Deep Vein Thrombosis

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GSN 0606 Pharmacology for Nurse Practitioners

Clinical Correlation

Deep Vein Thrombosis

Venous thromboembolism is a common and serious problem that can lead to premature mortality and long term morbidity (Lipchik & Presberg, 1996).

- Over 5M cases of DVT are estimated to occur/year in the US.
- Of these, 500,000 have pulmonary embolic event (PE).
- About 10% of these individuals die of PE
- Approximately 90% of clinically significant PE arise from deep veins of the lower extremities.

Case study

Patient presented to ED with the chief complaint of “my calf is very painful and swollen”.

HPI:

Marjorie Wagner is a 69 year old non-obese female with a history of DVT approximately eight yrs ago after outpatient knee surgery. She was on warfarin for three months with no subsequent thromboembolic episodes until yesterday morning when she experienced calf pain with tenderness, which worsened over the past 24 hours. She admits to sitting in front of the television for several hours each day with no exercise as part of her routine activity.

PMH:

HTN

Heart Murmur

DVT, ® leg after knee surgery 8 yrs ago

Osteoporosis

FH:

Noncontributory

SH:

Denies tobacco or alcohol use

Meds:

Amlodipine 5 mg PO QD

Conjugated estrogens 0.625 mg PO QD

Denies use of OTC meds

Allergy:

NKDA

ROS:

Denies SOB, CP, fever, chills, N/V, or recent change in weight

PE:

Gen. – awake, alert, NAD

VS – BP 140/80. TPR 36.4 96 15 ht 150 cm Wt 50 kg

Cor – RRR II/VI HSM @ LLSB

Lungs – Crackles ® base on inspiration

Abd – Soft, NT/ND, normoactive bowel sounds x4, no masses, Neg. hepatosplenomegaly

Ext. – 3+ periph. pulses. 2+ edema ® posterior calf with

erythema.

(+) Homan's sign ® calf

Labs:

Na 142mEq/L, K 3.4 mEq/L, Cl 104 meq/L,

CO_2 26 mEq/L, BUN 17 mg/dl, Cr 0.8mg/dL

H/H 12.5g/dL, 36.9%

Plt 256,000/mm^3, WBC 7000/mm^3

PT 12.8 sec, INR 1.2, aPTT 30 sec

Other:

Doppler ultrasound consistent with DVT ® anterior tibial vein

CXR NL lung fields with mild cardiomegaly

Problem Identification

A. Pathophysiology. DVT is a thrombus composed of cellular material (RBC,WBC,PLTs) bound together with fibrin bands which form in the venous portion of the vasculature. Most often it involves the veins of the lower extremities. The three primary components (Virchow's triad) that play an important role in thrombus formation is: venous stasis, vascular injury, and hypercoagulable state (Mansen, McCance & Field, 1998).

B. Risk factors for DVT in this patient include:

- Prior history of DVT

- Estrogen use
- Immobility/sedentary living
- Congestive heart failure
- Age >65 years old. It is not known if age itself is an independent risk factor, but the prevalence of many risk factors increase with age (Erdman, Rodvold, & Freidenberg, 1998).

Patients can be divided according to the degree of risk and their management directed accordingly. (Lipchik & Presberg, 1996)

1. Low risk group: those that experience DVT <0.5% of the time. These patients are < 40 years old; no other risk factor, underwent anesthesia < 30 minutes.
2. Medium risk: DVT can occur 2-10% of the time if left untreated. Patients who > 40 years old, had anesthesia > 30 minutes.
3. High risk: Patients who have clear predisposing underlying risk and DVT can occur >20% of the time in these individuals. Those with history of prolonged immobilization, cardiac problems (CHF, MI, Hx of DVT), inherited and acquired coagulation defects (hypercoagulable states), estrogen therapy poses varying risks with different compounds, malignancy, obesity, hip fx, pelvic or

lower extremity trauma or surgery.

C. Subjective evidence “My ® calf is swollen and painful”. Pain and tenderness are usually localized to the calf in patients with calf vein thrombosis and tend to be more diffuse and intense in patients with proximal vein thrombosis.

D. Objective evidences were:

Frequently, venous thrombi are clinically silent. Signs and symptoms develop as a consequence of venous outflow obstruction, inflammation of the vessel wall or peri-vascular tissue, or embolization of the thrombus to the pulmonary vascular bed.

