The Journal of the International Federation of Clinical Chemistry and Laboratory Medicine

eJIFCC

Advances in Oral Coagulants

Eleanor S. Pollak
Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, and Children's Hospital of Philadelphia and the Philadelphia VA Medical Center

Corresponding Author:

Eleanor S. Pollak, MD, FCAP
Associate Professor
Department of Pathology and Laboratory Medicine
Hospital of the University of Pennsylvania, and
Children's Hospital of Philadelphia and
the Philadelphia VA Medical Center
310B Abramson Research Center
3615 Civic Center Blvd.
Philadelphia, PA 19104
Office: (215)590-6117; Fax: (215)590-2320
e-mail: Pollak@mail.med.upenn.edu

Key words: oral anticoagulants, warfarin, pharmacogenetics, dabigatran, rivaroxaban, apixaban

Abstract

This article reviews current and future treatment practices concerning oral anticoagulants. In the second decade of the 21st millennium clinicians can finally treat thrombotic disease with long-awaited new oral anticoagulant medications. In addition, improvements have been made in managing warfarin, the traditional but far from obsolete medication. The first part of this review will cover current advances with warfarin treatment. The second portion will discuss specific active coagulation factor inhibitors, the new oral anticoagulants.

Advances in Oral Coagulants

Warfarin

The drug warfarin has remained the principal oral anticoagulant medication used to hinder the coagulation waterfall cascade of proteolytic enzymes.[1] Although warfarin was patented back in the 1940s and was followed by an onslaught of correlated scientific activity, the actual gene for the warfarin target, Vitamin K epoxide reductase (VKOR), was not identified until 2004.[2, 3] This discovery of VKOR has also allowed the medical field to focus on decreasing warfarin's dangerous safety profile by generating new complementary genetic tests.[4]

The warfarin preparation: Technically, the warfarin compound ($C_{19}H_{16}O_4$), [$C_{19}H_{15}NaO_4$ -- commonly known by the brand name: Coumadin ®], is a racemic mixture of the R- and S-enantiomers of 3-(α-acetonylbenzyl)-4-hydroxycoumarin. It is a crystallized form of warfarin sodium, an isopropanol clathrate, which essentially lacks any of the impurities of its amorphous form. In some countries, different coumarins with either shorter (acenocoumarol) or longer (phenprocoumon) half-lives are used in place of warfarin. Despite worldwide use, tremendous disadvantages still accompany warfarin. Notably, the prescribed drug dosage has a dangerously narrow therapeutic index. Vast variability exists for warfarin dosage needs depending in part on common patient genotypes. The frequent genotypes influencing this variability have focused on two principal genetic variant groups. These variants belong to vitamin K-epoxide reductase complex (VKORC1) enzymes as well as cytochrome P450-2C9 (CYP2C9) molecules and influence drug concentration and metabolism, respectively.[4]

Warfarin is contraindicated when the risk hazard is greater for hemorrhage than for the benefit provided by anticoagulation. The Prothrombin Time (PT) response due to warfarin may be influenced by a multitude of endogenous and exogenous factors. These not only include therapeutically prescribed medications, but herbal compounds as well as food consumed. In the United States, at the request of the FDA (United States Food and Drug Administration) in 2006, the company Bristol-Myers Squibb inserted a "black-box warning" label for Coumadin on the risk of major or fatal bleeding.
It is essential that a patient's PT/INR (Internationally Normalized Ratio) be determined on a frequent basis. Thus, warfarin use must be carefully watched when insufficient laboratory facilities would complicate monitoring. Care should be taken to avoid or prudently consider use with pregnancy [5], blood dyscrasias, and imminent surgery of the CNS, eye or large exposed surfaces. Additionally, unsupervised patients at risk for mishaps pose significant dangers. A non-profit website provides a validated calculation tool to assist with warfarin dosing decisions: http://www.warfarindosing.org.[6]

In the mid 1980s, the recognition of problems of non-uniform testing of the PT ultimately led to an international method to standardize and calibrate warfarin-like anticoagulant compounds. This resulted in the assignment of the World Health Organization (WHO) thromboplastin preparation with an International Sensitivity Index (ISI) of 1.1. A comparison ratio to this ISI is measured and reported for each laboratory's thromboplastin using the unit of the International Normalised Ratios (INR).[7]

Overall, the use of warfarin has improved for compliant, regularly monitored patients. However, many of the extant difficulties have been greatly decreased with the introduction of new drugs.

