LEADING ARTICLE

Drug Safety 2000 Jan; 22 (1): 13-18
0114-5916/00/0001-0013/$20.00/0

Should Antihypertensive Therapies be Given to Patients with Acute Ischaemic Stroke?

Larry B. Goldstein

Duke Center for Cerebrovascular Disease, Stroke Policy Program, Center for Clinical Health Policy Research, Duke University and Durham Veterans Administration Medical Center, Durham, North Carolina, USA

Abstract

Hypertension is a major risk factor for stroke and many patients with acute stroke have elevated blood pressures. The management of hypertension in the setting of acute ischaemic stroke remains a source of confusion and controversy. Lowering blood pressure in this setting may be hazardous because of impaired cerebral autoregulation. Treatment may be considered in patients who are otherwise candidates for thrombolytic therapy, patients who have severe hypertension or patients who have specific concomitant medical conditions including acute myocardial infarction, aortic dissection, hypertensive encephalopathy, or severe left ventricular failure.

In choosing an agent for acute treatment, drugs that can produce a precipitous decline in blood pressure (e.g. sublingual calcium antagonists) should be avoided. Drugs with the capacity to dilate cerebral vessels should be used with caution as they have the potential to increase intracranial pressure. Long term management of hypertension in poststroke patients is often required. The potential for certain classes of drugs (e.g. α_2-adrenergic receptor agonists and α_1-adrenergic receptor antagonists) to impair the recovery process should be considered when choosing an antihypertensive for treatment of these patients.

The management of hypertension in the setting of acute stroke remains a source of confusion and controversy. This reflects a general lack of prospective, randomised data to address this commonly encountered clinical problem. Most physicians recognise that hypertension is one of the primary risk factors for both ischaemic stroke and primary intracerebral haemorrhage.[1,2] Blood pressure is frequently elevated in patients presenting with stroke. This presents one incentive for physicians caring for patients presenting with stroke to treat elevations in blood pressure. However, because of pathophysiological changes that occur with acute stroke, aggressive lowering of the blood pressure is viewed as being hazardous.

The articles used for this review were identified through a Medline search and through examination of reference bibliographies.

1. Blood Pressure and Pathophysiology of Acute Ischaemic Stroke

Cerebral blood flow is determined by the relationship between cerebral perfusion pressure and cerebrovascular resistance.[3]

$$\text{cerebral blood flow} = \frac{\text{cerebral perfusion pressure}}{\text{cerebrovascular resistance}}$$

Cerebral perfusion pressure is determined by the difference between mean arterial pressure and venous back-pressure, where:

mean arterial pressure = (systolic blood pressure ÷ 2 × diastolic blood pressure)/3

In healthy individuals (i.e. those without increased intracranial pressure), venous pressure is negligible and cerebral perfusion pressure is reflected by the mean arterial pressure.[3] Therefore, the above equation can be rewritten as:

$$\text{cerebral blood flow} = \frac{\text{mean arterial pressure}}{\text{cerebrovascular resistance}}$$

As reflected by this equation, through a physiological response termed autoregulation, when arterial pressure is lowered, there is a compensatory reduction in cerebrovascular resistance though dilation of cerebral arterioles to maintain constant cerebral blood flow. In nonhypertensive adults, this autoregulation is effective for mean arterial pressures ranging from approximately 60 to 150mm Hg.[3] If mean arterial pressure decreases below the level that can be compensated by decreasing cerebrovascular resistance, cerebral blood flow decreases.

Cerebrovascular resistance (and therefore the autoregulatory relationship) is affected by the levels of respiratory gases (oxygen and carbon dioxide).[4] Local brain tissue levels of these respiratory gases are altered in the setting of ischaemia and can result in impaired autoregulation in both normotensive and chronically hypertensive patients (i.e. changes in cerebrovascular resistance may not occur in response to changes in mean arterial pressure).[5] Thus, in the setting of acute stroke, the zone of marginal perfusion surrounding an area of dense ischaemia (i.e. the 'penumbra') is potentially vulnerable to even small decreases in blood pressure.[6] Elevations in blood pressure observed in patients with acute stroke may represent a protective mechanism to maintain blood flow in this peri-infarct region.[7]

Patients with chronic hypertension may be at even greater risk from reductions in blood pressure in the setting acute ischaemic stroke than patients who were previously normotensive. Chronic hypertension lessens the vasodilatory capacity of cerebral arterioles causing an upward shift of the autoregulatory range.[3,8] Therefore, the lower limit of autoregulation is raised. Further, blood flow via collaterals is compromised in patients with chronic hypertension.[8] In addition to these pathophysiological observations that raise concern that lowering blood pressure in the setting of acute ischaemic stroke may be hazardous, lowering blood pressure also risks further decreasing distal perfusion on a haemodynamic basis in patients with high grade stenotic lesions.[9]