♦ (+) Homan’s sign, a discomfort in the calf upon dorsiflexion of the foot. It is not a specific nor a sensitive test for DVT (only 30% of patients tested with + Homan’s had DVT (Erdman et al. 1997)).

♦ palpable cord

♦ edematous/erythematous ® calf. Edema is related to proximal vein obstruction or vascular inflammation. Patient w/ DVT may exhibit discoloration as manifested by: cyanosis r/t large venous obstruction; paleness r/t reflex arterial spasm; redness r/t peri-vascular inflammation (Wells, 2000).

♦ Doppler (+) for DVT. Doppler ultrasonography is

noninvasive test that detects venous flow pattern. In a patient with DVT, there is absence of a spontaneous venous flow.

Desired Outcome

Goals of therapy include:

A. To prevent the development of PE. PE is the most serious and potentially fatal complication of DVT. It is estimated that >95% of PE originate as thrombi in the deep system of the lower extremities.

B. To prevent postphlebitic syndrome. Postphlebitic syndrome consists of symptoms ranging from chronic pain, edema of lower extremities to the formation of stasis ulcers and the development of infection.

B. To reduce morbidity from acute event

C. To relieve symptoms (pain, swelling)

D. To achieve these objectives with minimum adverse effects and cost.

Therefore, successful Rx of DVT should:

- prevent extension of thrombus
- prevent embolism to the lungs
- restore patency to the venous circulation, while
- maintaining venous valve function.

What are the feasible non-pharmacologic and pharmacotherapeutic options for DVT?

A. Non-pharmacologic.

There are some nonpharmacologic techniques that have proven to decrease venous stasis and therefore enhance venous return. These are:

1. Bed rest with feet elevated above the heart
2. Passive and active leg exercises
3. Elastic compression or thromboembolic deterrent (TED) stockings have graduated pressure that is highest in the ankle and decreases as it approaches the thigh, therefore enhancing blood flow to the proximal femoral vein.
4. Intermittent calf compression devise. Intermittent pneumatic calf compression also enhances venous flow to the proximal femoral vein as well as activating the fibrinolytic system.
5. Embolectomy is a more aggressive option in symptomatic DVT.

B. Pharmacotherapeutics

1. Anticoagulation should be initiated after the contraindications have been ruled out, to decrease the risk of further embolic event although it does not prevent the embolization of already established thrombus. Since Mrs. Wagner has no contraindication to anticoagulation, Heparin will be initiated immediately and Warfarin

will be given right on the 1st day of Heparin Rx (overlapped) to allow for the delayed onset of Warfarin effect and will be continued for at least three months.

Heparin is the mainstay for the prevention and treatment of DVT:

- MOA: Potentiates the action of antithrombin III, inactivating thrombin, coagulation factors IX, X, XI, XII and plasmin. It prevents the conversion of fibrinogen to fibrin.
- Metabolism: Hepatic
- Elimination: Renal
- Adverse effects: hemorrhage, thrombocytopenia, chills, fever, N/V, osteoporosis, increased liver enzymes

Warfarin

- MOA: Interferes with the synthesis of Vit K-dependent clotting factors resulting in the depletion of clotting factors VII, IX, X, II.
- Distribution: 97% protein bound
- Metabolism: Hepatic
- Elimination: Renal, GI
- Pregnancy category: X
- Adverse effects: hemorrhage, SOB, N/V, diarrhea, dermatitis, leukopenia, (PDR, 1999)

2. Thrombolytic Rx – The risk for bleeding far outweighs the benefit. PE is minimal when only calf vein is involved (Uphold & Graham, 1998).

Clinical Course:

Mrs. Wagner was admitted to the hospital.

Orders were:

- Bed rest, elevate feet above the heart
- Indomethacin 25 mg. PO TID with meals

Indomethacin was prescribed for leg pain.

