Oral Anticoagulants and Regional Anesthesia: A Perspective

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Anesthesiologists often encounter anticoagulated patients in two clinical settings: patients with medical conditions requiring chronic anticoagulation and patients receiving perioperative thromboembolism prophylaxis. In the United States, warfarin is the most commonly used oral anticoagulant and is the focus of this study. The use of neuraxial block in patients receiving warfarin, either chronically or for perioperative thromboembolism prophylaxis, is not a new issue. Although the preponderance of evidence suggests that as a specialty we have learned to safely practice regional anesthesia in these patient populations, we seek to emphasize the unknown. The actual incidence of complications from combining neuraxial blocks with warfarin therapy is unknown. We believe the numerator, the number of complications associated with neuraxial block and warfarin therapy, is probably underreported. The denominator, the number of neuraxial blocks placed in patients receiving or recently discontinued from warfarin therapy, is probably high but not well documented. This report will focus on the pharmacology of warfarin, how its anticoagulant effect is measured, and how that impacts the practice of regional anesthesia and analgesia.

Indications for Anticoagulant Therapy

Chronic oral anticoagulant therapy is indicated for patients with prosthetic heart valves, as well as other disorders associated with an increased risk of thromboembolism, including atrial fibrillation, rheumatic valvular heart disease, acute transmural anterior wall myocardial infarction, dilated cardiomyopathy, venous thromboembolism, and intracardiac thrombus. Chronic oral anticoagulation may also be indicated for the prevention of recurrent stroke and myocardial infarction. For most of these, moderate anticoagulation with a target international normalized ratio (INR) of 2–3 is appropriate (1). Although there is no consensus on the optimal perioperative management regimen, most strategies involve cessation of warfarin at least 48 hours before surgery, monitoring of INR, and avoidance of surgery until INR is 1.4 or less. Regional anesthesia is often the anesthetic technique of choice in these high-risk patients and can be administered safely with appropriate monitoring of the patient and their coagulation status.

Adjusted-dose warfarin (INR = 2–3) is the most common agent used for thromboembolism prophylaxis after hip and knee replacement surgery. The most appropriate timing of the first dose of warfarin (e.g., the night before or the night of surgery) and the total duration of oral anticoagulation therapy remains uncertain. Regional anesthesia has been used in conjunction with this type of thromboembolism prophylaxis therapy for many years with few reported complications. Again, appropriate neurological monitoring of the patient and the coagulation function is essential to minimize risk.

Pharmacology of Warfarin

Warfarin acts on both the intrinsic and extrinsic arms of the coagulation cascade. It inhibits vitamin K-dependent post-translational gamma-carboxylation of procoagulant factors II, VII, IX, and X, and the anticoagulant proteins C and S (2). Of these, factor VII and protein C have the shortest circulating plasma half-life (6–8 hours). Thus, factor VII

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Table 1. Drug Interactions With Warfarin

Pharmacokinetic (Drugs That Change Warfarin Levels)	Pharmacodynamic (Drugs That Do Not Change Warfarin Levels)	Mechanism Unknown (Drugs Whose Effect on Warfarin Levels Is Unknown)
Prolongs prothrombin time	**Prolongs prothrombin time**	**Prolongs prothrombin time**
Stereoselective inhibition of clearance of S isomer	Inhibits cyclic interconversion of vitamin K	Evidence for interaction convincing
Phenylbutazone	2nd and 3rd generation cephalosporins	Erythromyci
Metronidazole	Other mechanisms	Anabolic steroids
Sulfinpyrazone	Clofibrate	Evidence for interaction less convincing
Trimethoprim sulfamethoxazole	Inhibits blood coagulation	Ketoconazole
Disulfiram	Heparin	Fluconazole
Stereoselective inhibition of clearance of R isomer	Increases metabolism of coagulation factors	Isoniazid
Cimetidine*	Thyroxine	Piroxicam
Omeprazole*		Tamoxifen
Nonstereoselective inhibitions of clearance of R and S isomers		Quinidine
Amiodarone		Vitamin E (mega dose)
		Phenytoin
Reduces prothrombin time	**Inhibits platelet function**	**Reduces prothrombin time**
Reduces absorption	Aspirin	Penicillins
Cholestyramine	Other nonsteroidal anti-inflammatory drugs	Griseofulvin†
Increases metabolic clearance	Ticlopidine	
Barbiturates	Moxalactam	
Rifampin	Garbenicillin and high dosages of other penicillins	
Griseofulvin		
Carbamazepine		

