Show-Me SCRIPT

Missouri Society of Health-System Pharmacists Bi-Monthly Newsletter

FEBRUARY 2015

Diane's Musings

by Diane McClaskey, RPh, BCPS

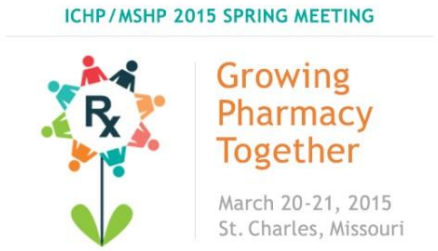
Greetings, everyone! Are you enjoying the milder weather? Winter is my favorite season; however, I'm thankful we are not getting what the Northeast is right now! I am enjoying that the daylight is getting longer now, too! I've got all of the gardening catalogs lined up for this weekend to start planning what I'll be planting. Who knew there were so many varieties of cucumbers? It sure is fun to try different varieties to see what works the best in my amended Ozark soil. If only there was a market for rocks!

I wanted to take a minute and send out a very special thank you to UMKC School of Pharmacy and the St. Louis College of Pharmacy. Each year, they help MSHP sponsor a wonderful reception at ASHP Midyear. And this year was no exception! The food was delicious, the fellowship was even better, and it was a delight to highlight the colleges and the students involved in the Clinical Skills Competition. So the next time you see Dr. Pieper from St. Louis and Dr. Melchert from UMKC, please let them know just how much we appreciate their continued support of MSHP. Gentlemen, thank you!

As you know, the Missouri Legislative Session is in full swing. And even though it was a successful year for pharmacy last year, we still need to continue working for our patients in Missouri. Do you know who is your Representative and Senator is for your district? Here is a great tool for looking up your Senator: http://www.senate.mo.gov/LegisLookup/default.aspx/leg_lookup.aspx and your Representative: http://www.house.mo.gov/legislatorlookup.aspx. It's easy to reach out to them, and they want to hear from you! Last year, a technician was meeting with their local senator and they were discussing preparing chemotherapy. The senator asked if they received enough training, and the technician stated that they would like more. It was a great opportunity for the senator to get an idea of what health-system pharmacy technicians in Missouri are currently doing. Also, your Public Policy team from MSHP is closely watching the issues as well. Christine Swyres (cms8937@bjc.org) is the Chair and David Wolfrath (wolfrathd@health.missouri.edu) is the Vice-Chair for that group, and they meet monthly to discuss key items. Please don't hesitate to reach out to them to discuss concerns.

Before I close, will I get to see you in March? It's time for our Spring Meeting, and I would love to see everyone and get a chance to visit! The meeting dates are March 20-21, and it will be held in St. Charles, MO. MSHP is co-hosting with Illinois, and it is going to be a great meeting! It's a little earlier this year, so I wanted to get this reminder out to you – time is going fast! Here is a link for meeting registration: https://events.ichpnet.org/events/ichpmshp-2015-spring-meeting-register/.

I'll see you in St. Charles!
Diane



Featured Job Posting on Page 11!

Table of Contents:

Hospital Pharmacy Regulatory Update

by Bert McClary, RPh

SB 808 Implementation

The relationships between health system entities based on ownership, operations responsibility and facility location create difficulties in the interpretation of Board of Pharmacy and Department of Health and Senior Services rules for distribution of medications, prescription and medication order processing, and MTS protocol implementation. One goal of the SB 808 legislation was to provide flexibility within health systems in performing these activities, resulting in better and more efficient patient care. Now that the statutory language is in place, it is important to provide guidance for its implementation.

MSHP and others have requested that BOP reconvene the Hospital Pharmacy Working Group that developed the language for SB 808. The Missouri Hospital Association invited about 20 pharmacists, administrators and regulatory agency representatives to participate in a telephone conference to prioritize the issues. The group focused on four areas: the new Class B hospital pharmacy license, MTS, distribution of medications between health system facilities and joint rulemaking by BOP and DHSS. A follow-up survey asked the participants to rank the importance of questions based on these four areas. The survey questions were provided to BOP for discussion during a BOP webinar scheduled for January 23. Since the deadline for this newsletter issue is prior to the webinar date, a summary of the presentation will be provided in the next newsletter. The recorded presentation will be made available to those who were unable to participate in the webinar.

