International Normalized Ratio (INR)

More than 2 million Americans are estimated to be treated with warfarin (National Center for Statistics, 1984). As with any medical treatment the weighing of risks and benefits must be carefully balanced. Anticoagulation agents have a narrow therapeutic index, and the more narrow the therapeutic index, the greater the chance for adverse effects, *i.e.*, bleeding (Ortel, 1995). To achieve optimal effects and evaluate the patient's response to warfarin, the clinician must keep in mind several important concepts. First, the intensity and duration of the therapy depends on the identified need for treatment. Second, the dose of warfarin must be patient specific, and lastly, periodic assessment of effectiveness is necessary due to warfarin's narrow therapeutic index. Considering the aforementioned facts, the blood test chosen to monitor the patient's response to warfarin must be accurate, reliable and cost effective (Ortel, 1995).

The traditional method of determining the efficacy of anticoagulation therapy is the prothrombin time (PT). This was first described by Armand J. Quick in 1935. He used thromboplastin derived from rabbit brains to prove his assumption that patients with bleeding abnormalities secondary to obstructive jaundice was due to a deficiency of prothrombin. This is now known to result from reduced levels of liver-produced vitamin K-dependent blood coagulation factors II, IX, and X (Florell & Rodgers, 1996).

Today a blood sample is collected in a tube containing citrated sodium, in the laboratory the sample is spun in a centrifuge, and a specific volume of thromboplastin reagent is added to the sample. The time until a fibrin clot forms, measured in seconds, is reported as the PT (Ortel, 1995). The thromboplastin reagent can be either an extract of mammalian tissue (lungs heart or brain of animals) rich in tissue factor, or a recombinant proportion of human tissue factor in combination with phospholipids (Hirsh & Poller, 1994).

Because thromboplastins are produced using different methods and from different sources, the sensitivity of an individual thromboplastin to another can vary greatly. The more sensitive the thromboplastin reagent, the longer the resulting PT. Conversely, the less sensitive the reagent the shorter the resulting PT. Variance can even occur within a single batch depending on shelf time (Ortel, 1995). This variability in sensitivity and its effect on PT outcomes can have a major detrimental effect on the management of warfarin therapy in patients requiring anticoagulation. This variability has also caused great international debate and concern for several decades (Florell & Rodgers, 1996).

To help standardize this difference two formats were developed, the first was the International Sensitivity Index (ISI) and the second was the International Normalized Ratio (INR). The INR was developed to incorporate the ISI values and attempt to make PT results uniformly useable. The manufacturers assign an ISI to each batch of reagent after comparing each batch to a "working reference" reagent preparation. This "working reference" has been calibrated against internationally accepted standard reference preparations which have an ISI value of 1.0 (Ortel, 1995). By definition, the more sensitive thromboplastins have an ISI of less than 1.0 and the less sensitive are greater

than 1.0. The ISI value is critical for calculation of the INR, because the ISI value is the exponent in the formula. Consequently, small errors in the ISI assignment may affect the calculated INR substantially (Florell & Rodgers, 1996).

To resolve the problem of highly variable PTs, the use of the INR has been recommended for monitoring patient's oral anticoagulant therapy. This recommendation is supported by the American College of Chest Physicians, the National Heart, Lung and Blood Institute and the British Society for Hematology (Nichols & Bowie, 1993).

It is important to emphasize that the INR is not a new laboratory test. It is simply a mathematical calculation that corrects for the variability in PT results attributable to the variable sensitivities (ISI) of the thromboplastin agents used by laboratories.

A target INR range of 2.0 to 3.0 is recommended for most indications, such as treatment or prophylaxis of DVT, prevention of further clotting in MI's and other preventive measures for patients with atrial fibrillation. An INR of 2.5 to 3.5 is recommended for patients with prosthetic heart valves (Ortel, 1995).

Using the INR in other medical conditions, such as coagulopathy or liver disease has not been deemed appropriate as of this time, because INR was originally developed using anticoagulated patient populations. Despite its usefulness during routine monitoring of warfarin therapy, the use of INR for monitoring during the induction phase of therapy has not been fully supported (Hirsh & Poller, 1994). Reliability is lost during the initial days of therapy because of the varying rates of plasma clearance of vitamin K-dependent clotting factors. These factors are what the thromboplastin reagents are sensitive to and in turn what the INR and PTR are actually reporting. In addition, individual thromboplastin reagents vary in their sensitivities to the vitamin K-dependent clotting factors (Ortel, 1995).

The INR system can be precise and valid when a sensitive thromboplastin and manual method of clot detection are used. However, it loses precision and accuracy when used to convert PT ratios obtained with less-sensitive thromboplastin reagents or when automated clot detection systems are used. These problems can be avoided by using reagents with low ISI's and proper calibration of machinery.

Although the INR system is far from perfect, it is the only practical solution currently available. With all of its faults, it is much better than an unadjusted PT system. Although the clinician would like a system with little or no variability, the goal is unattainable unless a standardized sensitive reagent is universally adopted.

