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

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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 the PT of a normal control or in some laboratories to a normal range.

Limits of the PT for Monitoring Oral Anticoagulants For decades physicians have used a PT ratio (patient PT/control PT) to monitor oral anticoagulants. However, 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 levels 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 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 does of chronic 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.

Since there is great diversity among American thromboplastins, it is recommended that patients receiving warfarin be monitored by the INR to prevent both overdosing and underdosing. Currently, an increasing number of laboratories in the United States are adopting the use of the INR in reporting PT results since studies support the enhanced safety afforded by its use. In addition, the improved understanding of the variations in the PT has led to lower, more appropriate dosing level of oral anticoagulants in the United States.

For similar reasons, consideration is currently being given to the development of an INR for the APTT. This may be available in the future to improve the monitoring of patients receiving heparin therapy.

Summary The introduction and the use of the INR has improved the monitoring of patients on oral anticoagulants by correcting for variations in the PT caused by differences in the sensitivities of various thromboplastins. Use of the INR has probably also encouraged the use of lower but equally efficacious doses of oral anticoagulants. Copies of Transfusion Medicine Update can be obtained by calling (412) 622-7254. ■

References:

Hirsh J, Dalen JE, Deykin D, Poller L: Oral anticoagulants: Mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest (Supplement) 102:312-326, 1992.

Hirst J: Oral anticoagulant drugs. New Engl J Med 324:1865-1875, 1991.

Correction: The previous *Transfusion Medicine Update* entitled "Hematopoietic Stem Cell Transplants" for May 1995, was authored by Alan Winkelstein, M.D and Joseph E. Kiss, M.D.

The Institute for Transfusion Medicine is offering a full-day seminar on Saturday, September 23, 1995, entitled "Transfusion Medicine Update-1995." The seminar will be held at the Sheraton Hotel, Station Square in Pittsburgh. If you are interested in receiving a brochure, please call Patricia Simko, (412) 647-9541.