Pharmacy Technicians

One of three professional development objectives in the current MSHP Strategic Plan is development of technician training standards that will support expanded technician practice roles. In 2009 MSHP joined the ASHP Pharmacy Technician Initiative, formed a technician committee that developed a position statement advocating for nationally accredited education, training and certification, and forwarded the statement to the BOP. This resulted in a BOP public forum on technicians with published minutes, and a 2011 BOP Working Group that thoroughly evaluated current technician training and activities. The Working Group was not allowed to discuss expanded roles, but did produce a list of prohibited activities. The Working Group discussions of training and prohibited activities became the basis in 2013 for language that BOP hopes to publish as a proposed rule.

Because of continued requests from MSHP members for advanced practice activities by technicians, this became a priority Strategic Plan objective and the Public Policy Committee formed a technician subcommittee to develop a draft proposal. Discussions in the technician subcommittee and the Public Policy Committee have focused on a future standard requiring nationally accredited training and certification, recognition of different levels of technician authority and responsibility, interim recommendations for education and training because of the limited number of accredited training programs in Missouri, and renewed discussions of technician roles among state pharmacy, health care and regulatory organizations. The committee hopes to have a draft proposal finalized in February for the MSHP executive board, to then be distributed to the membership for input.

MSHP R&E Foundation News

by Laura Butkievich, PharmD, BCPS

Happy New Year for the MSHP Research and Education Foundation! The R&E Foundation has been busy planning many upcoming activities that will occur over the next couple of months. Here we will highlight some of these events.

Call for Research Posters and Platform Presentations

The MSHP Annual Meeting will be held March 20-21, 2015 in St. Charles, MO and the R&E Foundation will be sponsoring the annual poster and platform presentation sessions. All MSHP members and students enrolled in a Missouri School of Pharmacy are eligible to submit abstracts. The research

categories to submit under include: original research, research in progress, encore presentation, and student presentation. The four abstracts with the highest review scores in the original research category will be invited to deliver platform presentations on their research at the annual meeting. Awards will be given for the following categories:

- **Best Platform Presentation** - $250 (one award)
- **Platform Presentation** - $100 (three awards)
- **Best Original Poster** - $200
- **Second Place Original Poster** - certificate
- **Best Encore Poster** – certificate
- **Best Student Poster** - $100

Please consider submitting your research for a poster or platform presentation. This is a great opportunity for practitioners, residents, and students to share their research with colleagues. The **deadline for abstract submission is February 1, 2015.** Please see the MSHP website for additional details: http://www.moshp.com/education/.

Call for Best Practice Award Submission

The R&E Foundation will be awarding the Best Practice Award at the MSHP Annual Meeting. This award recognizes innovation and outstanding performance in pharmacy practice. **This year's theme is: "What innovative practices have health-systems utilized to better manage drug shortages?"** If you or your organization is working on a project related to this year's theme, please consider submitting your work for this award. The recipient of this award will present their project and be honored at the R&E Foundation breakfast at the MSHP Annual Meeting. **Deadline to submit a project for this award is February 1, 2015.** Directions for submission can be found on the MSHP Website.

Call for Thomas J. Garrison Award Nominations

The Garrison Award was established in 1985 to recognize individuals who have had sustained contributes to MSHP and pharmacy practice within the state of Missouri. Deserving candidates have contributed in multiple ways to include:

- Outstanding accomplishment in practice in health-system pharmacy;
- Outstanding poster or spoken presentation at a state or national meeting;
- Publication in a nationally recognized pharmacy or medical journal;
- Demonstrated activity with pharmacy students from St. Louis or the UMKC Schools of Pharmacy;
- Development of an innovative service in a health-system pharmacy in either education, administration, clinical service, or distribution;
- Contributions to the profession through service to ASHP, MSHP and/or local affiliates

Please consider nominating someone for this prestigious MSHP award. Directions for nominee submission can be found on the MSHP website. **Deadline for submission of nominees is February 1, 2015.**

Call for R&E Board Nominations

Two Board Member positions for the MSHP R&E Foundation will be expiring 2015. R&E Foundation Board Members participate in monthly calls to discuss and plan activities of the MSHP R&E Foundation. Please consider nominating yourself or a colleague to apply for one of these open positions. Nominations can be submitted to Andy Smith at smithandr@umkc.edu.

Research Corner

Are you or a colleague in your organization doing some interesting research? If so, consider being highlighted on the R&E Foundation Research Corner located on the MSHP website. (http://www.moshp.com/research-education-foundation/research-corner/). If you or someone you know is willing to share your research with colleagues throughout the state of Missouri, please contact Paul Juang at paul.juang@stlcop.edu.

