



Saint Luke's Regional Laboratories Clinical Laboratory Letter

November 2013

What You Need to Know About NOAC Testing

New oral anticoagulants (NOAC) have been approved by FDA for reducing the risk of stroke in patients with nonvalvular atrial fibrillation. In addition, rivaroxaban can be used for prevention of deep vein thrombosis. Dabigatran Etexilate (Pradaxa®) is a reversible direct inhibitor of thrombin (factor IIa) while rivaroxaban (Xarelto®) and apixaban (Eliquis) are reversible direct inhibitors of factor Xa.

One of the major problems with NOAC is the unavailability of FDA approved companion diagnostic tests to measure their concentration or anticoagulant effect. Another problem is that these drugs interfere with routine coagulation tests in an unpredictable fashion. Both factor II and factor X are in the common pathway of the coagulation cascade. Usually, a deficiency or inhibitor of a coagulation factor in the common pathway elevates both the protime (PT) and activated plasma thromboplastin time (aPTT). However, this general rule does not hold true for NOAC.

Supra-therapeutic concentrations of dabigatran result in modest elevations of the PT and INR (<2.0). However the effect on INR is variable and unpredictable. PT and INR should not be used as a measure of the anticoagulant effect of dabigatran. There is a reasonable, non-linear correlation between dabigatran plasma concentration and the aPTT. An aPTT >2.5 x control may indicate over-anticoagulation. APTT can be used to detect an anticoagulant effect, but it cannot be used for quantitation of dabigatran concentration.

Thrombin time (TT) may be elevated as much as 10 to 20 times normal in patients with therapeutic plasma concentrations of dabigatran. TT is too sensitive for routine monitoring, but a normal thrombin time can be used to rule out clinically significant concentrations of dabigatran. A dilute thrombin time is being developed to measure dabigatran concentration.

Rivaroxaban at the recommended dose of 10 to 20 mg once daily usually elevates the PT. The protime reagent used at SLHS is increased in a linear and concentration dependent manner. The aPTT reagent used at SLHS is not very sensitive to rivaroxaban. Therefore, PT is preferred over APTT.

Rivaroxaban interferes with the anti-factor Xa assay that is routinely used to monitor heparin. A low result can be used to rule out a clinically relevant rivaroxaban concentration, but an elevated result does not provide an accurate drug level since this assay was calibrated with heparin. A specific anti-Factor Xa assay for rivaroxaban is not currently available

Unlike rivaroxaban, apixaban has little effect on the PT or aPTT. Neither test is helpful in determining the presence or absence of drug. Apixaban will interfere with a chromogenic anti-factor Xa assay calibrated to monitor heparin. A low result can be used to rule out clinically relevant apixaban concentration. An anti-factor Xa assay using a specific calibrator is not available.

An audit of coagulation tests ordered for patients receiving NOAC during October was undertaken to determine if the appropriate coagulation tests were being ordered. The medical records were reviewed for 21 patients anticoagulated with dabigatran, 20 with rivaroxaban and 36 with apixaban.

Physicians ordered coagulation tests for 15 of the 21 patients receiving dabigatran. In many cases only a PT/INR was ordered, which is not the optimal test. PT ranged from 14.3-19.0 with a median value of 16.4 (*normal 11.7–14.2 seconds*). APTT ranged from 45–61 with a median of 48 (*normal 22–34 seconds*).

Coagulation tests were ordered for 15 of the 20 patients treated with rivaroxaban. PT ranged from 12.7 to 23.4 with a median of 16.6 seconds. APTT ranged from 22 to 38 with a median of 31 seconds.

Coagulation tests were ordered at admission for 34 of the 36 patients treated with apixaban. About half the time only a PT/INR was ordered. PT ranged from 12.1 to 14.6 with a median of 13.5 seconds. APTT ranged from 31 to 35 with a median of 33 seconds.

Unlike warfarin, which has a long-lasting effect and can be monitored with an INR drawn at any time, NOAC have short half lives. Knowing the timing of the last dose is critical for interpretation of results. For example, rivaroxaban elevates PT at 4 hours after the last dose, but not at 12 hours. Caution must be exercised in interpreting a single coagulation test result.

All of the NOAC are given at fixed doses and do not require routine coagulation monitoring because of their predictable pharmacokinetics. Ordering of coagulation tests for patients receiving NOAC should be reserved for clinical situations such as life threatening bleeding, urgent invasive procedures or suspected overdose. In these situations the preferred test is listed below.

| NOAC | Present | Future |
|-------------|----------|-----------|
| Dabigatran | aPTT | Dilute TT |
| Rivaroxaban | PT | Anti-FXa |
| Apixaban | Anti-FXa | Anti-FXa |

Clinical Significance of Red Cell Antibodies

When a physician orders a red blood cell transfusion, the blood bank performs compatibility testing which includes an ABO and Rh type and an antibody screen. The antibody screen detects alloantibodies and autoantibodies in patient plasma. Approximately 95% of patients have a negative antibody screen which means that naturally occurring or *expected* anti-A and/or anti-B are the only red cell antibodies found in their plasma. If the antibody screen is negative, crossmatch compatible blood can be available within 15 minutes.

But what about those patients whose antibody screen is positive, indicating the presence of an *unexpected* red cell antibody? The answer is, it depends on the antibody detected. Red cell antibodies are not alike and are categorized according to their clinical significance. Some antibodies are capable of causing hemolytic transfusion reactions and/or hemolytic disease of

the newborn and fetus while others are not. The table below categorizes the most common red cell antibodies by their clinical significance.

| Significant | Insignificant |
|--|--|
| Duffy (Fy ^a , Fy ^b) | A1 |
| Kell (K,k) | Bg |
| Kidd (Jk ^a , Jk ^b) | Chido/Rodgers |
| Rh (D, C, c, E, e) | Cs ^a |
| Vel | HTLA |
| | JMH |
| | Kna |
| | Lewis (Le ^a /Le ^b) |
| | Lutheran (Lu ^a /Lu ^b) |
| | M,N |
| | McC ^a , Yk ^a |
| | P ₁ |
| | Sd ^a |
| | Xg ^a |

If an antibody is clinically significant, the transfusion service needs to provide red blood cells that are antigen negative for the corresponding antibody. For example, if a patient has anti-Kell antibody, they will be transfused with Kell negative blood. When a patient has multiple clinically significant antibodies (i.e. anti-K, anti-E, anti-Fya), the task of finding compatible blood becomes more challenging. Many times a large number of units must be antigen typed to find a single compatible unit of blood. This may necessitate sending the specimen to the consultation lab of our local blood center which maintains a larger inventory of red blood cells. The time required to find a sufficient number of compatible units can range from hours to days depending on the complexity of the case.

If an emergent transfusion is required for a patient with one or more red cell antibodies, the transfusion service may not have time to supply compatible antigen-negative blood. In this situation, the risk to benefit ratio of transfusing incompatible blood to a patient with life threatening hemorrhage must be considered. Transfusion of incompatible blood is usually beneficial in these situations because most clinically significant antibodies do not destroy transfused red cells immediately. The transfusion service at Saint Luke's Hospital and the clinical pathologists are available on a 24x7 basis for consultation.