency at 3 months [22]. Based on these observational data, the ideal SBP is 140-150 mmHg in the context of acute ischemic stroke.

There is limited and conflicting evidence regarding the benefits of BP-lowering treatment in acute ischemic stroke, in part due to the heterogeneity of time to treatment, entry criteria, type and severity of stroke, and degree and speed of BP control across clinical trials. Table 1 describes important trials in this area and their key findings. The totality of the evidence to date is that ***modest BP lowering with oral agents*** within the first 48 h after the onset of ischemic stroke is safe,

Table 1 Important Randomized, Controlled Trials of Intervention versus Control in BP Management Following Stroke. All trials included patients with ischaemic stroke and ICH

Name (year)	Number of participants	Initial median SBP (mmHg)	Time to treatment (hours)	Treatment	Outcome measures	Key findings
SCAST (2013) [31•]	2,029	171	17.8	Candesartan PO*	Composite endpoint of vascular death, myocardial infarction, or stroke during the first 6 months Functional outcome at 6 months	No beneficial effect seen in treatment group
COSSACS (2010) [32]	763	150	23.5	Previously taken antihypertensive agents	Death or dependency at 2 weeks	No differences between groups in primary outcome, vascular events or serious adverse events.
CHHIPS (2009) [33]	179	181	17.4 – 20.5	Labetalol PO, IV† Lisinopril PO, SL‡	Death and dependency at 2 weeks	No difference in primary outcome between groups (numbers small). Reduced 3 month mortality in treatment group. Active treatment not associated with increased early neurological deterioration.
IMAGES (2004) [34]	2,589	MAP 108	7	Magnesium IV	Death and disability at 90 days	Non-significant trend toward better outcome in treatment group. Significant trend toward better outcome in subgroup with high BP (MAP > 108)
INWEST (1994) [35]	295	159 – 161	10.5 – 11.5	Nimodipine IV	Neurological outcome at day 21 Functional outcome at day 21	Increased rate of poor outcome in treatment group
BEST (1988) [36]	302	Not published	22 – 25.3	Atenolol, propranolol PO	Mortality, neurological and functional state at day 8, 1 month and 6 months.	Increased mortality in treatment group (though groups unbalanced in terms of stroke severity)
CATIS (2013) [37•]	4,091	167	15	Stepped agent protocol enalapril (first-line), calcium channel blocker (second-line), diuretic (third-line)	Mortality and major disability at 14 days; mortality and major disability at 90-days	No difference between groups in the primary or secondary outcomes;

* PO: Per Os

† IV: Intravenous

‡ SL: Sub-lingual

SCAST: The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial

COSSACS: Continue or Stop post-Stroke Antihypertensives Collaborative Study

CHHIPS: Controlling Hypertension and Hypotension Immediately Post Stroke

IMAGES: Intravenous Magnesium Efficacy in Acute Stroke

INWEST: Intravenous Nimodipine West European Stroke Trial

BEST: Low dose beta blockade in acute stroke

CATIS: China Antihypertensive Trial in Acute Ischemic Stroke

but there is uncertainty about whether this improves long-term outcomes (Table 1) [31•, 33, 38, 39]. Whilst the Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) trial showed that early treatment (within 36 h) was safe and halved mortality compared to placebo at 3 months, Scandinavian Candesartan Acute Stroke Trial (SCAST) concluded that there was no benefit of treatment with an angiotensin-receptor blocker and potential harm on the basis of a non-significant trend towards increased poor functional outcome at 6 months [31•, 33]. Most recently, the large-scale China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) showed no beneficial (or adverse) effects of an angiotensin converting enzyme inhibitor (ACE-I) based regime of BP lowering within 48 h of acute ischemic stroke [37•]. However, all of these studies may be limited by the treatment being initiated relatively late (12 – 24 h) after the onset of symptoms in relatively mild cases of stroke, and in achieving relatively modest BP reductions to target over 24 h.