R&E Foundation Donation

Many activities are produced by the R&E Foundation that support the research and education efforts of Missouri health-system pharmacists. Consider making a donation to support these ongoing activities. A donation to the MSHP R&E Foundation can be made online or by downloading the pledge card on the MSHP website. Click the following link to be directed to the site: http://www.moshp.com/research-education-foundation/contributors/. Thank you for your support!

Member Spotlights

Congratulations to the following members who have been recently recognized:

Megan Musselman, PharmD, MS, BCPS was recently published:

- Thomas MC, Musselman ME, and Shewmaker J. "Droperidol for the treatment of acute migraine headaches." **Ann Pharmacother**. 2015; 49(2): 233-40.

GKCSHP recently recognized several members:

- Pharmacist of the Year: **Michael Kallenberger, PharmD, BCPS**
- Student of the Year: **Annie Heble, PharmD Candidate** – KU School of Pharmacy
- Technician of the Year: **Dave Campbell**

MSHP would also like to welcome **Robin Moser** as our new Executive Director with Centric!

Pharmacy School Update

by Dean Bruce Canaday, STLCOP

150th Celebration

St. Louis College of Pharmacy recently celebrated 150 years of educating future pharmacy innovators and practitioners. The highlights of the sesquicentennial events were a black-tie gala and a convocation featuring John Gans, Pharm.D., associate dean at Philadelphia College of Pharmacy and former executive vice president and chief executive officer of the American Pharmacists Association. It I was wonderful seeing so many familiar faces in attendance who have contributed so much to the profession in this state and across the country.

STLCOP CARES

Many students, faculty, and staff also contributed their time to the largest STLCOP C.A.R.E.S. initiative (Community Awareness Reaching Everyone in St. Louis) ever held. This annual event focuses on making a difference in the community. Our students conducted medication reviews and health screenings in a variety of settings across the region and volunteered at numerous community service projects. In all, they contributed thousands of hours of their time and helped improve the lives of hundreds of people across our region.

Service recognition

Our commitment to community service has been recognized by the federal government. The College was recently named to the 2014 President's Higher Education Community Service Honor Roll. The program is administered by the Corporation for National and Community Service (CNCS). In addition to helping patients get the most out of their medicine, the College is a recognized leader in the efforts to safely remove and dispose of medications from the home.

Members of the College community also regularly volunteer to clean up parks and other public spaces around the region, wrap Christmas gifts for children in need, and fill donated book bags with school supplies.

Building progress

Even in the depths of winter construction on our 213,000 square foot academic and research building and library continues. I am happy to say we have passed the halfway point. We remain on schedule to open this summer. It is an exciting time at the College. I invite each of you to come by and see what we are doing in support of, and to advance, the profession.

Featured Articles:

Strategies for Emergently Reversing Oral Anticoagulation

Brandon P. Mullins, PharmD – Clinical Pharmacy Specialist – Critical Care – St. Luke's Hospital – St. Louis

The arrival of the new oral anticoagulants (NOACs) dabigatran, rivaroxaban and apixaban has given prescribers new options for treating coagulation disorders. As with all anticoagulants, the NOACs pose a risk of hemorrhage with the risk of life-threatening bleeding ~2%.[1-3] Currently, pharmaceutical manufacturers are working on developing medication-specific reversal agents for these new products, but availability will likely be delayed several years before obtaining FDA approval. Until recently, warfarin was the go-to oral anticoagulant for patients that required long-term anticoagulation. With the FDA-approvals of the NOACs, the use of warfarin is likely decreasing in favor of the new agents. While the concern of bleeding is relatively the same with the newer agents compared to warfarin, the NOACs currently have no direct reversal agent such as vitamin K for warfarin reversal.

This article will discuss the current literature surrounding reversal of the NOACs as well as the newly available reversal agent for vitamin k antagonists (VKA), Kcenta®.

