Updates from the AHA/ASA statement on the rationale for the inclusion and exclusion criteria for tPA

Sapna Shah, PharmD

About the author: Sapna Shah recently published an article entitled “New Rationale Statement for tPA Inclusion and Exclusion Criteria” in the national online pharmacy publication, Pharmacy Times. We are pleased to publish excerpts from this article in our newsletter. The article can be read in its entirety online at: http://www.pharmacymtimes.com/contributor/sapna-shah-pharmd/2016/02/new-rationale-statement-for-tpa-inclusion-and-exclusion-criteria

Approximately 800,000 people in the United States experience a stroke yearly. Of these, more than 690,000 strokes per year are caused from decreased perfusion to an area of the brain due to a blood clot. Strokes cause 1 in 20 deaths among Americans becoming the 5th leading cause of death in the US. This critical and life threatening medical emergency requires urgent medical attention to prevent further damage to the brain. 1, 2

The American Heart Association/American Stroke Association (AHA/ASA) has partnered with hospitals nationwide to participate in the “Get with the Guidelines” initiative, which stresses the importance of maintaining the window of eligibility to administer tPA. During a stroke, every minute without treatment equates to losing close to 2 million neurons. IV alteplase also known as tPA (tissue plasminogen activator) lysed the blood clot, returning blood flow to the brain to prevent further injury and neurological deficit. 3, 4

The Joint Commission and AHA/ASA promote a 60 minute window (“the golden hour”) for the door-to-needle time for patients arriving to the emergency room subsequently diagnosed with stroke. Data collected by the “Get with the Guidelines” database showed only 5-8% of patients with stroke arrived within the tPA eligible time period. In addition, 77% of the tPA eligible patients were actually given tPA within the allotted time frame. Many clinicians attribute this number to the stringent inclusion and exclusion criteria associated with the use of tPA. 3, 4

Stroke experts nationally consider some of the exclusion criteria and/or contraindications to be relative, while others may be absolute; research showed that there was a broad variation among what would experts would or would not treat. The new AHA/ASA statement on the rationale for the inclusion and exclusion criteria tPA is meant to serve as a guide to practitioners to maximize the benefit of thrombolysis in patients with stroke. A strong emphasis is placed on ensuring the therapeutic benefit outweighs the risks. Each adverse event that has been outlined in the statement has been evaluated for substantial evidence behind the possibility of it occurring.5

The new recommendations allow for the use of tPA in elderly patients over 80 years of age although the risk of tPA therapy is increased with these patients > 80 years of age. Additional recommendations include patients with severe stroke, mild stroke, and prior stroke history. Patients with diabetes, hyperglycemia, and hypoglycemia are also now eligible for tPA. Lastly, patients with prior intracranial hemorrhage (not recent) may also be considered based on stroke, mild stroke, and prior stroke history. Patients with diabetes, hyperglycemia, and hypoglycemia are also now eligible with these patients > 80 years of age. Additional recommendations include patients with severe stroke, mild stroke, and prior stroke history. Patients with diabetes, hyperglycemia, and hypoglycemia are also now eligible for tPA.

An antibiotic is a chemical or a substance that inhibits the growth of, or kills bacteria. Antibiotics work by identifying the difference in bacteria and host cell structures. They prevent proliferation of the bacteria cells, allowing the immune system to fight off the remaining bacteria. This is carried out in a variety of ways, including inhibiting the synthesis of cells walls, proteins, and nucleic acids, as well as interfering with metabolic processes.

Our research was conducted using combinatorial chemistry. The advantage of this method is that it aims to synthesize a large library of compounds on a small scale and screen for a specific biological activity. In this case, we were focused on antibiotic growth using Escherichia coli. Resources were conserved by eliminating the need to individually synthesize, identify, and characterize compounds. Twenty-five compounds were able to be synthesized in a three to four hour time frame. Sixteen different hydrazones were formed by combining four different aldehydes with four different hydrazine derivatives in the presence of acid via a nucleophilic acyl substitution reaction.

