

Case studies in anticoagulation management

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Published online: 1 October 2007
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Keywords Anticoagulation · Bridging · Low molecular weight heparin · Warfarin

Introduction

As one of the most complex and widely prescribed drugs in North America, warfarin is a “hassle” drug due to its narrow therapeutic index, individualized dosing, INR monitoring, drug interactions, and high risk of bleed and patient noncompliance [1]. Fear of warfarin has led to under prescribing, subtherapeutic dosing and increased risk of thromboembolic events [1–5].

The objective of this article is to highlight problems, pitfalls and strategic approaches in warfarin management, using five complex and/or uncommon warfarin case studies. The five case studies are titled: #1 bridging dilemma, #2 warfarin resistance, #3 true HIT or not, #4 warfarin-induced alopecia, and #5 unstable and labile INRs.

Case #1: bridging dilemma

WW was a 47-year-old white male (110 kg), with a history of mitral valve replacement (MVR), right thalamic stroke (CVA) (post-MVR) with bilateral vision loss, three

transient ischemic attacks (TIAs) due to subtherapeutic INRs, pericarditis (post-MVR), Class I congestive heart failure (CHF), chronic pain due to intercostal neuralgia, benign prostatic hypertrophy, peptic ulcer disease, narcotic dependence, recreational marijuana use, history of alcohol abuse and warfarin noncompliance (with subtherapeutic INR results and warfarin dosing by his wife). His medications include warfarin 5–8 mg/day, enteric coated ASA 81 mg/day, folic acid 5 mg/day, hydromorphone 2–4 mg/day, acetaminophen 500–1000 mg/day PRN, and terazosin 10 mg/day.

In November 2006, WW required four dental extractions under general anesthesia. His family physician and dental surgeon were informed that WW was a high risk MVR patient who would require no warfarin reduction, interruption or discontinuation pre/post dental surgery [6, 7]. Unfortunately, the dental surgeon would not operate unless warfarin was discontinued. The anticoagulation clinic staff complied & recommended the following bridging regimen for pre-operative and post-operative anticoagulation:

- (1) Last dose of warfarin 3 days pre-op
- (2) Start enoxaparin 110 mg (1 mg/kg) SC BID 2 days pre-op
- (3) Check POCT INR at the clinic 1 day pre-op
- (4) Last dose of enoxaparin 110 mg SC on evening before surgery
- (5) Dental surgery
- (6) Restart enoxaparin 110 mg SC BID post-op on evening day of surgery
- (7) Take warfarin 10 mg PO/day × 2 doses starting evening day of surgery
- (8) Next POCT INR at the anticoagulation clinic 2 days post-op & likely return to his previously stable warfarin maintenance dose of 7 mg/day

Disclosure: Research investigator/coordinator, speaker, panelist and/or consultant for Apotex, AstraZeneca, BMS, Bayer, Leo, Pharmacia, Roche, Sanofi-Aventis, Taro and other antithrombotic manufacturers.

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To our surprise, the family physician wanted a second opinion and consulted a clinical hematologist for WW's pre-dental surgery assessment. The clinical hematologist disagreed with the anticoagulation clinic and prescribed the following bridging regimen:

- (1) Last dose of warfarin 5 days pre-op
- (2) Start nadroparin 171 U/kg SC/day 3 days pre-op
- (3) Last dose of nadroparin SC 1 day pre-op
- (4) Dental surgery
- (5) Start warfarin 7 mg/day post-op on evening day of surgery (no loading doses)
- (6) Start nadroparin 171 U/kg SC/day 24 hrs post-op & continue until INR ≥ 2.5 (no minimum number of LMWH days specified)
- (7) Next INR 5 days post-op

WW did follow the clinical hematologist's pre-op instructions, but chose to return to the anticoagulation clinic immediately post-op. Full dose low molecular weight heparin and warfarin were started on evening at the anticoagulation clinic.

Discussion

Dental procedures such as multiple tooth extractions do not require warfarin reduction, interruption or discontinuation pre/post dental surgery [6, 7]. WW would be classified as a medically unreliable patient due to his history of substance and alcohol abuse. Our minimum recommended interval for INR monitoring for medically unreliable patients is every 3 weeks.

WW would also be classified as a very high risk patient for thromboembolic events due to his history of MVR, three TIAs and one CVA [7]. In general, the recommended therapeutic range for MVRs is INR 2.5–3.5, with a target INR of 3.0 [7]. Bridging therapy is highly appropriate for MVR patients due to a stroke rate as high as 91% depending upon the type of valve [7–14].