Functional Class: NSAID

Chemical Class: Propionic Acid Derivative

<u>FDA approved uses of NSAIDs</u>:

- Analgesic - inhibits prostaglandins peripherally at site Of injury
- Anti-inflammatory of musculoskeletal conditions
- Antipyretic - reduces prostaglandin effect centrally in the thermoregulatory center in the hypothalamus

<u>Contraindications</u>

- Hypersensitivity
- Bleeding disorders
- Renal disease (Mg containing NSAID)
- Proctitis (Indomethacin suppositories)

The following anticoagulation regimen was initiated:

Day	aPTT (secs.) (aPTT Ratio)	Heparin Dose	PT/INR	Warfarin Dose
1	Baseline 30 (1.0) 6 hr post: 55 (1.8)	4000 u IV bolus 900 u/hr IV drip	12.8/1.2	10 mg
2	67 (2.2)	900u/hr IV drip	14.2/1.6	10 mg
3	85 (2.8)	(¯ by 2 u/kg)	17.4/2.7	5 mg
4	60 (2.0)	800u/hr IV drip	19.1/3.4	Dose held
5	52 (1.7)	800u/hr IV drip	17.9/2.4	5 mg
6	Not checked	Off	16.5/2.4	5 mg

Laboratory control aPTT 20 to 30 secs, which is equivalent to a heparin concentration of 0.2 to 0.4 u/ml by protamine titration.

The warfarin dose was adjusted to maintain an INR between 2.0 and 3.0. The nursing staff observed appropriate bleeding precautions. The patient was discharged on the 6th hospital day on warfarin 5 mg. PO QD. The physician scheduled outpatient clinic visit 3x a week for the next 2 weeks to monitor PT/INR.

Optimal Plan

Are these ordered interventions appropriate?

- **Bed** rest with legs elevated is appropriate to enhance venous return is definitely appropriate.
- **Indomethacin**. Anticoagulated patients are already at risk for bleeding. Concurrent use of NSAID is probably not appropriate.
- **Heparin** 4000 u IV bolus (80u/kg) followed by 900 u/hr (18u/kg/hr). A recent randomized controlled trial

concluded that weight-based Heparin dosing resulted in a shorter period of time (and more patients) to achieve therapeutic aPTT (Erdman, et al., 1998). This supports the use of weight-based algorithms to provide effective and safe heparin Rx. Once the desired degree of anticoagulation was determined, aPTT was monitored and necessary adjustment was made.

❖ **Warfarin**. Clinical trials have shown that initiation of warfarin therapy on the first or second day of heparin therapy as soon as a therapeutic aPTT is reached, results in a decreased length of hospital stay (Mehta 1997). Other studies (Erdman, et al., 1998)) with acute thromboembolic disease have established the effectiveness and safety associated with 4-5 day course of continuous IV Heparin with Warfarin started on the 1st day of Heparin, compared to the traditional 10-day course. Both groups showed no difference in the rate of recurrence of thromboembolism. The overlapping allowed for the delayed onset of warfarin's effect.

❖ **Clinic follow-up**. Anti-thrombolytic effects of Warfarin may not occur until 2-7 days post initiation of therapy, therefore the order to return 3x/week for 2 weeks was not necessary.

Assessment Parameters

A. Clinical

1. Relief of signs and symptoms (calf pain, edema, erythema)
2. Absence of hemorrhagic complications (hematochezia, hematemesis, hematuria, hematomas, ecchymosis, etc).

B. Laboratory parameters to evaluate safety and efficacy of anticoagulation therapy are:

1. aPTT 1.5-2x the control (to evaluate Heparin)

Studies have shown that a delay in achieving a therapeutic aPTT or allowing the aPTT to fall into a nontherapeutic range increases the risk of recurrent thrombosis from 7-15x, whereas in patients with adequate anticoagulation, recurrent thrombus occurs in <5% (Lipchik & Presberg, 1996).

2. PT 1-1.5x/INR 2-2.5x the control (to evaluate Warfarin). INR (International Normalized Ratio) or ratio of patient PT/control PT ^{ISI} (International Sensitivity Index) is now considered the standard of practice for monitoring warfarin therapy. The WHO has prepared a thromboplastin standardization of oral anticoagulation Rx by allowing any commercial thromboplastin reagent to be calibrated against this reference standard. It allows reporting of therapeutic range to be universally

applicable (Erdman, et al.,1998).

Platelet count to monitor for heparin induced thrombocytopenia.

Clinical Course

On the 8th day post discharge, Mrs. Wagner attended the Coagulation Clinic for PT/INR follow-up.
(PT 14.6 and INR was 1.6)

- Warfarin regimen was continued
- She was scheduled for another clinic appointment in two weeks
- She did not display any s/s of thromboembolic recurrence at this time.