THE INR (INTERNATIONAL NORMALIZED RATIO) FOR MONITORING ORAL ANTICOAGULANT THERAPY

Introduction: The PT test

The prothrombin time (PT) has traditionally been used to monitor the use of oral anticoagulants since these drugs, typified by Coumadin, lower the levels of the vitamin K dependent factors II, VII, IX, and X. Decreases in the levels of these factors result in a prolonged PT since factor II, VII, and X are in the PT or extrinsic pathway. The PT evaluates the extrinsic pathway factors by measuring the ability of a patient's recalcified plasma to clot when mixed with a crude mixture of a tissue factor activator and phospholipid, known as thromboplastin. Common sources of thromboplastins are rabbit brain or lung extracts. The patient's PT is usually reported as the clotting time, in seconds, and is compared with a normal range.

Limits of the PT for Monitoring Oral Anticoagulants

The marked regional differences in the sensitivity of thromboplastins have made inter-center comparisons of clinical trials evaluating oral anticoagulant drug regimens extremely difficult. This has hampered progress towards making appropriate recommendations regarding anticoagulation for patients at risk for thrombosis in various clinical settings. In addition, the lack of standardization of thromboplastins has made it difficult for practicing physicians to compare patient PT values done in different laboratories. Variability of thromboplastins has contributed to the problem of American physicians overanticoagulating their patients compared to their British counterparts, since Europeans have traditionally used more sensitive thromboplastins.

The INR and International Sensitivity Index (ISI)

The World Health Organization (WHO) recognized the variation in PT as a serious problem and formed a committee to establish uniformity of the PT test. This led to the development of the concept of the international sensitivity index (ISI) which is a correction factor for the response of different thromboplastins to oral anticoagulants. The ISI must be determined empirically for every combination of reagent and laboratory method. Each thromboplastin has a unique ISI value, with low ISI values assigned to sensitive thromboplastins which give relatively high PT values and high ISI values indicating thromboplastins relatively insensitive to the effects of oral anticoagulants. PTs obtained using different thromboplastins can then be compared by the calculation called the International Normalized Ratio (INR). The INR is defined as the ratio of a patient PT compared to the mean PT or normal donors raised to the power of the ISI or:

$$INR = \left(\frac{\text{Patient PT}}{\text{Mean Normal PT}} \right)^{ISI}$$

This calculation (i.e. of the INR) basically converts all PT results performed by different methods to a uniform scale despite the use of different thromboplastins. By using the INR, target values for therapeutic patient doses or oral anticoagulants become comparable from laboratory to laboratory. Determining the ISI is impractical for most laboratories, so many commercial vendors provide an ISI for their reagents in combination with the most commonly used instruments.

Limits of the INR

Often the clinical reason for requesting the PT is not specified and therefore some laboratories convert all PTs to an INR. It should be remembered that the INR only has meaning for patients on a stable doses of anticoagulants. The INR should not be used to evaluate the coagulation status of patients who have not been anticoagulated for at least one week or in those with an abnormal PT for other reasons, e.g., liver disease.

CALIBRATIONS

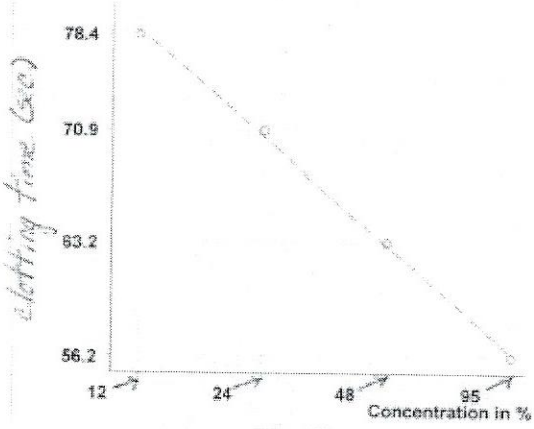
Date: Tuesday November 16, 2010, 06:45 AM

Methodology: Factor VIII Assay

Type: Clot-based
Abbreviation: F VIII
Stago Abbreviation:
Calibration Mode: Linear

Calibration n°1 Thursday october 01, 2009. 11:52 AM

Measure in Sec.



	ID	Product Name	Lot
Ra	GKVIII	gkviii	66g1
Rb	12203	STA-PTT A	102922
Rc			
Rd	11851	CaCl2 0.025 M	999999

Log(c) = (- 6.2161 * Log(t)) + 12.8634

r = - 0.999

patient has 95% VIII activity at 56.2 sec.

Dil'n	Concent.	Measure	M/D	Interpol.	Calibrator	Calibrator name	Lot
1/2	95 %	56.2 Sec.		97 %	12350	STA-UNICALIB.	104345
1/5	48 %	63.2 Sec.		47 %	12350	STA-UNICALIB.	104345
1/10	24 %	70.9 Sec.		23 %	12350	STA-UNICALIB.	104345
1/20	12 %	78.4 Sec.		12 %	12350	STA-UNICALIB.	104345