* Causes minimal prolongation of the prothrombin time.
† Has been proposed to cause increased metabolic clearance.
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activity decreases rapidly after an initial dose of warfarin. The initial increase in the prothrombin time (PT) or INR predominantly reflects reduction in factor VII activity. However, the therapeutic effect of warfarin anticoagulation is most dependent on the reduction in factors II and X activities. Because these factors have a circulating half-life of 36 to 48 and 72 to 96 hours, respectively, patients may not be adequately anticoagulated immediately after starting warfarin therapy, although the INR exceeds the lower limit of the therapeutic range. Conversely, factors II and X activities are the slowest to return to normal after the cessation of warfarin therapy. Consequently, an INR of 1.4 does not guarantee normal coagulation in these patients. Although no studies have directly examined the risk of procedure-related bleeding and INR in patients recently discontinued from coumadin, careful consideration should be given before performing neuraxial blocks in this subset of patients.

Many drugs interact with warfarin to either increase or decrease the intensity of warfarin anticoagulation (Table 1). Most of these interactions cause changes measured by PT INR. However, some drugs increase the bleeding risk without altering the PT. For example, nonsteroidal anti-inflammatory drugs, which have antiplatelet effects, may be associated with a higher rate of bleeding. This has been documented in patients taking high dosages of aspirin, and has also been reported with ketorolac (3). The concomitant use of warfarin with heparin to bridge the delay in anticoagulation during the initiation of warfarin therapy is also associated with increased bleeding.

The measured response to anticoagulant therapy at the initiation of treatment varies significantly. Some of the variability may be attributed to drug interactions, but there are patient variables that influence the response to oral anticoagulants (Table 2). Age is the primary determinant of dose response to warfarin. Age-related decreases in the free plasma warfarin concentration required to produce a given anticoagulation effect and decreased clotting factor synthesis lead to smaller dose require-

Table 2. Summary of Patient Characteristics Associated With Increased Sensitivity to Warfarin

Age >65 yr
Female gender
Weight <100 lb.
Excessive surgical blood loss
Liver, cardiac, and renal disease
Asian ancestry

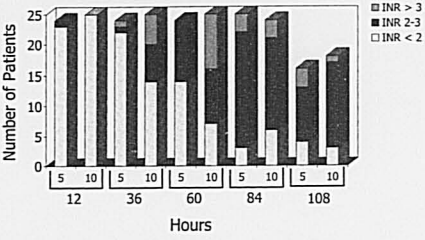

Fig. 1. International normalized ratio (INR) response to coumadin loading dosages of 5 mg and 10 mg. (Reprinted with permission [6]).

ments (4). An age of greater than 65 years is an independent risk factor for bleeding during the initiation of warfarin therapy (4). Female gender may also be associated with an enhanced response to warfarin (5). Concomitant medical problems, including liver, cardiac, and renal disease, are associated with an increased sensitivity to warfarin therapy. Patients of Asian ancestry require lower dosages than Caucasian patients during chronic therapy (4). In addition, dietary intake of vitamin K also influences the anticoagulant effect of warfarin.

In a study of postsurgical orthopedic patients receiving warfarin for thromboembolism prophylaxis, Rivey et al. (5) identified three variables related to an enhanced PT response to warfarin. Female gender, lower weight, and increased blood loss during surgery were associated with a PT of greater than 20 seconds when warfarin was given by a protocol-driven formula. There were few women less than 65 years old in this study; therefore, age was not identified as a significant risk factor.

Another variable influencing the rate of prothrombin prolongation is the initial loading dose of warfarin. Harrison et al. (6) compared initial loading dosages of 10 mg and 5 mg of warfarin. Patients in the 10-mg group had a supratherapeutic INR and required vitamin K reversal more often than patients in the 5-mg group. The vitamin K reversal led to a greater lag time in reaching the target INR in the 10-mg group compared with the 5-mg group (Fig. 1).

Monitoring of Warfarin Activity

The anticoagulant effect of warfarin is monitored by INR. INR was developed to minimize the inconsistencies of the PT test. The PT test is performed by adding calcium and thromboplastin to citrated plasma (1). The thromboplastins used for this test vary widely in their sensitivity to oral anticoagulant effects, which creates difficulty in interpreting PTs between laboratories and even between reagents within a laboratory. The INR standardizes PT reporting by referencing each thromboplastin preparation to an international standard.