Patient Counseling

A key to effective outpatient management of thromboembolic disease is patient education. Any antithrombotic agent, no matter how highly effective could fail as a result of inadequate patient education (Haines, 1998).

Important Issues to be discussed with patient/family about Warfarin Rx are:

1. Emphasize need for strict compliance: taking medications as directed, same time each day to minimize the influence of circadian variation; not to d/c or add new med. Without

clinician’s advice; following instructions about follow-up visits.

2. Review side effects: The sites and signs of excessive bleeding e.g., easy bruising, nose bleeds, bleeding gums, black stools, red/brown urine, weakness, dizziness, as well as instructions on when and who to call if bleeding occurs. Be careful to avoid cutting self, to use soft bristle toothbrush, avoid contact sports, use night light to avoid falls at night.

3. Dietary instructions: Avoid sudden changes in eating habits, drinking alcohol while taking this med., food with excessive quantities of Vit K e.g., asparagus, broccoli, cabbage, brussels sprout, spinach, turnips, milk, cheese, as hey may antagonize the effect of Warfarin Rx.

4. Frequent PT. The patient needs to be aware of the required monitoring of PT to evaluate how well the med. is working and should be addressed early in the course of treatment.

5. Inform about drug interactions: That other drugs can greatly influence the effect of Warfarin and should be told not to d/c or add new med. e.g., OTC meds. like antacids, analgesics, and cold products without clinician’s advice

6. Inform other healthcare providers (MDs, DDS, NPs) about being on Warfarin Rx.

Mechanism of Food-Drug and Drug-Drug Interaction and Effects on Coagulation

There are more food-drug and drug-drug interactions reported with Warfarin than any other drug (Erdman, et al., 1998).

- Altered Vit K availability
- Decreased Warfarin absorption
- Changes in Warfarin absorption
- Effects on Warfarin metabolism
- Changes in receptor affinity for Warfarin
- Decreased in Vit. K dependent clotting factor levels
- Independent effect on hemostatic metabolism

The clinician must be aware of the medications and substances like alcohol as a cause of increased or decreased of warfarin effect. Each patient's response needs to be closely monitored and additional INR determination may be indicated whenever other meds. added or discontinued, or an alteration in consumption of Vit. K containing foods.

Reversing the Effect of Warfarin

Excessive anticoagulant effect and bleeding from Warfarin can be reversed by stopping the drug and administering Vit. K and fresh frozen plasma or factor IX concentrate. The disappearance of effect is not correlated

with plasma Warfarin concentration but rather with the reestablishment of the normal clotting factor activity (DiPiro, 1998).

Clinical Situation	Recommended Rx Action
INR >20 mins. (Serious bleeding)	-Vit. K 10 mg IV (over 20-30 -May repeat Vit. K Q 12 H, supplement w/ plasma or factor concentrate
Serious Warfarin OD (life threatening bleeding)	-replacement with factor concentrate, Vit. K 10 mg. IV -May repeat Vit. K PRN pending on INR

Low Molecular Weight Heparin (LMWH)

Low molecular weight heparins (LMWH) have revolutionized the approach to DVT prophylaxis. They belong to a class of anticoagulants to which standard heparin also belongs. LMWHs are derived from unfractionated heparin (UFH) by various methods to elaborate compounds with smaller (mean of 5,000 Daltons compared to up to 30,0000 Daltons in standard heparin), more standard average masses than unfractionated heparin, which is very heterogeneous (Erdman, et al., 1998). Safety and efficacy studies (Belcaro, 2000; Sadovsky, 1999; Erdman, et al., 1998; Cate, 1999; Dunn & Coller, 1999) have shown that LMWH have these

favorable properties over the standard heparin:

- ✓ decreased patient variability
- ✓ fewer major bleeding complications
- ✓ more predictable response
- ✓ increased bioavailability
- ✓ fewer episodes of thromboembolic recurrences
- ✓ there is no need for routine laboratory monitoring
- ✓ well absorbed
- ✓ can be self administered in an outpatient setting
- ✓ reduces the number of inpatient hospital days.

Overall, clinical trials have shown LMWH to be at least as safe and as effective as UFH. However, further large scale studies are needed to more clearly define the role of individual LMWH for these clinical indications. UFH and Warfarin currently remain the drugs of choice (Wells,2000).