Stepwise Anticoagulation with Warfarin for Prevention of Intravenous Catheter Thrombosis

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Warfarin is the most commonly used anticoagulant for prevention and therapy of thrombosis. Warfarin is a vitamin K antagonist and inhibits synthesis of clotting factors II, VII, IX, and X, and anticoagulant proteins C and S. Whereas there is extensive information about the efficacy of warfarin and target International Normalized Ratio (INR) for patients with artificial heart valves, atrial fibrillation, pulmonary emboli, deep venous thrombosis, and lupus anticoagulant, there is little in the literature on the role of warfarin in maintaining the patency of hemodialysis catheters. Much more is reported about the value of minidose warfarin in maintaining the patency of infusion catheters. Many centers have tried low-dose warfarin (1 mg per day), and found this not to be effective in preventing catheter thrombosis in many patients. Although most support the use of warfarin following catheter problems, individual units have their own guidelines, with doses ranging from 2 mg per day (normal INR) to formal systemic anticoagulation with INR from 1.5 to 3.0.

Stepwise anticoagulation with warfarin is emerging as useful in preventing catheter-associated thrombosis. With this method, patients are placed on low-dose warfarin after the first clotting episode. With each subsequent episode, the dose is increased, raising INR by 0.5 until clotting episodes do not recur. Warfarin doses similar to those in patients with artificial heart valves have been used in selected patients (target INR 3.0 – 4.0) to prevent clotting.

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Key words

Warfarin, thrombosis, infusion catheters, hemodialysis catheters, artificial heart valves

Introduction

Warfarin is the most commonly used anticoagulant for prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism. Another major indication is prophylaxis and/or treatment of thromboembolic complications associated with atrial fibrillation and/or artificial heart valves. Warfarin is also indicated to reduce thromboembolic events related to myocardial infarction. Finally, warfarin is used in patients with artificial blood conduits, stents, and chronic intravenous catheters.

As early as the mid-19th century, Rudolf Virchow postulated that three factors predispose to phlebothrombosis: hypercoagulable state, vein wall damage, and blood stasis. These three factors are still judged to be most important and have to be considered in planning preventive measures. With a foreign body in the blood vessel, an additional factor becomes important, foreign material, which, contrary to the vascular endothelium, initiates the intrinsic clotting pathway by activating factors XII and XI. Intact endothelial cells have anticoagulant properties. These include mucopolysaccharides (heparin sulfate, dermatan sulfate) and thrombomodulin, which binds thrombin and enhances the activation of protein C. Finally, platelet adhesion to endothelial cells is inhibited by prostacyclin and endothelium-derived relaxing factor (EDRF, or nitric oxide).

It is not surprising that any foreign body in the vascular system causes formation of clots adhering to it. Those clots break away and cause strokes and other thromboembolic phenomena if a foreign body is in the arterial system. Clots on foreign bodies in the venous system may remain silent for a long time. Small clots, once broken away, migrate to the lungs and are dissolved by their potent fibrinolytic system without causing symptoms. Fibrin sheath on intravenous catheters interferes with catheter function if the tip becomes involved. Whereas tips in infusion catheters must be grossly covered with the clot to interfere with function, even a small clot covering a hemodialysis catheter inflow bore interferes with blood inflow by a valve-like mechanism.

Prevention of thromboembolic phenomena and catheter dysfunction may be achieved by anticoagulation with antiplatelet agents and anticoagulants. Of the latter, warfarin is the most commonly used. In fact, warfarin is the most frequently prescribed medication.

Warfarin is a vitamin K antagonist and is a dicoumarol derivative. Dicoumarol, first isolated from spoiled sweet clover hay has been used as an anticoagulant for decades. Warfarin is much better and faster absorbed. After absorption, 99% is bound to plasma proteins, mostly albumin. It is completely metabolized by the liver to inactive hydroxylated metabolites and warfarin alcohols, which are excreted in urine and bile. Although in patients with normal renal function,

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92% of metabolites are excreted in urine, no dose adjustment is needed in patients with renal failure [1]. Vitamin K is necessary to synthesize clotting factors II, VII, IX, and X, and anticoagulant proteins C and S. The half-life of these clotting factors is, for II, 60 hours; VII, 4 – 6 hours; IX, 24 hours; X, 48 – 72 hours; protein C, 8 hours; protein S, 30 hours. The resultant *in vivo* effect of warfarin is a sequential depression of factor VII, protein C, factor IX, protein S, factor X, and factor II [1]. Vitamin K promotes the synthesis of γ-carboxyglutamic residues in proteins, which are essential for their biological activity. Warfarin blocks reductases, which convert inactive oxidized (epoxide) vitamin K into its reduced form, thus inhibiting the regeneration of vitamin K [2].