Theoretical benefits of treating hypertension in the setting of acute ischaemic stroke include lessening the risk of haemorrhagic transformation, reduction of oedema formation, and preventing further vascular damage.[3] The potential impact of lowering blood pressure on reducing the risk of haemorrhagic transformation of an ischaemic stroke remains hypothetical.[3] There are no clear data demonstrating that acutely elevated blood pressures worsens stroke-related neurological deficits. As pointed out by Powers,[3] Britton and Carlsson[10] found no relationship between severe hypertension on hospital admission (systolic blood pressure ≥200mm Hg and diastolic blood pressure >115mm Hg) and progression of stroke symptoms.[10] A large community-based study found that stroke progression was inversely related to

systolic blood pressure on admission; the higher the blood pressure, the lower the risk of stroke progression (the relative risk of progression decreased by 0.66 per 20mm Hg increase in admission blood pressure).[11] However, Chamorro and co-workers[12] found that a 20 to 30% drop in mean arterial pressure on the second day after stroke almost tripled the odds of full neurological recovery. Brain oedema was less frequent in patients with a greater drop in blood pressure. Of 49 patients with a drop in mean arterial pressure of >30%, 8% worsened neurologically. This retrospective study (patients were not randomised to treatment or control conditions) did not include patients treated with parenteral agents.

It is important to recognise that acute elevations in blood pressure in patients with ischaemic stroke often spontaneously decline. In 1 study, blood pressure was elevated at the time of hospital admission in 85% of 334 consecutive stroke patients.[13] Systolic blood pressure declined an average of 20mm Hg and diastolic blood pressure decreased by an average 10mm Hg over the ensuing 10 days without specific antihypertensive therapy. Other studies have reported similar findings.[12,14-16]

2. Blood Pressure Management in Acute Ischaemic Stroke

If treatment of hypertension in the setting of acute ischaemic stroke is potentially hazardous, under what circumstances should intervention be considered? Detailed guidelines have been developed by the American Heart Association.[17] Based on the pathophysiological considerations previously reviewed, it is recommended that treatment of acute hypertension generally be deferred unless the patient is otherwise a candidate for thrombolytic therapy, has severe hypertension or has specific concomitant medical conditions including: (i) acute myocardial infarction; (ii) aortic dissection; (iii) hypertensive encephalopathy; or (iv) severe left ventricular failure. Parameters for severe hypertension are not clearly defined, but thresholds of systolic blood pressures >220mm Hg, diastolic blood pressures >120mm Hg, or mean arterial pressures >130mm Hg have been used based on the upper limits of autoregulation in healthy individuals. When considering treatment, elevated blood pressure should be documented by at least two readings obtained 5 minutes apart. Automatic monitoring devices are useful for providing semi-continuous blood pressure data.

When treating hypertension in the setting of acute ischaemic stroke, the use of sublingual agents such as nifedipine should be avoided as they can produce a rapid drop in blood pressure that is difficult to reverse. In general, drugs such as sodium nitroprusside, calcium antagonists and hydralazine are to be avoided except in stroke patients with very severe hypertension as they are cerebral vasodilators that can increase cerebral blood flow, impair autoregulation, and increase intracranial pressure.[3] In contrast, β-blockers and ACE inhibitors do not significantly affect blood flow.[3] As with other β-blockers, labetalol should be avoided in patients with asthma, congestive heart failure, or cardiac conduction abnormalities. Enalapril is a reasonable alternative for these patients. Nitropaste, a topical formulation of nitroglycerin (glyceryl trinitrate), is easily applied and can be removed if blood pressure drops too rapidly. However, nitropaste may also dilate cerebral vessels. Table I summarises preferred treatment guidelines.

Many stroke patients have been previously prescribed antihypertensives. Because of the risk of rebound hypertension with some agents (i.e. clonidine), the drug may be continued if the patient has been reliably taking the medication and if the blood pressure is not low. However, as patients will be closely monitored in the acute setting, it is often reasonable to withhold antihypertensives until they are neurologically stable.

Table I. Antihypertensive guidelines for nonthrombolytic candidates[17]

Blood pressure	Treatment	Comments
DBP >140mm Hg	Sodium nitroprusside 0.5 μg/kg/min	Target is 10 to 20% DBP reduction
SBP >220mm Hg DBP >120mm Hg MAP >130mm Hg	Labetalol 10 to 20mg IV over 1 to 2 min Repeat or double q 20 min to a maximum of 150mg	Alternative is enalapril

DBP = diastolic blood pressure; **MAP** = mean arterial pressure; **q *x* min** = every *x* minutes; **SBP** = systolic blood pressure.