New Oral Anticoagulant Medications
In this decade new oral anticoagulants are becoming the preferred therapy for indications when warfarin had been the only available oral anticoagulant therapy for over the previous half a century. The medications, dabigatran, rivaroxaban, abixaban, betrixaban, and edoxaban are small-molecule, selective inhibitors that bind to the active site of coagulation vitamin K dependent factors IIa or Xa. These recently developed new oral anticoagulants possess general similarities to the chemical structure of warfarin. Molecular weights of these new oral anticoagulants are approximately 1.5 to 2 times that of warfarin. (see Table 1).
The new oral anti-coagulants are attractive to patients, many healthcare providers, and healthcare system suppliers in part because laboratory monitoring is not routinely required; standard fixed doses are prescribed to patients with normal weights and renal function. This saves time and energy for those patients who would have normally been required to travel to a testing site for frequent warfarin monitoring. The new anticoagulants also reduce other drawbacks of warfarin including multiple drug interactions and problematic pharmacogenetics. Three of the novel new oral anticoagulants, dabigatran, rivaroxaban, apixaban have each been tested head-to-head against warfarin in large clinical trials for the indication of treatment of atrial fibrillation (AF).[8-10] Although no trial has prospectively tested these agents against each other, several meta-analyses provide added perspective regarding the utility and benefits that may be provided by these medications.[11] A semisystematic review and meta-analysis of 44,563 patients showed the new oral anticoagulants to be superior to warfarin in patients without heart failure regardless of gender or the presence of diabetes. However, additional benefits were not seen alongside the concurrent conditions of heart failure nor nonparoxysmal atrial fibrillation.[12]

Table 2 provides the specifics of the targeted enzyme, the drug half-life, the bioavailability, the % renal excretion, the doses /day of medication, possible method of testing if needed, the year of FDA approval for human use, the name of trial and safety risks of bleeding. All of these new drugs reach peak plasma levels between 1 and 4 hours after administration.

However, there remain patient characteristics that commonly influence the safety, efficacy and pharmacokinetics of the new oral anticoagulants. These include obesity, reduced hepatic, gastrointestinal and renal organ function, and contemporaneous prescriptions of interfering medications. It should be noted that factor Xa inhibitors are not devoid of problems and still do have potential interactions with other compounds including inhibitors and inducers of cytochrome P450 and the P-glycoprotein (P-gp) transporter-mediated drug interactions. Drugs that may be contra-indicated include: NSAIDs, ASA, anti-platelet drugs, proton pump inhibitors, and inhibitors or inducers of P-gp transport or CYP3A4.[13] [14] [15] The following populations were not included in most of the major new oral anticoagulant trials: pediatric, pregnant, elderly, and chronically ill patients. In addition, to the cited comparisons with warfarin (see Table 2), new oral anticoagulant apixaban was also shown to be more effective than aspirin in stroke risk reduction in the AVERROES trial. [15]

Despite the overall attraction of the new anticoagulants, other advantages must be carefully balanced. The major benefit in the use of warfarin remains the large ratio of its efficacy to its cost and availability. Besides the difficult issue with the new anticoagulants compliance due to the lack of regular monitoring the current high cost of the medications may result in patients saving money by not filling their prescriptions or reducing the number of pills the patient takes.
The most dangerous aspect of the new anticoagulants is the lack specific antidotes to reverse the medication should there be