Effects of BP lowering may depend on initial BP level, time to treatment, stroke severity, history of hypertension, intensity of treatment, and the agents used. There is no clear answer as to the ideal agent (Table 1). More positive outcomes were found in other trials where BP lowering was commenced earlier after stroke onset, although the use of nimodipine was shown to have an adverse effect [33, 35]. In particular, secondary analyses of the Intravenous Nimodipine West European Stroke Trial INWEST and SCAST suggest that rapid and large decreases in BP are associated with poor outcome, whereas rapid but moderate early BP reduction appears to be safe [35, 40]. Further data on BP lowering are expected from the Efficacy in Nitric Oxide (ENOS) trial, where nitric oxide was compared with placebo (and continuing versus stopping current antihypertensive therapy), which has completed recruitment of over 4,000 patients within 48 h of stroke onset [41].

Cochrane systematic reviews and several international guidelines report ongoing uncertainty as to the optimal management of BP in the context of acute ischemic stroke [8, 42–46]. Both American and European guidelines recommend against lowering BP in most patients during the initial 24 h of acute ischemic stroke unless the BP levels are extreme, that is, systolic >200 mmHg, or there is a concomitant specific situation that would warrant such treatment. When BP management is indicated, targets are based on best clinical judgment and observational data, with cautious lowering of SBP by 15 % and close monitoring for neurological deterioration [1, 9, 45–47]. Arterial monitoring of BP should be considered in critically ill patients who require frequent titration of intravenous BP-lowering agents.

More specific guidance is available for patients who are candidates for thrombolytic therapy (BP >180/110 mmHg being a contraindication to thrombolysis). If BP is >185/110 mmHg, intravenous labetalol (10 to 20 mg) or nicardipine (5 mg/h) are popular agents given with dose titration used as necessary. Other agents (for example, nitroglycerin, hydralazine, urapidil [not available in the US] and enalaprilat) may also be considered [1, 45–47]. Though guidelines recommend a cautious approach to BP lowering, the available evidence suggest potentially greater benefits may be derived from more aggressive BP lowering in the context of thrombolysis. The ongoing Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED, ClinicalTrials.gov: NCT01422616), which compares intensive (systolic target 130 – 140 mmHg) versus guideline recommended BP reduction (systolic target <180 mmHg), as well as low dose (0.6 mg/kg) versus standard dose (0.9 mg/kg) recombinant tissue plasminogen activator (rtPA), in thrombolysis eligible patients, will provide solid evidence regarding BP management in the peri- and immediate post-thrombolysis period [48].

Acute ICH

ICH accounts for 10 to 15 % of all strokes in high-income Western countries, but between 20 – 50 % of those in low- to middle-income developing countries [19, 49, 50]. Elevated BP is a frequent occurrence, often to markedly elevated levels, in patients with acute ICH [21, 51]. As in ischemic stroke, BP generally falls spontaneously within several days after onset. Elevated BP following ICH is associated with poor outcomes, though the exact pathophysiological mechanisms remain unclear [51–54]. While some studies report a link between SBP and hematoma growth, others do not [52, 54, 55]. There has been an extrapolation from the penumbra of ischemic stroke to a risk of inducing cerebral ischemia in the perihematomal edematous region from rapid lowering of BP, though recent careful studies with advanced cerebral imaging are more reassuring against such hazard [56]. A systematic review, and a large multicenter study in China show that a SBP greater than 140 – 150 mmHg within 12 h of ICH is associated with a more than doubling in the risk of subsequent death or dependency [51, 57]. In contrast to the U-shaped relationship between SBP and outcome in ischemic stroke, only one study in ICH has shown a poor outcome at very low levels of SBP [58].

Current guidelines for BP management in ICH are outlined in Table 2, although these were published prior to the completion of two important recent studies [60••, 61]. Their recommendations were based mainly on observational studies which suggest that a reduction in MAP by 15 % was associated with decreased CBF [62]; reducing SBP to <160 mmHg within 6 h of onset is associated with a trend toward improved outcome [63]; higher baseline SBP is associated with growth of ICH [52]; and rapid BP lowering may be hazardous [64].