Warfarin is a tricky drug. The dose is dependent on a multitude of factors including liver function, blood dyscrasias, diarrhea, fever, hyperthyroidism, malnutrition, concomitant use of other medications, and diet. The list of factors and medications interfering with warfarin response exceeds 250 in the latest *Physicians' Desk Reference* [1]. A list of the most common drugs that interfere with warfarin is shown in Table I. Every person needs a different dose, which must be adjusted by measurements of prothrombin time, or protime (PT). A PT measures the time required to clot plasma after addition of thromboplastin to which calcium has been added. Calcium is needed for the PT because citrate plasma is used for testing. The PT ratio is the PT, in seconds, divided by the control PT measured using the same preparation of thromboplastin. Because laboratories use various thromboplastins, the International Normalized Ratio (INR) was introduced to better guide warfarin therapy. European centers have been using this standardization method for many years. Developed at the Karolinska Institute in Stockholm, Sweden, the INR standardizes the methods for comparison among different laboratories. By running the patient's test against a known standard, a value can be calculated that is more consistent from place to place than the traditional PT values were. The thromboplastin used in any laboratory is assigned an International Sensitivity Index (ISI). Highly sensitive thromboplastins have low values assigned, and *vice versa*. After running the PT, the INR is calculated with the following formula [2]:

$$\text{INR} = (\text{PT ratio})^{\text{ISI}}.$$

For example, for high sensitivity thromboplastins (ISI = 1.0), INR equals PT ratio. If PT ratio equals 1.5 and ISI is 2, then INR is 1.5^2, or 2.25.

The most extensive experience with anticoagulation for a foreign body in the vascular system has been acquired in artificial heart vales. According to the Haemostasis and Thrombosis Task Force of the British Society for Haematology, all patients with mechanical prosthetic valves should be kept on warfarin indefinitely, with average INR of 3.5 and range from 2.5 to 4.9 [3]. This recommendation was based on a large Dutch study of 1608 patients followed for 6475 patient-years [4]. There was a sharp rise in thromboembolic events if INR was below 2.5, and a sharp increase in hemorrhagic complications when INR was 5.0 or higher. The authors concluded that the intensity of anticoagulant therapy for patients with prosthetic heart valves is optimal when the INR is between 2.5 and 4.9. They recommended a target INR of 3.0 – 4.0 to achieve this optimal level of anticoagulation. There are, however, several studies advocating lower anticoagulant intensity, with INR around 2.5 [5,6].

TABLE I Drugs that prolong the prothrombin time.

Allopurinol	Disulfiram	Omeprazole
Amioradone	Erythromycin	Phenylbutazone
Anabolic steroids	Fluconazole	Piroxicam
Cephalosporins	Isoniazid	Quinidine
Chloramphenicol	Ketoconazole	Sulfinpyrazone
Cimetidine	Ketoprofen	Tamoxifen
Clofibrate	Metronidazole	Thyroxine
Co-trimazole	Naproxen	Trimethoprim-sulfamethoxazole

Drugs that reduce the prothrombin time

Barbiturates	Colestipol	Rifampin
Carbamazepine	Gluthetimide	Vitamin K
Cholestyramine	Griseofulvin	

There is much less experience of warfarin use in patients with intravenous catheters. A Medline search yielded 7130 articles on warfarin (or Coumadin or coumarin); 3926 articles on vein or venous catheter or catheters; and 20 articles on both anticoagulation with warfarin (or Coumadin or coumarin) and vein or venous catheter or catheters. Most of the experience comes from cancer patients with catheters for chemotherapy and from patients on total parenteral nutrition.

In a prospective randomized study of infusion catheters, Bern *et al.* [7] used 1 mg of warfarin, beginning 3 days before catheter insertion and continuing for 90 days. Of 42 patients receiving warfarin, 4 had thrombosis. Of 40 patients not on warfarin, 15 had thrombosis. The small dose of warfarin did not influence PT. They concluded that very low doses of warfarin could protect against thrombosis without inducing a hemorrhagic state.

Boraks *et al.* [8] compared thrombotic episodes in patients with infusion catheters for chemotherapy of hematological malignancies. Five (5%) of the 108 patients on minidose warfarin (1 mg) developed a thrombosis a median of 72 days from the day of catheter insertion. In the historic control group of 115 patients who did not receive warfarin, 15 (13%) developed a catheter-associated thrombosis a median of 16 days post catheter insertion ($p = 0.03$). INR in patients given warfarin was always less than 1.6. The authors concluded that minidose warfarin reduces the incidence of central venous catheter-related thrombosis in patients with hematological malignancies.

