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Hospitalist Update

Real Warfarin Resistance or Medication Noncompliance?

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INTRODUCTION:

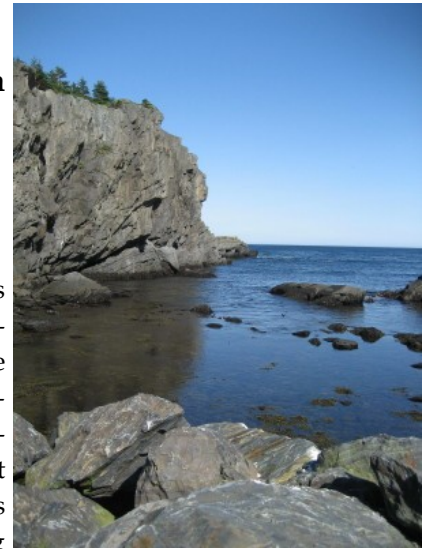
The word noncompliance comes too many times in the physicians' notes, particularly when the outcome is not in sync with the standard of care these days. True, many times, for various reasons, patients are noncompliant with the prescribed regimen; at times, however, the patient is not at fault and, perhaps out of ignorance, the clinician falls back on that explanation. We present an interesting

case of warfarin resistance and discuss possible reasons for that resistance in light of a current literature review.

Warfarin works by inhibiting the activation of vitamin K-dependent clotting factors II, VII, IX and X. Normally, reduced vitamin K is oxidized to vitamin K 2,3 epoxide, a cofactor in the gamma-carboxylation of these clotting factors. Warfarin blocks the conversion of vitamin K 2,3 epoxide back to vitamin K via its inhibition of vitamin K reductases. This produces therapeutic anticoagulation primarily via an effect on the extrinsic clotting pathway, as measured by the International Normalized Ratio (INR) [1].

Warfarin is well absorbed from the gastrointestinal tract after oral or rectal dosing, with an absolute bioavailability of up to 100%. Its onset and duration of action are also predictable [1-4]. Resistance to the action of warfarin is not common and may be either hereditary or acquired [1,2,5-7]. Hereditary resistance is rare and is presumed to be autosomal dominant, based on family studies; interestingly, because the absorption and clearance of warfarin is normal, the mechanism of resistance is likely at the molecular level, involving an enhanced formation of reduced vitamin K or resistance of vitamin K reductases to the action of warfarin [3-5, 8-12].

Acquired resistance may result from noncompliance, excessive vitamin K ingestion, gastrointestinal conditions that lead to malabsorption, or due to the use of drugs that alter warfarin pharmacokinetics, inhibiting its absorption or enhancing its biotransformation [3-6, 13]. We present a case of warfarin resistance secondary to a variant in the gene encoding VKORC1.



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CASE REPORT:

A fifty year old AA female was admitted to the hospital with chest pain and palpitations which were found to be due to atrial fibrillation. She had a thirty year history of hypertension for which she was taking maxide and verapamil. She also had bilateral carpal tunnel syndrome and had undergone a hysterectomy for menorrhagia. She worked as a chef and denied use of alcohol, tobacco or illicit drugs. Her family history was unremarkable.

On physical exam, her BP was 140/90, pulse 72 (irregularly irregular), respirations 16 and temperature 99 F. Clinical findings were normal except for the atrial fibrillation. Hematologic and biochemical parameters were normal. EKG demonstrated atrial fibrillation with a ventricular rate of 63-116. CXR was remarkable for cardiomegaly. Anticoagulation was initiated with enoxaparin and warfarin. Despite escalating doses of warfarin (ingestion supervised and documented by nursing), the INR remained sub-therapeutic; she eventually required 25 mg of warfarin daily to produce a therapeutic INR; drug interactions had been ruled out and the patient was maintained on a warfarin-safe diet. Genetic testing revealed that she had one copy of the VKORC1 1639 GA mutation.

