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MISSOURI HOSPITALIST

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Hospitalist Update

New Oral Anticoagulant Options in the Treatment of Atrial Fibrillation

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The oral anticoagulant market has recently become a lot more crowded and warfarin is no longer the only option that practitioners will have to choose from. Dabigatran (Pradaxa) is an oral direct thrombin inhibitor that has received FDA approval for the treatment of patients with nonvalvular atrial fibrillation [1]. Rivaroxaban (Xarelto) and apixaban (Eliquis), both oral Factor Xa inhibitors, have also recently been studied in comparison to warfarin for patients with nonvalvular atrial fibrillation [2,3]. Rivaroxaban is currently FDA approved for postoperative prophylaxis in knee and hip replacements and there are active efforts to obtain FDA approval for atrial fibrillation; apixaban has yet to be approved by the FDA. A brief summary of major efficacy and safety trial data where all three of these new drugs were compared to warfarin (in patients with atrial fibrillation) is provided in table form on the following page.

First impressions of the trial data reveal positive outcomes for each of the three new oral anticoagulants; they all demonstrated non-inferiority for the primary outcome of stroke and systemic embolism when compared to dose adjusted warfarin. However, there is some essential safety data to evaluate along with important pharmacokinetic and pharmacodynamics issues to consider. Safety outcomes of major bleeding and hemorrhagic stroke were either improved on unchanged when the three agents were compared to warfarin. The incidence of hemorrhagic stroke, in particular, was reduced with all three novel anticoagulants; however, with both dabigatran and rivaroxaban, this benefit was offset by a statistical increase in major gastrointestinal bleeding. In fact, based on the calculated NNT and NNH, nearly two major GI bleeds will occur with dabigatran for every hemorrhagic and/or ischemic stroke that is prevented when compared to warfarin; if rivaroxaban was selected over warfarin, at least three major GI bleeds would occur for each stroke prevented. While strokes may be more clinically detrimental than a major GI bleed, it is important to consider this shift in the safety profile when selecting one of these two agents over warfarin, especially in patients with a history of peptic ulcer (cont)

(cont) disease or past GI bleeding. Lastly, since there is no required monitoring of the anticoagulation effect with any of the these new agents nor a readily available antidote, particular attention should be paid to the effects of liver and renal impairment and drug interactions on the change in AUC (total drug exposure) for each of the novel oral anticoagulants [4-7].

New Oral Anticoagulants Compared to Dose-Adjusted Warfarin for Nonvalvular Atrial Fibrillation

Outcome*	Stroke and Systemic Embolism (Primary Outcome)	Ischemic Stroke	Major Bleeding†	Hemorrhagic Stroke	Major GI Bleeding	Hospitalization	Death
	% per year	% per year	% per year	% per year	% per year	% per year	% per year
Dabigatran 150mg bid	1.11vs. 1.69 NNT: 173	0.92 vs. 1.20 NNT: 358	3.11 vs. 3.36 NSD	0.10 vs. 0.38 NNT: 358	1.51 vs. 1.02 NNH: 204	20.2 vs. 20.8 NSD	3.64 vs. 4.13 NSD
Rivaroxaban 20 mg daily	2.1 vs. 2.4 NSD	1.34 vs. 1.42 NSD	3.6 vs. 3.4 NSD	0.26 vs. 0.44 NNT: 556	1.96 vs. 1.34 NNH: 162	Not reported	1.87 vs. 2.21 NSD
Apixaban 5mg bid	1.27 vs. 1.60 NNT: 303	0.97 vs. 1.05 NSD	2.13 vs. 3.09 NNT: 105	0.24 vs. 0.47 NNT: 435	0.76 vs. 0.86 NSD	Not reported	3.52 vs. 3.94 NNT: 238

***Outomes reported as the experimental event rate vs. warfarin (INR 2-3) event rate**
Major bleeding included Hgb fall ≥ 2 g/dL, transfusion of≥ 2 units, bleeding in a critical area or fatal bleeding
NNT=number needed to treat for new oral anticoagulant NNH =number needed to harm for new oral anticoagulant
NSD=no statistically significant difference