In patients on long-term, home, total parenteral nutrition (HTPN), Veerabagu *et al.* [9] compared a minidose warfarin, defined as 1 – 2 mg, which does not prolong the PT, to a therapeutic dose warfarin, defined as the dose that increases PT ratio to 1.2 – 1.5. Thrombotic episodes were more frequent on minidose than on therapeutic dose warfarin ($p < 0.005$). Patients with thromboses on minidose had significantly fewer thrombotic episodes after switching to the therapeutic dose warfarin. There were no hemorrhagic complications in the minidose warfarin group, and four nonfatal hemorrhagic complications in the therapeutic dose warfarin group ($p > 0.05$). The authors concluded that a therapeutic dose of warfarin is effective in reducing the incidence of thromboses in patients who experience central venous thrombosis, despite minidose warfarin, with a minimal increase in hemorrhagic complications.

There is even less experience with warfarin in hemodialysis catheters than that in infusion catheters. A Medline search in January 2000 yielded 7130 articles on warfarin (or Coumadin or coumarin), and 131 articles on hemodialysis catheter or central vein catheter, but only 1 article on these search topics combined, and this was my paper on high-dose intradialytic urokinase [10], where I mentioned the use of warfarin for catheter thrombosis prevention. There were two other articles, published in 1998 and 1999, describing warfarin use for patients with hemodialysis catheters, that were not picked up in the Medline search [11,12]. This scarcity of publications on warfarin in patients with hemodialysis catheters does not mean that warfarin is not used. Although Lockridge *et al.* [13] did not mention warfarin in their publication, they reported warfarin use during the presentation at the 5th Home Hemodialysis Symposium [14]. Many hemodialysis centers use warfarin but have not published their experience. Pierratos *et al.* [11,12] use a protocol similar to ours. Patients are started on low-dose warfarin after the first episode of malfunction and the dose is raised with each subsequent episode until there is no recurrence. According to the 1998 report [11], the average ±SD dose of warfarin was 2.1 ± 1.6 mg per day, and average ±SD INR was 1.5 ± 0.9.

In the above-mentioned retrospective analysis of the results with hemodialysis catheters in the 546-day period from November 1995 to April 1997, warfarin was given to patients who required repeated doses of urokinase to open clotted catheters [10]. Originally, a minidose with INR around 1.0 was used as recommended by Bern *et al.* [7] for infusion catheters. In patients who required repeated urokinase infusions in spite of low-dose warfarin, dose was increased to keep INR between 1.5 and 2.5. Of 104 patients, 68 required warfarin therapy to maintain catheter patency.

From January 1998 to January 2000, various INR values were aimed for in different patients in Dialysis Clinic, Inc. (DCI) in Columbia, Missouri. The population of patients on chronic hemodialysis ranged from 105 to 124. A cross-sectional analysis of demographics and blood access practices in DCI in January 1999 and January 2000 is shown in Table II.

Table II Cross-sectional analysis of demographics and blood access practices in Dialysis Clinic, Inc., Columbia, Missouri, U.S.A.

January 15, 1999		January 15, 2000	
Patients	107	Patients	107
Males	61	Males	60
Females	46	Females	47
African American	50	African American	49
Caucasian	57	Caucasian	57
Arteriovenous access	75	Arabic	1
On warfarin	17	Arteriovenous access	69
Catheter	32	On warfarin	17
Insertion site		Catheter	38
Right jugular	19	Insertion site	
Left jugular	8	Right jugular	22
Right subclavian	3	Left jugular	10
Left subclavian	2	Right subclavian	4
Catheter type[a]		Left subclavian	2
PermCath	17	Catheter type[a]	
Tesio	10	PermCath	17
Vas Cath	4	Tesio	10
Access Cath	1	Vas Cath	3
Warfarin	15	OptiFlow	8
INR 0.8–1.1	10	Warfarin	17
INR 1.2–1.9	3	INR 0.7–1.1	9
INR 2.6	1	INR 1.2–1.9	6
INR 3.2	1	INR 2.8	1
		INR 5.6	1

INR = International Normalized Ratio.

[a] PermCath, Kendall Healthcare Products, Mansfield, MA; Tesio and Access Cath, Medcomp, Harleysville, PA; Vas Cath and OptiFlow, Bard, Salt Lake City, UT, U.S.A.

