American Society of Health-System Pharmacists

Edward H. Lee, PharmD

The 2010 ASHP meeting, which took place from December 4 to 9 in Anaheim, Calif., is the largest gathering of pharmacy professionals in the world. This year's meeting attracted over 20,000 attendees and more than 250 exhibitors to learn about the newest advances in pharmacy via interactive sessions, keynote speakers, and networking opportunities. This article reviews the lecture series that discussed acute ischemic stroke, which remains an area in which the expertise and experience of a clinical pharmacist can be invaluable.

Role of the Pharmacist in the Management of Acute Ischemic Stroke

Stroke: A Neglected Disease of Modern Society

- Heather Draper Eppert, PharmD, BCPS, Clinical Specialist, Emergency Medicine; and Assistant Professor of Clinical Pharmacy, University of Tennessee College of Pharmacy, Knoxville, Tenn.

According to the American Heart Association Heart Disease and Stroke Statistics 2011 update, approximately 795,000 people experience a new or recurrent stroke each year. Strokes are responsible for one in every 18 deaths in the U.S. and remain one of the leading causes of serious, long-term disability. Stroke also accounted for a staggering $73.7 billion in health care costs in 2010.[1]

Despite the past serious efforts made in stroke prevention in the health care arena, acute ischemic stroke remains "a neglected disease of modern society," according to Dr. Eppert. Based on her review of community-based awareness studies, she found that a large proportion of stroke patients were not aware of the signs and symptoms of a stroke. For example, in patients presenting to the emergency department with a possible stroke, 39% could not identify signs and symptoms of stroke; further, 43% of these patients could not identify the risk factors.

The lack of stroke awareness often results in a delay in seeking professional care and may help explain why more than 50% of stroke patients die outside of the health care system. In one analysis, the median time from the onset of stroke symptoms to presentation was 16 hours, and in 66% of the cases, a bystander made the decision to seek treatment for the patient. In cases of prolonged time lapse from stroke onset to seeking professional care, treatment options and their effectiveness are significantly reduced.

However, Dr. Eppert noted that educational gaps regarding stroke might also be present among the medical community. In a survey of 308 internal medicine residency-training programs, only 47% required a rotation in neurology; by contrast, 97% required a rotation in cardiology. In addition, a study found that in states requiring a neurology rotation, age-adjusted stroke mortality was lower ($P = 0.015$).

Dr. Lee is a Health Economics and Outcomes Research Fellow in the Jefferson School of Population Health at Thomas Jefferson University in Philadelphia, Pa.

In a separate survey of emergency physicians, 40% stated that they were unlikely to use thrombolytics for acute stroke, even in ideal situations; this may explain why only 1.12% of acute-stroke patients who were eligible for thrombolytic agents actually received them between 1999 and 2004.

In order to combat the obstacles in delivering optimal acute-stroke care, stroke centers were developed based on the effectiveness of trauma centers. Dr. Eppert emphasized that the availability of specialized resources (i.e., staffing and infrastructure) allows stroke centers to improve the efficiency of patient care, achieve improved outcomes, enhance the use of acute-stroke therapies, reduce morbidity and mortality, and lower health care costs.

To Treat or Not to Treat: Management Of Hypertensive Crisis in Acute Stroke

- Patrick J. Bridgeman, PharmD, RPh, Emergency Medicine Pharmacist, Robert Wood Johnson University Hospital, New Brunswick, N.J.

Dr. Bridgeman noted that treating hypertensive crisis in acute-stroke patients is a "clinical conundrum." Although 67% of patients with acute stroke present with a systolic blood pressure (BP) above 140 mm Hg, both elevated and decreased BPs have been associated with poor outcomes. For example, in a study by Castillo et al., both a 10-mm Hg systolic BP decrease below and a 10-mm Hg systolic BP increase above 180 mm Hg were associated with a 25% and 23% increase, respectively, in poor neurological outcomes, based on the Rankin scale.[2]

Dr. Bridgeman presented several reasons why hypertensive acute-stroke patients should not be treated. He noted that within 24 hours, many patients experience an average of a 28% drop in their admission BP without medical treatment. Treating hypertensive crisis may also lead to hypoperfusion of ischemic areas, resulting in a larger infarct volume that can worsen neurological outcomes and lead to death.

