Published in final edited form as:
Am J Cardiovasc Drugs. 2013 February ; 13(1): . doi:10.1007/s40256-013-0007-6.

Drug Treatment of Acute Ischemic Stroke

Sameer Bansal[1], **Kiranpal S. Sangha**[2], and **Pooja Khatri**[3]

[1]Visiting Student, Department of Neurology, University of Cincinnati, College of Medicine, Cincinnati, OH, USA

[2]Clinical Pharmacy Specialist – CNS, UC Health University Hospital, University of Cincinnati, College of Pharmacy, Cincinnati, OH, USA

[3]Department of Neurology, University of Cincinnati, College of Medicine, Cincinnati, OH, USA

Abstract

Acute ischemic stroke (AIS) is the fourth leading cause of death and the leading cause of adult disability in the USA. AIS most commonly occurs when a blood vessel is obstructed leading to irreversible brain injury and subsequent focal neurologic deficits. Drug treatment of AIS involves intravenous thrombolysis with alteplase (recombinant tissue plasminogen activator [rtPA]). Intravenous alteplase promotes thrombolysis by hydrolyzing plasminogen to form the proteolytic enzyme plasmin. Plasmin targets the blood clot with limited systemic thrombolytic effects. Alteplase must be administered within a short time window to appropriate patients to optimize its therapeutic efficacy. Recent trials have shown this time window may be extended from 3 to 4.5 hours in select patients. Other acute supportive interventions for AIS include maintaining normoglycemia, euthermia and treating severe hypertension. Urgent anticoagulation for AIS has generally not shown benefits that exceed the hemorrhage risks in the acute setting. Urgent antiplatelet use for AIS has limited benefits and should only promptly be initiated if alteplase was not administered, or after 24 hours if alteplase was administered. The majority of AIS patients do not receive thrombolytic therapy due to late arrival to emergency departments and currently there is a paucity of acute interventions for them. Ongoing clinical trials may lead to further medical breakthroughs to limit the damage inflicted by this devastating disease.

1. Introduction

Stroke is the fourth leading cause of death and the leading cause of disability in the elderly in the USA. Every year, about 795,000 new or recurrent strokes occur, which cost an estimated US$73.7 billion in 2010 alone. Ischemic stroke, or disruption of blood flow to the brain, accounts for about 85 % of all strokes.[1]

We discuss the medications related to ischemic stroke care in the context of the overall treatment approach towards the patient. This approach consists of four main goals:

- The first goal of the evaluation of a suspected ischemic stroke is to exclude intracranial hemorrhage with neuro-imaging.

Correspondence: Dr *Pooja Khatri*, MD, MSc, Department of Neurology, University of Cincinnati, 260 Stetson St, Ste 2300, ML 0525, Cincinnati, OH 45267-0525, USA., pooja.khatri@uc.edu.

Financial Disclosures:
SB: None
KSS: None

- Second, the advisability for acute treatment with thrombolytic agents and endovascular device therapies must be considered, and general supportive care must be administered.
- Third, acute medical or neurologic complications of stroke must be anticipated.
- Finally, the most likely pathophysiology and etiology is considered and treatment is directed towards preventing recurrent ischemic events.

2. The Role of Medications in General Supportive Care

2.1 Oxygenation

Maintaining adequate tissue oxygenation is important during periods of acute cerebral ischemia in order to prevent hypoxia and potential worsening of the neurologic injury. Supplemental oxygen should be administered if there is evidence of hypoxia by blood gas determination or desaturation detected by pulse oximetry. Elective endotracheal intubation should be considered if there is a decreased level of consciousness to suggest aspiration risk.[2,3] The role for supplemental oxygenation by normobaric and hyperbaric means in the setting of adequate oxygenation by pulse oximetry remains to be determined by clinical trials.

2.2 Antihypertensives

In the setting of AIS, many patients will have elevated blood pressure for the first 24–48 hours. Although severe hypertension is a contraindication for thrombolytic therapy, there are no data to define the levels of arterial hypertension that mandate emergent management.[3] The consensus is that antihypertensive agents should be withheld unless the diastolic blood pressure is above 120 mmHg or unless the systolic blood pressure is above 220 mmHg (Table 1). When treatment is indicated, lowering the blood pressure should be done cautiously to minimize the chance of relative hypotension. Parenteral agents such as labetalol that are easily titrated and that have minimal vasodilator effects on cerebral blood vessels are preferred. In some cases, an intravenous (IV) infusion of nicardipine or labetalol may be necessary for adequate blood pressure control and this allows for careful titration. Patients also can be treated with oral agents, such as labetalol or lisinopril, for more sustained blood pressure lowering if dysphagia is not a concern. Sublingual use of a calcium channel antagonist, such as nifedipine, should be avoided because of rapid absorption and a secondary precipitous decline in blood pressure.[4]

Among patients who are candidates for treatment with thrombolytic agents, careful management of blood pressure is critical before and during the administration of alteplase (recombinant tissue plasminogen activator [rtPA]), and for the ensuing 24 hours. Excessively high blood pressures are associated with intracerebral hemorrhage after thrombolytic administration.[5]

Thrombolytic therapy is not given to patients who have a systolic blood pressure above 185 mmHg or a diastolic blood pressure above 110 mmHg despite non-aggressive blood pressure-lowering attempts. While there is no established definition of “non-aggressive” blood pressure reduction, a common approach is to use a maximum of two to three attempts with parenteral medications, with options including labetalol, enalaprilat or nicardipine. Uncontrolled blood pressure is an uncommon reason for ineligibility of IV alteplase for AIS.[6]

2.3 Insulin

Hypoglycemia can cause focal neurologic signs that mimic stroke and can itself lead to brain injury. Additionally, several clinical studies have associated hyperglycemia with poor

outcomes.[7,8] Therefore, prompt measurement and normalization of serum glucose concentration is important. Subcutaneous insulin is administered to keep glucose less than 180 mg/dL. A clinical trial is underway to determine whether stricter glucose management to glucose concentrations of 80–130 mg/dL improves clinical outcomes after acute ischemic stroke.[9]

2.4 Antipyretics

Increased body temperature in the setting of acute ischemic stroke has been associated with poor neurologic outcome, possibly due to increased metabolic demands, enhanced release of neurotransmitters, and increased free radical production. Maintaining normothermia might improve the prognosis of patients with severe events using antipyretic medications and cooling devices.[10,11] Hypothermia has been shown to be neuroprotective after experimental animal models of global and focal hypoxic brain injury, and it is currently under clinical study for acute ischemic stroke.[10,11] Antipyretic therapy is indicated for temperatures above 37.5 °C.