VKA reversal – Kcentra® (4-factor Prothrombin Complex Concentrate)

A new agent that has gained FDA-approval for reversing vitamin VKAs in acute, major bleeding is now available.[4] In a phase III, multicenter, open-label, non-inferiority trial, patients who needed urgent VKA reversal were treated with either Kcentra® (4-factor prothrombin complex concentrate [PCC]) or plasma.[5] Effective hemostasis was achieved in 72.4% of patients that received 4-factor PCC compared to 65.4% of plasma patients achieving non-inferiority. Rapid INR reduction (INR<1.3 at 30 minutes) was achieved for 62.2% of patients receiving 4-factor PCC compared to only 9.6% of plasma patients, demonstrating superiority (difference, 52.6% [95% confidence interval, 39.4 to 65.9]). It is important to note that all patients in this trial also received vitamin K as the pro-hemostatic effects of 4-factor PCC will not last beyond 24 hours. Equally as important to note, Kcentra® is contraindicated in known heparin-induced thrombocytopenia given the medication contains small amounts of heparin. In addition to FDA-approval, the Chest guidelines recommend patients with VKA-associated major bleeding have anticoagulation reversed with four-factor PCC rather than with plasma.[6]

Pradaxa® (dabigatran)

Dabigatran is the only oral direct thrombin inhibitor on the market in the United States. It is FDA-approved for the treatment of DVT/PE and for prevention of stroke due to atrial fibrillation. Currently, there is sparse data to suggest a pharmacologic antidote for dabigatran-induced bleeding. Eerenberg and colleagues evaluated the reversal of dabigatran's anticoagulant activity in 12 healthy male volunteers.[7] Subjects were given dabigatran 150 mg twice daily for 5 doses followed by a 50 unit/kg dose of 4-factor PCC. The observed elevation in the activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), and thrombin time was not reversed after receiving the dose of PCC. A case report by Dager and colleagues, describes a patient treated with dabigatran that developed severe bleeding secondary to drainage of cardiac tamponade after undergoing an ablation procedure.[8] The patient received a 26 unit/kg dose of factor eight inhibitor bypassing activity (FEIBA®) with cessation of bleeding occurring soon after initiation of the infusion. Lastly, in an *ex vivo* study of blood samples obtained after a single dose of dabigatran given to healthy volunteers, authors reported that both FEIBA and recombinant factor VIIa (rFVIIa) normalized prolongation of lag time whereas 4-factor PCC did not.[9] With the paucity of literature regarding pharmacologic reversal of dabigatran, a strong (or even moderate) recommendation cannot be made for one agent over the other. It is important to note that in acute ingestions activated charcoal should be used if dabigatran has been taken within two hours.[10] Additionally, hemodialysis can be an effective means of eliminating dabigatran from the circulation, with a reduction of serum concentrations up to 60% given dabigatran's lower protein binding.[11]

Factor Xa Inhibitors - Xarelto® (rivaroxaban) and Eliquis® (apixaban)

Rivaroxaban and apixaban are the only two oral factor Xa inbihitors (fXaI) on the market in the United States, although edoxaban is likely to be available soon. These agents have gained FDA approval for the treatment of DVT/PE, prevention of stroke due to atrial

fibrillation as well as postoperative thromboprophylaxis after hip or knee replacement. Similar to the literature surrounding dabigatran reversal, the available data for pharmacologic reversal of the fXaI is equally as unimpressive. In the aforementioned study by Eerenberg and colleagues, the reversal of rivaroxaban was also evaluated in the same patients after a washout period.[7] Patients received rivaroxaban 20mg twice daily for five doses followed by the same 50 unit/kg dose of 4-factor PCC. Contrary to what was observed with dabigatran-treated patients, the 4-factor PCC reversed the elevated prothrombin time (PT) and ECT in the rivaroxaban treated patients. In a similar ex vivo study, blood from healthy patients who were administered rivaroxaban was subsequently treated with different non-specific reversal agents.[12] Both FEIBA and 4-factor PCC reversed the rivaroxaban-induced effects on the endogenous thrombin potential (ETP). The author's stated that these results should be taken with caution because in a rabbit model the reversal agents were not successful in reducing bleeding.[12] While these results might shed a more favorable light on the use of PCC for the reversal of the fXaI, this cannot be conclusively stated until randomized, phase-III trials have been conducted. Unlike with dabigatran, dialysis is not effective at reducing concentrations of the fXaI as these medications have higher protein binding. In acute ingestion, activated charcoal should be considered if within two hours of the dose.

The use of oral anticoagulants is a necessity for patients with coagulation disorders. With the increasing life expectancy and the ever-growing population of elderly patients it can be expected that the number of patients with need for anticoagulation will continue to increase. Future studies should be aimed at identifying effective means of rapidly reversing the effects of the NOACs. Until that time, we are left with difficult decisions about whether or not to use these pro-hemostatic agents for life-threatening bleeding due to NOACs.