However, there are also several reasons to treat these patients. If the patient is eligible for a tissue plasminogen activator (tPA) but the systolic BP exceeds 185 mm Hg or the diastolic BP is greater than 100 mm Hg, treatment should be considered; there is an increased risk of hemorrhagic conversion (bleeding in the brain) when tPA is used in hypertensive patients. In addition to tPA-eligible patients, those patients

with a systolic BP above 220 mm Hg, a diastolic BP above 140 mm Hg, or a significant comorbid condition (acute renal failure, aortic dissection, or encephalopathy) should be treated, according to the stroke guidelines.

Dr. Bridgeman then reviewed a selective list of medications used to treat hypertensive crisis in tPA-eligible patients:

1. ***Labetalol*** (Trandate, Prometheus) is an alpha$_1$ and beta$_1$ antagonist with potential intrinsic sympathomimetic beta$_2$ activity to help stimulate vasodilation and control hypertension. It is the most commonly used agent in patients eligible for tPA with a systolic BP above 185 mm Hg. The recommended bolus dose is 10 to 20 mg, up to a maximum total dose of 300 mg. Continuous infusion should be used if further hypertensive control is warranted after the bolus dose. There is also a minimal effect on cerebral blood flow; therefore, the risk of decreasing blood flow to an already ischemic area is low.

2. ***Esmolol*** (Brevibloc, Baxter), a beta blocker, is associated with a relatively complicated administration schedule. A bolus dose of 500 mcg/kg is recommended at the start of the infusion and between every titration. Typically, the continuous infusion starts at 50 mcg/kg per minute; responses are generally seen when a rate of 150 mcg/kg per minute is achieved. The drug's half-life is nine minutes, which allows for quick recovery of BP after the medication is discontinued.

3. ***Nitroglycerin*** (e.g., Nitrostat, Pfizer), direct vasodilator, is generally used when the patient is expected to receive tPA in a short time frame and when labetalol is not an appropriate option. An inch or two of nitroglycerin paste is applied to the patient. An intravenous (IV) infusion, at a rate of 10 mcg/minute, is also an option, but headache associated with IV administration may pose a challenge. The effects of nitroglycerin disappear in five to 10 minutes after treatment is discontinued.

4. ***Sodium nitroprusside*** (e.g., Nitropress, Abbott), also a direct vasodilator, has an immediate onset and a five- to 10-minute duration of action. The infusion should be initiated at 0.25 mcg/kg per minute and titrated upward to a maximum of 10 mcg/kg per minute. This agent should be considered in cases of resistant BP when nicardipine (Cardene) and labetalol fail to achieve BP goals. There is a potential for cyanide toxicity at high doses and in patients with renal impairment.

5. ***Nicardipine*** (Cardene, Roche/Baxter/PDL BioPharma) is a dihydropyridine calcium-channel blocker. A continuous infusion should be started at 5 mg/hour and titrated every five minutes to a maximum of 15 mg/hour. When the target BP is reached, the infusion rate is reduced to 2 to 3 mg/hour, as recommended in the package insert. The onset of action is approximately 10 minutes, and the effects can last for two to six hours after treatment is withdrawn.

In most cases, BP should ideally be reduced by 15% to 20% over a 24-hour period. Selection of therapeutic agents should be based on the patient's assessment. To date, no specific medication has proved superior in treating hypertension in acute ischemic stroke. Although the optimal BP ranges for tPA treatment are not known, the goal for systolic BP in stroke patients receiving tPA is approximately 180 mm Hg or lower. In patients who are not eligible for tPA therapy, treatment should usually be withheld.

But I Don't Want the Patient to Bleed: Thrombolytics for Acute Ischemic Stroke

• Renee M. Petzel, PharmD, Emergency Medicine/Medical Toxicology Clinical Pharmacist, Loyola University Medical Center, Maywood, Ill.