Table 1
New Oral Anticoagulants

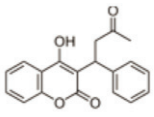
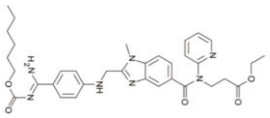
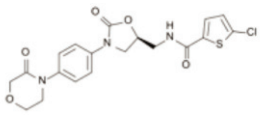
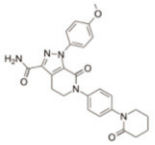
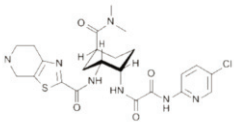
Anti-coagulant Drug	Chemical Formula and Molecular Weight	Tradename & Company	Chemical Structure
Warfarin	$C_{19}H_{16}O_4$ 308 g/mol	COUMADIN® Bristol-Myers Squibb	
Dabigatran etexilate	$C_{34}H_{41}N_7O_5$ 628 g/mol	PRADAXA® Boehringer Ingelheim	
Rivaroxaban	$C_{19}H_{18}ClN_3O_5S$ 436 g/mol	XARELTO® Bayer/ Janssen Pharmaceutical	
Apixaban	$C_{25}H_{25}N_5O_4$ 459/mol	ELIQUIS® Pfizer and Bristol-Myers Squibb	
Edoxaban	$C_{24}H_{30}ClN_7O_4S$ 548 g/mol	LIXIANA® Daiichi Sankyo	

Table 2
Oral Anticoagulant Characteristics

Anti-coagulant Drug	Targeted Enzyme	Half-Life (hrs)	% Bio-avail-ability	Renal Excretion	Method of testing if needed	Dose/ day	FDA approval	Name of Trial	Safety risks for major bleeding vs. warfarin
Warfarin	Vitamin K dependent Enzymes	40		92	Prothrombin Time (PT)	1	1954* in humans	----	----
Dabigatran	Thrombin	12 to 17	6	80	Thrombin Time (TT) or Dilute TT	2	2010	RE-LY	Comparable
Rivaro-xaban	Factor Xa	9	80	65	anti-Xa	1	2011	ROCKET AF	Comparable
Apixaban	Factor Xa	9 to 14	50	25	anti-Xa	2	2012	ARIS-TOTLE	Superior

a problem with bleeding. This is particularly relevant in the case of catastrophic bleeding due to excess medication. Guidance on treatment includes quickly providing routine supportive care. Because the new anticoagulants have short durations of effectiveness discontinuing the anticoagulant most commonly resolves the problem of excess
medication.[13] However, if necessary, activated charcoal may be an option if the ingestion is within several hours of the treatment. As dabigatran is only 1/3 bound by albumin, hemodialysis is a possibility reversal of dabigatran, particularly in cases when poor renal function delays natural drug elimination.[16]. Vitamin K has no indication in the scenario of reversing action of the new anticoagulants. However, another major benefit of warfarin includes the effectiveness of administering Vitamin K as an antidote in the event of over-anticoagulation.
Specific drug-directed neutralizing antibodies are under development for oral anticoagulants dabigatran and apixaban against Factors IIa and Xa, respectively.[17, 18]
The challenge to physicians is clear. Warfarin's use since the 1950s provides practioners with expertise not yet available when

using the newer oral anticoagulants. Cost considerations are an extra burden that new medications add to decision-making. The solution to the age-old cost/benefit conundrum and the necessary substantial familiarity with the new drugs are issues to be solved by experience and time. The end result will be better outcomes for our patients, our guiding mission.