In patients with arteriovenous (AV) access, heparin was given in doses keeping the activated clotting time (ACT) over 190 seconds; in patients with central vein catheter, ACT was kept over 270 sec. The method for determining a patient's dose of heparin has been described in detail elsewhere [15]. Seventy to 80% of catheters were dual lumen (PermCath, Kendall Healthcare Products Co., Mansfield, MA; Access Cath, Medcomp, Harleysville, PA; and OptiFlow, Bard, Salt Lake City, UT, U.S.A.), the remaining were Tesio (Medcomp). In January 1999, among 75 patients with AV fistulas and grafts, only 17 (23%) used warfarin for various reasons; among 32 patients with catheters, 15 (47%) used warfarin. In 10 of these patients, INR ranged from 0.8 to 1.14; in 3 patients, INR ranged between 1.2 and 1.5; in 1 patient, INR was 2.59; and in the remaining 1 patient, INR was 3.19. In January 2000, among 69 patients with AV fistulas and grafts, only 17 (25%) used warfarin for various reasons; among 38 patients with catheters, 17 (45%) used warfarin. In 9 of these patients, INR ranged from 0.7 to 1.1; in 6 patients, INR ranged between 1.2 and 1.9; in 1 patient, INR was 2.8; and in the remaining 1 patient, INR was 5.6. The last patient's clinical course is described in more detail below. Usually patients were started on a minidose of warfarin after the first clotting episode, then the dose was increased as needed if a smaller dose could not prevent catheter clotting. During the period in which high-dose urokinase was available (until March 1999), this protocol

was very convenient. Recently, patients with clotted catheters needed hospitalization for catheter locking with tissue plasminogen activator, stripping, or replacement. These options are less convenient for patients and more expensive. There was no pattern of warfarin requirement in relation to sex, race, age, diagnosis, and catheter type; however, the number of patients with catheters was too small for any meaningful statistical analysis. No systematic coagulation studies were performed to discern a relationship between warfarin requirement and coagulation test results.

Case report

One patient in the study required a higher dose to keep his catheter open. The patient was an obese Caucasian man, born in 1939, with diabetic nephropathy, neuropathy, retinopathy, neurogenic bladder, and severe arteriosclerotic disease. In 1993 he had right-below-knee amputation because of gangrene. Hemodialysis started in August 1994 using a PermCath catheter, and a left forearm AV fistula was created. In December 1994, a steal syndrome developed with gangrene of the left ring finger. The fistula was ligated and the finger was amputated. In January 1995, the catheter clotted and was stripped; however, flow was not fully restored. A right groin loop bridge AV graft fistula was created. The catheter was removed and the patient was dialyzed on the graft fistula. At the same time, the patient developed ischemic ulcer on the left foot. In December 1995 the graft fistula clotted and the patient developed thrombosis of the popliteal vein. The fistula was declotted and the patient was started on minidose warfarin. In August 1996 the graft fistula became infected and had to be excised. Another PermCath was inserted into the left jugular vein. Warfarin, which was stopped during surgery, was resumed with INR running between 0.84 and 1.06. For the next 900 days the catheter had to be opened 14 times with high-dose intradialytic urokinase and twice with stripping to restore its function. The clinical course in relation to INR is shown in Fig. 1. The catheter functioned well for the next 300 days while average INR was kept at 3.0.

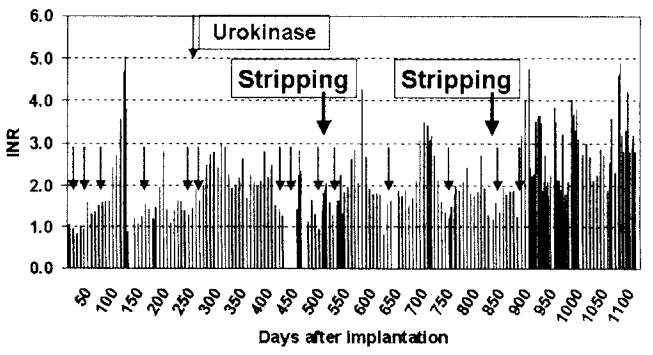

FIGURE 1* International Normalized Ratio (INR) values and catheter function in a patient with thrombophilia.

In this patient it became clear that, to keep his catheter open, the INR had to be similar to that recommended for artificial heart valves. Lower doses, with INR below 1.5 and even below 2.0, were insufficient. The longest period of excellent catheter function was achieved with a dose of warfarin that kept the INR at an average of 3.0. No bleeding episodes occurred throughout the whole course of warfarin therapy. Judging by clotting of the previous catheter, AV graft, and phlebothrombosis, this patient had some kind of thrombophilia; however, no coagulation tests were performed in this patient. The dose of warfarin ranged from 6 to 15 mg and was very difficult to adjust because of changes in food intake and multiple medical problems requiring use of various medications that influenced warfarin efficacy.

In conclusion, only less than 50% of patients do not require oral anticoagulation to prevent thrombosis of hemodialysis catheters. Of the remaining 50%, the majority needs small doses of warfarin, which do not influence INR. In a small group of patients, stepwise dosing of warfarin is emerging as useful in preventing catheter-associated thrombosis. Some patients may require a dose of warfarin that keeps INR at an average of 3.0, the anticoagulation level similar to that recommended for patients with artificial heart valves. Because of considerable fluctuations in INR values with the same dose of warfarin, the INR must be run at least once weekly and a physician or a trained pharmacist should adjust the warfarin dose. The results of the stepwise approach are sufficiently promising that randomized controlled studies should be initiated.

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