The purpose of bridging therapy is to provide instant anticoagulation with heparin or low molecular weight heparin (LMWH) when warfarin is initiated or temporarily discontinued [8–14]. After warfarin is initiated, the peak INR may be delayed by 3–5 days, increasing the patient's risk of a thromboembolic event [5]. Bridging therapy includes a minimum of 5 days of LMWH (with warfarin initiated on day 1 of LMWH) and continued until two consecutive, therapeutic INR results have been obtained [9–16].

Case #2: warfarin resistance

AZ, a 21-year-old female (97 kg), was admitted for her 4th deep vein thrombosis (DVT) after being diagnosed with

Protein C deficiency. This DVT appeared in her right arm after missing warfarin, 15 mg/day, for the past 5 days.

AZ's hypercoagulable history included her 1st DVT and spontaneous abortion at age 16 years old; her 2nd at age 18 years old; her 3rd proximal DVT at age 20 years old while on oral contraceptives (OCP). Between the ages 22–32 years old, AZ was diagnosed with 4 more DVTs; admitted for pulmonary embolism (PE) once; had two more abortions and two live births. AZ's family history included her mother who also had "blood clots." AZ's medications included: sumatriptan 100 mg PO/day PRN; warfarin 10–50 mg/day; unfractionated heparin 10,000 U SC/day or LMWH full dose (enoxaparin or tinzaparin) when INR less than 2.0 (under physician supervision).

AZ was admitted to the Outpatient DVT Treatment Program after one night of observation, as requested by her family [17]. Full dose LMWH was started as an inpatient and continued until two consecutive, therapeutic INR results were reached with warfarin [17]. Based upon AZ's history of high warfarin doses exceeding 15 mg/day and a baseline INR of 0.90, warfarin 20 mg/day was prescribed for the first 2 days.

By day 3 of warfarin, her INR of 1.24 was still subtherapeutic. The hematologist was hesitant to increase her warfarin dose more than 50%, therefore 30 mg/day was ordered for 2 more days. By day 5, AZ's subtherapeutic INR of 1.50, warranted more aggressive warfarin dosing of 40 mg/day. By day 7, warfarin was increased 60 mg/day in response to an INR of 1.76. By day 9, her INR was still subtherapeutic at 1.90. AZ tolerated warfarin 80 mg/day and by day 11, a therapeutic INR of 2.1 was finally achieved. LMWH was discontinued by day 13 when two consecutive, therapeutic INRs were recorded. Usually our Outpatient DVT Treatment Program aims for a maximum of 5 days of LMWH [17]. AZ's LMWH requirement was prolonged due to warfarin resistance.

Discussion

AZ's thromboembolic events were in part increased due to noncompliance with warfarin, with INR testing, clinic visits and LMWH therapy. Warfarin resistance requires aggressive, escalating warfarin doses to reach therapeutic INR results as safely as possible [18]. However, identifying warfarin resistant patients is subjective without real-time pharmacogenomic testing.

Warfarin resistance has been defined as an inability to achieve or maintain therapeutic INR despite high warfarin daily doses over 15 mg/day [19–22]. Daily doses are 5–20 times greater than average warfarin doses in resistant patients [20]. Several explanations have been proposed including: a change in affinity of the warfarin receptor

causing increased need for warfarin levels to achieve anticoagulant effect; a gene mutation of the vitamin K epoxide reductase multiprotein complex; and/or warfarin drug interactions [18, 21, 22].

Risk factors for warfarin resistance may include a history of coagulopathy (e.g. lupus, Factor V Leiden, Protein C deficiency) and/or active malignancy [18, 21, 22]. One hint of warfarin resistance is 3 consecutive, subtherapeutic INR results in patients under age 65 years old. Dosing a warfarin resistant patient requires two key strategies: daily INRs for the first 5–7 days and aggressive, escalating doses. At our clinic, if we see a change in INR that is <0.5 over 24 h, the day 3 warfarin dose is increased by 50–100% (e.g. 15–20 mg). This strategy has been successful at our clinic in reaching therapeutic INRs as safely and quickly as possible.

Case #3: heparin-induced thrombocytopenia or not?

