Clinical Utilization of the International Normalized Ratio (INR)

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The prothrombin time (PT) is one of the most important laboratory tests to determine the functionality of the blood coagulation system. It is used in patient care to diagnose diseases of coagulation, assess the risk of bleeding in patients undergoing operative procedures, monitor patients being treated with oral anticoagulant (coumadin) therapy, and evaluate liver function. The PT is performed by measuring the clotting time of platelet-poor plasma after the addition of calcium and thromboplastin, a combination of tissue factor and phospholipid. Intra- and interlaboratory variation in the PT was a significant problem for clinical laboratories in the past, when crude extracts of rabbit brain or human placenta were the only source of thromboplastin. The international normalized ratio (INR), developed by the World Health Organization in the early 1980s, is designed to eliminate problems in oral anticoagulant therapy caused by variability in the sensitiv-

ity of different commercial sources and different lots of thromboplastin to blood coagulation factor VII. The INR is used worldwide by most laboratories performing oral anticoagulation monitoring, and is routinely incorporated into dosage planning for patients receiving warfarin. Although the recent availability of sensitive PT reagents prepared from recombinant human tissue factor (rHTF) and synthetic phospholipids eliminated many of the earlier problems associated with the use of crude thromboplastin preparations, local instrument variability in the INR still remains a problem. Presently, the use of plasma calibrants seems the best solution to this problem. Standardizing the point-of-care instruments for INR monitoring is another dilemma faced by the industry. Ultimately, new generations of anticoagulant drugs may eliminate the need for laboratory monitoring of anticoagulant therapy. *J. Clin. Lab. Anal.* 14:101–114, 2000. © 2000 Wiley-Liss, Inc.

Key words: prothrombin time; International Normalized Ratio; thromboembolic disease; oral anticoagulants

INTRODUCTION

Laboratory determination of the prothrombin time is used to monitor patients receiving oral anticoagulant therapy (OAT). The prothrombin time (PT) measures the extrinsic pathway of coagulation, which includes the vitamin K-dependent factors II, VII, and X. In the determination of the PT, extracts of thromboplastin (phospholipids + tissue factor) and ionized calcium are added to patient plasma to initiate clotting for laboratory measurement. Unfortunately, differences in the sensitivity of various thromboplastin preparations and other specimen and laboratory variables can cause interlaboratory and intralaboratory variations in the prothrombin time of ten seconds or more. Under these circumstances, the international normalized ratio (INR) was developed to standardize prothrombin time values for anticoagulation. To calculate the INR, commercial manufacturers of thromboplastin provide a number (international sensitivity index, ISI) which mathematically compares the reagent lot to an international reference standard. The World Health Organization (WHO), American College of Chest Physicians/National Heart, Lung, and Blood Institute, College of American Pathologists, and other agencies recom-

mended that clinical laboratories monitoring OAT patients should provide the INR, as well as measurements of the PT, for the management of patients receiving oral anticoagulants. These agencies also have developed specific guidelines for the use of INR values in patient care management.

Rabbit-brain extracts were the primary thromboplastin reagents in the past, but thromboplastins prepared by recombinant technology are preferred at present because of their relatively high sensitivity to the effect of warfarin and potential capability to more accurately regulate OAT. Even with these attempts at standardization, problems still remain because PT determinations are affected by local instrumentation and reagent variables, as well as patient factors such as diet, disease states, and other medications. Because of these problems, a meticulous quality assurance program is neces-

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Received 2 September 1999; Accepted 31 January 2000

sary for laboratories monitoring OAT patients. In this regard, stringent specimen collection, transportation, and processing criteria are essential, and local verification of the ISI with each thromboplastin/instrument combination used in the laboratory is preferable. Extreme care must also be exercised in calculating and reporting the INR. All physicians using oral coagulant therapy must be knowledgeable about the pharmacology of warfarin, the laboratory determination of the PT, and the present problems that exist with the INR, while patients receiving OAT must be educated in the importance of complying with physician dosage orders and the effect of diet and medications. Guidelines for laboratory analysis of the PT and INR in patients receiving OAT were recently published by a consensus conference of the College of American Pathologists (1). This a comprehensive review of the subject, emphasizing practical problems in laboratory monitoring, quality assurance, and clinical utilization of the PT and INR.

PATHOPHYSIOLOGY OF ORAL ANTICOAGULANTS

Crystalline warfarin sodium (Coumadin, Panwarfin, Sofarin, Coufarin, Athrombin-K) is the most widely used oral anticoagulant in the world. Warfarin is a coumarin derivative originally isolated from sweet clover in the 1940s during an investigation of the cause of hemorrhagic "sweet clover disease" in cattle. Initially utilized as a rodent poison, the capacity of warfarin to effectively prevent human thromboembolic disease became apparent from the first clinical trials in the early 1950s. Warfarin sodium [sodium 3-(α -acetyl-

benzyl)-4-hydroxycoumarin, $C_{19}H_{15}NaO_4$] is a racemic mixture of R and S enantiomers and has a molecular weight of 330.32 daltons (2).

Warfarin interferes with the hepatic synthesis of the vitamin-K dependent coagulation factors (factors II, VII, IX, X, protein C, protein S) by inhibiting the reduction of oxidized vitamin K, Fig. 1.) (2–4). As a result, the glutamate residues of these coagulation factors cannot be γ -carboxylated, and the molecules are dysfunctional and inactive because they cannot bind calcium. Therefore, a functionally effective prothrombinase complex cannot be formed, thrombin generation is inhibited, the conversion of fibrinogen into fibrin is delayed, and clotting is reduced. Therapeutic doses of warfarin decrease the synthesis of the active form of each vitamin K-dependent clotting factor by 30–50%. However, since functional circulating clotting factors are not affected by warfarin, a week or more of oral coagulant therapy is required to achieve an optimal therapeutic effect in a patient beginning treatment with warfarin. The approximate half-lives of the clotting factors are as follows: factor II (60 hours), factor VII (4–6 hours), factor IX (24 hours), factor X (48–72 hours), protein C (8 hours), protein S (30 hours).