3. Treatment of Acute Ischemic Stroke

3.1 Overview

Intravenous thrombolysis with alteplase is the mainstay medical treatment for acute ischemic stroke (AIS). While antiplatelet therapy with aspirin (acetylsalicylic acid) has been shown to decrease the risk of early recurrent stroke when initiated within 48 hours of ischemic stroke onset, it does not actually treat the stroke that has already occurred. Newer antiplatelet agents, alone and in combination with aspirin, have shown promising results for further prevention of early recurrence, and clinical trials are ongoing. Acute therapeutic anticoagulation with unfractionated heparin (UFH) and low molecular weight heparin (LMWH) administered to unselected patients have not demonstrated clinical benefits in the acute ischemic stroke setting over antiplatelet agents. More studies are needed to demonstrate the role of acute anticoagulation in specific circumstances in which the risk of early stroke recurrence is high.[12]

3.2 Thrombolysis

Intravenous administration of alteplase is the only US Food and Drug Administration (FDA)-approved medical therapy for treatment of patients with acute ischemic stroke. Its use is associated with improved outcomes for a broad group of patients. Recent trials have shown the therapeutic window may be extended out to 4.5 hours in selected patients.[13] Earlier treatment is more likely to result in a favorable outcome.[14]

Alteplase and other plasminogen activators such as streptokinase and urokinase promote thrombolysis by hydrolyzing the arginine-valine peptide bond in plasminogen to form the active proteolytic enzyme plasmin.[15] During physiologic fibrinolysis, the activity of circulating plasmin is inhibited rapidly by α2-antiplasmin (α2-plasmin inhibitor). The fibrinolytic activity of plasmin is maintained within the thrombus. It is minimized systemically because plasminogen is incorporated selectively into the thrombus when it is formed and because the active site and lysine-binding sites of plasminogen (and thus plasmin) at which fibrin binds are the same sites at which α2-antiplasmin binds. Fibrin-bound plasmin within the thrombus, therefore, is relatively protected from inactivation by α2-antiplasmin. Thrombolytic agents such as streptokinase and urokinase activate both fibrin-bound and circulating plasminogen indiscriminately; systemic activation of plasminogen results in the release of large amounts of plasmin into the circulation.

Excess plasmin eventually depletes α2-antiplasmin, leading to a 'systemic lytic state' that is characterized by marked systemic fibrinogenolysis and degradation of other plasma procoagulant proteins. Unlike streptokinase and urokinase, alteplase is a relatively fibrin-selective plasminogen activator. After binding to fibrin, alteplase acquires a high affinity for plasminogen. The binding of alteplase and plasminogen to the fibrin clot is associated with a conformational change in either alteplase or plasminogen. This binding increases the availability of plasminogen locally, which results in more efficient activation of plasminogen at the fibrin surface than that occurring in circulation. In vitro studies suggest that the enhanced activation of plasminogen by one- or two-chain tPA in the presence of fibrin is related to the increased affinity of fibrin-bound alteplase for plasminogen and to an increased catalytic efficiency. Inactivation by α2-antiplasmin of plasmin generated at the fibrin surface within the thrombus occurs 100-fold more slowly than inactivation of circulating plasmin because the binding sites of α2-antiplasmin on plasmin are occupied by fibrin.[15]

Alteplase initiates local fibrinolysis when administered intravenously. The FDA approved the use of intravenous alteplase in 1996 based on the results of the NINDS (National Institute of Neurological Disorders and Stroke) Stroke Study. In this study, which consisted of two trials, 624 patients were treated with alteplase (0.9 mg/kg) or placebo within 3 hours of onset of symptoms of AIS.[17] As a part of the protocol, half of the patients were treated within the first 90 minutes after stroke onset. There were significantly better outcomes among those treated with IV alteplase based on the primary end point, which was a clinical outcome combining the Barthel Index, modified Rankin Scale (mRS), Glasgow Outcome Scale (GOS) and the National Institutes of Health Stroke Scale (NIHSS) scores at 3 months. The alteplase-treated patients had a 30 % higher probability of recovering with little or no deficit after 3 months. The absolute percent difference in favorable clinical outcomes in the alteplase-treated patients was 11–13 % compared with placebo. This clinical benefit of alteplase treatment was seen despite a 5.8 % increase in the absolute risk of symptomatic intracerebral hemorrhage (ICH) within 36 hours among alteplase-treated patients (6.4 % vs. 0.6 %).[18] Practically, alteplase is an expensive medication that may not be quickly retrieved from an institution's pharmacy. Therefore, it is suggested that the medication be stored in automated dispensing machines (e.g., Pyxis®) where it can be quickly retrieved at any time of day. This helps ensure safe and rapid administration, and appropriate capture of charges. Key inclusion criteria for IV alteplase are given in Table 2.

