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Strategies for Reversal of Anticoagulants, Part I: Warfarin, Unfractionated Heparin and Low Molecular Weight Heparins

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INTRODUCTION

Many patients are treated with anticoagulant medications and physicians frequently have to address strategies for their reversal in the event of life-threatening bleeding or for invasive procedures. In Part 1 of this review, we will summarize some of the traditional anticoagulant medications and strategies for their reversal.

WARFARIN (COUMADIN)

Warfarin (Coumadin) is a vitamin K antagonist. Vitamin K is a cofactor necessary for production of coagulation factors II, VII, IX, and X. Warfarin also inhibits production of natural anticoagulant factors such as protein C and protein S.

Half-life: In therapeutic doses, warfarin has a half-life of 35 to 48 hours. It is commonly used as rat poison and is occasionally ingested by humans either by mistake or for suicidal/homicidal purposes. In such cases, its half-life can be weeks to months.

Monitoring: The INR (international normalized ratio) is used to monitor warfarin therapy. For most indications the INR therapeutic range is 2 - 3. The main exception is for prosthetic heart valves where the target INR is higher. Warfarin has a narrow therapeutic window and an unpredictable response which makes maintaining optimal anticoagulation difficult. The incidence of major hemorrhagic events associated with warfarin is in the 2 to 4% range annually (6 -10% for minor bleeding). Bleeding risk rises with INR > 4.

A patient's genetic makeup may influence response to warfarin. Specifically, patients with variations in two genes may need lower doses than those without these genetic variations. The two genes are called CYP2C9 and VKORC1. The CYP2C9 gene is involved in the metabolism of warfarin and the VKORC1 gene helps regulate the ability of warfarin to prevent clotting.

Antidotes: vitamin K, fresh frozen plasma (FFP), Prothrombin complex concentrate (PCC), and recombinant activated factor VII (rFVIIa).

Reversal of warfarin anticoagulation:

For elective surgeries, warfarin can be held three to five days prior to surgery and the patient's aPTT, PT and INR can be checked prior to surgery.

If a reversal of anticoagulation is needed sooner (e.g. in cases of urgent surgery, supratherapeutic INR>5 or lower INR with symptoms of bleeding), warfarin reversal can be achieved with administration of vitamin K. The route of administration and appropriate dose of vitamin K should be based on the patient's current INR level, target INR level and presence or absence of signs of bleeding. Vitamin K should be administered either orally or intravenously depending on the clinical situation. Subcutaneous administration is not recommended because of unpredictable and sometimes delayed response.

The half-life of vitamin K is 1.5 to 3 hours. The full effect of vitamin K is only achieved 12 to 24 hours after administration; therefore in cases of serious bleeding, administration of FFP, PCC or, occasionally, recombinant factor VIIa is needed. There are a number of factors that could potentially affect response to vitamin K, including: body weight, level of INR elevation, active cancer and drugs. Elderly patients may require lower vitamin K doses.

In cases of serious bleeding, vitamin K can be administered IV 5-10 mg as an adjunctive therapy. If the INR is >5 and <9 without active bleeding, vitamin K can be given orally 1- 2.5 mg for rapid reversal (within 24 hours) to patients that are at risk for bleeding. If the INR is >9 with no clinically significant bleeding, 2.5- 5 mg of oral vitamin K can be given. For an INR> 20, 10 mg of vitamin K by slow intravenous infusion can be administered. As mentioned above, in cases of serious bleeding vitamin K should be used only as adjunctive therapy. If the INR remains significantly elevated, additional doses of vitamin K can be repeated at 12 hour intervals. It should be noted that intravenous administration of vitamin K has been associated with anaphylactoid reactions. Also, vitamin K (both oral and parenteral) is ineffective in patients

with severe liver failure, due to poor synthesis of coagulation factors by the liver.

For patients with serious or life-threatening bleeding, administration of vitamin K is not sufficient; therefore fresh frozen plasma, PCC or recombinant factor VIIa may be needed. The volume of plasma needed to correct a high INR to 1.5 or less (no increase in bleeding risk) is 10- 20 ml/kg (4-6 units FFP or about 1 to 1.5 liters in an adult). This amount, however, is difficult to infuse quickly, especially in elderly patients and in patients with congestive heart failure and volume overload. In PCCs, the concentration of vitamin K dependent factors II, VII, IX, and X is much higher than in FFP, therefore a much smaller volume is required (25-50 units/kg). While PCCs are widely used in Europe, they are not currently widely used or readily available in the United States. Plasma remains the most widely used approach for urgent reversal of warfarin. However, risk vs. benefit should be considered in each patient due to possible adverse effects, including: volume overload, Transfusion-Related Acute Lung Injury, allergic reactions and the small risk of transfusion-transmitted viral infection.

Recombinant factor VIIa has been used "off label" for emergency reversal of warfarin effect in patients with intracerebral hemorrhage (ICH). The effect of shortening the PT is immediate and the half-life of rFVIIa is 2-3 hours. There is no consensus regarding the dose of rFVIIa to be used for reversal of warfarin effect in cases of ICH, but a dose of 40 - 90 mcg/kg has been used in a number of studies.

UNFRACTIONATED HEPARIN

Unfractionated heparin (UFH) inhibits coagulation by binding to antithrombin III and potentiating its activity about 1000-fold. Antithrombin III inhibits circulating thrombin, Xa, IXa, and VIIa.

Half-life: 1.5 hours.

Monitoring: The dose is adjusted to attain a target aPTT of 1.5 to 2 times normal or an anti-factor Xa heparin activity assay in the therapeutic range (0.3 - 0.7 units/mL), with monitoring and dosage adjustment at 6-hour intervals after initiation of heparin infusion until stabilization. Monitoring thereafter is once daily at the same time of day. Hematocrit and platelet count (potential for heparin-induced thrombocytopenia) should be monitored periodically during therapy.

Antidote: Protamine sulfate at 1 mg IV per 100 units of heparin. The maximum dose is 50 mg per 10 minutes (administered at 5 mg/minute). Therapy should be guided by monitoring aPTT every 5 to 15 minutes. A dose can be repeated in 10 to 15 minutes, if needed. Dosage adjustment can be made based on the time from heparin administration, i.e. a smaller dose is needed if more than one hour has elapsed after heparin administration. Vital signs should be monitored during administration of protamine sulfate since it can be associated with side effects such as hypotension, bronchoconstriction and anaphylaxis due to histamine release.

LOW MOLECULAR WEIGHT HEPARINS

Low molecular weight heparins (LMWH) work primarily by inhibition of factor Xa.

Half-life: 3 - 12 hours based on the type of LMWH: enoxaparin (Lovenox): 4.5-7 hours; dalteparin (Fragmin): 3-5 hours; tinzaparin (Innohep): 3-4 hours.

Dose: depends on the type of LMWH used and its indication for prophylaxis vs. treatment.

Elimination: renal

Monitoring is usually not required; however in certain circumstances (patients with renal impairment, bleeding or abnormal coagulation parameters, pregnancy, obesity or low body weight, and children) anti-Xa activity can be used. Target peak range should be measured at 3-4 hours post-dosing and also depends on prophylaxis vs. treatment regimen.

Reversal: Protamine sulfate can be used; however it only partly neutralizes the effect of LMWH. It reverses only about 60% of the anti-factor Xa activity of LMWH. Dose of protamine is 1 mg IV per 100 units (or 1mg) of LMWH. Repeated doses may be required. Dose adjustment can be made based on the time from LMWH administration and its half-life. In cases of life-threatening ICH rFVIIa has been used “off-label”.

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