Warfarin is essentially completely absorbed from the upper intestinal tract by passive diffusion after oral ingestion, and reaches peak plasma levels within one hour (2). Approximately 98–99% of warfarin in the circulation is bound to plasma proteins (5). Warfarin is principally metabolized (by cytochrome P450 oxidase enzymes in the microsomal fraction of the hepatic endoplasmic reticulum) to inactive hy-

Fig. 1. The properties of warfarin. (a) The molecular structure of warfarin. (b) A simplified schematic of the vitamin-K cycle, showing the effect of warfarin on the synthesis of vitamin-K dependent coagulation factors. In the cycle, vitamin K₁ or K₂ are reduced to their hydroquinone forms (KH₂). A further stepwise oxidation of KH₂ to vitamin K epoxide (KO) occurs, during which descarboxyprothrombin (descarboxy-II) is converted to prothrombin by carboxylation of glutamate residues (*Glu*) to γ -carboxyglutamate

(*Gla*). Enzymatic reduction of the epoxide requires reduced nicotinamide adenine dinucleotide (*NADH*) as a cofactor and is sensitive to warfarin (solid bar). The R sidechain on the vitamin K molecule is a 20-carbon phytyl in vitamin K₁ and a 5- to 65-carbon prenyl side chain in vitamin K₂. Adapted from Gilman AG, Goodman LS, Rall, and Murad F, editors. Goodman and Gilman's The pharmacological basis of therapeutics. 7th ed. New York: MacMillan Publishing Co.; 1985. p. 1346.

droxylated metabolites, including dehydrowarfarin, two diastereoisomer alcohols, 4'-, 6-, 7-, 8- and 10-hydroxywarfarin (2). The inactive metabolites are conjugated with glucuronic acid and ultimately excreted into the urine and feces. The functional half-life of warfarin is approximately 40 hours, with R-warfarin having a longer half-life than S-warfarin (2). The recommended maintenance dose range for warfarin is 2–10 mg/day (0.029–0.14 mg/kg/day).

Warfarin is a safe agent for the prophylaxis of thrombosis if the correct dosage is given and the patient is carefully monitored (6,7). However, serious bleeding complications, especially intracranial hemorrhage, can occur with excessive anticoagulation and thromboembolic complications are a risk with inadequate coagulation. The patient response to warfarin may be influenced by many factors, including age, changes in diet, travel, other diseases, and medications. Therefore, accurate laboratory measurements of the prothrombin time (PT) are critical in the management of patients receiving OAT. This monitoring should be performed on a regular basis, usually monthly, with more frequent determinations during and after hospitalization and a change in medication type or dosage. Hemorrhaging at any site may occur with warfarin overdose, but epistaxis, bleeding gums, gastrointestinal bleeding, excessive bruising, and hematuria are the most common signs. Hemorrhagic shock and paralysis secondary to cerebral hemorrhage occurs in fatal cases of warfarin overdose. The oral lethal dose in adult humans is approximately 50–500 mg/kg (one to two teaspoons).

LABORATORY MONITORING OF ORAL ANTICOAGULANT THERAPY

Prothrombin Time

The one-stage prothrombin time (PT) of Quick has been used for more than forty years as a laboratory assay to monitor the anticoagulant effects of warfarin. The PT measures the function of the extrinsic (tissue factor) coagulation pathway and is extremely sensitive to the vitamin-K dependent clotting factors (factors II, VII, and X) affected by warfarin (Fig. 2). During the early stages of warfarin therapy, the PT is prolonged primarily because of depressed factor VII levels, but during maintenance therapy it is also sensitive to decreased levels of factor II and X (8).

To determine the PT, a phospholipid-protein extract of tissue (thromboplastin) is added to platelet-poor plasma, and clotting is initiated by the addition of calcium (Fig. 3). The appearance of fibrin strands signals the clot endpoint of the reaction, which can be detected by manual-visual, photo-optical, electromechanical, viscoelasticity, nephelometric, or other techniques. The result is reported in seconds (prothrombin time), or as a ratio compared to the laboratory mean normal control (prothrombin ratio, PTR). The PT is critically dependent on the characteristics of the thromboplastin used in the assay. Both components of thromboplastin, tissue fac-

Fig. 2. A simplified diagram of the coagulation system.

tor and phospholipid, are necessary for the activation of factor X by factor VII. Tissue factor (factor III) is a transmembrane protein, widely expressed on cells of nonvascular origin, which activates factor VII during the initiation of the extrinsic coagulation pathway. Different thromboplastin preparations vary considerably in their ability to initiate coagulation in the presence of decreased clotting factors. For example, “responsive” thromboplastins produce less rapid activation of factor X by factor VII than “unresponsive” thromboplastins, resulting in a relatively greater prolongation of the PT for a given decrease in vitamin K-dependent coagulation factors. The PT result is also influenced by the instrument used in the assay, the plasma standard, drug–drug

Fig. 3. The prothrombin (PT) assay. Clotting is initiated by the addition of thromboplastin reagents (tissue factor, phospholipids, and calcium) to citrated plasma. The endpoint of the reaction is the appearance of fibrin strands. The PT assay can be performed manually, but automated coagulometers are used in most clinical laboratories. These instruments use a variety of methods (electromechanical, photo-optical, nephelometric, etc.) for endpoint detection.

interactions, drug–food interactions, and other factors (9,10). With current thromboplastin reagents, the PT determined by the automated clotting assay has a normal range of 8.8–11.6 seconds (11). The normal range may be different for instruments using other techniques of endpoint detection.

