REVIEW ARTICLE

INTERNATIONAL NORMALIZED RATIO (INR)

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Prothrombin time (PT) and its derived measures Prothrombin Ratio (PR) and International Normalized Ratio (INR) are the measures of extrinsic pathway of coagulation. They are used to monitor the warfarin dosage, liver damage and vitamin K status. The reference range for PT is usually 12-15 seconds and for INR is 0.8-1.2.[1]

PT measures factors II, V, VII, X and fibrinogen.[1,2,3] It is used in conjunction with the activated partial thromboplastin time (APTT) which measures the intrinsic pathway.[4,5,6] Prothrombin time is the time taken by the plasma to clot after addition of tissue factor (obtained from animals). It measures the quality of the extrinsic pathway (as well as the common pathway) of coagulation.

Prothrombin time can be measured roughly on whole blood as in neonates, but is more commonly measured from plasma. Blood is taken into a vacutainer containing liquid citrate. Citrate acts as an anticoagulant by consuming all the calcium in the sample. The blood is mixed and centrifuged to separate blood cells from the plasma. The plasma is placed in a coagulation machine which takes a sample of the plasma. An excess of calcium is added, which enables the blood to clot again. Tissue factor or thromboplastin is added and the time taken by the sample to clot is measured optically.

The prothrombin ratio is the PT of a patient divided by that of control.[7,8,9]

INR is a world-wide routinely used factor in the monitoring of oral anticoagulation therapy. However, it was reported that other factors, e.g. factor II may even better reflect the therapeutic efficacy of oral anticoagulation therapy and therefore may be potentially useful for this purpose.

As with any medical treatment the weighing of risk and benefit must be carefully balanced. Anticoagulant have a narrow therapeutic index, and the more narrow the therapeutic index, the greater the chance for adverse effects, *i.e.* bleeding.[5,10,11,12]

The traditional method of determining the efficacy of oral anticoagulant therapy is to monitor PT. This was first described by Armand J. Quick in 1935. [4,13,14] He used thromboplastin derived from rabbit brain to prove his assumption that bleeding abnormalities secondary to obstructive jaundice were due to 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.[4]

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 is measured in seconds and reported as PT.[15,16,17]

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.[1,2,18]

Because thromboplastin is 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. The variability in sensitivity and its effect on PT outcomes can have major detrimental effects on the management of warfarin therapy in patients requiring anticoagulation. This variability caused great international debate and concern for several decades.[4]

To standardize this difference two formats were developed; the first was the International Sensitivity Index (ISI) and the second 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 it 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.[4] By definition, the more sensitive thromboplastin 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.[3,4]

To resolve the problem of variable PT, the use of INR has been recommended for monitoring the 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.[16,19,20]

INR 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. Because of differences between different batches and manufacturers of tissue factor the INR was devised to standardize the results. Each manufacturer gives an ISI (International Sensitivity Index) for any tissue factor they make. This ISI says how their tissue factor compares to that of other companies.

INR is the ratio of a patient's prothrombin time to a normal control sample, raised to the power of the ISI

$$INR \quad \frac{PT_{test}}{PT_{normal}}^{ISI}$$

Prothrombin time ratio (PTR) is the patient's observed PT (in seconds) divided by laboratory's calculated mean normal PT (in seconds).[10,20,21]

A target INR range of 2.0 to 3.0 is recommended for most indications, such as the treatment or prophylaxis of deep vein thrombosis (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.[16,22]

Using the INR in other medical conditions, such as coagulopathy or liver disease has not been deemed appropriate because INR was originally developed to monitor anticoagulant therapy. 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.[1,2] 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.[4,15,23]

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 and proper calibration of machinery.[10,24]

Although the INR system is far from perfect, it is the only practical solution currently available. With all its faults, it is much better than an unadjusted PT system.

An INR is useful in monitoring the impact of oral anticoagulants such as warfarin (coumadin). Patients with atrial fibrillation often take anticoagulant medications to protect against clots that can cause thromboembolic strokes. While taking warfarin, patients have regular blood tests to monitor their blood coagulation status by testing INR.

In healthy people, the INR is about 1.0. For patients on anticoagulants, the INR typically should be between 2.0 and 3.0 for patients with atrial fibrillation, or between 3.0 and 4.0 for patients with mechanical heart valves. However, the ideal INR must be individualized for each patient.[8,24,25]

An INR can be too high; a number greater than 4.0 may indicate that blood is clotting too slowly, creating a risk of uncontrolled bleeding. An INR less than 2.0 may not provide adequate protection from clotting.

Among various vitamin K-dependent plasma proteins, the coagulation factors II, VII and X showed the most significant association with INR. Of these variables, the two-component model, including factors II and VII deserves special attention, as it largely explains the overall variability observed in INR estimates.[26]

Some substances such as alcohol can affect the PT/INR. Antibiotics, aspirin, and cimetidine can increase the PT/INR. Barbiturates, oral contraceptives, hormone-replacement therapy (HRT) and vitamin K either in a multivitamin or liquid nutrition supplement can decrease PT. Certain foods (such as beef and pork liver, green tea, broccoli, chickpeas, kale, turnip greens, and soybean products) contain large amounts of vitamin K and can alter the PT results.

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