New Oral Anticoagulant Pharmacologic & Pharmacodynamic Characteristics

PK/PD Parameter	Dabigatran	Rivaroxaban	Apixaban
Bioavalability	3-7%	80-100%	66%
Protein Binding	35%	92-95%	87%
Metabolism	Esterase-catalyzed hydrolysis (dabigatran etexilate to dabigatran)	Hepatic CYP450 3A4, 3A5 & 2J2	Hepatic cyp450 3A4
Excretion	Renal (80% as unchanged drug)	Renal (36% unchanged)	Renal (25% unchanged)
Half-life:			
CrCl >30cc/min	12-17 hrs	5-9 hrs	12 hrs
CrCl ≤30cc/min	27.5 hrs	9.5 hrs	not reported
AUC & CrCl			
CrCl 50-79	AUC increased 75%	AUC increased 44%	not reported
CrCl 30-49	AUC increased 174%	AUC increased 52%	not reported
CrCl 15-29	AUC increased 583%	AUC increased 64%	not reported
AUC & Child-Pugh			
Score A	Negligible AUC change	AUC increased 15%	not reported
Score B	Negligible AUC change	AUC increased 127%	not reported
BMI extremes	Unknown effect on AUC	Little or no correlation	not reported

(continued)

AUC & Relevant Drug Interactions

	Dabigatran	Rivaroxaban	Apixaban
	P-glycoprotein (P-gp) mediated	CYP450 3A4 & P-gp	CYP450 3A4 & P-gp
Enzyme Inhibitors:	Amiodarone (AUC up 58%)	Ketoconazole (AUC up 160%)	Not Reported
	Dronedarone (AUC up 1.7-2x)	Ritonavir (AUC up 150%)	
	Verapamil (AUC up 2.4x)	Clarithromycin (AUC up 50%)	
	Ketoconazole (AUC up 153%)	Erythromycin (AUC up 30%)	
Enzyme Inducers:	Rifampin (AUC down 66%)	Rifampin (AUC down 50%)	Not Reported
Pharmacodynamic:	Pantoprazole (PPIs)	None identified	Not Reported
	- AUC down 22%		

Patients were excluded in the dabigatran and rivaroxaban studies if their creatinine clearance (CrCl) was less than 30 cc/min and less than 25 cc/min in the apixaban study. Although the FDA did approve a reduced dose of dabigatran (75mg BID) for patients with a CrCl of 15-20 cc/min, it was done so based on pharmacokinetic data. Until properly designed studies report patient-oriented outcomes data which demonstrate safety and efficacy, great caution should be used with all of these agents in patients with a CrCl of less than 30cc/min. Similarly, it would be advisable to avoid noted drug interactions and concomitant use of dual antiplatelet therapy as safety and efficacy could also be significantly affected. In summary, after more than 50 years, clinicians now have alternatives to warfarin therapy for preventing stroke in patients with atrial fibrillation. These new oral anti-coagulants possess some improvements over the standard of care but are not without their own limitations. Only careful selection of patients, based on specific inclusion and exclusion criteria from the respective trials, will ensure similar risk-benefit rations in real-world practice.

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7. Stangier, J et al., Influence of Renal Impairment on the Pharmacokinetics and Pharmacodynamics of Oral Dabigatran Etexilate, Clin Pharmacokinet 2010; 49:259-268

CASE OF THE MONTH Drs. Imran Ashraf, Delene Musielak, Shafaq Paracha, Sonya Addison & Monika Arya

A 79 year old Caucasian female was transferred to University Hospital from an outside facility due to progressive weakness in her extremities over several weeks, spreading from her legs to her arms; at the time of admission, she was unable to walk, She also complained of urinary incontinence over the past week and reported an intermittent pounding headache, associated with photophobia and phonophobia. The patient denied any history of trauma and had not experienced back pain, spinal problems, visual problems, sensory deficits, speech disturbance or dysphagia. Her husband reported that she had been confused at times and that her memory had recently become impaired.

There was no history of recent fever, chills, night sweats or acute infection. No new medications were recently started and she did not recall any insect bites. There were no known sick contacts and no family history of similar musculoskeletal problems. Recent travel had been limited to Texas where she and her husband have a winter home.

The patient's past medical history was remarkable for hypertension, hyperlipidemia and two episodes of pneumonia in the past four months. She was diagnosed with colon cancer in 2002 which was treated with a partial colon resection; a follow-up colonoscopy in 2005 was normal and no other signs of recurrence had been documented. Other past surgeries included a hysterectomy, cataracts and a cholecystectomy. The patient is a former smoker but quit 20 years ago; alcohol use is limited to a glass of wine with her evening meal and she denied illicit drug use. She had been very active prior to the onset of her weakness and was still playing golf several months prior to admission. She lives with her husband; they have a summer home in Missouri and a winter home in Texas.