References:

1. Pradaxa® [package insert]. Burlington, Ontario, Canada: Boehringer Ingelheim Canada Ltd; 2014.
2. Xarelto® [package insert]. Toronto, Ontario, Canada: Bayer Inc; 2014.
3. Eliquis® [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2014.
4. Kcentra® [package insert]. Kankakee, IL: CSL Behring; 2013.
5. Marlu R, Hodaj E, Paris A, et al. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban. A randomised crossover ex vivo study in healthy volunteers. *Thrombosis and Haemostasis*. 2012;108:217-224.
6. Guyatt GJ, Akl EA, Crowther M, et al. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012 Feb;141(2 Suppl):7S-47S.
7. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate. *Circulation.* 2001;124:1573-79.
8. Dager, WE, Gosselin RC, and Roberts AJ. Reversing Dabigatran in Life-Threatening Bleeding Occuring During Cardiac Ablation with Factor Eight Inhibitor Bypassing Activity. *Critical Care Medicine*. 41(5):e42-e46.
9. Marlu R, Jodaj E, Paris A, et al. Effect of Non-Specfic Reversal Agents on Anticoagulant Activity of Dabigatran and Rivaroxaban: a Randomized Crossover ex vivo Study in Healthy Volunteers. *Thrombosis and Haemostasis.* 2012;108:217-24.
10. Alikhan R, Rayment R, Keeling D, et al. The acute management of haemorrhage, surgery and overdose in patients receiving dabigatran. *Emergency Medicine Journal*. 2014;31(2):163-8.
11. Wagner F, Formella S, Weigart E, et al. Effective elimination of dabigatran with haemodialysis: a phase I single centre study in patients with end stage renal disease. *Thrombosis and Haemostasis.* 2013;109(4):596-605.
12. Sarode R, Milling T, Refaai M, et al. Efficacy and Safety of a 4-Factor Prothrombin Complex Concentrate in Patients on Vitamin K Antagonists Presenting With Major Bleeding. *Circulation*. 2013;128:1234-1243

New Oral Anticoagulants and Preoperative Management

Ashley Ausmus, Pharm.D., BCPS; Thomas Sandifer, Pharm.D., BCPS – University of Missouri Health System

University of Missouri Health System

Background

Preoperative management of patients who are chronically anticoagulated has always been a topic of discussion. A benefit to using the new oral anticoagulants (NOACs) over vitamin K antagonists (VKAs) for diseases such as atrial fibrillation and thrombosis has been the lack of need to monitor for therapeutic levels. However, lack of monitoring also indicates a lack of ability to ensure safe levels of medication in the preoperative setting, when weighing a patient's risk of bleed versus clotting is often imperative for best management. With increasing use of NOACs, an understanding of their pharmacokinetics and how this affect preoperative management is necessary.

The primary goal when managing any anticoagulated patient preoperatively is to weigh their risk of bleeding versus their risk of thromboembolism. The purpose of this review will be to help provide guidance in how to stratify these risks and to review parameters that should be considered to make patient-centered decisions in the management of patients chronically anticoagulated with a NOAC prior to surgery.

Risk of thromboembolism

There are many suggested tools often used to help quantify the risk of thromboembolism. The first step is to evaluate the patient's reason for chronic anticoagulation. For patients with risk factors for venous thromboembolism (VTE), it is important to determine if this is the patient's first incidence or if it is a recurrence, and in what time period the patient has been previously anticoagulated. For patients with atrial fibrillation on a NOAC for stroke prevention, use of a scoring tool such as $CHADS_2$ or CHADS2-VaSC is recommended.[5,6] The CHEST guidelines suggest risk stratification for atrial fibrillation and VTE.

Table 1: Risk Stratification for Thromboembolism[1]

Risk Stratification	Indication for NOAC	
	Atrial Fibrillation	Venous Thromboembolism
High	$CHADS_2$ score of 5 or 6 $CHADS_2$-VASC score of Recent stroke/TIA ≤3 months	Recent VTE ≤3 months
Moderate	$CHADS_2$ score of 3 or 4 $CHADS_2$-VASC score of No recent or previous stroke/TIA	Previous VTE (within 3 to 12 months) Recurrent VTE
Low	$CHADS_2$ score of 2 or less $CHADS_2$-VASC score of No prior stroke or TIA	Previous VTE (>12 months) and no other risk factors

Evaluating risk of preoperative bleeding

When considering risk of bleeding there are two major considerations in play. The first is risk of bleeding due to the anticoagulant itself. Evaluating this often involves consideration of basic pharmacokinetic principles of the anticoagulant. The second consideration is the risk of bleeding due to surgery.

