Factors That Influence INR system Comparisons

The time required to convert fibrinogen into fibrin, in the presence of thromboplastin and calcium, is known as the prothrombin time or PT. Prothrombin time (PT) is the test of choice for monitoring patients on oral anticoagulants.

Standardization of PT

PT was reported for many years as the clotting time in seconds. However, different PT reagents (thromboplastins) have different sensitivities to the various proteins involved in the clotting process. This can cause very large differences in the prothrombin times when one sample is tested using multiple reagents. The early thromboplastins, first used in the 1960's commercially prepared reagents, varied in their sensitivities, which lead to patient management issues due to the inherent variability in the clotting time expressed in seconds.

To address this issue, the International Normalized Ratio or INR system was introduced by the World Health Organization WHO in 1983, to standardize patient results across different test systems. [1,2]

The INR is PT ratio raised to the power of the ISI according to the following equation:

$$INR = (PT/MNPT)^{ISI}$$

The *International Sensitivity Index* (ISI) is a measure of the sensitivity of the PT reagent. The ISI for a PT reagent is determined by comparing that reagent to the WHO standard. Using the INR scale theoretically eliminates differences between PT reagents by standardizing to the WHO and allows results to be compared between labs regardless of the type of thromboplastin.[3,4]

Errors in PT determination

When the INR system was introduced, it was believed that it would eliminate the differences seen between PT reagents. However, there were a number of variables that were not quantifiable at the time that continue to cause differences when comparing systems including: [5]

- Errors in PT determination
  - Pretest variables
  - Variations in manual technique
- Incorrect mean normal value (MNPT)
- Incorrect ISI of Thromboplastin
  - Incorrect calibration
  - Change in ISI over time
  - Poor distribution of warfarin samples
  - Incorrect choice of reference
- Incorrect transformation of PT Ratio to INR
- Rogue plasmas
- Effects of instruments

The factors above can cause problems when comparing prothrombin time systems to each other. Problems with comparisons between systems can also arise due to the following:

- Lack of comparability of INR between reagents when used at onset of warfarin treatment
- Loss of accuracy and precision when using reagents with high ISI
- Loss of accuracy with different instrumentation
- Lack of reliability of ISI provided by manufacturer
- Incorrect calculation of INR from use of inappropriate control plasma to determine the MNPT.

Interfering Factors [6,7]

Factors that affect warfarin mechanism or metabolism can contribute to differences when comparing systems. Such factors include:

- Illness (e.g. congestive heart failure, hyperthyroidism, hypothyroidism, hepatic failure)
- Drugs
- Diet (vitamin K and alcohol)
- Also factors that affect the PT test itself can cause differences when comparing systems.

These factors are relevant when comparing a whole blood finger stick to a plasma based lab system:

- Contaminated line (Heparin)
- Antiphospholipid antibodies
- Hematocrit

References

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