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Sublingual administration of warfarin: a novel form of delivery

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Abstract: Current therapy for venous thromboembolism (VTE) includes the initiation of short acting parenteral agents, heparin, low-molecular-weight heparin, or fondaparinux, with subsequent conversion to oral warfarin therapy for the duration of anticoagulation. We present two patients who required long-term anticoagulation for VTE but because of gastrointestinal dysmotility issues were unable to use standard oral anticoagulation. Warfarin is water soluble and absorbed across the epithelium; therefore, we elected to administer warfarin sublingually in an effort to avoid the dysmotility issues while trying to achieve therapeutic anticoagulation. Using sublingual warfarin dosing we were able to achieve therapeutic anticoagulation without complications. Both patients required approximately 6 days to achieve a therapeutic International Normalized Ratio (INR). Neither patient reported adverse side effects related to the sublingual dosing. This unique form of warfarin delivery may be considered for patients with gastrointestinal dysmotility or other gastrointestinal issues which prevent oral use of medications.

Key words: anticoagulation; catheter-related thrombosis; deep venous thrombosis; pharmacology; venous thromboembolism; warfarin

Introduction

Estimates suggest that 31% of all patients discharged from the hospital are at increased risk for venous thromboembolism (VTE).[1] Population studies estimate the rate of venous thrombosis to be approximately 117 per 100,000 person years.[2] The underlying risk for venous thrombosis relates to alterations in the integrity of the vessel wall, venous stasis, or underlying hypercoagulable states. Most patients affected by VTE are successfully treated with short-acting parenteral agents, unfractionated heparin (UFH), low-molecular-weight heparins (LMWH), or fondaparinux, with eventual conversion to oral anticoagulation for the duration of their therapy. However, current guidelines do recommend extended LMWH therapy for 3–6 months in patients with VTE and underlying malignancy.[3] In addition, in some patients the use of oral anticoagulants is not practical; for example, in pregnancy given the risk of warfarin fetopathy or in patients who are unable to take oral medications. In these populations extended use of LMWH has become accepted practice. Small studies have demonstrated the efficacy of this approach. Kucher *et al.* compared extended therapy with enoxaparin to standard therapy with enoxaparin as a bridge to oral warfarin in patients with acute symptomatic pulmonary embolism and demonstrated no difference in recurrent VTE or bleeding between the therapies.[4]

Long-term LMWH therapy is not free of potential complications. Though LMWH has reduced activation of osteoclasts compared to unfractionated heparin (UFH), osteopenia may still result with the use of LMWH.[5] Injection site complications such as a mild to moderate discomfort and ecchymosis may also make this less appealing to patients. In addition, long-term LMWH may be cost-prohibitive for patients without adequate insurance coverage for their medications. We present two patients requiring long-term anticoagulation in whom long-term parenteral therapy was suboptimal and for whom oral anticoagulation was not tolerated. In both cases we administered sublingual (SL) warfarin with good tolerability and with clinical success.

Case history 1

A 26-year-old woman weighing 47 kg with long-standing multiple sclerosis (MS) was admitted

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through the emergency department for fever and visual changes in her right eye. She had gastrointestinal dysmotility related to the MS and was maintained on long-term total parenteral nutrition (TPN). She had had recurrent line infections, both bacteremic and fungemic, as well as recurrent line-related deep venous thrombosis (DVT) and pulmonary embolism (PE) related to the chronic indwelling venous access.

During this admission for line-related fungemia and optic neuritis, vascular medicine was consulted for management of her anticoagulation. Her current outpatient anticoagulation regimen included enoxaparin 50 mg subcutaneously every 12 hours. During a prior attempt to use oral warfarin she failed to achieve the anticipated increase in her International Normalized Ratio (INR) and was found to have multiple intact warfarin tablets in retained gastric contents related to gastroparesis. Since that time she had been committed to using subcutaneous enoxaparin for long-term therapy.

Prior to this admission she had been seen by another vascular specialist who advised against continued use of the enoxaparin because of concerns related to bone demineralization. She was interested in receiving intravenous warfarin via her central venous catheter to achieve anticoagulation. Because of her history of recurrent line-related bacteremia and fungemia this was felt to be a poor option as it would increase the utilization of her central line and potentially increase the likelihood for infection.