Pharmacokinetics

The pharmacokinetics of NOACs are often considered appealing in the preoperative setting due to a faster onset and offset of action versus VKAs. In theory, anticoagulation could be held for 12 to 24 hours before surgery and restarted 12 to 24 hours after surgery to rapidly restore anticoagulant effect, rendering bridging with heparin or low-molecular weight heparin unnecessary. However, in patients with renal failure, hepatic impairment, drug interactions, low body weight, or other factors that may result in altered drug levels, these assumptions may be inaccurate. Based on these factors, the patient may actually have therapeutic (or supratherapeutic) levels for longer periods which would actually predispose the patient to bleeding in an intraoperative setting. Additionally, holding the medication for longer than necessary may lead to increased risk of thromboembolism. It is for these reasons, there must be consideration of some key pharmacokinetic principles (Table 2). [4,5,6]

Table 2: Pharmacokinetic Principles of NOACs[4,5]

	Rivaroxaban	Apixaban	Dabigatran
Mechanism of Action	Factor Xa inhibitor	Factor Xa inhibitor	Direct thrombin inhibitor
Dosing Frequency	Once daily	Twice daily	Twice daily
Half-life	5 – 15 hours	12 hours	8 – 15 hours
Percent renally excreted	66%	25%	80%
Factors that may increase exposure	Renal Failure Drug interactions	Renal Failure Low body weight Drug interactions	Renal Failure Drug interactions
Factors that may decrease exposure	Increased body weight Drug interactions	Increased body weight Drug interactions	Drug interactions

The main area for concern with regards to pharmacokinetics is regarding patients who may have prolonged activity and an increased risk of bleeding when going to surgery. Many of these concerns stem from the high renal clearance of these medications or a high-degree of drug-interactions through the CYP-system or P-glycoprotein pumps. Other factors suspected to alter levels outside of therapeutic range include extremes in body weight, hepatic impairment, or low-protein states (due to degree of protein binding of the drug).[4]

Unlike VKAs, NOAC's activity is not reliably measured by laboratory markers to predict anticoagulant activity. In some cases, prothrombin time (PT), activated partial thromboplastin time (aPTT), or other markers may be used, but the reliability of these tests may be decreased in certain situations (e.g. timing of the laboratory draw). For example, PT is more sensitive with supratherapeutic concentrations of rivaroxaban, but therapeutic levels of rivaroxaban have been shown to have little effect on PT. Further studies are needed to validate these tests and their utility in the clinical setting.[2,3,4,14]

To better evaluate the risk of bleeding due to surgery, types of surgeries are often first stratified by elective versus emergent, and then: low risk, moderate risk, or high risk (Table 3). Spyropoulos et al proposed this risk stratification mechanism to be applicable to both VKAs and NOACs when assessing bleed risk for procedure.[12] In addition, the HAS-BLED tool (Table 4) is often used to help weigh risk versus benefits of chronic anticoagulation may have use in assessing bleed risk preoperatively. Omran et al found that a HAS-BLED of 3 was indicative of higher risk of procedural bleed when looking at patients on vitamin K antagonists and undergoing elective procedure (HR 11.8, 95% CI [5.6-24.9]).[10]

Emergent surgeries are an area of major concern for NOACs, mainly due to concern of lack of reversal agent and the high risk for bleed. If urgent hemostasis is needed, blood products will be the mainstay of therapy for any patient, whether anticoagulated with a NOAC or VKA. Agents such as factor products may also be used, but their utility is not well understood.

