"Antibiotics? But what about my warfarin?"

DALHOUSIE UNIVERSITY
Inspiring Minds

Sam G. Campbell, MB BCh, CCFP(EM) CHE; and Peter J. Zed, BSc, BSc(Pharm), ACPR, PharmD, FCSHP

Mary's case

Mary, a 63-year-old lady presents with signs, symptoms and urinalysis findings of a urinary tract infection (UTI). Her vital signs are within normal limits and she has no features suggesting the need for hospitalization. You decide to treat her with oral antibiotics and to follow-up with her FP. Following abdominal surgery a month previously, she suffered a pulmonary embolism, for which she has been anticoagulated with warfarin, with her current dosage being 2 mg q.d. and her current INR is 2.8 (target INR 2-3).

Questions & Answers

1. What are the issues with the use of antibiotics in patients on warfarin?

The benefits of warfarin in patients with venous thromboembolic disease have been clearly established. Unfortunately, the established benefits of warfarin must be weighted against the potential risks, most importantly major bleeding, which occurs at an annual rate of 2.2% and which carries a mortality of 13%. The risk of bleeding complications increases as the INR exceeds therapeutic levels. There are many factors which predispose patients to elevated INR and increased bleeding risk. Drugs that potentiate the effects of warfarin are a common cause of supratherapeutic INR.

All antibiotics can alter the coagulation status of patients receiving warfarin. There are two primary mechanisms by which antibiotics interact with warfarin. First, warfarin is metabolized by the cytochrome P450 isoenzyme 2C9; thus, antibiotics that inhibit this isoenzyme will impair the metabolism of warfarin and thus potentiate the anticoagulation effects of warfarin. Second, antibiotics suppress vitamin K producing bacteria in the gut, thereby decreasing the anti-warfarin effect of vitamin K in the body. In addition to these two drug-related mechanisms, it has been suggested that infection itself can alter warfarin metabolism and increase the INR via stimulation of the immune system, increasing levels of pro-inflammatory cytokines and by reducing dietary intake (and thus vitamin K).

Table 1

Indications for anticoagulation and benefits thereof

Indication for warfarin	Risk of complications of primary condition	Benefits of adequate anticoagulation with warfarin	Notes
Atrial fibrillation (non-rheumatic)	Overall average risk of CVA in patients with atrial fibrillation is 5% a year (2-7 times the risk in patients without atrial fibrillation), but ranges from 1.9% in those with no risk factors to 18.2% in the highest risk categories	Risk of stroke is reduced by 66%	Determination of annual risk of stroke without prophylaxis is determined by CHADS2 score. CHADS2 Score: 0 (1.9%), 1 (2.8%), 2 (4.0%), 3 (5.9%), 4 (8.5%), 5 (12.5%), 6 (18.2%)
Mechanical prosthetic heart valve	20% of patients with valve prostheses have an embolic stroke by 15 years after valve replacement. The annual risk of systemic embolization (predominantly stroke) is 4.0% with no anticoagulation and 2.2% with ASA alone. Patients with mitral valve prostheses are at approximately twice the risk as those with aortic valve prostheses.	In patients with mechanical valves who are treated with warfarin, embolization occurs at a frequency of approximately 0.7%-1.0% per patient per year	Independent risk factors for stroke include: age > 75 years, female gender and smoking. Atrial fibrillation, coronary disease and tilting-disc mechanical prostheses were also independent predictors of embolic stroke after aortic valve replacement. Preoperative left ventricular dysfunction was an independent risk factor in patients with mitral prostheses
VTE – "Unprovoked"	Cumulative annual risk of recurrence is 10%	The weighted incidence of recurrent VTE is 0.052 events/person-year in patients on long-term and 0.072 events/person-year for those on short-term anticoagulation therapy	Greatest risk of recurrence is in first 6 months. Presence of active cancer carries the greatest risk for recurrent VTE following discontinuation of anticoagulant therapy. The risk of VTE recurrence is increased by: - More proximal initial DVT - Male gender (1.5-3 times risk of recurrence) - Older age (risk of recurrence increases by 17% per decade) - Body habitus (risk of recurrence increases by 24% per 10 kg/m^2 increase in BMI) - Intrinsic coagulation disorders all have an increased risk of recurrence, risk varying with the specific disorder
VTE – "Provoked" by a minor risk factor	Annual risk for recurrence is 5%		
VTE – "Provoked" (*e.g.*, by major surgery)	Annual risk for recurrence is 3%		
PE	Recurrent PE: 15% mortality rate		
DVT	Recurrent DVT: 2% mortality rate		

CVA: Cerebrovascular accident
VTE: Venous thromboembolism
PE: Pulmonary embolism
DVT: Deep vein thrombosis

2. *Are certain drugs more likely to cause problems than others?*

Antibiotics that inhibit the cytochrome P450 isoenzyme 2C9 are the most problematic. The antifungals fluconazole and miconazole and antibacterials metronidazole and sulfamethoxazole/trimethoprim (co-trimoxazole), being primary inhibitors of the cytochrome P450 enzyme CYP2C9 are the most notorious offenders. However, fluoroquinolones, particularly ciprofloxacin and macrolides such as erythromycin have also been associated with significant interactions with warfarin. Despite these more established and pronounced interactions, a supratherapeutic INR can result with concomitant use of any antibiotic due to alterted vitamin K gut synthesis.