Three of the four aldehydes were benzene rings which were substituted with an electron-withdrawing nitro group at the ortho, meta, and para positions, while the fourth aldehyde was a furan ring. Of the sixteen compounds that were tested, the lead active compound was found to be guanofuracin, prepared via a nucleophilic acyl substitution by treatment of commercially available 5-nitro-2-furaldehyde with aminoguanidine in the presence of acid. The process for this research involved an agar cup diffusion method, in which autoclaved agar plates were divided into three sections, with a well created in each section. The plates were then smeared with a strain of E. coli mixed in tryptic soy broth. Once the hydrazones were synthesized, 1% dimethyl sulfoxide was added to each one. Each hydrazone was then micropipetted into each well in the agar plates. Once completed, the plates were placed into an incubator for 24 hours. After these 24 hours, the plates were removed from the incubator in order to measure the zones of inhibition around each of the wells, which was a clear ring around the well that had inhibited the bacterial growth. The average diameter of each zone was measured in order to determine which hydrazone had the greatest antibacterial activity. The data showed that a 5-nitro substituent in conjunction with the heterocyclic furan aldehyde was more biologically active than its benzene aldehyde counterparts with various electron-donating or electron-withdrawing groups at the para-position. After conducting this research from fall 2013 through spring 2015 semesters, guanofuracin continuously proved to be the most active hydrazone.

References:
1. Ludvigsen R, Makar M, Milstein N, Carreon J (Faculty advisor). Synthesis of Hydrazones as Antibiotics. [Poster]

**Question:**
What is the difference between the tablet and capsule formulations of Depakote®?

**Answer:**
Depakote®, an anticonvulsant agent, is available in several dosage forms, including:
- delayed-release capsules (Depakote Sprinkles®)¹
- delayed-release tablets (Depakote®)²
- extended-release tablets (Depakote ER®)³

Due to multiple dosage forms with the same name, the potential for confusion and medication errors is very high with Depakote®. According to the United States Pharmacopeia (USP), delayed-release tablets and capsules are enteric coated so that the active medication is not released from the tablet until it has left the stomach. This is often done to prevent gastric mucosa irritation and to prevent the drug from being destroyed by gastric juices. Extended-release tablets, however, release the active drug over an extended period after swallowing, which means the contents of the tablet/capsule are released slowly, not all at once.⁴ As a result, dosing frequency varies for both; Depakote® DR is usually dosed more frequently, while Depakote® ER is usually dosed once daily.¹²³⁴

Depakote DR and Depakote ER are on the ISMP’s “Do not confuse” list as significant adverse events can result from confusing the two formulations.⁵ The best way to be mindful of a mix up and prevent these types of errors from happening is clarifying with the doctor, nurse, and pharmacist if there is a concern, as well as checking a home medication list if available to ensure the proper formulation is being ordered. Overall, there are two distinct formulations of Depakote® and they are NOT bioequivalent nor interchangeable.

Reference:
Recently Resident Program Director Carlo Lupano, co-resident Melanie Stewart and I had the opportunity to meet with Congressman Scott Garrett. As a pharmacy resident, I spend most days analyzing patient cases, preparing for rounds, and performing medication reviews. Thus, meeting with a Congressman to advance the pharmacy profession and improve the healthcare system as a whole, is considered an eventful day. During our discussion, I elaborated on our role in healthcare and provided concrete examples on how pharmacists play an intricate part in optimizing patient care. Our conversation ranged from medication streamlining to cost waste minimization. The aim of our discussion was to generate a stronger understanding of the various ways pharmacists could improve patient care while reducing costs, if recognized as providers.

The Pharmacy and Medically Underserved Areas Enhancement Act (H.R. 592/ S. 314) is bipartisan legislation that will amend the Social Security Act to include pharmacists on the list of recognized healthcare providers. As providers, pharmacists that undergo special post-doctorate training such as a PGY-1 residency or achieve a National Board of Pharmacy certification will be allowed to bill for their specialized services. The services include, but are not limited to: Medication Therapy Management (MTM), reducing emergency room and acute care visits by providing sound clinical counseling and reinforcement, and optimizing medication regimens through streamlining medication therapies.