Table 3: Risk stratification for surgical bleeding risk[8]

Surgery type	Operative Bleeding Risk	
	Low[1]	High[2]
Cardio-respiratory procedure	• Bronchoscopy with or without biopsy • Non-coronary angiography • Atrial fibrillation ablation • Pacemaker/cardiac defibrillator insertion	• Coronary artery bypass
Dental/General surgery	• Simple dental extraction • Abdominal hernia repair • Abdominal hysterectomy • Axillary node dissection • Biopsies: cutaneous, bladder, thyroid, breast, and lymph node • Carpal tunnel repair • Cholecystectomy • Hemorrhoidal removal • Hydrocele repair • Gastrointestinal endoscopy	• Multiple tooth extractions • Endoscopy guided fine needle aspiration • PEG placement • Polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilatation • Colon resection • Major cancer resection
Orthopedic surgery	• Arthroscopy	• Hip and knee arthroplasty • Surgery of shoulder, foot, or hand
Urological/ Gynecological surgery	• Dilatation and curettage	• Kidney biopsy • Transurethral prostate resection
Others	• Central venous catheter removal • Cataract surgery • ***Lumbar puncture??***	• Abdominal aorta aneurysm repair • Laminectomy

[1]Low: risk defined as: 2-day risk of major bleed less than 2%
[2]High risk defined as 2-day risk of major bleed of 2 to 4%

Table 4: HAS-BLED[10]

Characteristic	Score
Hypertension (SBP > 160 mmHg)	1
Abnormal renal function • Chronic dialysis • Renal transplant • SCr ≥ 200 mmol/L Abnormal liver function • Cirrhosis • Bilirubin 2-3 times upper limits of normal • AST/ALT >3 times upper limits of normal	1 to 2 (1 point for each)
Stroke	1
Bleeding tendency or predisposition (e.g. antiplatelet)	1
Labile INRs (if on warfarin, <60% therapeutic range)	1
Age > 65 years	1
Drugs or alcohol	1 to 2 (1 point each)

Recommendations

Two sources, Lai et al and Levy et al report suggested algorithms for holding new oral anticoagulants.[5,6,7] These recommendations take into consideration creatinine clearance (Table 5). Clinical judgment should be used in evaluating the risk of bleeding from surgery when considering the range of time anticoagulation should be held. In addition, other patient factors such as patient weight, age, and concomitant medications should be considered. For emergent surgery, if the start of the surgery can safely be delayed at least one to two half-lives of the NOAC, this is preferable. However, if urgent emergent surgery cannot be delayed, blood products are the mainstay of management. Factor products may also be considered.[9]

Table 5: Suggested interruption of NOAC

Creatinine Clearance (ml/min)	Dabigatran	Rivaroxaban	Apixaban
> 50 ml/min	≥ 48 – 72 hours	≥ 24 – 48 hours	≥ 24 – 48 hours
30 – 50 ml/min	≥ 48 hours – 96 hours	≥ 36 – 72 hours	≥ 48 – 72 hours
15 – 29 ml/min	N/A	≥ 48 – 96 hours	≥ 48 - 96 hours
<15 ml/min or dialysis	N/A	N/A	Not well studied

Overall, the need for bridging is considered unnecessary due to the fast offset and onset of action. Bridging may be necessary when a patient is considered high thromboembolic risk and is unable to take oral medications post-surgery. In this case, a parenteral agent such as unfractionated heparin or low-molecular weight heparin may be utilized until oral agents may be resumed. Additionally, some practitioners have taken to discontinuing NOACs and bridging with parenteral agents until surgery, especially in the acute setting where patients may be on an unpredictable procedure schedule. In this way, unfractionated heparin or low-molecular weight heparin may be held for 12 to 24 hours prior to surgery more predictably, and anti-Xa levels may be utilized if needed.[1,2,4]

Summary

Preoperative management of the patient chronically anticoagulated with a NOAC requires attention to the pharmacokinetic properties of the drug, patient factors that can alter pharmacodynamics, and the patient's personal risk of thromboembolism versus bleeding. Use of risk stratification tools may be useful to the practitioner, but patient-centered care is prudent. Further research is emerging regarding possible monitoring tools for NOACs and for reversal agents for emergent situations.