DISCUSSION:

Warfarin is used for the long term prevention of thromboembolic events in patients with atrial fibrillation. In 2003, 21.2 million prescriptions were written for warfarin (a derivative of coumarin) in the U.S. alone [14]. However, the use of warfarin poses two challenges: first, a safe and effective stabilization dose must be determined during the initial period of therapy and, second, the maintenance dose must be monitored and adjusted to compensate for changes in the patient's weight, diet, health and medication regimen. In addition, studies have shown that genetic factors can affect outcomes, despite close attention to this protocol. Specifically, patients with the common, functionally defective *2 and *3 allelic variants of the cytochrome P-450 enzyme 2C9 (CYP2C9) require significantly lower maintenance doses, have longer times to dose stabilization and are at higher risk for serious and life-threatening hemorrhage [15]. This warfarin sensitivity is explained by the fact that CYP2C9 is responsible for the metabolic clearance of the more pharmacologically potent S-enantiomer of warfarin [16].

In contrast to the rather common, genetically-determined cases of increased warfarin sensitivity, as described above, are the rare cases of warfarin resistance. A potential pharmacodynamic mechanism underlying warfarin resistance has been elucidated with the recent discovery of the warfarin target gene, which encodes the vitamin K epoxide reductase complex 1 (VKORC1) [17,18]. This complex recycles reduced vitamin K, which is essential for the post-translational gamma-carboxylation of vitamin K-dependent clotting factors II (prothrombin), VII, IX and X. Several rare mutations that lead to amino acid changes in the VKORC1 protein have been found in warfarin-resistant patients but not in the general population [17], suggesting that coding region variants of VKORC1 are severely detrimental and that they likely play no role in the typical, minor variability of warfarin dosing (2-10 mg/day) requirements that we encounter in practice. Recently, a single, noncoding polymorphism was found to be associated with these normal range variations [19], suggesting that other regulatory polymorphisms in VKORC1 may influence the pharmacodynamic response to warfarin.

Warfarin anticoagulation is the standard of care for the treatment and prevention of thromboembolic events. Nevertheless, it is associated with considerable morbidity and mortality due to its rather narrow therapeutic index and to inter-individual variability in drug sensitivity. The warfarin dose is adjusted in accordance with its pharmacodynamic effects on clotting, as measured by the INR, and the INR value has been closely correlated with risks for thrombosis (under-anticoagulation) and bleeding (over-anticoagulation) [20]. The daily dose of warfarin to maintain the INR in the recommended, therapeutic range, is quite variable; nevertheless, patients who require more than 105 mg per week (15 mg/day) should be considered warfarin-resistant. Warfarin resistance is distinct from warfarin failure, defined as a new thromboembolic event despite achievement of a therapeutic INR; this situation is most commonly observed in patients with malignancy. An important feature of warfarin resistance is that patients need much smaller doses of vitamin K to reverse the warfarin effect [21].

Steady-state warfarin dose requirements are strongly affected by genetic variants of VKORC1 and CYP2C9; initial variability in the INR response is more closely associated with VKORC1 than with CYP2C9 [22]. The ability to achieve a therapeutic INR on a relatively low dose of IV warfarin but not on high doses of oral warfarin strongly suggests an inherent warfarin malabsorption [23].

Patrick et al. suggested that the use of genotyping before warfarin initiation would be cost effective for patients with atrial fibrillation only if this testing was shown to reduce out-of-range INR values by more than 5-9%, compared with usual care [24]; genotyping is unlikely to be cost effective for typical patients with non-valvular atrial fibrillation but may be cost effective in patients at high risk for hemorrhage [25]. Li, et al., stated that some of the predictive information provided by VKORC1 and CYP2C9 genotypes about warfarin sensitivity early in therapy is reflected in the early INR response.; in their cohort of 214 patients, after a week of dose titration guided by the INR response, pharmacogenetic data did not contribute significantly to predicting the first stable warfarin dose beyond what could be inferred from the clinical information provided by the INR response to warfarin dosing [20]. It remains unclear whether these expensive genetic tests add much to dosing decisions beyond the initial INR response; hopefully, the EUPACT trial will shed light on this controversy [26].

Ethnic differences may also explain some of the variability in warfarin dose requirements. While CYP2C9 and VKORC1 genetic variants may play a role, they do not totally explain some of the inter-ethnic differences in warfarin sensitivity; dietary and environmental factors, unique to the culture of various ethnic groups, may also be involved.