Noncommercial extracts of human brain prepared by standardized techniques were used as the source of thromboplastin in the 1950s and 1960s (12). However, due to expense, ethical considerations, and other factors, the less responsive rabbit brain or human placenta extracts became commercially available in the 1970s 1980s and gradually replaced the human brain extracts. Unfortunately, the effect of the change in thromboplastin source on the PT was not considered by the medical community, and physicians inadvertently increased warfarin doses in order to maintain a prothrombin ratio of 2.0–2.5 (3). Interlaboratory variations in the PT also became a significant problem when different commercial preparations of thromboplastin, prepared from different animal species and tissue sources, and through different extraction techniques, became available. In addition, the responsiveness of thromboplastin preparations varied between reagent lots, creating serious intralaboratory PT variations. The problem was further compounded by increasing laboratory automation of the PT, by an increasing diversity of commercial coagulometers using different means of endpoint clot detection, and by differences in the relative concentrations of nonthromboplastin components of the PT reagent formulation, including calcium (13). Furthermore, the PT was found to be affected by a wide variety of other factors, including patient diet, medications, and other physiologic and pathologic conditions; the type of specimen container; the type and amount of anticoagulant; specimen collection (e.g., traumatic venipuncture, overfill or underfill of specimen containers, inadequate or over-vigorous mixing of specimen, contaminated collection tubes, etc.); failure to correct for the hematocrit of patients with elevated packed red cell volumes (> 0.55); transportation and storage conditions; incubation time and temperature, and other factors (14,15). More recently, the introduction of recombinant tissue factor, produced from molecular cloning and sequencing of cDNA tissue factor, has created an additional variable (16,17).

Besides the previously discussed variables in laboratory instruments and reagents, many physiologic factors can influence the PT as well. The PT is prolonged in cord blood and newborns due to relatively low levels of vitamin K-dependent clotting factors, which may not increase to the normal adult range until several weeks after birth. Lipemia, hyperbilirubinemia, and hemolysis interfere with the detection of clot formation by photo-optical methods and cause falsely elevated values. Heparin at therapeutic doses usually does not interfere with the PT, but PT prolongation can result in patients receiving higher doses of heparin. In fact, due to variability in the sensitivities of different thromboplastins to heparin, a falsely prolonged PT can occur during initiation of warfarin

treatment when the patient is simultaneously receiving heparin (18).

PT also can result from dysfibrinogenemia, iatrogenic agents which deplete fibrinogen and/or factor V (e.g., streptokinase, anicard, tissue plasminogen factor, etc.), vitamin-K deficiency, gastrointestinal disease, liver disease, disseminated intravascular coagulation, and specific or nonspecific factor inhibitors (antiphospholipid antibodies, inhibitors specific for factors II, V, VII, or X) (10). The PT may be falsely shortened by the use of oral estrogen-containing contraceptives or by coagulation activation during or after specimen collection, which can occur as a result of contamination with tissue fluid, delayed mixing with anticoagulant citrate, or storage in soda lime or borosilicate glass tubes for prolonged times at cold temperatures (10).

The International Normalized Ratio

The international normalized ratio (INR) was introduced by the World Health Organization (WHO) in the early 1980s as a means of standardizing PT results (19). Because there is a linear relationship between the logarithms of the PT ratios obtained with different extracts of human and rabbit brain, a calibration system was developed to relate any PT ratio to a WHO standard. For this purpose, a very responsive batch of human brain extract was designated as the first international reference preparation (IRP), and a correction factor (international sensitivity index, ISI) was developed to correlate the sensitivity of commercial thromboplastin preparations to the IRP (20–23). By definition, the ISI of the first IRP was 1.0. An additional term, the INR, was introduced to compare a given prothrombin ratio measurement to the IRP. Thus, the INR represents the prothrombin time that would have been obtained if the IRP had been used as a reagent in the test. “Responsive” thromboplastins have lower ISIs and produce longer prothrombin times than “unresponsive” thromboplastins (24). A low ISI is a desirable reagent property. When a reagent with a low ISI is used, the analytical precision of the prothrombin time is increased, there is better discrimination of normal and warfarin-treated patients, and a wider therapeutic range exists, enabling clinicians to make fine adjustments in anticoagulation dosage (23,25). Recent studies have shown that the ISI of thromboplastins used in the United States varies from 0.8 to 2.24 (26). One study, however, suggests that even the latest highly sensitive thromboplastin reagents (ISI < 1.2) fail to achieve true standardization of the PT value (27).

Commercial suppliers of thromboplastin preparations supply the ISI with each reagent lot. If the ISI is known, the INR is easily calculated by the formula

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

where the mean (geometric mean) normal PT is determined from at least 20 fresh plasma specimens obtained from healthy individuals (28). A logarithmic version of the formula is

$$\text{INR} = \text{antilog} (\text{ISI} \times \log \text{PR}) .$$

The INR also can be read directly from graphic nomograms when the prothrombin ratio and ISI are known, thus obviating the need for mathematical calculations (29,30) (Fig. 4).

Quality Assurance Considerations

The PT and INR are indirect measures of the biologic effect of warfarin, and are not direct measurements of warfarin concentration. Therefore, the results are affected by patient, specimen, and laboratory variables other than warfarin concentration, including the following:

- Preanalytic variables
 - Patient factors
 - Specimen collection and storage
 - Type and concentration of anticoagulant
 - Specimen preparation and storage
- Analytic variables
 - Type and sensitivity of thromboplastin
 - Assay conditions (i.e., incubation time and temperature)

ISI calibration
Instrumentation effects
Heparin, lupus anticoagulants, and other substances

- Postanalytic variables
 - INR calculation
 - Result reporting
 - Physician education

The induction and maintenance of a steady state with warfarin therapy requires strict patient compliance. Ultimately, either failure to understand or failure to comply with the physician's orders is responsible for most undesired INR results and most adverse responses to warfarin therapy (31). In one study, noncompliance with warfarin therapy was statistically greatest in young, male patients who had no regular physician and who had not yet suffered a thromboembolic episode (32). The advantages of thorough patient education facilitated by a checklist have been emphasized (33).

