The Laboratory has started to use a new reagent for the Prothrombin Time (PT) test which has affected not only the normal values but also the relationship of the PT value to the International Normalized Ratio (INR).

The PT, reported in seconds to clotting, measures the integrity of the extrinsic and common coagulation pathways. PT prolongation is most commonly caused by a factor deficiency involving Factor VII (extrinsic pathway), or fibrinogen or Factors II, V, or X (common pathway). Acquired causes of factor deficiency are more common than congenital causes. The liver synthesizes all coagulation factors except VIII (it synthesizes only some) and liver disease will effect both the PT and the PTT but the effect on the PT is earlier and more prominent. This is in part due to the short half life of Factor VII which is only 4-6 hours. Vitamin K deficiency and warfarin therapy, which impairs vitamin K, impair synthesis of Factors II, VII, X and IX.

PT results cannot be compared between labs. The PT value is very dependent on (1) pre-analytical variables, such as a traumatic phlebotomy, heparinization or tube fill, (2) biological variables such as hematocrit, warfarin therapy, vitamin K deficiency, antibiotics or liver disease and (3) analytical variables associated with the specific reagent and instrument being used for the assay. In addition, the normal PT range varies with age. It is higher in younger infants and gradually approaches the “adult” value somewhere between ages 6-12 months or in some studies even later. Normal ranges for pre-mature infants are at best approximate.

This variability becomes especially important when monitoring oral anticoagulation therapy. Vitamin K dependent coagulation proteins have different initial concentrations & half lives; different absorptions & metabolic clearance patterns, both within and between patients. The steady state level during therapy is affected by concomitant medications, co-morbid conditions, changes in diet, patient compliance and the growth and development of the child.

Partial compensation for analytical variability associated with reagents is achieved by calculating the Internationalized Normalized Ratio (INR). Reagents for the PT assay are compared by manufactures for sensitivity to reductions in procoagulants induced by oral anticoagulation therapy and assigned an International Sensitivity Index (ISI). This comparison uses the “gold standard” manual tilt tube method. In reality this calibration is at best a third generation comparison to the WHO standardized reagent and still has a variation of 5-9% and does not incorporate instrument variability, which is incorporated by using the lab specific geometric mean normal value. In addition the ISI value can drift since its original determination. An ISI of 1.00 is considered “standard”. A reagent with an ISI < 1 is more sensitive and a reagent with an ISI > 1 is less sensitive to factor deficiencies. Using the assigned ISI the INR is calculated as:

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\text{INR} = \frac{\text{Patient PT}}{\text{Geometric Mean Normal PT in the specific lab}} \text{ISI}
\]

It had been many years since we extensively evaluated the normal PT values and drift not detected in our on-going evaluations was inevitable. Knowing that we would be switching reagents, including a change in the ISI, we undertook an extensive evaluation of the PT assay. We evaluated the following…

1. The normal range with the old reagent using one year’s worth of data from “healthy” patients > 1 year old.
2. The normal values using both the old and new reagents using prescreened healthy employees. We established a correlation.
3. The sensitivity of the new reagent to single factor deficiencies
4. A comparison of the INR using the new and old reagents over a broad range of values. We established a correlation.

Normal PT Range: In consultation with Dr. Wicklund, the new normal range was set at 11.3-15.6.
Sensitivity to Factor Deficiencies: The old ISI was 1.86 and the new ISI is 1.24. The new reagent is more sensitive to factor deficiencies. It is very rare for a patient to have 100% of all factors but one, and you can reasonably expect that the PT will be significantly elevated before a single factor is as low as indicated below.

Factor % when PT > 15.6:      F VII (64.6%)  F V (50.0%)  F II (27.9%)  F X (54.5%)

INR: As depicted in the graft below the relationship of the ISI and INR is complex. In addition the new results have hopefully corrected for drift in the old data over the last few years. The old ISI was 1.86 and the new ISI is 1.24. It will be a year before I am sure but I believe the new data is more accurate.

The simplest guidelines for the relationship of the old INR to the new INR are:

- Previous INR < 1.5:  New INR is unchanged
- Previous INR 1.5-2.5  New INR is 0.10 lower
- Previous INR > 2.5  New INR is 0.35 lower

The therapeutic range for warfarin therapy is a clinical decision but an INR of 2-3 is generally a good range for most indications and an INR of 2.5-3.5 is a good range when a higher amount of anticoagulation is desired.

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CME Series
Sponsored by Department of Pathology & Laboratory Medicine

Date:  CANCELED for September
Time:  Noon – 13:00
Location:  Lab Conference Room 2206.10 WT

Charles Barnes, PhD; Linda Cooley, MD, FCAP, FACMG; Uttam Garg, PhD, DABCC, DABFT, FACB; Marilyn Hamilton, MD, PhD; Carol Saunders, PhD, FACMG; Rangaraj Selvarangan, PhD, D(ABMM); Lei Shao, MD; Vivekanand Singh, MD; Eugenio Taboada, MD; Shihui Yu, MD, PhD.; David Zwick, MD