Most recently, three studies have demonstrated safety, feasibility and potential efficacy of early intensive BP lowering in acute ICH: The Antihypertensive Treatment of Acute Cerebral

Table 2 Summary of Current International Guidance on Management of Elevated BP Following ICH

BP level (mmHg)	Treatment Options	Monitoring
*SBP>200 or †MAP >150	Consider aggressive BP lowering with IV infusion of short acting antihypertensive, e.g. labetalol/nicardipine	Monitor BP every 5 min
SBP >180 or MAP >130 with possible raised ‡ICP	Consider monitoring ICP and reducing BP with IV infusion	Maintain ICP ≥60 mmHg
SBP >180 or MAP >130 with no evidence of raised ICP	Consider modest reduction in BP with IV infusion	Re-examine patient and monitor BP every 15 min Target BP = 160/90 mmHg

[17, 47, 59]

*SBP = Systolic blood pressure

†MAP = Mean Arterial Pressure

‡ICP = Raised Intracranial Pressure

Hemorrhage trial (ATACH), Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) and the Intracerebral Haemorrhage Acutely Decreasing Arterial Pressure Trial (ADAPT), [61, 65]. The pilot phase INTERACT, which was undertaken in 404 patients who could be treated within 6 h of ICH onset, showed a trend towards attenuation in hematoma growth in the intensive treatment group, with no excess of neurological deterioration or other adverse events. The ATACH study demonstrated safety of a nicardipine-based BP-lowering regime in acute ICH, while the ADAPT randomized trial showed that BP lowering to a target SBP of <150 versus <180 mmHg within 24 h of onset did not produce any clinically meaningful change in CBF within the immediate perihematomal region or hemispheres, as measured by CT perfusion [56].

The definitive, main phase INTERACT2 trial, randomly assigned 2,839 patients with spontaneous ICH and elevated SBP (≥150 and ≤220 mmHg) to a strategy of intensive (SBP <140 mmHg within 1 h) versus guideline-recommended (SBP <180 mmHg) lowering of BP within 6 h [60••]. In those assigned to intensive treatment, intravenous and oral antihypertensive agents were given, according to pre-specified protocols based on local availability. The results showed a borderline significant reduction in poor outcome at 90 days, defined by death or major disability (odds ratio [OR] 0.87, 95 % confidence interval [CI] 0.75–1.01; P=0.06), with a significant favourable shift in an ordinal analysis of the distribution of scores on the modified Rankin Scale (pooled OR for shift 0.87, 95 % CI 0.77–1.00; P=0.04). Moreover, intensive BP lowering was shown to be safe, and resulted in significantly better health-related quality of life.

In conclusion, current evidence suggests that early intensive BP lowering is safe and may improve outcome from ICH. The ongoing randomized ATACH2 trial and the Field Administration of Stroke Therapy - Magnesium (FAST-Mag) trials will provide further information on the role of early BP lowering, while guidelines are currently being updated to reflect these advances.

Hypertensive Encephalopathy

Hypertensive encephalopathy accounts for 16 % of all hypertensive emergencies [5]. When MAP significantly exceeds the upper limit of cerebral autoregulation, vasodilation occurs resulting in over perfusion. While this reaction may occur at BP levels as low as 160/100 mmHg, higher BP levels may be needed to overwhelm autoregulation in those with chronic hypertension. The pathogenesis of this disorder is poorly understood, though dysfunction of cerebral endothelium and blood brain barrier are likely to be instrumental, with increased permeability leading to microhemorrhages and cerebral edema, which give rise to clinical symptoms of headache, vomiting, confusion, visual disturbance, and seizures [66]. If not treated promptly, progressive cerebral edema and ICH can lead to raised ICP and ultimately, death.

There is no randomized evidence to guide the most appropriate drug or optimal manner of BP lowering in this condition. Patients should be monitored in an intensive care or high dependency setting to allow close monitoring, with consideration given to arterial BP and ICP monitoring. Treatment recommendations are for SBP to be reduced cautiously by 20 to 25 %, or a DBP to 100 – 110 mmHg in the first 1 – 2 h, using titratable intravenous agents [8, 66]. More rapid BP reduction may lead to cerebral hypoperfusion. Particular caution is necessary in older patients and in those with pre-existing hypertension, as they appear at increased risk of hypoperfusion and stroke [66, 67]. Nicardipine and labetalol are commonly used, whereas sodium nitroprusside has the potential to raise ICP and is reserved for resistant cases [67–69]. The use of anticonvulsive therapy to control seizures may also help reduce BP [70].