3.2.1 Expanding the Time Window for Thrombolytic Treatment—The results of the randomized clinical trial ECASS (European Cooperative Acute Stroke Study) III and the large-scale registry SITS-ISTR, published in 2008, demonstrated the efficacy and safety of alteplase 3–4.5 hours after the onset of ischemic stroke symptoms.[19,20] The ECASS III trial showed that alteplase administered between 3 and 4.5 hours after onset of symptoms had a benefit over placebo (52.4 % vs. 45.2 % excellent outcome; $p = 0.04$). Important exclusions of the ECASS III trial, compared to the prior NINDS study for the 3- hour time window were for: age over 80 years, current treatment with oral anticoagulants, NIHSS above 25, and a history of both stroke and diabetes. Other trials such as the ATLANTIS (Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke) trial, which was significantly underpowered to accurately evaluate a treatment difference in this time window, showed no excess detriment from the use of alteplase with the extended time to treatment.[21] While treatment with alteplase is associated with an increased risk of symptomatic intracranial hemorrhage, it has not been demonstrated to increase the rate of mortality. Table 3 lists recommendations for monitoring after alteplase administration.

3.2.2 Intravenous versus Combined Intravenous and Intra-Arterial Thrombolysis—The persistence of proximal arterial occlusion after IV thrombolysis,

often present in those with baseline NIHSS scores ≥10, is a poor prognostic sign. Furthermore, the rate of partial or complete recanalization of occluded proximal middle cerebral artery (MCA) after IV alteplase is approximately 25 %, as compared to higher rates of 50–60 % commonly reported after intra-arterial (IA) therapies.[22–29] Combined intravenous and IA (IV+IA) thrombolytic therapy may, therefore, be more efficient than either technique alone by offering the benefits of a rapid administration of IV thrombolytic and a higher recanalization rate achieved with IA therapy. The dose of IA alteplase used in previous and ongoing clinical trials is up to 22 mg. This has shown safety, and ongoing clinical trials of the combined IV/IA approach, including mechanical embolectomy, are underway. [28,31,32]

3.2.3 Other Thrombolytic Agents—Clinical trials of streptokinase were halted prematurely because of unacceptably high rates of hemorrhage, and this agent should not be used to treat acute ischemic strokes in clinical practice.[33–36] Tenecteplase was compared to alteplase in a recent initial trial for acute ischemic stroke.[37] This study enrolled a total of 75 patients into three groups: alteplase IV 0.9 mg/kg, tenecteplase IV 0.1 mg/kg, and tenecteplase IV 0.25 mg/kg. Patients were enrolled within 6 hours of symptoms based on CT-based penumbral imaging selection (with potentially reversible penumbra estimated to be at least 20 % or larger than the presumed irreversible infarct core). Tenecteplase was associated with better outcomes than alteplase without an increase in bleeding or other serious adverse events in this open-label study. A large Phase IIb/Phase III trial (but without imaging selection) was stopped prematurely at 112 subjects due to poor recruitment, and showed no benefit.[38] Further studies are needed to verify any benefit of tenecteplase over alteplase. The intravenously administered desmoteplase is also under study.[94,95]

3.3 Device Therapies

Mechanical thrombectomy delivered endovascularly is another option for clot removal, either as an adjunct to thrombolysis or for patients who are ineligible for IV alteplase. Appropriate patient selection for this approach is currently under study in several ongoing trials. These will not be reviewed here, as they are beyond the scope of this review.

3.4 Anticoagulants

Data suggest that urgent anticoagulation in unselected acute ischemic stroke patients leads to symptomatic intracranial hemorrhage that outweighs any potential benefit. The precise timing for initiation of long-term anticoagulation for secondary stroke prevention is debatable. Specific circumstances for consideration of early anticoagulation may include extracranial arterial dissection or the presence of a high-risk cardiac thrombus. Physicians must weigh the risk of hemorrhagic transformation based on the severity of neurologic impairments or the extent of infarct on CT and the risk of stroke recurrence in specific clinical settings.

3.4.1 Heparin—UFH has a mean molecular weight of 15,000 Daltons. It has its anticoagulant effects by inactivating thrombin and activated factor X. This is achieved by binding to antithrombin. The inactivation of thrombin by UFH prevents fibrin formation and inhibits thrombin-induced activation of platelets and factors V and VIII. The main limitations of UFH are the binding to plasma proteins with resulting variable anticoagulant response and frequent monitoring required.

The International Stroke Trial (IST) tested two doses (5,000 units/day or 25,000 units/day) of subcutaneously administered heparin started within 48 hours of AIS.[39] The benefits of heparin were counteracted by the increase in bleeding seen with it. The subgroup of patients with atrial fibrillation in the IST also did not show a benefit of the subcutaneous heparin.[41]

Two smaller trials recently tested the utility of unfractionated heparin (bolus with dose adjustment) in treating patients within 12 hours of stroke. No significant differences in outcomes, recurrent ischemic stroke, hemorrhagic worsening, or death were noted between the two treatment groups.[42–44]

3.4.2 Low Molecular Weight Heparin and Danaparoid—Low molecular weight heparins (LMWHs) have a mean molecular weight of 5,000 Daltons. Compared to UFH, LMWHs have a decreased ability to bind thrombin. The decreased binding to cells and plasma proteins is responsible for the more predictable dose-response relationship of LMWHs, the longer plasma half-life and the lower risk of heparin-induced thrombocytopenia (HIT). Some of the available LMWHs are enoxaparin, dalteparin, nadroparin, tinzaparin, and certoparin.

A trial of two different doses of nadroparin started at 10 days or more after stroke showed no benefit at 3 months.[45] A German trial compared four different doses of certoparin; no differences in rates of favorable outcomes were noted among the groups, but the rate of serious bleeding complications was highest among the group that received the largest dose of the LMWH.[46] A randomized, double-blind, placebo-controlled trial tested the utility of a continuous intravenous infusion of the LMW heparinoid danaparoid in improving outcomes after acute ischemic stroke.[40,47] The trial was stopped because of an increased risk of symptomatic intracranial hemorrhages. The medication did not reduce the risk of recurrent stroke, even in the subgroup of patients with cardio-embolic events. No improvement was found in the rate of having a favorable outcome at 3 months.