EB was a 43-year-old female dialysis patient, admitted with a superior vena cava thrombosis most likely due to the dialysis port. She was treated with a continuous infusion of unfractionated heparin (UFH) for several weeks. EB's platelets decreased from 216,000 to 97,000 between day #18 and day #20 of UFH therapy. EB was managed for possible HIT by discontinuing UFH; testing for the ELISA HIT antibody; and changed to a non-heparin anticoagulant, argatroban. EB received argatroban 1.7 mcg/kg/min with plans for chronic anticoagulation with warfarin.

The ELISA HIT antibody was positive. One day after the antibody was sent, the patient's 10-day antibacterial course of linezolid was also discontinued. Because the thrombocytopenia occurred at the same time of linezolid therapy and HIT was suspected, a more specific serotonin release assay (SRA) was sent to confirm the HIT diagnosis.

While on argatroban, EB's platelet count increased to 161,000/ul. The SRA test of 7% was negative (i.e. positive SRA >20%), indicating the absence of true HIT. With the negative SRA test, EB was cautiously restarted on UFH and bridged to warfarin therapy.

Limited data is available for transitioning a patient from argatroban to UFH [23, 24]. Argatroban was discontinued and an UFH IV bolus of 2,500 units (46 units/kg) was given 4 h later. EB's platelet count was 165,000 at baseline and subsequently 179,000 1 h after the UFH IV bolus was given. With no anamnestic response or decrease in platelets that would suggest true HIT, UFH 800 units/h (15 units/kg/h) was started. Platelets were monitored again with no decrease, while maintaining therapeutic aPTT results and aiming for two consecutive, therapeutic INR results between 2.0 and 3.0.

Discussion

The clinical picture of HIT was not convincing from presentation with linezolid the most likely cause of thrombocytopenia [25–27]. Linezolid is a synthetic Gram-positive antibacterial from the oxazolidinone class [25–27]. Thrombocytopenia has been reported in doses \leq 600 mg Q12H for up to 28 days of linezolid [25–27]. Its active metabolites have decreased clearance in renal dysfunction [25–27].

In phase 3 comparator-controlled trials, the percentage of patients who developed a substantially low platelet count (<75% of lower limit of normal and/or baseline) was 2.4% with linezolid and 1.5% with a comparator [25–27]. Thrombocytopenia associated with the use of linezolid appears to be dependent on duration (generally 2 weeks or more) [25–27]. The platelet counts for most patients returned to the normal range/baseline during the follow-up period [25–27].

HIT may be caused by either unfractionated heparin or low molecular weight heparin (LMWH) [28–36]. There are two types of HIT. Type 1 HIT has an incidence of \sim 5% and is characterized by transient, mild, non-immune mediated decrease in platelets, typically within the first 3 days of heparin [28–36]. In contrast, Type 2 HIT has a lower incidence of 1–5%, but is associated with a severe, immune-mediated drop in platelet, typically occurring with 4 days or more of heparin therapy [28–36].

Of those who develop HIT, the incidence is lower with LMWH compared to UFH. In Type 2 HIT, the risk of thrombosis is greater than the risk of bleeding, despite severely low platelet counts [28–36]. The risk of thrombosis without further treatment is 10–15% in 2 days, 40% in 1 week and 53% in 1 month [28–36]. The type of thromboembolic events is 50% DVT, 25% PE, 5–10% acute limb ischemia, 20% amputation and 3–5% acute myocardial infarction (AMI) [28–36]. HIT mortality may be as high as 30–50% [28–36].

Thrombosis occurs due to antibodies that bind to a platelet–heparin complex, thus increasing platelet activation and aggregation. Activated platelets release prothrombotic particles that trigger thrombin generation [28–36].

Clinically, Type 2 HIT may be detected by a platelet drop greater than 50% from baseline or a platelet count <150,000; usually within the first 4–6 days of heparin [28–36]. Type 2 HIT may also initially present as a new thromboembolic event while on heparin therapy such as DVT, PE or CVA [28–36].

Prevention and early detection of HIT is needed for all UFH and LMWH patients. A prudent strategy is to monitor platelets at baseline, then every 3 days for the first 2 weeks of heparin therapy [28–36].

If HIT is suspected, heparin must be discontinued and lab tests must be done immediately [28–36]. The serotonin-release assay (SRA) is most specific for pathogenic IgG (HIT) antibodies [28–36]. The ELISA test is more sensitive, but less specific for HIT [28–36]. Depending upon each site's resources, clinicians may expect delay in lab confirmation of HIT and must manage the patient as a suspected Type 2 HIT case until ruled out by SRA and/or ELISA.