3. *Which conditions suggest a higher risk for temporary discontinuation of anticoagulation?*

Of the several indications for anticoagulation, the three most common are: treatment or prophylaxis of venous thromboembolism (VTE) disease (deep vein thrombosis or pulmonary embolism) and stroke prophylaxis in patients with atrial fibrillation and in those with prosthetic heart valves. Although disruption of warfarin therapy should be avoided if possible, each of the above conditions must be evaluated to determine if temporary discontinuation may be feasible. It might not be appropriate to disrupt therapy in patients with prosthetic heart valves, but in some patients with VTE or lower risk of stroke due to atrial fibrillation, temporary discontinuation of warfarin may be an option. The risks and benefits of discontinuing warfarin may be estimated by considering the items listed in Table 1.

4. *What should we do in Mary's case?*

Under most circumstances, temporary discontinuation of warfarin will not be desirable and, assuming the antibiotic is

Mary's case cont'd

Issues facing the emergency practitioner to consider:

- Is this actually a UTI, or chronic asymptomatic bacteriuria (that is common in older patients and does not require antibiotic treatment)?
- Does the risk of over-anticoagulation as a result of antibiotic-warfarin interaction exceed the benefit of the antibiotic?
- If antibiotics are indicated, is the indication for warfarin of sufficiently low risk that it might be preferable to temporarily stop the warfarin until the antimicrobial course is completed?
- Is she, because of the new illness, at greater risk of trauma due to falls, that would swing the risk benefit ratio away from warfarin?

Dr. Campbell is an Associate Professor, Emergency Medicine, Dalhousie University, Halifax, Nova Scotia.

Dr. Zed is a Clinical Coordinator, Department of Pharmacy; Pharmacotherapeutic Specialist, Emergency Medicine, Queen Elizabeth II Health Sciences Centre; and Associate Professor, College of Pharmacy and Department of Emergency Medicine, Dalhousie University, Halifax, Nova Scotia.

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definitely indicated, co-administration of these two medications will happen. An appropriate approach in this circumstance is to increase the frequency of warfarin monitoring both clinically and with more frequent INR measurement. Patients should be reminded to observe any signs of bleeding and to report any bleeding complications to the FP as soon as possible. It would also be reasonable to measure INR twice weekly while on antibiotic therapy and for the week after antibiotic treatment has been discontinued (*i.e.*, drug interaction removed), adjusting the warfarin dose as necessary. Some have advocated empirically reducing the warfarin dose when initiating an interacting drug. This approach may be problematic as, due to the large interpatient variability in warfarin response, not all patients will actually require a dosage adjustment. For Mary, a baseline INR should be obtained and the level repeated every three to four days while on antibiotic treatment and in the week following antibiotic discontinuation. Given her INR is already at the upper limit of the desired INR range 2 to 3, it would be reasonable to empirically reduce her warfarin dose to 1.5 mg q.d. when initiating antibiotic therapy.

5. *Are there other "blanket concerns" for emergency physicians to consider when treating patients on warfarin?*

It is prudent to consider every patient on warfarin, one in whom coagulation status could change rapidly and catastrophically. Patients should understand the importance of constant surveillance for signs of over-anticoagulation. Any change in treatment or medical condition should suggest the need for increased monitoring of the INR and more intensive follow-up by the FP. Dx

A useful guideline is posted at:
Guidelines and Protocols Advisory Committee: Initiation and Maintenance of Warfarin Therapy: http://www.bcguidelines.ca/gpac/pdf/warfarin_therapy.pdf. Accessed: November 29, 2009.

Resources
1. Adcock DM: Recurrence of Thromboembolism: Determining Risk. Clinical Hemostasis Review. 2005;19(1). http://www.esoterix.com/files/ch_review/chreview2005_Q1.pdf. Accessed: November 29, 2009.
2. Gage BF, Waterman AD, Shannon W, et al: Validation Of Clinical Classification Schemes For Predicting Stroke. Results From The National Registry Of Atrial Fibrillation. JAMA 2001; 285(22):2864-70.
3. Risk Factors For Stroke And Efficacy Of Antithrombotic Therapy In Atrial Fibrillation. Analysis Of Pooled Data From Five Randomized Controlled Trials. Arch Intern Med 1994; 154(13):1449-57.
4. Ost D, Tepper J, Mihara H, et al: Duration Of Anticoagulation Following Venous Thromboembolism: A Meta-Analysis. JAMA 2005; 294(6):706-15.

This is one of a series of articles dedicated to the memory of Leslie Ann Walsh, our patient who died following a gastro-intestinal bleed associated with over-anticoagulation following an antibiotic prescription.