During an ischemic stroke event, blockage of the blood supply to the brain results in a cascade of biological processes that ultimately lead to cell death. Treatments are often focused on recanalization of the vessels, depending on various factors (the occlusion site, age and composition of the thrombus, and the presence and efficacy of the collateral circulation). Several therapeutic options have been studied, including streptokinase (Streptase, Hoechst Marion Roussel/AstraZeneca) and tenecteplase (TNKase, Genentech/ Roche). Since 1996, however, recombinant tPA (r-tPA) has been used most often in the U.S.

r-tPA, a fibrin-enhanced enzyme, converts plasminogen to plasmin, initiating local fibrinolysis to restore blood flow to the brain in an effort to minimize the effects of tissue hypoxia. The main adverse effect associated with r-tPA for stroke is bleeding; one in 18 reported adverse events are related to major or minor bleeding. Other adverse effects include anaphylactoid reactions, cerebral edema, cerebral herniation, seizure, and the occurrence of a new ischemic stroke.

Dr. Petzel briefly reviewed some of the more prominent r-tPA studies, as follows.

ECASS: Intravenous Thrombolysis with r-tPA for Acute Hemispheric Stroke: European Cooperative Acute Stroke Study. In a double-blind, randomized, placebo-controlled trial, researchers measured the difference in activities of daily living and disability using the Barthel Index and modified Rankin scale after 90 days. There were no significant differences between the r-tPA and placebo groups in primary and secondary outcomes, including mortality at 30 days. However, this might have been a result of the treatment window of six hours used in the study. Upon examination of the short-term efficacy parameters, including neurological change within a week, duration of hospital stay, and the National Institutes of Health Stroke Scale (NIHSS) at 24 hours, r-tPA was significantly better than placebo. The authors concluded that treatment with r-tPA might improve some functional measures and neurological outcomes in a subpopulation of ischemic stroke patients. A *post hoc* analysis showed potential benefit in patients receiving r-tPA within three hours.

NINDS: National Institute of Neurological Disorders and Stroke r-tPA Stroke Study. This randomized, double-blind, placebo-controlled trial was conducted to measure the difference in neurological improvement at 24 hours and the proportion of patients achieving complete or nearly complete neurological outcomes three months after stroke. The results of this study were used to gain FDA approval of r-tPA in the U.S. The exclusion criteria in this study are currently used to help determine r-tPA eligibility in stroke patients. In addition, the three-hour treatment window that determines r-tPA eligibility is based on the findings of this study.

A lower r-tPA dose of 0.9 mg/kg, compared with 1.1 mg/kg in ECASS, was used in an effort to reduce the incidence of

bleeding; this is currently the dose used in clinical practice. Although not all results were statistically significant, patients receiving r-tPA performed better on the NIHSS and experienced improved outcomes three months after the stroke, as assessed by the modified Rankin scale, the Barthel Index, and the Glasgow Outcome Scale. The incidence of symptomatic brain hemorrhage, however, was elevated with r-tPA when compared with placebo (6.4% vs. 0.6%, respectively).

ECASS II. This trial was similar to ECASS I, but the investigators decreased the r-tPA dose and made the exclusion criteria more stringent. No significant differences in modified Rankin Scale scores or mortality rates were noted at 90 days or at 30 and 90 days, respectively. Rates of intracranial hemorrhage were higher with r-tPA (8.8%) than with placebo (3.4%).

ECASS III. This double-blind, parallel-group, placebo-controlled trial tested the safety and efficacy of r-tPA administered at 3 to 4.5 hours after symptom onset in an effort to expand the treatment window from 3 hours to 4.5 hours. The primary endpoint was disability at 90 days with the modified Rankin Scale. Safety endpoints included overall mortality at 90 days and the incidence of intracranial hemorrhage, symptomatic intracranial hemorrhage, symptomatic edema, and other adverse events. The median time to r-tPA administration was 3 hours 59 minutes. Patients receiving r-tPA treatment were 34% more likely to experience a favorable outcome, as measured by the modified Rankin Scale ($P = 0.04$).

