EDUCATIONAL COMMENTARY – ORAL ANTICOAGULANT THERAPEUTIC MONITORING AND POINT-OF-CARE TESTING

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Learning Outcomes
Upon completion of this exercise, the participant will be able to:

- Understand how warfarin exerts its anticoagulant effect.
- Discuss the reasons that laboratory testing is crucial for oral anticoagulant therapy.
- Describe the potential advantages and disadvantages of point-of-care INR testing.

Oral Anticoagulant Therapy
Oral anticoagulant therapy with vitamin K antagonists is commonly employed in the treatment and prevention of venous thromboembolism. Warfarin is the most frequently used vitamin K antagonist. Vitamin K is an essential cofactor in the post-translational carboxylation of glutamic acid residues of coagulation factors II, VII, IX, and X, and the anti-thrombotic proteins C and S. These factors are synthesized as inactive forms, but become functional as carboxylation creates calcium-binding sites.

Mode of Action of Warfarin
Dietary vitamin K is reduced to vitamin K-H₂ by the enzyme vitamin K reductase. Vitamin K-H₂ is converted to vitamin K epoxide during the carboxylation of coagulation factors. Vitamin K epoxide is returned to vitamin K by the enzyme vitamin K epoxide reductase. A single molecule of vitamin K may be involved in many carboxylations. This cycle is illustrated in the following figure.

[Diagram of vitamin K cycle]

Warfarin inhibits the enzymes vitamin K reductase and vitamin K epoxide reductase, preventing formation of vitamin K-H₂. Thus, warfarin is not a direct anticoagulant, but exerts its antithrombotic effect by decreasing the rate at which the vitamin K-dependent factors are carboxylated. The onset of the warfarin effect is related not only to the degree of inhibition of the vitamin K cycle enzymes, but also to the
half-lives of the vitamin K-dependent factors (factor II ~60 hours; factor VII ~6 hours; factor IX ~24 hours; factor X ~48 hours; protein C ~8 hours; protein S ~30 hours). With the initiation of warfarin therapy, factor VII levels fall quickly due to the short half-life and produce a measurable effect in laboratory tests, but the full therapeutic effect is delayed until factor X and factor II levels fall over several days.

Importance of Laboratory Monitoring

Laboratory monitoring of warfarin is important for a number of reasons.

- First, warfarin has a relatively narrow therapeutic window. When the anticoagulant effect is within this window, warfarin is both safe and effective, but subtherapeutic anticoagulation increases the risk of recurrence or extension of thrombosis and supratherapeutic anticoagulation increases the risk of hemorrhage. Either hemorrhagic or thrombotic complications may lead to morbidity or death.

- The dose-response of warfarin is highly variable between individuals and even in the same individual over time, so the level of anticoagulation cannot be reliably predicted from the warfarin dose.

- The effect of warfarin is affected by a large number of medications. For example, warfarin is potentiated by acetaminophen, erythromycin, fluconazole, isoniazid, miconazole, propranolol, and cimetidine and inhibited by nafcillin, rifampin, cholestyramine, barbiturates, prednisone, and carbamazepine. Herbal supplements and herbal medications are a frequently overlooked source of changes in dose-response.

- Warfarin’s effect is influenced by dietary changes. Foods rich in vitamin K include green leafy vegetables, butter, margarine, liver, milk, ground beef, coffee, pears, olive oil, and soybean oil. The half-life of vitamin K is only 1.5 days, so continual intake is required and changes in vitamin K intake affect the anticoagulation level within days.

- Co-morbidities may change the baseline risk of hemorrhage or thrombosis and lead to changes in either the therapeutic targets or intensity of monitoring.

- Patient compliance with prescribed therapy is variable.

Prothrombin Time and INR Testing

The test most commonly used to monitor warfarin therapy is the one-stage prothrombin time (PT) due to it being affected by 3 of the 4 vitamin K-dependent factors (II, VII, and X). The PT test measures the time of the following reaction:

\[ \text{Plasma} + \text{Thromboplastin} + \text{Ca}^{2+} \rightarrow \text{Fibrin Clot} \]

Unfortunately, PT values do not agree well between different laboratories. A large variety of thromboplastins and coagulation analyzers are commercially available and used in clinical laboratories and PT results are not standardized. Consequently, the PT, by itself, is unsuitable for assessing warfarin effect.
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The International Normalized Ratio, or INR, was developed to standardize PT values. Under the INR system, a thromboplastin is assigned an International Sensitivity Index (ISI) value. The ISI indicates the relative prolongation of the PT, or sensitivity, of the thromboplastin compared to an international reference thromboplastin. If a thromboplastin has the same sensitivity as the reference thromboplastin, then its ISI is 1.0. A higher ISI value indicates that a thromboplastin is less sensitive than the reference thromboplastin. The ISI is used in the following formula to calculate an INR value from a PT value.

\[
\text{INR} = \left( \frac{\text{patient } PT}{\text{mean normal } PT} \right)^{\text{ISI}}
\]

The ISI is usually determined by the thromboplastin manufacturer. Because the PT is also affected by the coagulation analyzer, a thromboplastin is generally assigned different ISI values for different models or classes of coagulation analyzers. The mean normal PT is determined in each laboratory by averaging the PT values from at least 20 healthy individuals.