3.4.3 Warfarin—Warfarin is a vitamin K antagonist. It inhibits factors II, VII, IX, X and the anticoagulant proteins C and S. There are no data showing that urgent anticoagulation with warfarin for AIS provides an acute benefit. It is, however, well established for the prevention of recurrent stroke among patients with atrial fibrillation. EAFT (the European Atrial Fibrillation Trial) and the SPAF III (Stroke Prevention in Atrial Fibrillation) trial showed a risk reduction of up to 50 % with an INR of 2–3 as the optimal goal with the lowest bleeding risk.[48–50]

3.4.4 Dabigatran—Dabigatran is an oral anticoagulant that acts as a direct thrombin inhibitor. It was recently tested in a large multicenter trial and FDA-approved for stroke prevention in patients with non-valvular atrial fibrillation. The RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy, Warfarin, Compared with Dabigatran) study enrolled 18,113 patients with AF at risk for stroke from 967 centers in 44 countries.[51] The trial showed that 110 mg of dabigatran twice daily was as effective as a conventional adjusted-dose warfarin regimen in reducing the occurrence of stroke and that 150 mg of dabigatran twice daily was better than warfarin in this patient population.[51,52] In addition, 110 mg twice daily of dabigatran was associated with lower rates of major hemorrhage and 150 mg twice daily with similar rates, compared with warfarin.[51] This dichotomy between the 110 mg twice-a-day group and the 150 mg twice-a-day group suggests that dosing of this new drug could potentially be customized: the lower dose for patients at lower embolic risk but higher bleeding risk and the higher dose for patients at greater stroke risk. A significant concern with the use of dabigatran is the absence of an antidote in the setting of hemorrhage. The FDA has only approved the 75 mg and 150 mg dosage strengths for use and therefore the 110 mg strength is not an option in the USA. Practically, it should be noted that dabigatran capsules should not be opened as this results in a significantly elevated exposure and increased risks such as bleeding.

3.4.5 Rivaroxaban—Rivaroxaban is an oral anticoagulant that is an inhibitor of factor Xa. It was also recently approved by the FDA based on a large, randomized trial. Specifically, the Rocket-AF (Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) was a randomized, double-blind, double-dummy trial comparing rivaroxaban 20 mg daily (15 mg daily if creatinine clearance [Cr_{CL}] <30 mL/min) versus dose-adjusted warfarin (Goal INR 2–3).[53] This study enrolled 14,264 patients and the primary endpoint was stroke (ischemic or hemorrhagic) and systemic embolism. Safety was evaluated as a composite of major and non-major clinically relevant bleeding. Rivaroxoban showed non-inferiority to warfarin as per the protocol and intent-to-treat analysis ($p < 0.001$ for both analyses). Rivaroxaban is also limited by an inability to reverse its actions in the setting of hemorrhage.[54]

3.4.6 Apixaban—Apixaban is another direct thrombin inhibitor. Its efficacy in preventing secondary stroke was compared to warfarin in the Aristotle (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trial. This study enrolled 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke and demonstrated a decrease in secondary stroke occurrences (hemorrhagic stroke 0.24 % vs. 0.47 % with warfarin, $p < 0.001$; ischemic stroke 0.97 % vs. 1.05 %, $p = 0.42$), less bleeding (2.13 % vs. 3.09 % with warfarin, $p < 0.001$) and lower mortality (3.52 % vs. 3.94 % with warfarin, $p = 0.047$) with the use of apixaban.[55] Apixaban has been submitted for approval by the FDA.

A summary of the results of the large trials for dabigatran, rivaroxaban, and apixiban is given in table 4. The clinical role of these newer oral anticoagulants will continue to be delineated with their more widespread use and more safety data.

4. Antiplatelet Agents

4.1 Aspirin

Aspirin irreversibly inhibits cyclooxygenase, which prevents the conversion of arachidonic acid to thromboxane A2 (TXA2). Thromboxane A2 is a vasoconstrictor and stimulator of platelet aggregration. Platelets are inhibited for their full life cycle (5–7 days) after exposure to aspirin. Aspirin also inhibits prostacyclin activity and this inhibits platelet aggregration. The effects of aspirin on prostacyclin are dose related.

Acute use of aspirin after AIS was tested in CAST (the Chinese Acute Stroke Trial) and IST (the International Stroke Trial).[56,57] In ISTl, aspirin 300 mg/day reduced stroke recurrence within the first 2 weeks without an effect on early mortality. In CAST, aspirin 160 mg/day reduced the risk of recurrence and death in the first 28 days. In these two large studies the rates of long-term death and disability were not different to with placebo. Both of these trials showed small significant increases in the risk of hemorrhagic transformation. The data show a small but statistically significant decline in risk of mortality and morbidity when aspirin is initiated within 48 hours of AIS.[56,57] The effects of aspirin are due to a reduction of recurrent AIS rather than a reduction in the neurologic symptoms after the incident AIS. Specifically, there is approximately a 1 % risk reduction in stroke recurrence over the first 2 weeks after the incident event.

4.2 Clopidogrel

Clopidogrel irreversibly blocks ADP receptors on platelets and thus prevents the cascade resulting in activation of GP IIb/IIIa receptor. The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial tested clopidogrel 75 mg daily versus aspirin 325 mg daily in the prevention of cardiovascular and cerebrovascular events.[58] The primary

outcome measurement was a combined endpoint of the occurrence of myocardial infarction, ischemic stroke and vascular death. Event rates of 5.32 % and 5.83 % were associated with clopidogrel and aspirin therapy, respectively. Clopidogrel therapy resulted in a relative risk reduction of 8.7 % (confidence interval [CI] 0.3–16.5) compared with aspirin therapy (p = 0.043). Gastrointestinal hemorrhages occurred in 1.99 % of patients treated with clopidogrel and 2.66 % of patients treated with aspirin ($p < 0.002$). Post hoc analysis of the CAPRIE trial, the basis of the drug's FDA approval, showed no significant benefit of clopidogrel over aspirin in the stroke subgroup ($p = 0.26$).