The quality of the blood specimen is the most critical determinant of an accurate PT/INR result. In this regard, a nontraumatic venipuncture must be performed, with the blood specimen collected into the proper anticoagulant at the correct concentration. To avoid contamination with tissue thromboplastin, specimen tubes for the PT should be drawn last if multiple tubes of blood are being obtained. A traumatic venipuncture can activate coagulation factors, leading to a shortened PT. If the specimen for PT analysis is being obtained alone, 1–2 mL of blood should be drawn first and discarded. Specimens obtained from arterial lines or other indwelling lines can be utilized for the PT if 10–15 mL of blood is drawn first and discarded. The specimen must then be labeled correctly, promptly delivered to the laboratory, and correctly processed to produce platelet-poor plasma.

The PT should be performed within 24 hours after sample procurement if the unopened, centrifuged, or uncentrifuged specimen tube is refrigerated (2°–4°C.) or stored at room temperature (18°–24°C)(34). Frozen plasma stored at –20°C can be used within two weeks, or plasma stored at –70°C can be used within 6 months if the blood specimen is spun properly to remove all platelets and promptly frozen. Platelet-poor plasma (platelet count $<10 \times 10^9/\text{L}$) should be prepared by centrifuging the capped specimen tube at 1,500g for a minimum of 15 minutes at room temperature (34).

Buffered citrate at a concentration of 109 mmol/L (3.2%) is recommended by the Subcommittee on Coagulation of the National Committee for Clinical Laboratory Standards, the College of American Pathologists, and the WHO Expert Committee on Biological Standardization as the anticoagulant of choice for routine coagulation testing (1). This recommendation was initially based on studies which revealed that spurious PT results due to overfilling or underfilling of specimen tubes, variation in tube vacuum, high or low patient hematocrit, and other variables were minimized at a citrate concen-

Fig. 4. A nomogram for obtaining an INR from a measured prothrombin ratio (PTR). The ISI of the assay system must be known. In the example shown, an INR of 3.0 is obtained from plasma with a PTR of 2.0 if the ISI is 1.6.

tration of 109 mmol/L (35). The effect of citrate concentration on the PT and INR has also been documented. For example, in one study, both normal individuals and patients on OAT had longer PTs with plasma samples collected in 129 mmol/L citrate than for those collected in 105 mmol/L (36). In addition, ISIs for calibrations with plasmas collected in 105 mM were up to 10% greater than those with plasmas collected in 129 mmol/L citrate. The effect of citrate concentration is reported to be greatest with responsive thromboplastins, and in the analysis of specimens from patients receiving OAT, especially from patients receiving both heparin and OAT (37).

The type and sensitivity of the thromboplastin reagent used for PT/INR determination is the laboratory variable that has received the most attention. The use of thromboplastin reagents with low ISI values is critical, since the precision of the PT assay improves at a low ISI (38,39). Recently, both the Subcommittee on Coagulation of the National Committee for Clinical Laboratory Standards and the College of American Pathologists endorsed the use of thromboplastins with a manual international sensitivity index (ISI) between 0.9 and 1.7, preferably with the ISI toward the lower end of this scale (1). At present, thromboplastin reagents using recombinant human tissue factor are most suitable for this purpose. The reported use of recombinant human tissue factor as a reagent in PT analysis was quickly followed by commercially available thromboplastin reagents using recombinant human tissue factor and synthetic phospholipid (40). Early clinical investigations with thromboplastins based on recombinant tissue factors revealed many advantages over conventional sensitive rabbit brain or human placental thromboplastins. These include increased sensitivity to factor VII and factor X deficiencies, improved slope of calibration curve, low coefficient of variation on various instruments, good reagent stability and long shelf life, and good lot to lot consistency (16,41). In addition, capillary whole blood analysis of the PT/INR was possible with the recombinant reagents (16,42). However, since higher INR values are found for the recombinant reagents, especially in patients with INRs >3, physician education is necessary to avoid adverse consequences to patient care. In one large collaborative study using Lyophilised plasma samples, significant differences were found in the INRs determined with two recombinant thromboplastin reagents and two conventional thromboplastins (43).

The initial assumption that adoption of the INR system would eliminate interlaboratory variation in PT values and lead to standardization of the PT throughout the world proved overly optimistic. Early attempts to calibrate different rabbit thromboplastin preparations against the IRP on different types of coagulometers produced significantly different results, even using equivalent control and normal PTs and thromboplastin reagents with nearly identical ISIs (coagulometer effect). This led to a request of thromboplastin manufacturers that they provide instrument-specific ISI values (44,45). Although this

has been accomplished, specific local variables in reagents and instrumentation continued to compromise the INR system. Numerous reports of variability in INR determinations have appeared in the literature (46–48). Even the use of highly sensitive thromboplastins does not eliminate the problem of local INR variation (27,49,50).