SAH

SAH, most often due to rupture of an intracranial aneurysm, accounts for 5 – 10 % of all strokes, but with devastating consequences due to having an early case fatality near 45 %

[71–73]. Hypertension is an established risk factor [74]. Studies of the frequency and significance of elevated BP in SAH are lacking. As cerebral autoregulation is often disturbed in SAH, rapid BP lowering has the potential for inducing cerebral ischemia [14]. One observational study reported that elevated BP on admission with SAH was an independent poor prognostic factor [75], but another found no association between BP and prognosis [76]. Indeed, a recent observational study on the prognostic significance of admission BP in SAH concluded that a lower MAP was associated with a poor prognosis and increased mortality [77].

Recurrent hemorrhage (or re-bleeding) remains a serious consequence of SAH, with case fatality around 70 %. It affects 9 – 17 % of patients in the first 72 h [78]. Higher initial BP is a potential risk factor. One retrospective review found that re-bleeding occurred less frequently in those treated for high BP following SAH, and another reported that re-bleeding was more common in those with SBP >160 mmHg [79, 80]. A further large retrospective study, however, found no relationship between re-bleeding risk and BP [81]. Relative change in BP may be important with one review reporting that an acute BP increase occurred immediately prior to re-bleeding [82]. Interpretation of these findings is limited by their retrospective nature, confounding variables, and cause and effect relationships. Cerebral ischemia in the days following SAH may contribute to poor outcome. Traditionally, this has been attributed to cerebral vasospasm, though recent studies have shown that treatment of vasospasm does not necessarily translate to better neurological outcome [83]. Rapid BP lowering in the presence of impaired cerebral autoregulation may be implicated in adverse outcomes, though data are lacking. Thus, robust evidence related to the prognostic significance of elevated BP in SAH, and of the association between elevated BP (or its treatment) and re-bleeding or delayed ischemia, are urgently required.

Evidence regarding the optimal approach to hypertensive treatment in SAH is sparse. A 1960s study of 1,005 patients with SAH who were randomized to one of four treatment modalities – one arm of drug-induced BP lowering, another of bed rest alone, and the other two arms were carotid ligation and intracranial surgery – showed no effect of BP lowering on case fatality or re-bleeding at 6 months compared with bed rest [84, 85]. An observational study in the 1980s found that patients with treated hypertension had a higher rate of cerebral infarction but lower rate of re-bleeding compared to normotensive control patients, and a later observational study suggests that avoiding antihypertensive medication and increasing fluid intake may reduce the risk of cerebral infarction [79, 86].

It is not too surprising, then, that current guidelines state that BP management in SAH remains controversial [87]. A cautious approach to BP lowering should be considered, with close patient monitoring for stroke, hypertension-related re-bleeding, and the maintenance of cerebral perfusion pressure. When BP remains elevated (SBP 160 – 180 mmHg), despite administration of nimodipine (given for neuroprotection and vasospasm) and analgesia, a short-acting continuous-infusion intravenous agent is most appropriate. No robust evidence is available regarding drug type, though agents with a reliable dose-response relationship and favorable safety profile include nicardipine, labetalol, and esmolol. The magnitude of BP lowering has not been determined but a target SBP of 140 – 160 mmHg (i.e. maintain MAP >90 mmHg) seems reasonable. Centrally acting BP medication should be avoided (e.g. sodium nitroprusside) because of its tendency to raise ICP [76, 87].