CONCLUSION:

Although some patients do not adhere to their warfarin regimen, hampering efforts to achieve a safe but effective INR, drug resistance and inadequate patient education may also lead to adverse outcomes; this is of special concern during the immediate post-discharge period when a stable dose has often not been reached and when specific follow up arrangements are sometimes inadequate. Hospitalists must play an active role in both patient education regarding the risks of warfarin therapy (including over and under anticoagulation) and in ensuring that effective arrangements for monitoring and follow up care have been made.

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CASE OF THE MONTH**Jaya Buddineni, MD**

A 35 year old Hispanic male, with no significant past medical history, presented to the ER complaining of fever, cough and myalgias. The patient had gone to another ER 8 days prior to this presentation with less severe complaints and was diagnosed with a left lingular pneumonia; he was sent home on a course of Bi-axin. After initially improving, he developed left sided chest pain, productive cough, hemoptysis, fever, nausea and right upper quadrant abdominal pain. The patient lives with three healthy room-mates and denied a history of recent travel, sick contacts or exposure to animals. He works in a restaurant and reported a history of salmonella infection 3 years ago, for which he received antibiotics. He denied any history of tobacco, alcohol or illicit drug use.

On arrival, the patient was afebrile, tachycardic, and normotensive with a RR of 18/min and saturating 96% on RA. He appeared to be in mild distress and lung exam revealed diffuse, coarse rhonchi, greater on the left side. Abdominal exam revealed RUQ tenderness with normal bowel sounds and no organomegaly. The remainder of his physical exam was within normal limits.

Lab data revealed a low WBC, severe normocytic anemia and a platelet count of 43,000. He had mild hyponatremia, hypokalemia, hypochloridemia and normal renal function. Hepatic labs revealed a marked hypoalbuminemia, normal total protein, hyperbilirubinemia, elevated transaminases and a high alkaline phosphatase. A peripheral blood smear demonstrated numerous schistocytes with enlarged platelets; further workup revealed an elevated reticulocyte count, high LDH and decreased haptoglobin. A CXR showed progression of the left lingular infiltrate and an associated effusion. A hepatitis profile and legionella antigen were negative; an ultrasound of the RUQ was also WNL.

The patient was admitted to the IM service and, after appropriate cultures were obtained, he was started on IV Vancomycin, Zosyn and doxycycline. A CT of the chest demonstrated lingular and LLL consolidation, a left pleural effusion with loculations, a mild right pleural effusion and splenomegaly. CT Surgery was consulted and the patient underwent a VATS procedure for drainage and decortication; the pleural fluid was exudative, consistent with a parapneumonic effusion, but the gram stain and culture were negative; results of serologic testing for IgM and IgG are still pending. All cultures remained negative, lab abnormalities corrected, the patient's clinical status improved and he is currently undergoing pulmonary rehabilitation.

DISCUSSION: This is a case of partially-treated, community acquired pneumonia (CAP), presenting with severe complications of parapneumonic effusion, empyema, hemolytic anemia and pancytopenia. Common pathogens of CAP that may present with hemolysis include mycoplasma [3] and, less commonly, strep pneumonia with hemolytic-uremic syndrome. Pathogens that cause atypical pneumonia tend to produce more extra pulmonary manifestations than occurs in typical pneumonia. Atypical pneumonia can pose a diagnostic challenge for clinicians since there are no diagnostic tests for reliable and early detection of atypical organisms [2] and since partial treatment of CAP with antibiotics may mask important clinical signs. Serologic tests, including ELISA, indirect fluorescent antibody assay and particle agglutination to detect IgM and IgG, are increasingly used to diagnose atypical pneumonia. Although these tests may aid in the identification of the pathogen, delayed results and economic burden are significant barriers and they seldom help in early management decisions, including empiric antibiotic coverage. The 2007 IDSA/ATS consensus guidelines recommend diagnostic testing for a specific organism only when empiric antibiotic therapy fails to result in clinical improvement. Diagnostic testing for outpatient management of CAP is considered optional [1].