The PT measures the activity of vitamin K–dependent factors II, VII, and X. During chronic therapy, PT primarily reflects the activity of factor X and is a useful reflection of the level of anticoagulation. However, during the initiation of oral anticoagulant therapy, PT primarily reflects the rapid depletion of factor VII. The PT will be prolonged when factor VII activity is reduced to approximately 55% of normal (7). An antithrombotic effect occurs when factors II and X are depleted several days later. In Harrison et al's. (6) study of factor levels after different loading doses, the level of factor II did not decrease below the hemostatic range for 50 to 70 hours after the level of factor VII decreased to 50%, regardless of the loading dose.

A corollary to this is the early recovery of factor VII after chronic warfarin therapy is discontinued. The INR, primarily determined by factor VII, may normalize, although the levels of factors II and X are still depleted. Theoretically, there may be a time when the INR approaches a normal value because factor VII levels have been restored; however, factors II and X have not been restored to a hemostatic range of 40% activity (8–12).

Clinical Investigations of Patients Receiving Chronic Warfarin Therapy and Regional Anesthesia

There are no investigations of patients receiving chronic, uninterrupted oral anticoagulation therapy and regional anesthesia. Wille-Jorgensen et al. (13) reported a case of difficult epidural placement in a patient who was fully anticoagulated with phenprocoumon, a long-acting oral vitamin K inhibitor not used in the United States. The anticoagulant therapy was unknown to the anesthesiologist. There was no bleeding observed during catheter placement, although placement was technically difficult. Satisfactory anesthesia developed and apparently resolved. Three days after surgery, the patient developed paresis of the lower extremities and impairment of the rectal and bladder sphincters. An epidural hematoma was evacuated from T11 to L1, but the extremity paresis was not reversed. Postoperatively, the prothrombin/proconvertin test of clotting was 10% of normal.

The labeling of coumadin in the United States

specifically lists spinal puncture and lumbar block anesthesia as contraindicated during coumadin therapy, which is not interrupted before surgery (14). Numerous investigators have examined the appropriate timing of oral anticoagulant discontinuation before surgery (15–17). None of these studies have commented on the role of neuraxial blocks in this setting. Based on the pharmacokinetics of vitamin K–dependent clotting factors and the levels that are required for normal hemostasis, we believe this knowledge should be balanced with indications for the neuraxial block.

Clinical Investigations of Patients Receiving Perioperative Warfarin and Regional Anesthesia

Several studies have examined the use of regional anesthesia and analgesia in patients who received warfarin during the perioperative period for thromboembolism prophylaxis. No spinal hematomas were reported in any of the studies; however, the power of these studies to detect a rare complication was low.

Odoom and Sih (18) reported their experience with 1,000 patients who had continuous epidurals and received oral anticoagulants before surgery. Patients were excluded from the study for a thrombotest below 10%, previous heparin or aspirin therapy, thrombocytopenia, or other blood dyscrasias. The thrombotest and partial thromboplastin time test were prolonged in all patients at the time of epidural placement. Intraoperatively, the patients received heparin and their blood loss was replaced with fresh-frozen plasma. Sensory and motor examinations were performed before each top-up dose during epidural analgesia for 48 hours postoperatively. After catheter removal, the patients were tested once daily until discharge. No neurological complications were detected postoperatively.

Horlocker et al. (19) prospectively studied 192 orthopedic patients who received epidural anesthesia and analgesia in combination with low-dose warfarin. All their patients received very low dosages (initial dose, 4.6 ± 1.4 mg) of warfarin beginning with the night of surgery. The mean PT at the time of catheter removal was 13.4 ± 2 seconds (INR = 1.4). There were no signs of spinal hematoma in these patients. However, they did report a significant variability in the response to warfarin and prolonged PTs at the time of catheter removal (Fig. 2). They recommended frequent monitoring of the PT (INR) and neurological examination of the patient in this setting.

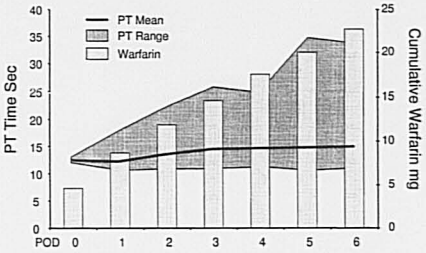

Fig. 2. Prothrombin time (PT) response to warfarin administration after total knee arthroplasty. Abbreviation: POD, postoperative day. (Reprinted with permission [19]).