Type 2 HIT is a potentially life-threatening, hypercoagulable state that requires immediate anticoagulation [28–36]. The 7th ACCP Antithrombotic Guidelines recommends non-heparin anticoagulants such as the thrombin inhibitors (argatroban, lepirudin, bivalirudin) or a heparinoid (danaparoid) to replace heparin in HIT [35].

Once the Type 2 HIT patient has been stabilized on a non-heparin anticoagulant, bridging with warfarin therapy will be required. Clinicians need to be aware of falsely elevated INR results with non-heparin anticoagulants, creating difficulty with therapeutic dosing of warfarin [24]. A bridging protocol from thrombin inhibitor to warfarin has been recently published [23].

Case #4: warfarin-induced alopecia

VC was a 70-year-old African American female treated with warfarin 7 mg/day for a unilateral superior vena cava DVT. Her medical history consisted of hypertension (HT), dyslipidemia, temporal arteritis and osteoporosis. VC's medications included: hydrochlorothiazide (HCTZ) 12.5 mg daily, enalapril 10 mg bid, amlodipine 5 mg daily, atorvastatin 20 mg hs, alendronate 70 mg weekly, and prednisone 10 mg daily.

Soon after starting warfarin, VC claimed that patches of her previously thick hair were falling out. The most severe affected areas were around her temples. VC denied any change in shampoo, conditioner, or application of any new hair products. Warfarin-induced alopecia was suspected due to the timing of the oral anticoagulant and the hair loss.

Discussion

Drug-induced alopecia has also been reported with amlodipine, atorvastatin, ACE inhibitors (enalapril) and hydrochlorothiazide [37–39]. Of note, prednisone is used to treat alopecia of the scalp associated with autoimmune disorders [40]. VC experienced hair loss despite daily prednisone for her temporal arteritis.

Earlier reports of warfarin and alopecia seem unbelievable, with incidences as high as 42–78% [41, 42]. Another report claims that diffuse alopecia, primarily

affecting the scalp, occurs up to 40% of warfarin patients [43]. Reversible, diffuse hair loss typically begins within a few weeks of warfarin initiation [41–43]. However, one case study described localized alopecia of the beard area after several months of stable warfarin therapy [43]. Since 1964, the CSM West Midlands Centre for Adverse Drug Reactions have only received 33 reports of warfarin-induced alopecia [43].

Age, warfarin dosage or warfarin duration are not risk factors [42]. Females have a higher incidence of warfarin-induced alopecia [42]. Warfarin appears to primarily affect the anagen (growing) phase of the hair cycle, thus, making the hair follicle enter the telogen (shedding) phase prematurely [40–43]. Warfarin does not affect the catagen (intermediate) phase [40–43].

VC's alopecia could have been caused by amlodipine, atorvastatin, enalapril, hydrochlorothiazide, warfarin and/or an undiagnosed autoimmune disorder such as lupus (SLE) or antiphospholipid antibody syndrome [37, 40].

Managing alopecia during short courses of warfarin therapy like this case may simply require educating and reassuring patients that the hair loss is reversible upon discontinuation of warfarin [41–43]. Switching warfarin to LMWH may not be the answer because alopecia has been also reported with several LMWH products [44, 45]. Depending upon the warfarin indication, a parenteral thrombin or Factor Xa inhibitor may be considered as a non-warfarin and non-heparin anticoagulant substitute.

For VC, it would be valuable to conduct 6-month and 12-month follow-up visits after the warfarin has been discontinued to reassess her hair thickness, new hair growth and the possible cause-and-effect of warfarin-induced alopecia. VC needs to be educated that alopecia may recur if warfarin is ever restarted [41].

Case #5: unstable and labile INRs

MD was a 53-year-old female on warfarin for antiphospholipid antibody syndrome (APA) and a stroke (CVA). Her past medical history includes Type 2 diabetes mellitus (DM), dyslipidemia, hypothyroidism, migraine headaches and uterine fibroids.

Because of the high risk of recurrent CVA, MD's therapeutic range was increased to INRs between 2.5 and 3.5. Her INRs were monitored weekly due to unstable (labile) INR results, ranging from 1.7 to 8.1. Her mean INR was 3.33 (therapeutic), median INR 3.15 (therapeutic) and standard deviation (SD) of 1.38.

Even with small warfarin dosing adjustments, MD's INR would dramatically increase or decrease. She reported taking acetaminophen occasionally for headaches (i.e. exact dosage unknown). MD denied any changes in her

diet, medications, exercise, alcohol consumption or illness.