Plasma calibrants appear to be the solution to specific (local instrument) and reagent variables, as well as to inaccurate assignment of thromboplastin ISI values. Plasma calibrants are reference-lyophilized plasmas with INR values assigned by the manual technique using a certified thromboplastin IRP (51–53). These reagents permit a laboratory to locally verify its range of accuracy for the INR for each thromboplastin/instrument combination used in patient care (local ISI calibration, system ISI calibration). Plasma obtained from coumarin-treated patients (“coumarin plasma”) has been used for this purpose, as well as normal plasma artificially depleted of vitamin-K clotting factors (“depleted plasma”). There is evidence that lyophilized plasma calibrants are accurate only when calibrated against an IRP of the same species, that coumarin plasma calibrants are superior to artificially-depleted plasma calibrants for system ISI calibration, and that a minimum of 12 plasma coagulants are required to assign an accurate system ISI (54,55). Various mathematical approaches have been used to calculate the system ISI value, but the preferred method is to utilize orthogonal regression analysis to determine the slope of the line relating normal plasma specimens used for the MNPT to the PT values obtained with the plasma calibrants (54,56). Simple linear regression analysis has been reported as inaccurate for this calculation, but an alternative method involving extrapolation from a calibration curve using freeze-dried “reference” plasmas has been reported (57,58). Several recent multicenter studies have confirmed the use of plasma calibrants to improve the accuracy of the INR (55,59,60). The most extensive use of plasma calibrants has occurred in France, where more than 4,000 laboratories have participated in nine national external quality assessment surveys conducted since 1977 (61). A reduction in interlaboratory variability from 12 to 6% was achieved in the latest survey with a coumarin plasma coagulant. Artificially depleted plasma calibrants were less efficient, although usable, and did not have the disadvantages of limited supply, cost, and batch-to-batch variability of coumarin plasma preparations. A recent investigation revealed in-house calibrants to improve the precision but not necessarily the accuracy of INR determinations (62).

Inaccurate calculation and reporting of the INR is another problem that has compromised patient care. This most commonly occurs because of the use of the PT of the control plasma rather than of the mean (geometric mean) normal PT to calculate the INR. In addition, the mean normal PT must be determined for each type of thromboplastin and for each clot detection system used in the laboratory. The values are not equivalent, and any error is magnified exponentially dur-

ing calculation of the INR (38,63,64). The problem of plasma volumetric errors and inaccurate measurement of other reagents as a source of error leading to an erroneous INR has also been documented by one investigator (65).

The increasing global utilization of OAT and the current emphasis on cost-efficient patient care has resulted in considerable interest in patient self-management and self-monitoring of OAT. In addition, medical institutions are increasingly interested in laboratory decentralization and point-of-care testing. Several portable monitoring devices have been developed for this purpose, although none have achieved widespread utilization at this time. For example, the CoaguChek System, developed by Boehringer Mannheim

Corporation (Indianapolis, IN), was approved by the U.S. Food and Drug Administration (FDA) in 1997. Initial clinical studies confirm the practical feasibility and acceptable accuracy of patient self-monitoring with the CoaguChek device, provided the patient is motivated and thoroughly educated (66–71). The Biotrack (Ciba Corning) whole-blood PT monitor, evaluated in a pediatric outpatient and home setting, was found to provide results comparable to those obtained from a coagulation laboratory ($r = 0.93$, $P = 0.001$) (72). In contrast to these devices, the Thrombolytic Assessment System (TAS, Cardiovascular Diagnostics, Raleigh, NC) analyzer was primarily designed for near-patient testing by nursing or other nonpathology staff. The TAS analyzer uses thromboplastin-containing test cards for the determination of the INR on either plasma or whole blood. Evaluations of the TAS device by several groups have revealed good precision and linearity, although INR values tend to be lower than those found by the conventional laboratory assay (73–75).

PRINCIPLES OF ORAL ANTICOAGULANT THERAPY

The use of the INR in patient management has been advocated by the WHO, the International Society for Haemostasis and Thrombosis, and the American College of Chest Physicians (ACCP), and other agencies. In addition, the International Society for Haemostasis and Thrombosis, the International Committee for Standardization in Hematology, and the ACCP have recommended inclusion of the INR in the scientific literature. The INR has achieved widespread use in foreign countries, including the United Kingdom, Canada, France, Italy, Germany, and the Netherlands (76). A recent survey of U.S. academic laboratories reported that 100% of 58 responding labs were using the INR; however, 79% of these labs did not confirm the accuracy of the ISI for their own analyzers (77).

The concepts of therapeutic anticoagulation have changed in the recent past. Based on prospective randomized trials which showed the efficacy of “less intense” oral anticoagulant regimens in providing antithrombotic protection without bleeding complications, the Food and Drug Administration

(FDA) approved the use of low-intensity warfarin anticoagulation in 1987 (78). In association with changes in the therapeutic range for warfarin therapy, physicians have recognized the need to incorporate the INR into dosage planning (79). Presently, two ranges (less intense and more intense) are recommended for oral anticoagulant therapy by the ACCP and the National Heart, Lung, and Blood Institute (Table 1) (80). An INR of 2.0–3.0 is presently advocated for most patients receiving oral anticoagulant therapy, with higher ratios for those with mechanical prosthetic valves or a history of myocardial infarction (3,81–83).

There are a number of factors that determine the appropriate clinical utilization of the INR. These include the identification of the appropriate patient to test, utilization of the correct ISI for the laboratory test system, and correct calculation and reporting of the results (63,84). Inappropriate physician use of the INR is one of the major problems. Because the INR was designed for use in patients receiving stable anticoagulation and the mathematical relationship is accurate only for these patients, it cannot be used for patients receiving unstable therapy or those with other hemostatic disorders (38,63,76,85). In particular, the INR must be used with caution in hospitalized patients, since they rarely achieve stable anticoagulation and frequently receive heparin and other drugs concurrently with oral anticoagulants, which may influence the determination of the PT (63). In this regard, the INR should only be used only in the management of “stable” patients who have received an oral anticoagulant for at least two weeks, who have reproducible prothrombin times, and who have responded appropriately to the drug (76). The INR is not appropriate for patients in the induction phase of therapy with oral anticoagulants, for patients in whom oral anticoagulants are being discontinued, or for patients with liver disease or vitamin-K deficiency (76).

Warfarin Administration and Monitoring

The appropriate dosage schedule for warfarin administration is of great concern for physicians (86). In the past, large

TABLE 1. Recommended therapeutic ranges for oral anticoagulant therapy*

Indication	Recommended INR
Venous thromboembolism	
Prophylaxis	2.0–3.0
Treatment	2.0–3.0
Prevention of systemic embolism	
Chronic atrial fibrillation	2.0–3.0
Acute myocardial infarction	2.0–3.0
Cardiomyopathy	2.0–3.0
Recurrent systemic embolism	2.0–3.0
Tissue cardiac valve prosthesis	2.0–3.0
Rheumatic mitral valve disease	2.0–3.0
Mechanical cardiac valve	2.5–3.5

*From Hirsh et al. Chest 1995; 108(Suppl.4):225S–522S. With permission.

loading doses of warfarin (50–75 mg or larger) were initially administered, based on the theory that this would rapidly maximize the effect of the drug. Although the PT does increase rapidly under these circumstances due to the depletion of active factor VII, the patient still remains at risk for thromboembolism since factors IX and X have much longer half lives and are not initially decreased. An alternative approach, first advocated in 1979 and still used today by some physicians, is to administer 10 mg doses of warfarin daily for three consecutive days. The daily warfarin maintenance dose is determined from a graph based on the PT ratio at the end of the three days. Unfortunately, this method is based on a PT ratio of 1.5–2.5 and is inappropriate with current low-intensity warfarin therapy and sensitive thromboplastin reagents. In contrast, the initiation of warfarin therapy with maintenance doses of warfarin (5–7.5 mg) appears to be the best approach (87,88). However, lower doses should be used in the elderly to avoid bleeding complications, since they tend to have reduced levels of factor synthesis. In elderly patients with atrial fibrillation, Oates and collaborators described an outpatient regimen in which the warfarin maintenance dose is calculated from an algorithm based on patient response to an initial warfarin dose of two mg daily for two weeks (89). There is recent evidence of the influence of racial background on warfarin responsiveness, with higher doses of warfarin required to maintain an INR between 2.0 and 3.0 in Asians and Afro-Caribbeans than in Caucasians (90).

Warfarin is contraindicated in pregnancy, and in patients with known blood dyscrasias and hemorrhagic tendencies, overt bleeding, ulcerations of the gastrointestinal, genitourinary, and respiratory tracts, or other conditions with a potential risk of hemorrhage, including cerebrovascular disease, aneurysms of the aorta or cerebral vasculature, pericarditis and pericardial effusions, bacterial endocarditis, vasculitis, and malignant hypertension (2,4,91). Warfarin should not be used in patients being treated with streptokinase or urokinase or in those undergoing major regional or block anesthesia or diagnostic/therapeutic procedures with a potential for uncontrollable bleeding, such as a lumbar puncture. Known hypersensitivity to warfarin or other components of the tablets is a contraindication, and it should not be used in uncooperative patients unsupervised patients with a history of senility, alcoholism, or psychosis. In addition, warfarin should not be considered at locations with inadequate laboratory facilities for patient monitoring. Caution should be used in patients with heparin-induced thrombocytopenia and deep venous thrombosis, severe to moderate hepatic or renal insufficiency, infectious diseases or disturbances of intestinal flora, diarrhea, indwelling catheters, severe to moderate hypertension, polycythemia vera, severe diabetes, and a known or suspected deficiency in protein-C-mediated anticoagulant response (4). Inactive metabolic products of warfarin appear in the milk of lactating mothers; the prothrombin time of nursing infants is not affected, but other effects are unknown. Maternal treat-

ment with warfarin during the first trimester of pregnancy may lead to nasal hypoplasia and stippled epiphyseal calcifications, while central nervous system abnormalities and fetal hemorrhage have been reported following fetal exposure during the second and third trimesters (2,92–94). The use of low-molecular-weight heparin has recently been advocated during pregnancy in women at risk of thromboembolism (95–97). The special problems of oral anticoagulation in pediatric patients have been recently reviewed by Streif and collaborators (98).

Warfarin is usually administered in the evening, and should be taken at the same time every day. During the initiation of warfarin therapy, daily PTs should be determined on morning blood specimens to assure that excessive hypoprothrombinemia does not occur in rare individuals who are unusually sensitive to warfarin. It is important to draw blood specimens consistently at the same time of day, because significant variations have been shown to occur in patients, with the highest PT values occurring in the morning and the lowest in the evening (99). Since the effect of warfarin on the PT is not evident for at least three days, the dosage should not be changed more frequently than every three to five days. During the initiation of warfarin therapy, the PT should gradually increase by 0.5 to 2 seconds per day. In order to avoid bleeding complications, the warfarin dosage should be reduced if the PT increases by 2 to 3 seconds or more on a given day. Conversely, if the PT fails to increase after 3 to 5 days, the dose of warfarin should be slightly increased (<50% of the previous dose). However, it must be strongly emphasized that the initiation phase of therapy cannot be shortened by giving the patient extra doses of warfarin, and this approach makes subsequent PTs much more difficult to interpret. One to two weeks may be necessary before the final effects on the PT are noted from a given dose of warfarin (86). Sun and Chang found computer modeling using five INR inputs a reliable method for predicting initialization dosages for OAT (100).

If temporary discontinuation of warfarin therapy for surgery is necessary, the INR decreases exponentially, with approximately 96 to 115 hours required for a decrease from between 2.0 and 3.0 to 1.2 (101). Gradual, stepwise discontinuation of oral coagulant therapy is recommended, since abrupt withdrawal is associated with more intense and long-lasting low-grade transient clotting activation ('rebound hypercoagulable state') secondary to increased generation of thrombin (102,103). Recent studies have also cast doubt on the need to withdraw warfarin in patients undergoing minor surgical procedures (104). If a patient is excessively anticoagulated (INR >5.0), withholding one or two doses of warfarin and administering 2.5 mg oral phytonadione (vitamin K₁) is a useful means of correction (105,106). For emergency reversal of anticoagulation, clotting factor concentrates provide the best therapy (107). In one study, statistically independent factors associated with an INR greater than six included medications known to potentiate warfarin, recent

diarrheal illness, decreased oral intake, and taking more warfarin than prescribed. In this study, acetaminophen ingestion was a previously unrecognized and statistically independent factor, while higher dietary vitamin-K intake and habitual alcohol consumption were not statistically significant (108). In a study of patients with INRs greater than eight, improper dose loading during the in-hospital initialization of OAT was the major cause. The incidence of major bleeding episodes in these patients was 12%, and two hemorrhage-related fatalities occurred (109).

The medical risks and complications of OAT are related to the intensity and duration of therapy, as well as to patient age, diet, use of other medications, and presence of underlying diseases. Hemorrhage, especially intracranial hemorrhage, is the most frequent complication of warfarin therapy, but there is also a small risk of systemic cholesterol microembolization, as well as of necrosis and/or gangrene of the skin and other tissues (110–113). Patients undergoing warfarin anticoagulation for thrombotic-induced cerebral ischemia are at higher risk of intracranial hemorrhage than patients with atrial fibrillation (114,115). The release of cholesterol emboli from atheromatous plaque can be precipitated by OAT, leading to the “purple toes syndrome,” and vascular compromise of the kidneys, pancreas, spleen, liver, and other organs. The purple toes syndrome usually occurs within 3–10 days of the initiation of OAT, and is characterized by pain and tenderness, and by a mottled purple color of the toes that blanches with pressure (116,117). Most cases of the purple toes syndrome are reversible, but severe gangrene and necrosis have been reported. Warfarin-induced skin necrosis is a rare complication that usually begins 3 to 10 days after the initiation of OAT (4,118,119). The skin of the extremities is most often involved, but involvement of adipose tissue and the skin of the penis and female breast has been reported. Recurrence of skin necrosis after discontinuation of warfarin has also been reported (120,121). There appears to be an increased risk of skin necrosis in patients with heparin-induced thrombocytopenia, protein-C and protein-S deficiency, hypoprothrombinemia, and activated protein-C resistance (122,123). Protein C concentrate has been reported as effect therapy in some patients with warfarin-induced skin necrosis (124,125).

The value of patient education and self-management in the management of OAT has recently been emphasized (126–129). Dietary management may be of assistance in poorly controlled patients (130, 131).

Abnormal Warfarin Responsiveness

Patients are said to be “resistant” to warfarin when the steady-state INR cannot be achieved with previously adequate maintenance doses of warfarin. The most common causes of warfarin resistance are drugs and dietary changes that diminish the anticoagulant effect of warfarin. For example, the balanced diet and increased vitamin K₁ in a hospital setting may

partially reverse the effect of warfarin in a patient who received a marginal diet prior to hospitalization. These patients are at risk for thromboembolism and may require additional warfarin while hospitalized. Other drugs, disease states, and dietary changes may induce “warfarin sensitivity” by enhancing the effect of warfarin and increasing the INR. This most commonly occurs in patients placed on a restricted diet because of gastrointestinal disease or other medical problems who become vitamin K deficient, with accentuation of the effect of warfarin. These patients may require a reduced dosage of warfarin and/or vitamin K₁ administration to prevent bleeding problems. Hypoprothrombinemia has also been reported in these patients (132). Oral, intravenous, and subcutaneous routes have been used for the administration of vitamin K₁ (106,133–136). Elderly patients may also be sensitive to warfarin and require smaller doses (137). Recently, a very low factor-IX level due to a mutation in the propeptide region of the factor-IX gene (Ala-10 mutation) was discovered as the etiology of an elevated activated partial thromboplastin time (aPTT) and as the cause of bleeding in patients on OAT (138–140). However, in a study of 734 patients on OAT, van der Meer, Vos, and Rosendaal were unable to find any patients with an Ala-10 mutation, and concluded that routine aPTT screening in OAT patients is not warranted (141). A more complex situation involving simultaneous vitamin-K deficiency and decreased warfarin absorption is seen in patients undergoing major gastrointestinal surgical procedures (i.e., bowel resection, short bowel syndrome, etc.), and in association with increased gastrointestinal transit time or certain malabsorption diseases. Warfarin resistance is usually present in these patients (33). In a recent study of 50 outpatients receiving warfarin and followed for at least 8 weeks, Lubetsky and collaborators found that 16 (32%) had a daily vitamin-K intake of >250 mg/day and required a higher maintenance dosage of warfarin than did other patients to maintain an INR >2.0 (142). Algorithms based on measurements of plasma warfarin concentration and plasma clearance in stable patients were published by Bentley et al. for use in predicting the cause of abnormal warfarin responsiveness (143).

Extreme caution must be exercised to avoid abrupt changes in the steady state in warfarin-sensitive or -resistant patients, since re-establishment of a steady-state situation can be very difficult in a patient given large doses of warfarin or vitamin K₁ (33,133,144). Likewise, gradual re-adjustment of the warfarin dosage should be undertaken after the patient is discharged from the hospital, with careful laboratory monitoring. Seasonal adjustment of the warfarin dosage may be necessary in some patients, particularly in the spring and summer, when large amounts of foods rich in vitamin K, such as the vegetables found in salads, are often consumed. Drugs should be prescribed cautiously in patients receiving warfarin. Drugs interfering with warfarin absorption or PT determination should be avoided, if possible, in patients receiving warfarin.

If these drugs must be used, careful adjustment of the warfarin dosage, dietary management, and close laboratory monitoring is necessary until a new steady state is achieved.

A few patients have been identified with an exceptionally low daily warfarin-dose requirement (1.5 mg/day) or less, accompanied by an increased risk of bleeding complications ("warfarin sensitivity"). Recent investigations have revealed an association between a low warfarin-dose requirement and allelic variants of the hepatic enzyme responsible for the metabolism of S-warfarin (cytochrome P450 CYP2C9) (145,146). CYP2C9 genotyping may be of value in patients who have difficulty during warfarin induction.

Direct measurement of warfarin in the serum can be utilized for toxicity assessment in patients who have ingested rodent poison or large quantities of the pharmacologic preparation of the drug. Various techniques, including high-performance liquid chromatography, gas-liquid chromatography, and UV spectrophotometry have been used for this purpose (147). The serum therapeutic range is 6.5–16.2 $\mu\text{mol/L}$ (2–5 $\mu\text{g/mL}$), with a panic range of $>32.4 \mu\text{mol/L}$ ($>10 \mu\text{g/mL}$) (148). Direct serum warfarin measurements do not detect bishydroxycoumarin and are not used at the present time in routine OAT monitoring.

Patient Factors Influencing Thromboplastin Sensitivity

Antiphospholipid antibodies (APA) are a unique cause of abnormal warfarin responsiveness. APAs are autoimmune antibodies (e.g., lupus anticoagulants, anticardiolipin antibodies) directed against anionic phospholipids or phospholipid/protein complexes, which are frequently associated with a variety of clinical problems, including venous thrombosis, arterial thrombosis, obstetrical complications, neurologic disease, hematologic abnormalities, dermatologic lesions (149).

Long-term oral anticoagulation is advocated by nearly all authorities for APA-positive patients with recurrent thromboembolic disease (150–154). In this regard, Khamashta found that high-intensity warfarin (INR of ≥ 3) treatment with or without low-dose aspirin (75 mg per day) to be significantly more effective ($P < 0.001$ by the log-rank test) than treatment with low-intensity warfarin (producing an international normalized ratio of < 3) with or without low-dose aspirin, or treatment with aspirin alone, in preventing further thrombotic events (recurrence rates per patient-year, 0.013, 0.23, and 0.18, respectively). The rate of recurrence of thrombosis was highest (1.30 per patient-year) during the first six months after the cessation of warfarin therapy (155). The more aggressive therapeutic regimens should not be discontinued until aPL concentrations have been normal for at least six months. Warfarin-resistant patients may also respond to aspirin, low-dose porcine heparin, low-molecular-weight heparin, or long-term subcutaneous heparin therapy. Thrombocytopenia in patients with APAs may also respond to warfarin therapy (156).

The monitoring of OAT in patients with APAs can pose a problem for the laboratory, since the antibodies have been postulated to interfere with prothrombin time determinations (157). Several recent studies have evaluated the sensitivity of thromboplastin reagents in the presence of APAs. Della Valle and collaborators found INRs obtained with a recombinant thromboplastin (Recombiplastin, Ortho Laboratories) to be significantly higher in lupus anticoagulant (LA)-positive, than in LA-negative patients, using the manufacturer's instrument-certified ISI, and questioned the validity of the INR system for monitoring OAT in LA-positive patients (158). Reagent-dependent thromboplastin sensitivity to LA was also reported in three later studies (159–161). Laboratory and patient-specific determinations of the effect of LAs on thromboplastin sensitivity, and the avoidance of reagents that show an LA influence is one solution to this problem. However, until a better solution can be found, CAP recommends the use of alternative tests in the monitoring of patients with lupus anticoagulants (1). The influence of ACAs on thromboplastin sensitivity has not been reported.

The effect of heparin on PT determinations can pose a problem in the laboratory monitoring of patients receiving both warfarin and heparin. For example, Solomon and coworkers reported a heparin-induced increase in the INR for some conventional thromboplastins, but not for a recombinant thromboplastin (Innovin, Dade) (18). For the thromboplastins showing heparin sensitivity, the effect of heparin was dose-dependent and reversed by protamine in a dose-related manner or by preincubation of the plasma with heparinase. These results were confirmed in a more recent study (162). The College of American Pathologists recommends that laboratories should determine the sensitivity of their PT to heparin and, if possible, select a thromboplastin that is insensitive to heparin in the therapeutic range (1).

SUMMARY

The INR is a special form of therapeutic drug monitoring for patients receiving oral anticoagulants. Since the INR corrects for intralaboratory and interlaboratory variations in prothrombin time-results caused by reagent and instrumental variables, failure to consider the INR can result in less than optimal therapy, or even life-threatening bleeding or thrombosis. Although the INR has been slow to gain acceptance in the United States, it is now recommended by the American College of Chest Physicians, the College of American Pathologists, and other professional organizations. In clinical practice, maintenance doses of warfarin should be used during the initiation of oral coagulant therapy, with careful monitoring of the PT and expected PT increases of 0.5 to 2 seconds per day. PT and INR values should be monitored during long-term oral anticoagulation, at least on a monthly basis.

Many problems are associated with the clinical utilization of the INR. Laboratory factors and physiologic factors can

all affect the INR; consequently, its utilization has failed to achieve perfect standardization of prothrombin times between various laboratories. Improper calculation and improper use of the INR have also complicated the issue. Attention to the aforementioned difficulties by clinicians as well as laboratory technicians should lead to improved understanding and, with the aid of improving technology, improve the care of patients requiring long-term anticoagulation.

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