After explaining the risks, benefits, and alternatives to SL warfarin, the patient agreed to proceed. A standard intact oral warfarin tablet was administered sublingually. It took about 1 hour to dissolve and had no taste. Medication doses and laboratory monitoring are as indicated in Table 1. On day 4 of her therapy, warfarin was held and enoxaparin was continued due to persistent fungemia and the need to replace the central venous catheter via the translumbar approach. Once all her procedures were completed, anticoagulation using enoxaparin and SL warfarin was resumed and dosed by her primary internal medicine team. She was discharged home to complete therapy with enoxaparin and SL warfarin. Recommendations were to continue enoxaparin until the INR was between 2 and 3 for 2 consecutive days. She was further monitored after discharge by her primary care physician.

Case history 2

A 62-year-old woman weighing 70.5 kg with a history of ischemic colitis requiring subtotal colectomy complicated by functional short bowel syndrome with a high output ostomy had been maintained on home electrolyte infusion. Four months previously she was admitted with an infected indwelling catheter to an outside hospital. During that admission, she developed chest pain raising suspicion for pulmonary embolism (PE). A ventilation/perfusion lung scan was interpreted as an intermediate probability for pulmonary embolus. During treatment with intravenous UFH she developed thrombocytopenia. Her heparin-induced platelet aggregation study (HIPA) was reportedly positive and she was discharged on a fondaparinux to warfarin conversion regimen. Owing to high ostomy output she had frequent intact pill discharge and was unable to achieve and maintain a therapeutic INR.

Table 1 Anticoagulation dosing administered during the hospital course for case 1

Anticoagulation day	Lovenox dose every 12 hours	Sublingual warfarin dose (mg)	INR[a]
1	50 mg	5	–
2	50 mg	5	–
3	50 mg	7.5	1.0
4	50 mg	7.5	1.5
5	50 mg	Held	3.2
6	50 mg	5	2.7
7–11	50 mg	Held for line change	2.1
12	50 mg	7	0.9
13	50 mg	10	0.9
14	50 mg	10	1.1
15	50 mg	10	None
16	50 mg	5	1.9; 2.2
17	Held	7	2.0
18	50 mg	10	1.3
19	50 mg	7	1.5
20	50 mg	10	1.6
21	50 mg	7	1.7
22	50 mg	10	1.9

[a]INR, International Normalized Ratio.

Approximately 4 months later she was admitted to our facility with acute renal failure secondary to increased stoma output and dehydration. Because of the history of PE she was initially treated with UFH but developed progressive thrombocytopenia. UFH was discontinued and bivalirudin was initiated due to the concern for heparin-induced thrombocytopenia (HIT). Her heparin:platelet-factor 4 antibody assay was initially positive at 0.559 with 85% inhibition. She was continued on bivalirudin and warfarin was initiated; however, the first two tablets passed undigested into her ostomy bag. After explaining the risks, benefits, and alternatives related to sublingual warfarin dosing, the patient agreed to proceed. A standard, intact warfarin tablet was administered sublingually. It took about 1 hour to dissolve and had no taste. The INR rose to 2.9 on day 4 of therapy (Table 2). This was likely due to the 7.5 mg dose she received on day 2 of therapy. Her bivalirudin was continued until her INR was between 2 and 3 for 2 consecutive days. She was discharged on SL 2.5 mg daily and followed by her local physician. Her HIPA and porcine serotonin release assay were both subsequently negative.

She was subsequently readmitted approximately 3 weeks later with line-related bacteremia. Anticoagulation was again managed with bivalirudin and SL warfarin. The INR increased as it had during the previous hospitalization. Once she had completed 6 months of therapy for the original PE all anticoagulation was withheld.