There were no significant differences in mortality, but rates of intracranial hemorrhage were significantly higher in the r-tPA group ($P = 0.001$). The authors concluded that although r-tPA was more frequently associated with symptomatic intracranial hemorrhage, patients receiving r-tPA 3.0 to 4.5 hours after symptom onset experienced improved outcomes.

Depending on the specific hospital protocol, usually based on the studies reviewed by Dr. Petzel, if the patient has met all the inclusion criteria and the decision is made to treat, r-tPA is given at 0.9 mg/kg (the maximum dose is 90 mg). Ten percent of the dose (0.09 mg/kg; the maximum dose is 9 mg) is given as an IV bolus over one minute, followed by the remaining 90% of the dose (0.81 mg/kg; the maximum dose is 81 mg), given as an IV infusion over 60 minutes. BP and neurological status must be monitored consistently.

In addition to IV r-tPA, an alternative route of administration utilizes the intra-arterial pathway, which may result in increased recanalization of the vessel. A potential downside is the time necessary to administer the drug via the intra-arterial route. The Emergency Management of Stroke (EMS) study investigators compared the use of bridge therapy (IV r-tPA plus intra-arterial r-tPA) with intra-arterial r-tPA alone. Overall, the bridge therapy group achieved better outcomes.

In conclusion, Dr. Petzel stressed the importance of becoming familiar with current guidelines and the benefits of having a pharmacist as a part of the multidisciplinary team. As Dr. Petzel quoted, "time is brain," and having a trained pharmacist familiar with the appropriate dosing and administration of r-tPA, based on the patient assessment, is critical to delivering optimal care.

It Starts With the Assessment: The NIH Stroke Scale and Certification

• Tony Casanova, PharmD, Emergency Department Pharmacist Specialist, St. Joseph Medical Center, Tacoma, Wash.

The NIHSS, the standard initial neurological assessment, must be completed upon patient admission, every 24 hours, upon any change in neurological status, and at discharge. The NIHSS contains 11 sections and 13 items that allow clinicians to quickly assess patients for neurological changes. The scores range from 0 to 42, with 42 being the worst, indicating severe stroke. A score of less than 5 indicates mild impairment; 5 to 14, moderately severe impairment; 15 to 24, severe impairment; and higher than 25, very severe impairment.

Dr. Casanova reviewed a prospective study linking NIHSS scores with outcomes. One additional point on the NIHSS decreased the likelihood of an excellent outcome at seven days by 24% and at three months by 17%. At three months, 46% of patients with NIHSS scores of 7 to 10 had excellent outcomes compared with 23% of patients with scores of 11 to 15. In a retrospective study examining 94 patients who were either discharged to a home or a nursing facility, patients with an NIHSS score greater than 13 were 10 times more likely to require rehabilitation than those with NIHSS scores below 5.

Although the NIHSS is a valuable clinical tool, it is not feasible to use for identifying stroke in the general public. Dr. Casanova explained that pharmacists should learn the acronym FAST to recognize stroke symptoms: *F*acial weakness or vision disturbance, *A*rm and leg weakness, *S*peech difficulty or mute, and *T*ime saved is brain function saved. This mnemonic has been shown to be very effective in the field, with 100% sensitivity and 92% specificity, when all three factors (FAS) are present.

Dr. Casanova concluded the lecture series by emphasizing the important role of the pharmacist as an integral member of the stroke team. He said that pharmacists must "assume that every situation is medication-related until proven otherwise." Pharmacists need to take a methodical approach to efficiently assess the patient by attaining valuable information from patient records and interviewing family members, and they should be prepared for a multitude of clinical scenarios. Equally important, pharmacists must have a thorough understanding of the patient's history of present illness, vital statistics, medical history, and medication history.

Pharmacists should be familiar with the eligibility requirements for tPA therapy, and they should be prepared to discuss and manage hypertensive crisis and thrombolytic therapy. Pharmacists' rapid access to thrombolytic therapy and their knowledge of appropriate dosage and administration are keys to successful therapy, and their participation remains crucial to effective stroke management.

REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 Update: A report from the American Heart Association. *Circulation* 2011;123(4):e18–e209.
2. Castillo J, Leira R, Garcia M, et al. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. *Stroke* 2004;35(2):520–526. ■