References

1. Davie, E.W., Fujikawa K., Kurachi, K., Kisiel, W., The role of serine proteases in the blood coagulation cascade. Adv Enzymol Relat Areas Mol Biol. , 1979. 48: p. 277-318.
2. Link, K.P. The discovery of dicumarol and its sequels. Circulation, 1959. 19(1): p. 97-107.
3. Li, T., Chang, C. Y., Jin, D. Y., Lin, P. J., Khvorova, A., Stafford, D. W, Identification of the gene for vitamin K epoxide reductase. Nature, 2004. 427(6974): p. 541-4.
4. Johnson, J. A., Gong, L., Whirl-Carrillo, M., Gage, B. F., Scott, S. A., Stein, C. M., Anderson, J. L., Kimmel, S. E., Lee, M. T., Pirmohamed, M., Wadelius, M., Klein, T. E., Altman, R. B., Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. Clin Pharmacol Ther, 2011. 90(4): p. 625-9.
5. Blickstein, D. and I. Blickstein, The risk of fetal loss associated with Warfarin anticoagulation. Int J Gynaecol Obstet, 2002. 78(3): p. 221-5.
6. Gage, B.F., Eby, C., Johnson, J.A., Deych, E., Rieder, M.J., Ridker, P.M., et al., Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clin Pharmacol Ther., 2008. 84(3): p. 326-31.
7. Thomson, J.M., Tomenson, J.A., Poller, L., The calibration of the second primary international reference preparation for thromboplastin (thromboplastin, human, plain, coded BCT/253). Thromb Haemost. 1984. 52(3): p. 336-42.
8. Connolly, S.J., Ezekowitz, M.D., Yusuf, S. et al, Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med, 2009. 361: p. 1139-51.
9. Patel, M.R., Mahaffey, K.W., Garg, J., et al., Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91. N Engl J Med 2011;365:883-91., 2011. N Engl J Med 2011;365:883-91.: p. 883-91.
10. Connolly, SJ, Eikelboom, J., Joyner, C., et al., Apixaban in patients with atrial fibrillation. N Engl J Med 2011. 363: p. 806-17.
11. Mantha, S. and J. Ansell, An indirect comparison of dabigatran, rivaroxaban and apixaban for atrial fibrillation. Thromb Haemost, 2012. 108(3): p. 476-84.
12. Ahmad Y, L.G., Apostolakis S., New oral anticoagulants for stroke prevention in atrial fibrillation: impact of gender, heart failure, diabetes mellitus and paroxysmal atrial fibrillation. Expert Rev Cardiovasc Ther., 2012. 10(12): p. 1471-80.
13. Kaatz, S., Kouides, P. A., Garcia, D. A., Spyropolous, A. C., Crowther, M., Douketis, J. D., Chan, A. K., James, A., Moll, S., Ortel, T. L., Van Cott, E. M., Ansell, J. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. Am J Hematol, 2012. 87 Suppl 1: p. S141-5.
14. Cabral, K.P. and J. Ansell, Oral direct factor Xa inhibitors for stroke prevention in atrial fibrillation. Nat Rev Cardiol, 2012. 9(7): p. 385-91.
15. Littrell, R. and Flaker, G. Apixaban for the prevention of stroke in atrial fibrillation. Expert Rev Cardiovasc Ther, 2012. 10(2): p. 143-9.
16. van Ryn, J., Stangier, J., Haertter, S., Liesenfeld, K. H., Wienen, W., Feuring, M., Clemens, A., Dabigatran etexilate--a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost, 2010. 103(6): p. 1116-27.
17. Portola Pharmaceuticals, Portola initiates phase 2 study of PRT4445, universal antidote for factor Xa inhibitor anticoagulants [press release]. 2012.
18. van Ryn, J., Litzenburger, T., Gan, G., Coble, K. and Schurer, J., In vitro Chacterization, Pharmacokinetics and Reversal of supratherapeutic doses of dabigatran-induced bleeding in rats by a specific antibody fragment antidote to dabigatran., in American Heart Association: Scientific Sessions. 2012.
19. Horton, J.D., and Bushwick, B.M., Warfarin Therapy: Evolving Strategies in Anticoagulation, Am Fam Physician., 1999 59(3):635-646.
20. Potpara, T. S., Polovina, M. M., Licina, M. M., Stojanovic, R. M., Prostran, M. S., Lip, G. Y., Novel oral anticoagulants for stroke prevention in atrial fibrillation: focus on apixaban. Adv Ther., 2012. 29(6): p. 491-507.
21. Doggrell, S.A., More light at the end of the tunnel - apixaban in atrial fibrillation. Expert Opin Investig Drugs, 2012. 21(8): p. 1235-9.
22. Hochtl, T. and Huber, K., New anticoagulants for the prevention of stroke in atrial fibrillation. Fundam Clin Pharmacol, 2012. 26(1): p. 47-53.
23. Pollack, C.V., Jr., New oral anticoagulants in the ED setting: a review. Am J Emerg Med, 2012.
24. Carter, K. L., Streiff, M. B., Ross, P. A., Wellman, J. C., Thomas, M. L., Kraus, P. S., Shermock, K. M. Analysis of the projected utility of dabigatran, rivaroxaban, and apixaban and their future impact on existing Hematology and Cardiology Anticoagulation Clinics at The Johns Hopkins Hospital. J Thromb Thrombolysis, 2012. 34(4): p. 437-45.
25. Esmon, C.T., What did we learn from new oral anticoagulant treatment? Thromb Res., 2012. 130(Suppl 1): p. S41-3.