Other studies support the need for frequent monitoring of PT (INR). Benzon and Esposito (20) reported that prolongation of the PT in orthopedic patients who received warfarin thromboembolism prophylaxis was even more rapid. In this retrospective study of 60 patients undergoing orthopedic procedures, he found a 38% incidence of patients with a PT greater than 15 seconds by the second postoperative day.

Wu and Perkins (21) reported a retrospective review of a large cohort of orthopedic patients receiving low-dose warfarin and neuraxial anesthesia and analgesia. Warfarin therapy was initiated the night before surgery and continued postoperatively. These patients had indwelling epidural catheters to provide analgesia for an average of 43 hours after surgery. Again, significant variability in the PT was documented. Twenty percent of the indwelling epidural catheters were removed when the PT was greater than 16 seconds. Four peripheral neuropathies were reported in this series, but there were no spinal hematomas.

There are two case reports in the literature describing spinal hematoma in patients who received perioperative warfarin for thromboembolism prophylaxis and regional anesthesia. There are very likely more cases that have not been reported. Woolson et al. (22) reported on an 85-year-old woman who underwent total knee arthroplasty with epidural anesthesia and analgesia. The patient was given a single preoperative dose of 10 mg warfarin. Her epidural catheter was removed on the second postoperative day, at which time her INR was 6.3. She developed paraparesis of the lower extremities, which required laminectomy. At 6 months follow-up, she continued to have bilateral lower extremity weakness. Badenhorst (23) reported on another female patient who underwent

bilateral total knee arthroplasty with epidural anesthesia and analgesia. This patient also received a preoperative dose of warfarin that was continued throughout the perioperative period. Her PT the morning of surgery was 14.3 seconds. On the third postoperative day, the epidural catheter was removed when her PT was 17.3 seconds. At that time, she complained of blurred vision and tingling and weakness in her right leg. On postoperative day 4, she had bilateral lower extremity sensory and motor deficits, which were more prominent on the right side. She underwent emergent decompressive laminectomy and had a near complete recovery with only a residual right-sided foot drop.

Recommendations

When oral anticoagulation therapy and neuraxial anesthesia are used together, physicians must be aware of the interactions of warfarin on the coagulation cascade and the role of the PT and INR in monitoring its effect. To minimize the risk of complications from this practice, we believe:

1. For patients on chronic oral anticoagulation, the anticoagulant therapy must be stopped and the PT (INR) measured prior to initiation of neuraxial block. Early after discontinuation of warfarin therapy, the PT and the INR reflect predominantly factor VII levels, and in spite of acceptable factor VII levels, factors II and X levels may not be adequate for normal hemostasis.

2. The concurrent use of medications that affect other components of the clotting mechanisms may increase the risk of bleeding complications for patients receiving oral anticoagulants and do so without influencing the PT and INR. These medications include aspirin and other nonsteroidal anti-inflammatory drugs, and heparin. One should reflect on these drug interactions when an indwelling neuraxial catheter is being considered for a patient.

3. For patients receiving an initial dose of warfarin before surgery, the PT and INR should be checked prior to neuraxial block if the first dose was given more than 24 hours earlier, or a second dose of oral anticoagulant has been administered.

4. Patients receiving low-dose warfarin therapy during epidural analgesia should have their PT and INR monitored on a daily basis and checked before catheter removal, if initial doses of warfarin are 36 or greater hours before. Initial studies evaluating the safety of epidural analgesia in association with oral anticoagulation used low-dose warfarin, with mean daily doses of approximately 5 mg. Higher-dose warfarin may require more intensive monitoring of the coagulation status.

5. Neurological testing of sensory and motor function should be performed routinely during epidural analgesia for patients on warfarin therapy. The type of analgesic solution should be tailored to minimize the degree of sensory and motor block. These checks should be continued after catheter removal for at least 24 hours and longer if the INR was greater than 1.5 at the time of catheter removal.

6. An INR greater than 3 should prompt the physician to withhold or reduce the warfarin dose in patients with indwelling epidural catheters. We can make no definitive recommendation for removal of neuraxial catheters in patients with therapeutic levels of anticoagulation during neuraxial catheter infusion. Clinical judgement must be exercised in making decisions about removing or maintaining these catheters.

7. Reduced doses of warfarin should be given to patients who are likely to have an enhanced response to the drug (Table 2).

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