Although empirically determined, treatment with alteplase (recombinant tissue plasminogen activator; rt-PA) under US National Institutes of Health protocol guidelines is generally not recommended for those patients with a systolic blood pressure >185mm Hg or a diastolic blood pressure >110mm Hg.[18] In patients who are otherwise candidates for alteplase, the application of 1 to 2 inches of nitropaste or the administration of 1 to 2 intravenous doses of labetalol 10mg may be used in an attempt to carefully reduce blood pressure to within these parameters.[17] If the blood pressure does not respond to these measures or is not maintained at these levels, thrombolytic therapy with intravenous alteplase should be withheld. Strict monitoring of blood pressure is required after alteplase is administered (every 15 minutes for 2 hours, then every 30 minutes for 6 hours, then every hour for 16 hours). Blood pressure management of patients who have been treated with alteplase are given in the table II.

Of the 624 patients in the National Institute of Neurological Diseases and Stroke rt-PA Stroke Trial, 19% had hypertension on admission and 60% had hypertension in the 24 hours after randomisation.[19] Prerandomisation treatment of hypertension had no effect on 3-month favourable outcomes for either alteplase or placebo-treated groups. For placebo-treated patients with hypertension in the 24 hours after randomisation, clinical outcome measures were similar for those who did and did not receive antihypertensive therapy. However, the proportions of placebo patients treated and not treated with antihypertensives having abrupt declines in blood pressure were similar. For alteplase patients with hypertension in the 24 hours after randomisation, those who were treated with antihypertensives were more likely to have abrupt declines in blood pressure and less likely to have a favourable outcome at 3 months. Careful attention to blood pressure and gentle management were recommended for patients treated with alteplase. However, it should be recognised that these analyses were carried out post hoc and the recommendation is not based on prospective, randomised data.

3. Postacute Management of Blood Pressure

Despite the decline in blood pressure seen during the acute hospitalisation in patients with ischaemic stroke, marked increases in both systolic and diastolic blood pressure occur in 2 out of 3 of patients examined 1 month after hospital dis-

Table II. Antihypertensive guidelines after thrombolysis[17]

Blood pressure	Treatment	Comments
DBP >140mm Hg	Sodium nitroprusside 0.5 μg/kg/min	
SBP >230mm Hg DBP >121 to 140mm Hg	Labetalol 10mg IV over 1 to 2 min Repeat or double q 10 min to a maximum of 150mg or give initial bolus followed by labetalol drip at 2 to 8 mg/min	Consider sodium nitroprusside if blood pressure not controlled with labetalol
SBP 180 to 230mm Hg DBP 105 to 120mm Hg	Labetalol 10mg IV over 1 to 2 min Repeat or double q 10 min to a maximum of 150mg or give initial bolus followed by labetalol drip at 2 to 8 mg/min	

DBP = diastolic blood pressure; **MAP** = mean arterial pressure; **q *x* min** = every *x* minutes; **SBP** = systolic blood pressure.

charge.[20] These elevated blood pressures remained stable over 1 year of follow-up. There is a clear relationship between chronic systolic and diastolic blood pressure after stroke and the rate of recurrent stroke.[21] Therefore, most stroke patients will eventually require pharmacological treatment for chronic hypertension. A meta-analysis of all available randomised controlled clinical trials assessing the effect of blood pressure lowering drugs on clinical outcomes in patients with prior stroke or transient ischaemic attack found that stroke recurrence was significantly reduced with treatment.[22] Perindopril Protection Against Recurrent Stroke Study (PROGRESS) is a multicentre, prospective, randomised, placebo-controlled trial designed to determine whether ACE inhibitor–based blood pressure lowering reduces the risk of recurrent stroke in patients with a history of cerebrovascular disease and will provide important data regarding treatment of poststroke hypertension.[23]

The choice of agent for long term management of blood pressure in patients recovering from stroke is often dictated by other medical concerns. However, data are accruing that suggest certain centrally acting antihypertensives may impair poststroke recovery.[24] These potentially detrimental antihypertensives include α_2-adrenergic receptor agonists (e.g. clonidine) and α_1-adrenergic receptor antagonists (e.g. prazosin). Until more data are available, these classes of drugs should be avoided if possible in patients recovering from stroke.