Admission vitals revealed T 36.2, P 87, R 18, BP 129/70, O2 sat 92% on RA. No rash or jaundice were noted and no meningeal signs were present. Her chest was clear, cardiovascular exam was normal and the abdomen was unremarkable. She was alert and cooperative; her speech was normal and cranial nerve function was intact bilaterally. Muscle strength was 3/5 in her proximal extremities and 4/5 distally; DTRs were diminished bilaterally but sensation, including vibration, was intact. Finger-nose testing was normal but her response was slow. Gait could not be assessed since she was unable to stand or walk.

Admission labs revealed WBC 10.3 (75 G, 13 L, 6 M, 4 E, 1 Baso), Hgb 13.3, MCV 88.2, Platelet Count 341, serum Na 125 (plasma osmolality 262, urine 744), K 4.1, glucose 102, BUN 15, Cr 0.45, Ca 9.7, normal LFTs, serum albumin of 4.0 and normal B12 and folate. CEA, AFP and CA-19 were normal. A lumbar puncture was performed which returned a WBC of 1050 (72 L, 3 E), RBC 200, Prot 338, G 21; the CSF was negative for HSV by PCR and AFB; India ink stain was negative and no fungal organisms were seen. Histoplasmosis antigen and VDRL were negative and her drug screen was unremarkable.

A PET/CT demonstrated nonspecific FDG uptake corresponding to a nodular lesion in the posterior aspect of the left lower lobe and the presence of multiple mediastinal and left hilar lymph nodes. An MRI of the brain did not show any restricted diffusions or abnormal enhancement; chronic small vessel disease and tiny, old infarcts in the basal ganglia and thalamic area were noted. An MRI of the spine revealed cervical spondylosis at C5-6 but no evidence of cord compression. A CT of the abdomen-pelvis was normal except for possible wall thickening in one area of the sigmoid, thought to be consistent with under-distention. Finally, a CT-guided biopsy of the pulmonary nodule revealed Cocciodes immitis.

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Infectious Disease was consulted and they agreed that her symptoms and clinical findings were consistent with Coccidiomycosis meningitis. They recommended that she be started on fluconazole, initially 400 mg BID and then 400 mg daily for life. The patient was discharged to a skilled nursing facility for recuperation and rehabilitation and she was scheduled for follow up by both Neurology and Infectious Disease.

DISCUSSION: Coccidioidomycosis is an infection caused by dimorphic fungi, either Coccidioides immitis or Coccidioides posadasii. Endemic to the Southwest U.S., from California to West Texas, this fungus is known for causing "Valley Fever" and "Desert Rheumatism." Infection with Coccidioides is via inhalation of spores; while most patients remain asymptomatic, some develop symptoms and clinical findings consistent with community acquired pneumonia. The pneumonia develops within 7-21 days of infection and may be associated with erythema nodosum or erythema multiforme; fatigue may persist for months. The primary infection may become disseminated, especially in immunocompromised patients, and can result in meningitis.

While Coccidioides causes more than 150,000 cases of symptomatic infection in the U.S. each year, less than 100 cases of Coccidioidal meningitis occur; if untreated, this CNS infection has a mortality rate of 95% within 2 years. The most common early symptom of Coccidioidal meningitis is a persistent headache and clinical findings may be absent early in the course; indeed, meningeal signs are uncommon. Over time, tremulousness, gait abnormalities and focal neurologic deficits may develop; the presence of papilledema suggests elevated intracranial pressure and/or hydrocephalus. Lab findings often include hyponatremia, secondary to SIADH, and nonspecific abnormalities such as a mild leukocytosis, peripheral eosinophilia and an elevated ESR. The CSF generally reveals the presence of leukocytes (predominantly lymphocytes), a low glucose and elevated protein; eosinophils may also be present. It is very difficult to isolate Coccidioides in the CSF and the diagnoses is often presumptive, based on the above findings and on the presence of anticoccidioidal antibodies.

Treatment of Coccidioidal meningitis is usually with fluconazole 400 mg per day; other options include itraconazole 200 mg BID or TID and intrathecal Amphotericin B (with or without an azole). The documentation of response to therapy is primarily based on a gradual improvement in symptoms. The CSF may be monitored after several weeks to demonstrate a gradual rise in glucose and follow-up serology can be helpful; a significant rise in antibody titer may correlate with progression of the disease. Serial MRIs of the brain and spine are recommended over the first two years to look for signs of focal infection or secondary complications and follow-up chest imaging should be performed to check for evidence of cavitation. In almost all cases, fatigue and weakness persist for weeks or months.