Certain patients show reduced responses to clopidogrel. This clopidogrel resistance may involve variable responses to some genotypes of the CYP2C19 gene. Additionally, some patients taking proton pump inhibitors such as omeprazole show less antiplatelet activity. Some of the proton pump inhibitors also interfere with the CYP2C19 enzyme required for the conversion of clopidogrel to its active metabolite.

4.3 Combination Antiplatelet Therapy

The MATCH (Management of ATherothrombosis with Clopidogrel in High-risk patients) trial compared clopidogrel in combination with aspirin to clopidogrel alone in secondary prevention of transient ischemic attack (TIA) or stroke. No difference was found for TIA or stroke prevention, but a significant increase in major bleeding complications (3 % vs. 1 %) was observed among those on combined therapy.[59] No benefit with this combination was seen in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial as well, which included a subgroup of patients with prior stroke or TIA.[60] Thus, use of clopidogrel in combination with aspirin is generally not recommended for long-term stroke prevention. Its potential short-term use for early stroke recurrence is under study.

Dipyridamole is an antiplatelet agent that inhibits the uptake of adenosine by a variety of cells. This accumulated adenosine is an inhibitor of aggregation. Since dipyridamole is absorbed erratically, depending on the stomach pH, a revised formulation combines timed-release dipyridamole 200 mg with aspirin 25 mg. This combination was tested in two trials. The ESPS II (European Stroke Prevention Study) II showed efficacy of both 50 mg aspirin and extended-release dipyridamole in preventing stroke, and a better risk reduction with the combination.[61] Another trial, ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial**)** , randomized 2,739 stroke or TIA patients treated with aspirin to dipyridamole 200 mg or no dipyridamole. Primary outcome events arose in 173 (13 %) patients on aspirin and dipyridamole and in 216 (16 %) on aspirin alone, which led to the conclusion by the authors of the study that the combination of dipyridamole and aspirin is superior to aspirin alone as an antithrombotic therapy after cerebral ischemia of arterial origin.[62] Randomized comparison of the combination of long-acting dipyridamole and 50 mg aspirin (Aggrenox) to clopidogrel showed that neither of the two treatments was superior to the other for secondary stroke prevention, although clopidogrel was better tolerated.[96]

Tirofiban and *eptifibatide* are antiplatelet drugs belonging to the class of glycoprotein IIb/IIIa inhibitors with potential to be adjuncts to thrombolysis acutely. Phase II data have suggested safety, and further studies are needed to determine efficacy.[63,64]

Newer antiplatelet agents including ticagrelor, cangrelor, and prasugrel have been studied in recent trials, although none were tested in AIS patients.[65–66] Ticagrelor and cangrelor block adenosine diphosphate (ADP) receptors of subtype $P2Y_{12}$. Prasugrel is also an irreversible ADP inhibitor. In contrast to the other antiplatelet drugs, ticagrelor has a binding site different from ADP, making it an allosteric antagonist, and the blockage is reversible.

4. Drugs Related to Treatment of Acute Neurological Complications

The most important acute neurologic complications of ischemic stroke are: (1)cerebral edema and increased intracranial pressure, which can lead to midline or transtentorial herniation, (2) seizures, and (3) hemorrhagic transformation of the infarction. We also review the occurrence of angioedema after thrombolysis, which is a rare but well-recognized phenomenon.

4.1 Cerebral Edema and Increased Intracranial Pressure

Brain swelling is due to a cytotoxic reaction mediated by multiple factors, including free radicals.[67] Brain swelling typically occurs in patients who have had an occlusion of the stem of the middle cerebral artery (MCA), and usually peaks at 3–5 days after stroke. Dramatic early swelling has been described and may be attributable to reperfusion edema and possibly effects of alteplase.[69–73] In patients with MCA infarctions who develop malignant brain edema, local pressure on additional arteries, such as the anterior communicating (ACA) and posterior communicating (PCA) arteries, can lead to extension of infarction in previously involved territories, followed by further edema and herniation. A global increased intracranial pressure can also result from acute hydrocephalus secondary to obstruction of cerebrospinal fluid pathways by a large cerebellar lesion such as a PICA infarction.[74,75]

Mannitol is an osmotic diuretic, typically used at 0.25–0.5 g/kg IV administered over 15 minutes. It lowers intracranial pressure, and can be given every 6 hours.[76] The usual maximal dose is 2 g/kg. Its effect in patients with ischemic brain swelling is still unknown, but it is often used as a temporizing measure before patients undergo decompressive craniectomy. There is limited evidence on the benefits of other medical options including hypertonic saline and hyperventilation.[3,97]

Despite intensive medical management, the mortality rate from malignant cerebral edema is estimated to be as high as 50–70 %.[77] The treatment of patients with raised intracranial pressure consisting of medical measures such as osmotic diuretics and hypertonic therapies should only be used as a bridge to decompressive surgery, which is the most effective option for malignant ischemic cerebral edema. This has been established by randomized trials, including HAMLET (Hemicraniectomy after middle cerebral artery infarction with life-threatening Edema trial), DECIMAL (DEcompressive Craniectomy In MALignant middle cerebral artery infarction), DESTINY (DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral artery), and DESTINY 2.[78–81] Surgery should be considered in patients with drowsiness and 4 mm or more of midline shift. Approximately 10– 20 % of patients develop edema that is significant enough to warrant decompressive hemicraniectomy.[68]