4. Conclusion

Lowering blood pressure in the setting of acute ischaemic stroke may be hazardous, and when required (severe hypertension, concomitant medical conditions, candidates for thrombolysis) should be done gently to avert rapid drops in mean arterial pressure. Drugs with a propensity to cause precipitous reductions in blood pressure and agents that may produce vasodilatation of the cerebral vasculature should be avoided. The potential effects on recovery should be considered when choosing drugs to treat chronic hypertension in poststroke patients. Data to definitively address issues related to acute and subsequent blood pressure management of stroke patients can only be obtained through appropriate randomised controlled trials.

References

1. Qizilbash N, Lewington S, Duffy S, et al. Cholesterol, diastolic blood pressure, and stroke: 13 000 strokes in 450 000 people in 45 prospective cohorts. Lancet 1995; 346: 1647-53
2. Kannel WB. Blood pressure as a contributor to stroke. Fed Pract 1995; 12: 14-20
3. Powers WJ. Acute hypertension after stroke: the scientific basis for treatment decisions. Neurology 1993; 43: 461-7
4. Wilson DA. On the contribution of respiratory gases to cerebral autoregulation. Adv Exp Med Biol 1997; 428: 695-702
5. Meyer JS, Shimazu K, Fukuuchi Y, et al. Impaired neurogenic cerebrovascular control and dysautoregulation after stroke. Stroke 1973; 4: 169-86
6. Paulson OB. Cerebral apoplexy. Pathogenesis, pathophysiology and therapy as illustrated by regional cerebral blood flow measurements in brain. Stroke 1971; 2: 327-60
7. Meyer JS, Denny-Brown D. The cerebral collateral circulation. 1. Factors influencing collateral blood flow. Neurology 1957; 7: 447-58
8. Baumbach GL, Heistad DD. Cerebral circulation in chronic arterial hypertension. Hypertension 1998; 12: 89-95
9. Britton M, De Faire U, Helmers C. Hazards of therapy for excessive hypertension in acute stroke. Acta Med Scand 1980; 207: 253-7
10. Britton M, Carlsson A. Very high blood pressure in acute stroke. J Int Med 1990; 228: 611-5
11. Jorgensen HS, Nakayama H, Raaschou HO, et al. Effect of blood pressure and diabetes on stroke in progression. Lancet 1994; 344: 156-9
12. Chamorro A, Vila N, Ascaso C, et al. Blood pressure and functional recovery in acute ischemic stroke. Stroke 1998; 29: 1850-3
13. Wallace JD, Levy LL. Blood pressure after stroke. JAMA 1981; 246: 2177-80
14. Wechsler LR, Koroshetz W. Therapy for acute ischemic stroke. In: Ropper AH, editor. Neurol Neurosurg Intensive Care. New York: Raven Press, 1993: pp 265-78
15. Harper G, Castleden CM, Potter JF. Factors affecting changes in blood pressure after acute stroke. Stroke 1994; 25: 1726-9
16. Carlberg B, Asplund K, Hägg R. Course of blood pressure in different subsets of patients after acute stroke. Cerebrovasc Dis 1991; 1: 281-7
17. Cummins RO. Acute stroke: advanced cardiac life support. In: Cummins RO, editor. Dallas: American Heart Association, 1997
18. Adams Jr HP, Brott TG, Furlan AJ, et al. Guidelines for thrombolytic therapy for acute stroke: a supplement to the guidelines for the management of patients with acute ischemic

stroke – a statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. Stroke 1996; 27: 1711-8
19. Brott T, Lu M, Kothari R, et al. Hypertension and its treatment in the NINDS rt-PA Stroke Trial. Stroke 1998; 29: 1504-9
20. Carlsson A, Britton M. Blood pressure after stroke: a one-year follow-up study. Stroke 1993; 24: 195-9
21. Rodgers A, MacMahon S, Gamble G, et al. Blood pressure and risk of stroke in patients with cerebrovascular disease. BMJ 1996; 313: 147
22. Gueyffier F, Boissel JP, Boutitie F, et al. Effect of antihypertensive treatment in patients having already suffered from stroke – gathering the evidence. Stroke 1997; 28: 2557-62
23. Neal B, Anderson C, Chalmers J, et al. Blood pressure lowering in patients with cerebrovascular disease: results of the PROGRESS pilot phase. Clin Exp Pharmacol Physiol 1996; 23: 444-6
24. Goldstein LB. Potential effects of common drugs on stroke recovery. Arch Neurol 1998; 55: 454-6

Correspondence and reprints: Dr *Larry B. Goldstein*, Duke Center for Cerebrovascular Disease, Stroke Policy Program, Center for Clinical Health Policy Research, Box 3651 – DUMC, Durham, NC 27710, USA.
E-mail: golds004@mc.duke.edu