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FROM THE JOURNALS

KYLE MOYLAN MD

Azithromycin for Prevention of Exacerbations of COPD

Albert, RK et al., NEJM 2011; 365:689-698

COPD exacerbations are frequently encountered by hospitalists and more effective strategies for prevention are needed. This randomized controlled trial tested the hypothesis that daily antibiotics could prevent acute COPD exacerbations; patients received azithromycin 250 mg or placebo daily. Those receiving azithromycin had fewer exacerbations, including the proportion of patients who went 1 year without an exacerbation (68% vs. 57%). However, patients receiving azithromycin developed more macrolide resistance and hearing impairment.

Holter Monitoring in syncope: diagnostic yield in octogenarians

Kuhne, M et al., J Am Geriatr Soc 2011; 59(7): 1293-1298

In this retrospective study, the medical records of 475 octogenarians who wore a Holter monitor for the evaluation of syncope were reviewed; abnormalities were found in 16.6% but only 11% were thought to be diagnostic. The author reports that the rate of similar abnormalities in patients < 80 years of age was 6%. This retrospective study cannot prove that the abnormalities caused the syncope but reinforces the fact that the evaluation of syncope is complex and should be guided by a careful history and physical before embarking on a reflexive workup. Other studies have demonstrated that the measurement of orthostatic blood pressure is one of the highest yield diagnostic tests and, of course, is much less expensive.

Trimethoprim-sulfamethoxazole induced hyperkalemia in elderly patients receiving spironolactone: nested case control study

Antoniou, T et al., BMJ 2011; 343:d5228 doi: 10.1136/bmj.d5228 (*Original*) PMID: 21911446

Trimethoprim is structurally similar to amiloride and can induce hyperkalemia via reduced tubular excretion. This case-control study examined almost 7000 admissions for hyperkalemia. Patients taking spironolactone who were given trimethoprim-sulfa had a 12-fold increased risk of admission for hyperkalemia compared to patients given amoxicillin. For patients on spironolactone who develop a UTI, the authors estimate that 60% of admissions for hyperkalemia could be avoided if trimethoprim was not used.

Risk of fractures requiring hospitalization after an initial prescription for zolpidem, alprazolam, lorazepam or diazepam in older adults

Finkle, WD et al., J Am Geriatr Soc doi: 10.1111/j.1532-5415.2011.03591.x

Zolpidem has been increasingly used as a "safe alternative" to benzodiazepines as a sleep aid in elderly patients. This retrospective cohort study demonstrated that new prescriptions for zolpidem were associated with an increased risk of nonvertebral fractures and dislocations; in fact, the risk of injury with zolpidem exceeded risks for alprazolam and lorazepam. There is currently no safe sedative-hypnotic for older patients with insomnia.

ID CORNER

WILLIAM SALZER MD

GUIDELINES FOR USE OF ANTIMICROBIALS IN NEUTROPENIA

The IDSA has updated its practice guidelines for the management of febrile neutropenia in cancer patients: Freifeld, AG et al., Clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by Infectious Disease Society of America, Clin Infect Dis 2011; 52:e56-e93

http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/FN.pdf

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MISSOURI HOSPITALIST CALENDAR

Pulmonary Vascular Symposium, October 15, 2011, Eric P. Newman Education Center, Washington University Medical Center and Kansas University Medical Center; register at http://cme.wustl.edu **LOCAL**

Kidney Disease: Management for Primary Care Providers, October 22, 2011, Eric P. Newman Education Center, Washington University School of Medicine; register at http://cme.wustl.edu **LOCAL**

Recent Advances in the Management of Valvular Heart Disease, October 29, 2011, Ritz-Carlton, St. Louis, Washington University School of Medicine; register at http://cme.wustl.edu **LOCAL**

Update in Hospital Medicine, Daniel Dressler MD, MSc, SFHM, Society of Hospital Medicine, St. Louis Chapter Meeting, Chase Park Plaza, St. Louis, November 10, Meet & Greet at 6:30 PM, Dinner at 7:30 PM. RSVP via phone at 314-362-1707 or via email: MRussell@dom.wustl.edu **LOCAL**

Please direct all comments, ideas and newsletter contributions to the Editor:

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Please forward this newsletter to Hospitalists that you might know!