References

1. Douketis JD, Spyropoulos AC, spencer FA, Mayr M, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest*. 2012; 141(2 suppl): e326S – e350S.
2. Douketis JD. Pharmacologic properties of the new oral anticoagulants: a clinician-oriented review with a focus on perioperative management. *Curr Pharm Des*. 2010; 16(31): 3436-441.
3. Garcia D, Barrett YC< Ramacciotti E, Weitz JI. Laboratory assessment of the anticoagulant effects of the next generation of oral anticoagulants. *J Thromb Haemost*. 2013; 11(2); 245-52.
4. Heidbuchel H, Verhamme P, Alings M, Antz M, et al. EHRA practical guide on new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J*. 2013; 34: 2094-106.
5. Lai A, Davidson N, Galloway SW, Thachil J. Perioperative management of patients on new oral anticoagulants. *BJS*. 2014; 101: 742 – 49.
6. Levy JH, Faraoni D, Spring JL, Douketis JD, et al. Managing New Oral Anticoagulants in the Perioperative and Intensive Care Unit Setting. *Anesthesiology*. 2014; 118(6): 1466 – 74.
7. Levy JH, Key NS, Azran MS. Novel Oral Anticoagulants. *Anesthesiology*. 2010; 113(3): 726 – 45.
8. Liew A, Douketis J. Perioperative management of patients who are receiving a novel oral anticoagulant. *Intern Emerg Med*. 2013; 8: 477-84.
9. Nutescu EA, Dager WE, Kalus JS, Lewin JJ, et al. Management of bleeding and reversal strategies for oral anticoagulants: clinical practice considerations. *Am J Health-Syst Pharm*. 2013; 70: e82 – 97.
10. Omran H, Bauersachs R, Rubenacker S, Goss F, et al. The HAS-BLED score predicts bleedings during bridging of chronic oral anticoagulation: BORDER. *Thromb Haemost*. 2012; 108(1): 65-73.
11. Pierre S, Samama CM, Godier A, Rosencher N, et al. Surgery and invasive procedures in patients on long-term treatment with direct oral anticoagulants: Thrombin or factor-Xa inhibitors. Recommendations of the Working Group on the perioperative haemostasis and the French Study Group on thrombosis and haemostasis. *Archives of Cardiovascular Disease*. 2011; 104: 669 – 76.
12. Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. *Blood*. 2012; 120(150: 2954 – 62.
13. Vandiver JW, Vondracek TG. Anti Xa Levels versus Activated partial Thromboplastin Time for Monitoring Unfractionated Heparin. *Pharmacotherapy*. 2012; 32(6): 546 – 58.

Continuing Education (CE) Article Information:

In case you missed it, here's a link to the last CE article released early last month, "Chronic Kidney Disease-Mineral and Bone Disorder: The Basics." https://mlsvc01-prod.s3.amazonaws.com/80119d75301/d7cd103e-32b3-4358-8fe5-ed5a4d86db0a.pdf

Please return the completed quiz to Robin Moser (rmoser@centrichq.com) or by fax to (785) 271-0166 by March 15th 2015 to receive credit.

Upcoming Newsletter and CE Article Topics:

- March/April 2015: Infectious Disease
- May/June 2015: Oncology
- July/August 2015: Cardiology
- September/October 2015: Transitions of Care

Featured Job Posting:

Company: Mercy Hospital Joplin
Position: Manager, Retail Pharmacy Services

Company Overview:

New State of the Art Hospital Set To Open March 2015 In Joplin, Missouri. Mercy is the sixth largest Catholic health care system in the U.S. and serves more than 3 million people annually. Mercy includes 32 acute care hospitals, four heart hospitals, two children's hospitals, three rehab hospitals and one orthopedic hospital, nearly 700 clinic and outpatient facilities, 40,000 co-workers and more than 2,100 Mercy Clinic physicians in Arkansas, Kansas, Missouri and Oklahoma. Mercy also has outreach ministries in Louisiana, Mississippi and Texas.

Position Overview:

Retail Pharmacy Managers are responsible for performing or supervising all duties associated with the provision of retail pharmacy services and for complying with all pharmacy laws, rules, and regulations pertaining to those retail pharmacy services. The manager is responsible for identifying potential and existing drug related problems and taking appropriate actions to prevent or resolve adverse drug events. These individuals are responsible for managing the pharmacy with specific responsibilities defined by the Missouri Board of Pharmacy. The pharmacy manager is responsible for the financial performance and operational issues of the pharmacy.

Position Requirements:

Education: Bachelor of Science in Pharmacy and/or Doctor of Pharmacy degree
Licensure: Current Missouri Pharmacist license in good standing
Experience: Three or more years in a retail pharmacy supervisory

Contact:
Sharon Perkins
417.659.6782
sharon.perkins@mercy.net

Mercy Hospital Joplin
1001 East 32nd Street
Joplin, MO 64804
www.mercy.net/careers

Questions/Comments

If you have any questions or comments about MSHP Newsletter, please don't hesitate to contact the Newsletter Chair, Cassie Heffern, PharmD, BCACP (cassie.heffern@coxhealth.com) or any other newsletter committee member.

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