RVCS

RVCS is a rare condition characterized by recurrent acute-onset severe headaches and reversible cerebral vasoconstriction with or without neurological deficits or seizure. It can occur spontaneously, or be evoked by pregnancy or use of a vasoactive drug. The major complication is stroke due to ischemia, ICH or SAH [88]. The pathophysiology is unknown but it is generally considered a transient disturbance in the control of cerebral vascular tone. Around a third of all patients with RCVS have an SBP ≥160 or DBP ≥90 mmHg during their acute headaches [88]. There are no large, prospective trials to guide BP or indeed of overall management, and no pharmacological treatment has proven efficacy. Data from small open-labelled trials in patients with thunderclap headache (including RCVS) suggests that headaches may respond to nimodipine given orally or IV (dose adjusted according to degree of vasoconstriction) [89]. However, in a more recent case series of 67 patients with RCVS, 30 % of those treated with the drug had recurrent headaches [90]. In those with ischemic or hemorrhagic complications, caution should be exercised with dose escalation of nimodipine, as BP reduction may have deleterious effects. Nicardipine, verapamil and intra-arterial milrinone have been used with success in case reports, but no higher level evidence on efficacy and safety exists [89–91].

Individual Antihypertensive Agents

A wide range of agents exist for the treatment of hypertensive neurological emergencies, but the lack of clinical outcome controlled trials and comparative-effectiveness studies means there is no one ideal drug specific to each neurological condition. Available agents, and evidence and prescribing guidelines related to each, are discussed in the following sections.

Labetalol

Labetalol is a combined selective alpha-1 adrenergic and non-selective beta adrenergic. It has a rapid onset (2 to 5 min) after intravenous administration and effects last 2 to 4 h [92]. It can be given by IV bolus or continuous infusion without the need for invasive BP monitoring. It reduces total systemic vascular resistance but maintains cerebral blood flow [93]. A recent systematic review of nicardipine versus labetalol in hypertensive crises found 10 comparative studies [2•]. Four were concerned specifically with hypertension in stroke patients. Comparable efficacy and safety data were reported, but nicardipine appeared to provide more predictable and consistent control of BP. Main adverse events were hypotension (17 %) and arrhythmia (20 %).

In a stroke population, the use of labetalol within 36 h of onset is safe, and effectively reduces BP [33]. There are no specific data in hypertensive encephalopathy or SAH. Labetalol can be used for all neurological hypertensive emergencies, is recommended by the American Stroke Association for the management of hypertension for thrombolysis in ischemic stroke, and is cited in European and American guidelines as an appropriate agent to use in the management of aneurysmal SAH.

Nicardipine

Nicardipine is a second generation dihydropyridine calcium channel blocker. It has cerebral and coronary arterial vasodilatory properties, and may improve cerebral perfusion [94]. It has an onset of action of 5 to 10 min. In a retrospective study comparing nicardipine with labetalol in patients with ICH, SAH and ischemic stroke, those allocated nicardipine had less variable reductions in MAP, were more likely to achieve their target BP within 1 h, and were less likely to need dose adjustments or additional antihypertensive agents. Safety was comparable [95]. A prospective, randomized trial found significantly less BP variability with nicardipine, but comparable rates of adverse events compared with other agents [96]. Among hypertensive patients in an intensive care setting, those who received nicardipine were less likely to require a second agent and had significantly shorter lengths of hospital stay as compared to those receiving other antihypertensive agents (including 44 % on labetalol as the "other antihypertensive agent") [97].

A small, prospective study found that a reduction of MAP with nicardipine or labetalol in those with ICH and severe hypertension did not reduce cerebral blood flow [62]. This may be of clinical importance given the concerns regarding potential for iatrogenic end organ damage. Main adverse effects are hypotension (15 %) and arrhythmia (20 %) [2•]. According to European and American Guidelines, nicardipine is recommended as a first line agent (along with labetalol) in ischemic stroke patients receiving thrombolysis, and it is safe in all neurological hypertensive emergencies.

Sodium Nitroprusside

Sodium nitroprusside is an arterial and venous vasodilator. Though easily titratable with reversible effects, sodium nitroprusside decreases cerebral perfusion with increasing ICP, so it should be used cautiously in neurological hypertensive emergencies. Invasive BP monitoring is required [98]. It is cited as an agent to consider in the management of hypertensive emergencies in recent European stroke and hypertension guidelines.