4.2 Seizures

Seizures after ischemic stroke occur in approximately 5–10 % of patients. They typically occur within 24 hours of stroke, and are of partial type, with or without secondary generalization. Prophylactic administration of antiepileptic agents (e.g., phenytoin) routinely after stroke are not recommended based on indirect evidence that recovery from stroke may be adversely affected.[82–84]

4.3 Hemorrhagic Transformation

Studies suggest that almost all infarctions have some element of minor hemorrhage. The use of all anticoagulants and thrombolytic agents, and antiplatelet agents to a lesser degree, increases the likelihood of serious hemorrhagic transformation.[17,85,87] Management of

patients with intracranial hemorrhage (ICH) depends on the amount of bleeding and its context. This includes emergent fresh frozen plasma (FFP) and platelet transfusions in the presence of thrombolysis, FFP and/or prothrombin complex concentrates (PCC), and vitamin K in the setting of warfarin, protamine to reverse heparin's activities, and/or clot evacuation in deteriorating patients.[88–90] A suggested protocol for ICH after IV alteplase as modified from the NINDS Trial Protocol is shown in figure 1.

4.4 Angioedema

Another potential adverse effect is the development of angioedema after IV alteplase, typically near the end of the 60-min infusion. Its incidence has been estimated to be 1–2 % of all alteplase-treated strokes, and it is more common in patients taking ACE inhibitors.[91] There are no standard guidelines available for management, and one proposed approach to management is provided in figure 2.

4.5 Other Adverse effects

Other rare adverse effects of thrombolytic therapy are severe hypotension and a systemic fibrinolytic state.[92,93]

5. Conclusions

We have provided an overview of the drugs potentially used in the care of the acute ischemic stroke patient. Drugs associated with supportive care include antihypertensives, antipyretics, and insulin. Drugs associated with treating, and potentially reversing, the effects of the ischemic stroke directly consist of thrombolytics. Drugs used to prevent recurrent strokes include anticoagulants and antiplatelet agents. Finally, drugs used to treat complications of strokes include osmotic diuretics and antiepileptics. Specific considerations for some commonly used agents are shown in table 5.

Acknowledgments

NIH/NINDS grant K23 NS 059843.

PK: Research Support (NIH, Penumbra, Inc as Neurology PI of THERAPY Trial), Travel Support (Genentech, Inc. as unpaid consultant), Consultant Fees (medical expert in medicolegal cases).

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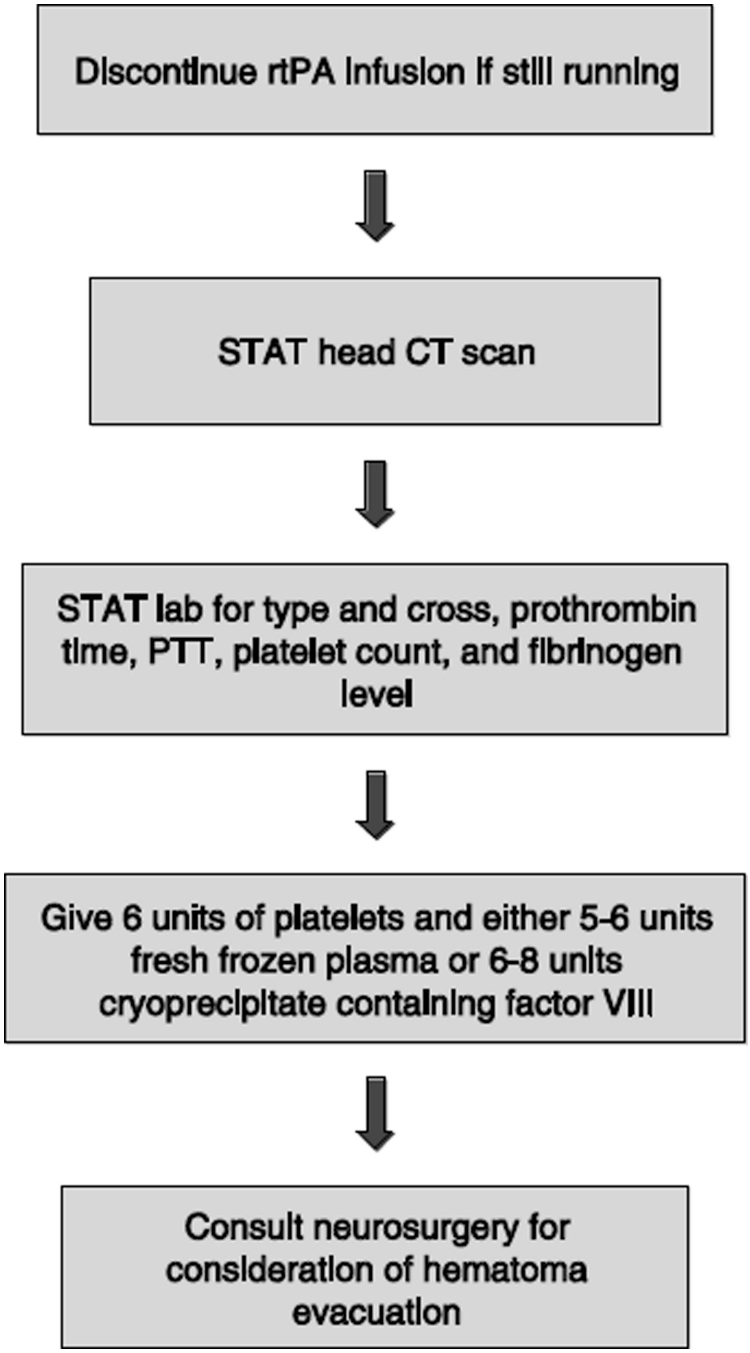

Fig. 1.
Treatment protocol for intracerebral hemorrhage (ICH) with recombinant tissue plasminogen activator (rtPA) as per NINDS (Modified NINDS ICH Management Protocol). *CT* computed tomography, *PTT* partial thromboplastin time