Theoretically, the INR is so standardized that if a patient were tested by more than one laboratory, all the resultant INR values would be equivalent. In practice, the INR falls short of this ideal, but is considerably more comparable than the PT and has become the standard for monitoring and adjusting warfarin therapy. Use of the INR rather than the PT enables therapy to be managed more effectively as patients travel, relocate, or obtain care from multiple physicians in different healthcare settings.

**Point-of-care Testing**

Because warfarin management is so heavily dependent on laboratory testing, recent years have seen a rise in the availability of point-of-care testing (POCT) for INR determinations. POCT is used in a variety of settings, including physicians’ offices, anticoagulation clinics, hospital rooms, surgical suites, and home care. Patient self-testing is common in Germany and has been approved since 1997 by the FDA in the United States.

**Advantages of POCT**

POCT offers several advantages compared to traditional laboratory testing.

- POCT offers rapid turnaround time. While traditional testing may take anywhere from 30 minutes to several hours or even overnight, depending on the setting, POCT results are available within minutes, with a number of resultant benefits. By having INR results available during patient visits, clinicians can discuss the results’ implications for efficacy and safety in person rather than by phone at a later time, improving clinical-patient interactions. Results are unlikely to be overlooked, suspicious results can be confirmed on the spot, the time from testing to therapeutic adjustment is shortened, and critical values can be addressed immediately.
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- POCT is more convenient for patients and clinicians. Patients may be able to avoid the inconvenience of several trips to the laboratory. Clinicians may be able to avoid the inconvenience of handling laboratory reports and tracking down patients to relay results and instructions. Greater convenience facilitates more frequent testing, and more frequent testing has been shown to increase the proportion of time in the therapeutic range.
- Most POCT methods use very small specimen volumes that decrease iatrogenic blood loss. Furthermore, when fingerstick specimens are used, as is the case with most POCT methods, problems associated with venipuncture specimens can be avoided, including needlestick injuries, inadequate mixing of blood and anticoagulant, improper blood-to-anticoagulant ratio, mislabeled specimen tubes, and transportation effects.

**Disadvantages of POCT**

Although POCT methods are often marketed as being simple and error-proof, there are some important potential disadvantages that must be addressed.

- POCT methods vary considerably in their precision and accuracy, so POCT results may be less reproducible and significantly different from traditional laboratory results. The differences tend to be greater with high INR values, but some POCT methods are inaccurate even at therapeutic levels. Different POCT methods often yield widely discrepant results.
- Specimen quality is highly affected by technique. Coagulation tests are among the tests most seriously affected by specimen quality. Most POCT INR methods use fingerstick specimens, whose quality tends to be more difficult to control than that of venipuncture specimens. INR results can be dramatically skewed by inadequate blood flow, excessive squeezing, and delayed specimen application. Some POCT methods are also sensitive to the amount of blood applied. Furthermore, with fingerstick testing, the entire specimen is consumed so tests cannot be added on and specimens cannot be compared between laboratories to confirm results or troubleshoot instruments.
- POCT may be performed by non-laboratory personnel who are unfamiliar with good laboratory practices, regulations, safety, and analyzer failure modes. Fortunately, most POCT devices are designed to be operated by non-laboratorians and have built-in features to decrease the chance of producing invalid results; however, it is imperative that testing personnel understand the method’s limitations or else patients may be placed at risk from inaccurate results.
- Traditional laboratory results often become part of an integrated medical record that is available to a large number of practitioners or else lab reports can easily be provided to practitioners. On the other hand, POCT results are typically recorded in patients’ charts and are not readily accessible to other practitioners. Consequently, POCT may decrease the ability to effect true integration of care.
Implementing POCT
Before POCT is implemented, it is vital for patients’ safety that several critical steps be taken.

- A laboratory professional should be retained to assist with POCT method selection, test implementation, and ongoing quality assurance.
- POCT methods must be assessed for accuracy. This is best achieved by comparing results with a trusted traditional laboratory. If multiple POCT instruments are to be used, they must be compared against each other to assure equivalency of results.
- A robust quality assurance plan must be developed, including method validation, standard operating procedures, quality control procedures, result reporting, and action plans for extreme or unexpected results.
- Testing personnel must be adequately trained in specimen collection techniques and test performance procedures.

Summary
In summary, warfarin therapy is safe and effective in a relatively narrow therapeutic range and INR testing is required for proper therapeutic management. POCT INR testing has the potential advantages of improved timeliness, better clinical interactions, increased testing frequency, and greater convenience, but the potential disadvantage of decreased accuracy compared to other testing methods. By careful selection of POCT methods, a strong liaison with laboratory professionals, and a well designed and executed quality assurance program the potential disadvantages can be avoided and the potential benefits realized.

Suggested Reading

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