Clevidipine

Clevidipine is a new, third generation dihydropyridine calcium channel blocker. It has a rapid onset (<1 min), is easily titratable, and does not require invasive monitoring [99]. Clevidipine was safe and effective in reducing BP in 126 patients presenting to the emergency department or intensive care with hypertensive crisis [100]. Further studies have confirmed its safety in hypertensive emergencies in the cardiac surgery population, and direct comparisons have demonstrated similar efficacy and safety with nitroglycerin, sodium nitroprusside, and nicardipine in the perioperative setting [101]. The recently published Clevidipine in the Treatment of Patients with Acute Hypertension and Intracerebral Hemorrhage (ACCELERATE) trial in 35 hypertensive patients with acute ICH [102•], clevidipine alone quickly and safely achieved control of SBP. There are no data specific to other neurological hypertensive emergencies, and it is not cited in current guidelines.

Esmolol

Esmolol is a cardio-selective beta blocker (given as an IV bolus or infusion) with an onset of action within 1 min, and duration of 10 to 20 min. It is not dependent on renal or hepatic function, therefore may be useful in those with renal or hepatic impairment [7]. There are no specific trials in hypertensive neurological emergencies. It is cited as agent to consider in European SAH guidelines.

Nitroglycerin

Nitroglycerin is a venodilator that reduces preload. The onset of action is immediate, and the duration of action 3 to 5 min. Preload reduction is followed by a decrease in cardiac output that can potentially be detrimental to patients who already have compromised cerebral or renal blood flow [3]. It can be given IV or as a transdermal patch. Large trial data are scarce. A meta-analysis of two previous trials in acute stroke found no

clear effect on end-of-treatment death, combined death or deterioration with the transdermal patch [103]. The recently completed ENOS trial, designed to test the safety and efficacy of transdermal glyceryl trinitrate in acute stroke, may add to our understanding [41].

Enalaprilat

Enalaprilat is currently the only ACE-I that is commercially available in a parenteral formulation. It has an onset of action of 15 min and duration of action of 12 to 24 h. This property makes titration difficult, and hypotension can develop [104]. It is not often used in hypertensive neurological emergencies and data are limited.

Urapidil

Urapidil is a vasodilator acting on peripheral vessels by alpha-1 adrenoceptor blockade, and on central nervous system by alpha adrenoceptor blockade. It has an onset of action of 2 to 5 min and duration of 3 h. Wide individual variations in doses are observed. One systematic review of treatment of hypertensive emergencies suggested that intravenous urapidil gave the most desirable number needed to treat compared to other available agents [104]. A head to head study comparing it to sodium nitroprusside in hypertensive crises, showed it to be equally as effective and safe [105]. Given the large contribution of Chinese patients, urapidil was the most popular agent used in the INTERACT2 trial of ICH. It is an effective treatment of hypertensive crises, perioperative hypertension, and pre-eclampsia [106]. It is not explicitly mentioned in current international guidelines on stroke, ICH or SAH and is not currently available in the US

Conclusions

Neurological hypertensive emergencies have the potential for significant morbidity and mortality. Prompt but controlled BP reduction is necessary, and although shown to be safe in most circumstances, there remains uncertainty as to the optimal BP target, rate of decline, or most ideal antihypertensive agent. Indeed, there is probably no single ideal treatment strategy that covers all neurological hypertensive emergencies and given the significant heterogeneity in pathology, treatment should be tailored to the individual case disease. Rapid acting, readily titratable, parenteral agents, such as nicardipine, labetalol, clevidipine and urapidil, are reasonable first-line agents. Given that many of these patients are critically ill, have variable disturbance of cerebral circulation, and that elevated BP is dynamic, close monitoring is required ideally in an intensive care or high dependency setting. Invasive BP monitoring may be necessary where BP is difficult to control, or where there is raised ICP; the latter also prompts consideration of cerebral perfusion pressure monitoring. Randomized data in patients with ICH suggests that early intensive lowering of BP is safe and effective, whereas for those with ischemic stroke, early and more modest BP lowering is safe and may improve outcomes. In SAH and hypertensive encephalopathy, data for the effect of BP lowering is scarce. Ongoing large trials are likely to inform future clinical practice guidelines.

Compliance with Ethics Guidelines

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- • Of importance
- •• Of major importance

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