Discussion

Patients with VTE typically require anticoagulation for a minimum of 3–12 months depending on the clinical situation. In both of our patients the VTE was related to the indwelling central venous access. Complications related to indwelling venous access may include infection, VTE, venous stenosis or injury, catheter occlusion, vessel perforation, pneumothorax and hemothorax.[6] Studies have demonstrated up to 28% incidence of clinically manifest thrombosis related to central venous catheters.[7] Once an individual suffers thromboembolism related to an indwelling access, maintenance of anticoagulation to preserve line function and prevent recurrent events is indicated. Most patients can be adequately treated with UFH, LMWH, or fondaparinux with conversion to warfarin for long-term oral anticoagulation therapy. However, in our patients, the use of oral anticoagulation was complicated by gastrointestinal dysmotility disorders. In addition to patients with dysmotility issues, some patients may be strictly kept nil *per os* (NPO), thus limiting the administration of oral agents. In patients who are not able to take medications or nutrition orally, who have rapid gastrointestinal transport, or if malabsorption is suspected, alternative therapy using parenteral agents may be considered.

Adjusted dose UFH has been used historically but may be complicated by erratic subcutaneous absorption and the need for frequent dose adjustment. Long-term LMWH therapy is costly and may not be practical in all patients. UFH and to a lesser extent LMWH may also predispose patients to complications such as bone loss. This was a strong consideration in our first patient who was very young and will require an extended duration of therapy given her clinical situation. In addition, UFH and LMWH should not be used in patients with a history of HIT. Fondaparinux is also available for parenteral administration. However, cost considerations may again prevail for long-term use with this drug. In addition, it is unclear whether fondaparinux serves as a good alternative therapy in patients with a history of HIT as was the case for our second patient.[8]

Warfarin is water-soluble and is rapidly and completely absorbed by the epithelium. Given this pharmacologic profile we attempted to use SL administration of warfarin with good success. Warfarin competitively inhibits vitamin K and disrupts the γ-carboxylation of newly synthesized vitamin K-dependent coagulation factors II, VII, IX, and X, as well as the natural anticoagulants protein C and S. Warfarin has no effect on extant coagulation

Table 2 Anticoagulation dosing regimen for case 2

Anticoagulation day	Bivalirudin dose (mg/kg per hour)	aPTT[a] (s)	Sublingual warfarin dose (mg)	INR[b]
1	0.07	84.6	5	1.0
2	0.07	45.9	5	1.0
3	0.13	46.5	0	1.1
4	0.15	51.0	5	1.0
5	0.16	53.8	7.5	1.2
6	0.17	48.8	5	1.7
7	0.13	63.9	2	2.9
8	Held	57.4	2.5	2.9

[a]aPTT, activated partial thromboplastin time; [b]INR, International Normalized Ratio.

factors; therefore, the peak anticoagulant effect is dependent on the normal catabolism of pre-formed factors and replacement by newly manufactured dysfunctional proteins. Warfarin is available for oral and intravenous administration. It is completely absorbed after oral administration with the peak concentration attained in approximately 4 hours. Studies have demonstrated that most of the absorption occurs in the proximal portion of the small bowel; therefore, even patients with extensive bowel loss will typically absorb warfarin adequately.[9] However, clinically this is not always a consistent experience.

The effect of SL administration in our patients was consistent with oral dosing. The long half-lives of factors II and X result in a 3–4-day lag between warfarin dosing and the onset of anticoagulation, as is reflected in Tables 1 and 2. As anticipated, the INR rose over approximately a 5–6-day period into the target therapeutic range of 2 to 3. In case 1, the patient required interruption of anticoagulation for a catheter change on day 6 of therapy. When anticoagulation was resumed she once again had a fairly typical and expected rise in the INR (Table 1).

The limitations of this study include a small sample size, two case reports, and limited patient follow-up. After discharge from our facility both patients were followed by their local physicians for anticoagulation management. We cannot determine whether the ability to use SL dosing in these cases was the result of absorption via the oral epithelium or by absorption across the intestinal epithelium once the tablet was dissolved. Both of our patients had issues with gastrointestinal transit time which appeared to affect the expected absorption process. We frequently encounter patients who are strict NPO due to enterocutaneous fistulae or other intestinal abnormalities and this form of dosing may be a consideration for their care also. This route of dosing will require further study in a larger population of patients to confirm clinical success as well as assess feasibility. However, our initial success suggests this may serve as a viable route for dosing for patients who are unwilling or unable to use injections and are unable to take food or medications orally.

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