As providers, pharmacists will be able to deliver care to patients in federally defined medically underserved areas. Historically, pharmacists are paid when providing and dispensing a prescription medication to a patient. However, much of our work, such as the aforementioned, goes undocumented and financially overlooked. This has major implications on the future of our profession and healthcare. Under the current system, pharmacists are performing their duty pro bono. Therefore, without recognition and payment, this can eventually shape the education we receive and the methods by which we practice. Consequentially, patients will not receive optimal care without properly trained pharmacists and this will contribute to the exponentially rising costs of healthcare. Following the enacting of the Affordable Care Act, there is and will continue to be a large influx of patients into our healthcare system. Therefore, we can further utilize the skills that pharmacists have developed through their Doctorate level education and professional experiences.

Recently in California, the SB 493 bill was passed and now specialized pharmacists are recognized as providers. Furthermore, pharmacists can bill for 15-minute MTM sessions, order labs, start/change/discontinue medications regimens pursuant to an order by a patient’s treating prescriber and in accordance with established protocols. This recognition of pharmacists sets the precedent for how pharmacist will be educated and practice as healthcare continues to evolve. Pharmacists acting as providers will lower the costs to the health care system. Currently, Americans pay about $290 billion dollars for medications, that figure could be substantially lowered by reducing some of the 1.5 million preventable medication related health care problems. No one is better equipped with the skills and education than a specially trained pharmacist who can help prevent and fix these problems.

As we continue to navigate through the complex intricacies of the healthcare system, recognition of pharmacists as providers will legitimize their expertise and provide financial reimbursement for their services.
Beta-blockers During the Perioperative Period

By: Melanie Stewart, PharmD

Within the Valley Hospital, nurses are trained to always administer a beta-blocker during the perioperative period to patients who were taking a beta-blocker prior to admission. Although this is ordinary practice within the hospital, many are unaware of why this standard is followed. This practice is based on the guidance from the Surgical Care Improvement Project (SCIP). The SCIP is a national partnership of organizations interested in improving surgical care by using evidence-based medicine to significantly reduce surgical complications. The SCIP guidelines contain a core performance measure that recommends that surgery patients on beta-blocker therapy prior to admission receive a beta-blocker during the perioperative period, defined as 24 hours prior to surgical incision through discharge from post-anesthesia care/recovery.

Beta-blockers bind to beta-adrenoreceptors and prevent the binding of catecholamines, such as epinephrine and norepinephrine, to these sites. This prevents the effects of the sympathetic nerve stimulation. Beta_1-receptors are found in the heart and kidney, and Beta_2-receptors are found in the lung, peripheral blood vessels, and skeletal muscles. Non-selective beta-blockers act on both the Beta_1 and Beta_2 receptors. Examples of non-selective beta-blockers are carvedilol, labetalol, propranolol, and nadolol. Selective beta-blockers act only on the Beta_1 receptors. Examples of selective beta-blockers include metoprolol, atenolol, bisoprolol, and nebivolol.

When undergoing surgery, the patient can experience stress from surgical trauma, anesthesia, pain, intubation or extubation, hypothermia, bleeding, anemia, and fasting. This stress on a patient’s body causes increased catecholamine and cortisol levels, which in hand leads to an elevated blood pressure, heart rate, free fatty acids and relative insulin deficiency. Under these conditions, the body requires an increased oxygen demand, which can lead to myocardial ischemia and perioperative myocardial infarction. Beta-blockers can prevent this cascade, as both non-selective and selective beta-blockers reduce heart rate and blood pressure, reduce ischemia, increase myocardial oxygen delivery, prevent or control arrhythmias, and can protect against plaque rupture. However, patients who are not on beta-blockers prior to surgery should not be initiated on beta-blocker therapy in the perioperative period, because the use is associated with increased risk of stroke, death, hypotension, and bradycardia. Patient’s taking a beta blocker prior to admission should be continued on a beta-blocker in the perioperative period because sudden withdrawal of this medication in patients with underlying coronary disease can lead to rebound hypertension, irregular heart rhythm, heart palpitations, shortness of breath, blood sugar abnormalities, accelerated angina, myocardial infarction and sudden death.

Both pharmacists and nurses can help to identify all patients who were on a beta-blocker prior to arrival by performing appropriate medication reconciliation upon admission. When completing medication reconciliation, it is important to determine when the patient took their last dose of beta-blocker prior to arrival, and to document a reason if the patient did not receive a beta-blocker within the perioperative period. It is also important to note that even if a patient is NPO, the patient should still receive their beta-blocker.

References: