Blood clotting-- HEMOSTASIS -

Thrombosis, Warfarin, and Protimes

Thrombosis is the unexpected development of a blood clot in a vein or an artery that plugs the vessel. Blood in the blocked vessel cannot reach critical tissue, and the tissue dies. Thrombosis can occur in arteries, causing heart attacks and strokes, or in veins, causing thrombophlebitis, deep vein thrombosis, and pulmonary emboli.

Types of Thrombosis

Common Name	Clinical Name	Site of Clot	Type
Heart attack	Coronary thrombosis causing myocardial infarction	Coronary arteries that nourish the heart	Arterial
Stroke	Cerebrovascular accident	Cerebral arteries that nourish the brain	Arterial
Thrombophlebitis	Superficial venous thrombosis	Superficial leg veins	Venous
	Deep venous thrombosis	Deep leg veins that return blood to the heart	Venous
Pulmonary embolism	Pulmonary thrombotic embolus	Clots from deep leg veins travel to the lung and block arteries	Venous

Thrombosis is a major affliction of humankind. In the USA, at least one in a thousand people suffers a venous thrombotic event every year. The real number could be even higher since the symptoms of pulmonary emboli resemble other disorders and often go undiagnosed. Further, each year there are 500,000 deaths from heart

attacks and 500,000 strokes resulting in 100,000 deaths. Those who survive strokes are often faced with severe disabilities.
People with certain conditions have increased thrombosis risk requiring preventive treatment. Atrial fibrillation, diabetes, cancer, autoimmune diseases like systemic lupus erythematosis (SLE), knee and hip surgery, and chronic inflammatory conditions all may lead to thrombosis if no anticoagulant therapy is given.

Clot-dissolving Drugs are used First to Stop Thrombosis

When a thrombosis victim arrives at the hospital, the doctor stops the clotting process and prevents additional damage by directing a clot-dissolving drug to the clot via cardiac catheterization. The three 'clotbusters' used in the USA are tissue plasminogen activator (TPA), streptokinase, and urokinase.

All three are effective at rapidly reestablishing blood flow, but, without long-term treatment, the injured spot in the vessel may clot again. Repeat clotting, called *rethrombosis*, is life-threatening, so the doctor must start anticoagulant therapy soon after the clot-dissolving therapy is completed.

Anticoagulants Prevent Rethrombosis
Heparin
Anticoagulants are drugs that reduce the action of the blood clotting factors. Heparin, because it acts fast, is the first anticoagulant administered after a thrombotic event. Heparin is given intravenously and requires close supervision, so it is only given while the patient is in the hospital, and seldom for more than five days.

Oral Anticoagulant: Warfarin
Within a few hours after starting heparin therapy, the doctor starts the patient on oral anticoagulant therapy, or "blood thinners." Oral anticoagulant pills reduce the production of some of the blood coagulation (clotting) factors. Normal human blood has thirteen coagulation factors, identified by Roman numerals. The liver

produces coagulation factors and releases them into the blood. After about five days of treatment, oral anticoagulants slow the production of four of these factors: II, VII, IX, and X, the liver produces these four factors from dietary vitamin K, found in green, leafy vegetables and liver. Oral anticoagulants slowly neutralize vitamin K. Once the coagulation factor levels are reduced, the risk of rethrombosis becomes small, but, of course, the risk of bleeding increases. Most doctors prescribe oral anticoagulants for at least 6 months; longer if there is a concurrent risk factor like atrial fibrillation, infection, or diabetes.

The first oral anticoagulant was developed by scientists at the University of Wisconsin in the 1930s. They noticed that cows that ate spoiled clover had a tendency to hemorrhage. They soon isolated an anticoagulant chemical from the clover and named it Warfarin® to honor the Wisconsin Alumni Research Foundation. The first use of Warfarin was for rat poison: rats would eat the tablets and bleed to death. Today, Warfarin is manufactured synthetically and dispensed in safe therapeutic doses by several manufacturers using various trademarks (table 2).

Table 2 Oral Anticoagulant; USA Trademarks

- Warfarin
- Warfarin sodium (generic)
- Coumarin
- Panwarfin
- Sofarin
- Coumadin
- Dicumarol

The Protimes Test

Coumadin's dosage must be carefully controlled because the safe therapeutic target range is narrow. Each patient needs a different amount depending on their weight, diet, general health, and activity level. People taking Coumadin must adhere very closely to their dosages and schedule, and must have blood collected at regular intervals for 'protime' tests. The word protime is a contraction of *prothrombin time*, or 'PT,' a test of blood clotting that measures the

effects of Coumadin in the blood. The name comes from prothrombin, which is another name for coagulation factor II.

Here's how the protime works. The laboratory scientist collects a small blood specimen in a tube with an anticoagulant that keeps the blood from clotting. In the laboratory she separates the blood cells from the liquid portion by centrifuging the specimen. She then precisely measures a small amount of plasma (that's the liquid portion of blood), adds a chemical called 'thromboplastin' and measures how long it takes for the plasma to clot. The time interval from addition of thromboplastin to clotting is called the prothrombin time. For normal individuals the protime result is about 12 seconds, but in people taking Coumadin it is longer, up to 20 to 25 seconds.

Protime Variations

In a busy laboratory, scientists may perform 200 or 300 protimes a day using automated instruments. Protime results vary from laboratory to laboratory depending on the type of instrument, the brand of thromboplastin used, and the operator's technique. A patient taking Coumadin could, on one day, have a protime of 19 seconds at one laboratory, 21.5 at another, and 23 seconds at a third. If nothing were done about this variation, a person would have to always have their protimes done at the same laboratory each time to avoid repeated, and possibly erroneous, dosage adjustments.

In the 1980s, laboratory scientists learned to minimize the protime inter-lab variation problem by developing the *international normalized ratio* (INR). Every laboratory compares their protime results to an international standard and, using a mathematical formula, reports the product as an INR number. For example, blood from a person taking no Coumadin would have an INR near 1.0, whereas a person taking Coumadin should have an INR in the therapeutic target range of 2-3. The therapeutic range is extremely important. If a person who needs Coumadin has an INR result below 2, the dosage is too low, and there is a risk of rethrombosis. INRs between 3 and 3.5 are relatively safe, but above that, hemorrhage is likely. The doctor reviews the

INR each time a protime is done, and adjusts the Coumadin dosage to keep the INR in the therapeutic target range throughout the period of therapy.

Unexpected Protime Variations

Laboratory scientists have shown that all INR results vary slightly, so doctors do not usually adjust the dosage if successive results are within 15% of each other. Once in a while, however, a more extreme variation may be seen. Why? The most likely cause is a skipped or mistimed pill. It is important for the patient to take their Coumadin pills at the times and dosages prescribed, usually around 5 milligrams per day. If a pill is accidentally missed, the patient is instructed to take it as soon as he realizes the error and get a new protime done within the next few days. Diet may also cause variation. Lettuce, cabbage, broccoli, greens, and liver contain high vitamin K concentrations and can reduce Coumadin's effectiveness. Most people eat more fresh vegetables in the summer when they are readily available. Their INR drops, reflecting their dietary change (table 4).

Causes of Protime (INR) Variability

- Missed dosage
- Dietary changes: foods high in vitamin K
- Blood collection variations: short draw, clots, high temperature, delay cause high INRs
- Blood collection variations: long draw, prolonged chilling, shaking cause low INRs

Blood collection errors also cause protime changes. The laboratory scientist must ensure that the blood reaches the collection tube 'fill line' and must gently mix it within seconds of the time it is collected to make sure it does not clot. 'Short draws' or clotted blood both give erroneously high INRs. Blood that is transported at temperatures above 80° Fahrenheit or stored at room temperature for more than 24 hours also causes high INRs. On the other hand, if the scientist overfills the blood collection tube, or the blood is stored in the refrigerator for more than 24 hours, the INR will be falsely low. And

if the blood is shaken too vigorously in mixing, its cells may rupture, also causing false low values. If there is any suspicion that a collection error has occurred, the test should be repeated before the dosage is adjusted.

Summary

Coumadin therapy has saved many lives and is essential for the prevention of rethrombosis after a thrombotic event. It is also used to prevent thrombosis in high risk individuals. Coumadin is safe and effective, but it has a narrow therapeutic dosage range that requires regular laboratory monitoring. The protime test is the standard test of therapeutic effectiveness, and Coumadin dosages are adjusted to keep the protime within the therapeutic range, an INR of 2 to 3. Although protime results are normalized around the world through the application of the INR, patients, laboratory scientists, and doctors must watch carefully for variations caused by changes in dosage, diet, or specimen collection errors.