After 2 years of labile INRs, the anticoagulation clinic staff tried to stabilize MD's INRs with small daily doses of oral vitamin K, based upon published reports [46–49]. By April 2006, she agreed to take two soft calcium chewable tablets daily, each containing 40 µg of vitamin K per tablet. Over the next 11 months, MD's mean INR decreased to 3.03 (from 3.15 earlier) with a median INR of 2.72 (compared to 3.15 earlier) and a SD of 0.98 (compared to 1.38 earlier). There was no statistical difference in the percentage of time in the therapeutic INR range, before and after taking oral vitamin K 80 µg daily. The standard deviation of INR values from the target INR range did decrease from 1.38 to 0.98.

Discussion

The desire to stabilize MD's 2 year history of labile INRs is understandable. Clinicians must remember to screen for any changes in dosages of the interacting drugs that may affect INR and warfarin dosing. Weekly INR monitoring for 2 years is unusual and labor-intensive, even for labile INR patients. Using oral daily vitamin K is one strategy, although not currently supported by the literature for routine use [46–50]. Before considering vitamin K, it is good practice to rule out other causes of labile INRs such as alcohol binges, variable doses of acetaminophen or related products, new infections with fever and/or antibiotics, diarrhea, warfarin compliance (extra, missed or wrong doses), and warfarin self-dosing.

MD's anticoagulation response to two soft calcium chewable tablets daily each containing 40 µg of vitamin K per tablet produced mean INR decrease to 3.03 (from 3.15 earlier) with a median INR of 2.72 (compared to 3.15 earlier).

Anticoagulation clinics and services tend to draw the most complex warfarin patients. [1, 5, 17]. For patients like MD, elevated and unstable INR results and challenging warfarin dosing are expected with antiphospholipid syndrome patients [51–60]. Case reports and one clinical trial have used oral vitamin K doses ranging from 80–500 µg/day [46–50, 61]. The optimal oral vitamin K daily dose has yet to be established. In a case series, eight warfarin patients were selected with INRs fluctuating for reasons not associated with identifiable changes in diet, warfarin dosage, activity level, illness, or changes in drug therapy [47]. After starting oral vitamin K 100 µg/day, there was a significant decrease in the INR standard deviation ($P < 0.05$) [47]. The number of INRs within 0.2 units of the target range increased from 32% to 57% (relative increase 76%) [47]. Time in range also

increased by a similar degree [47]. The authors concluded that supplementation with daily low-dose oral vitamin K significantly increased the number of INRs in range as well as the time in range, and decreased INR fluctuation in this small series of selected patients [47].

An open label study enrolled nine patients with unstable INRs and gave them point-of-care (POC) INR monitors with oral vitamin K 500 µg/day for 9 weeks [49]. A decrease in INR variability was reported in 56% (5/9 patients), at 2–7 days after initiation of oral vitamin K [49]. However, therapeutic INRs were achieved as early as 2 days and as late as 35 days after vitamin K initiation. The authors reported that oral vitamin K (warfarin antagonist) was associated with warfarin dosage increases of 6–95% [49]. These results would suggest ongoing labile INRs and problems with warfarin dosing in 44% of patients, despite daily oral vitamin K.

Finally in 2007, the first double-blind study randomized 70 unstable warfarin patients to either oral vitamin K 150 µg PO/day or placebo for 6 months [61]. A statistically significant (SS) reduction in SD of INR was reported as vitamin K group 87% compared to the placebo group 59% [61]. The time in the therapeutic INR range was better with the vitamin K group 28% than the placebo group 15% [61]. As expected, increased warfarin dosage was required more frequently in the vitamin K group 16% compared to the placebo group 1.5% [61]. This clinical study suggests that selected warfarin patients may benefit from daily oral vitamin K. Further studies with larger patient populations are needed to confirm these results.

Conclusion

Anticoagulation clinics and services tend to draw the most complicated patients who are at highest risk of thromboembolic and/or hemorrhagic events, noncompliance, drug interactions and other challenges. The Anticoagulation Forum's 12 Consensus Guidelines emphasize the need for qualified personnel. These 5 anticoagulation case studies highlight problems, pitfalls and strategic approaches in warfarin management, using 5 complex and/or uncommon patient scenarios.

Acknowledgements Many thanks to Dr. Jack Ansell, the former chair of the Anticoagulation Forum (AF) for the past 16 years; and the AF participants who contributed 3 of these cases for discussion at the last AF Forum in May 2007.

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