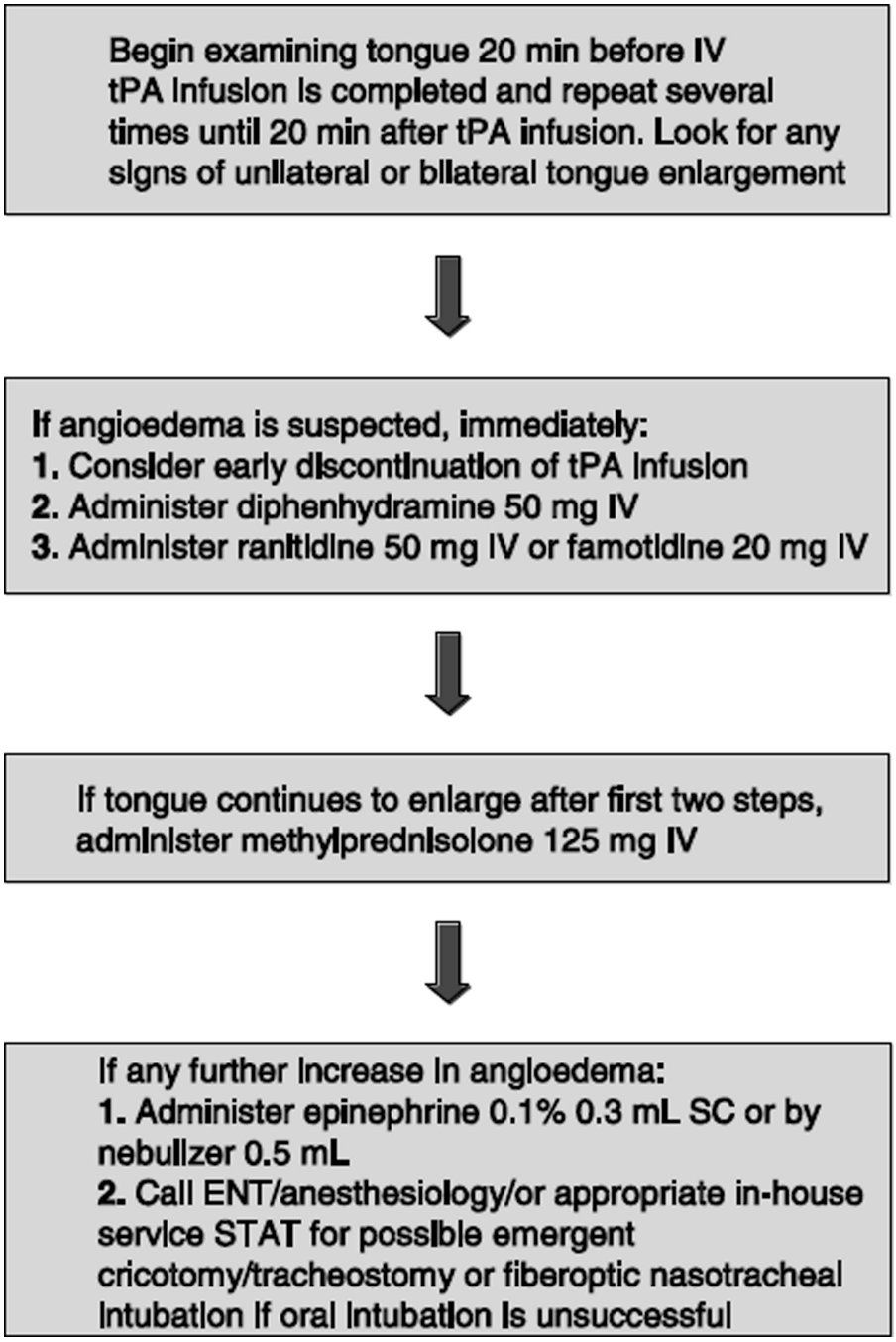

Fig. 2.
Greater Cincinnati/Northern Kentucky Stroke Team Angiodema protocol. *ENT* ear nose and throat, *IV* intravenous, *SC* subcutaneous, *tPA* tissue plasminogen activator

Table I

Emergent management of hypertension in patients with acute ischemic stroke (AIS)

Therapy for AIS	Blood pressure situation	Recommendations
Not an rtPA candidate	Systolic BP <220 mmHg Diastolic BP <120 mmHg	Observe BP unless there is end-organ involvement such as aortic dissection, renal failure, or myocardial infarction that would mandate emergent management
	Systolic BP >200 mmHg Diastolic BP 121–140 mmHg	Labetalol 10–20 mg IV over 1–2 min. May repeat or double every 10 min to a maximum of 300 mg or an IV infusion Nicardipine 5 mg/h IV infusion, titrate to desired effect, to a maximum of 15 mg/h (target 10–15 % reduction)
	Systolic BP >220 mmHg or Diastolic BP > 140 mmHg	Sodium nitroprusside 0.25 μg/kg/ min IV with continuous BP monitoring if nicardipine is infective (target 10–15 % reduction)
rtPA candidate	Systolic BP >185 mmHg Diastolic BP > 110 mmHg	IV labetalol 10–20 mg IV over 1–2 min, may repeat at double doses; or nitropaste 1–2 in (2.5–5 cm); or nicardipine infusion, 5 mg/h, titrate up by 2.5 mg/h at 5- to 15-min intervals, maximum dose 15 mg/h; when desired BP attained, reduce to 3 mg/h. If BP is maintained >185/110 mmHg, do not give alteplase

Note: Other oral antihypertensive medications (e.g., diuretics, captopril,clonidine, metoprolol, and hydralazine) may be utilized for maintenance therapy if the patient has passed a dysphagia screening