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FROM THE JOURNALS

Robert Lancey MD

Ford, MK et al., *Systemic Review: Prediction of Perioperative Cardiac Complications and Mortality by the Revised Cardiac Risk Index*, *Annals Int Med*, January 5, 2010; 152:26-35

See also: Lee Goldman, *The Revised Cardiac Risk Index delivers what it promised*, *Ann Int Med*, January 5, 2010; 152:57-58

This meta-analysis by investigators from the University of Toronto abstracted data from several studies to determine the effectiveness of the Revised Cardiac Risk Index (RCRI). The RCRI was first published in *Circulation* in 1999 by Lee et al. as a new risk score for the prediction of cardiac events in patients undergoing noncardiac surgery. It has since been utilized as the scoring system for medical risk in the 2007 ACC/AHA Guidelines on Perioperative Evaluation and Care for Noncardiac Surgery. The authors abstracted data from 24 studies utilizing the RCRI, including the original study by Lee et al., and found that the RCRI had moderate success in discriminating between patients at low versus high risk for cardiovascular complications following mixed noncardiac surgery. It remains the best cardiac risk index in widespread use to this day.

Daniels,, JM et al., *Antibiotics in addition to systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease*, *Am J Respir Crit Care Med*, 2010 Jan 15; 181(2):150-157

Investigators in Amsterdam, The Netherlands, conducted a small, randomized, double-blinded, placebo-controlled trial of doxycycline for hospitalized COPD patients. All enrolled patients were given oral corticosteroids and standard inhaler therapy plus either doxycycline 200 mg/day or placebo. Outcomes were determined at days 1, 10 and 30, which showed that the doxycycline group had a significant clinical improvement over placebo at day 10 but not at 30 days. The doxycycline group also showed significant improvements in microbiological cure, symptom improvement and decrease in CRP at 10 days but not at 30 days. In summary, this study serves to reiterate the lack of clear evidence for the use of antibiotics in patients with COPD exacerbations. However, this study may strengthen the argument for use of antibiotics in patients admitted for COPD exacerbation since they demonstrated a significant short-term benefit.

(continued)

FROM THE JOURNALS (cont)

Chan, PS et al., *Rapid Response Teams: A Systemic Review and Meta-analysis*, Arch Int Med 2010 Jan 11; 170(1):18-26

See also: Edelson, DP, *A weak link in the Rapid Response System*, Arch Int Med 2010; 170:12-13

Hospital rapid response teams (RRTs) have come into widespread use in the last several years as a way to augment patient safety by lowering hospitalized patient's risk of cardiac arrest and in-hospital mortality. This current meta-analysis abstracts data from 18 publications and analyzed for a lowering of the risk of cardiac arrest and in-hospital mortality as a result of the institution of rapid response teams in hospitals. The meta-analysis found a lowering of the cardiac arrest rate outside of the ICU but showed no difference in the hospital mortality rate. When analyzed in the pediatric population, improvement was shown in both the rate of non-ICU cardiac arrest and, less robustly, in hospital mortality. To summarize, this meta-analysis sheds more light on the lack of impact by RRT's on in-hospital mortality but does reinforce the benefit of lowered incidence of non-ICU cardiac arrest. The accompanying editorial highlights these results while warning hospital administrators that RRTs need to be improved, not discarded.



ID CORNER

William Salzer MD

DIAGNOSIS AND TREATMENT OF INTRA-ABDOMINAL INFECTIONS

The IDSA has recently updated its guidelines for the management of complicated intra-abdominal infections. Solomkin, JS et al., Diagnosis and management of complicated intra-abdominal infections in adults and children: Guidelines by the Surgical Infection Society and the Infectious Disease Society of America, Clin Infect Dis 2010; 50:133-164

<http://www.journals.uchicago.edu/doi/pdf/10.1086/649554>

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MISSOURI HOSPITALIST CALENDAR

Hospital Medicine 2010, April 8-11, Washington, DC, information online at www.hospitalmedicine.org

48th Annual USC Weil Symposium on Critical Care & Emergency Medicine, April 11-15, Westin Mission Hills, Rancho Mirage, CA, 800-USC-1119 or register online at www.peopleware.net/0128 and select course #2580

Internal Medicine 2010, American College of Physicians, April 22-24, Toronto, register online: www.acponline.org

American Geriatric Society, Annual Meeting, May 12-15, Orlando, information and registration via www.americangeriatrics.org

Hospitalist Conference, Missouri ACP Meeting, September, 2010; presentations from MU, UMKC, Washington University; details to follow

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!