BP blood pressure, *IV* intravenous, *rtPA* recombinant tissue plasminogen Activator

Table 2

Key inclusion criteria for intravenous tissue plasminogen activator (rtPA) treatment (adapted from 2007 American Hypertension Association [AHA] guidelines)[16]

- Diagnosis of ischemic stroke causing measurable neurologic deficit
- The neurologic signs should not be minor as suggested by a potentially non-disabling deficit
- The symptoms of stroke should not be suggestive of subarachnoid hemorrhage
- Onset of symptoms <4.5 h before beginning treatment
- No head trauma or prior stroke in previous 3 months
- No gastrointestinal or urinary tract hemorrhage in previous 21 days
- No major surgery in the previous 14 days
- No arterial puncture at a non-compressible site in the previous 7 days
- Blood pressure not elevated (systolic <185 mmHg and diastolic <110 mmHg)after non-aggressive treatment
- No evidence of active bleeding or acute trauma (fracture) on examination
- Not taking an oral anticoagulant or, if anticoagulant being taken, INR ≤1.7
- If receiving heparin in previous 48 hours, aPTT in normal range
- Platelet count ≥ 100,000 mm^3
- CT scan does not show a clear, large hypodensity (such as >1/3 cerebral hemisphere)

aPTT activated partial thromboplastin time, *CT* computed tomography, INR international normalized ratio

Table 3

Post-recombinant tissue plasminogen activator (rtPA) therapy monitoring (adapted from 2007 American Hypertension Association [AHA] guidelines)[16]

- Admit the patient to an intensive care or stroke unit for close neurologic monitoring
- Perform neurologic assessments and blood pressure monitoring every 15 min during the first 2 h, every 30 min thereafter for the next 6 h, and then hourly until 24 h after treatment
- If the patient develops headache, acute hypertension, nausea, vomiting, or neurologic worsening, discontinue the infusion (if alteplase is still being administered) and obtain emergent non-contrast CT scan of the brain
- Increase the frequency of blood pressure measurements if a systolic blood pressure is >180 mmHg or if a diastolic blood pressure is >105 mmHg; urgently administer antihypertensive medications to maintain blood pressure at or below these levels
- Consider delaying placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters until 24 h after alteplase administration
- Obtain a follow-up brain CT scan at 24 h to rule out asymptomatic intracranial hemorrhage before starting anticoagulants or antiplatelet agents for secondary prevention of stroke

Table 4

Summary of trial results: dabigatran (RE-LY), rivaroxaban (Rocket-AF),and apixiban (Aristotle)

Study	Study groups		Results [RR, 95% CI] (*p* value)
RE-LY (n = 18,113)	Dabigatran		
	150 mg bid	Warfarin	
Primary endpoint	1.1 % per year	1.7 % per year	0.66, 0.53–0.82
			(< 0.001)
Major/non-major	16.4 % per year	18.2 % per year	0.91, 0.86–0.97
bleeding			(< 0.001)
ICH	0.3 % per year	0.74 % per year	(< 0.001)
Rocket-AF (n = 14,262)	*Rivaroxaban*		
	20 mg daily	*Warfarin*	
Primary endpoint	1.7 % per year	2.2 % per year	0.79, 0.66–0.96
Major/non-major	14.9 % per year	14.5 % per year	1.03, 0.96–1.11
bleeding			
ICH	0.5 % per year	0.7 % per year	(0.02)
Aristotle (n = 18,201)	*Apixaban*		
	5 mg bid	*Warfarin*	
Primary endpoint	1.3 % per year	1.6 % per year	0.79, 0.66–0.95
Major/non-major	4.1 % per year	6 % per year	0.68, 0.61–0.75
bleeding			
ICH	0.33 % per year	0.8 % per year	(*p* < 0.001)

bid twice daily, *ICH* intracranial hemorrhage

Table 5

Specific drug therapy considerations for acute ischemic stroke

Typical adult dose/route	Mechanism	Monitoring/adverse effects
Antihypertensives		
Labetalol 10–20 mg IVP or 1–5 mg/min CIV	β-blocker α-blocker	BP, HR, nausea, wheezing
Nicardipine 2.5–15 mg/h CIV	Calcium channel antagonist	BP, HR, volume overload
Nitropaste 1–2 in (2.5–5 cm)	Nitrate	BP
Topical nitroprusside 0.25 μg/kg/min CIV	Vasodilator	BP, HR, cyanide toxicity
Labetalol 100–2400 mg/day PO	β-blocker	BP, HR
Lisinopril 5–40 mg/day PO (multiple other ACEI)	ACEI	BP, HR, cough
Hydralazine 20–100 mg/day PO 5–40 mg/day IV	Vasodilator	BP
Thrombolytics		
Alteplase (tPA) 0.9 mg/kg IV 10 % of dose as bolus and 90 % as 60-min infusion	Thrombolytic	Bleeding, BP
Antiplatelets		
Aspirin 80–325 mg/day PO	Inhibits TXA_2/PGI2	GI intolerance, use EC forms
Clopidogrel 75 mg/day PO	Inhibits ADP	Diarrhea, rash
Aspirin+ER dipyridamole 25+200 mg 1 cap PO twice daily	See aspirin	Headache
Anticoagulants		
Heparin SC 5000 units 2–3 times per day		For DVT prophylaxis
Warfarin 2.5–10 mg/day PO	Vitamin K antagonist	INR, Bleeding

ACEI angiotensin-converting enzyme inhibitor, *ADP* adenosine diphosphate, *BP* blood pressure, *CIV* continuous IV, *DVT* deep venous thrombosis, *EC* enteric coated, *ER* extended-release, *GI* gastrointestinal, *HR* heart rate, *INR* international normalized ratio, *IV* intravenous, *IVP* IV push, *PGI2* prostacyclin, *PO* oral, *SC* subcutaneous, *TXA_2* thromboxane A_2