i. Thrombolytics

Coumadin, with its narrow therapeutic range and time to steady-state (peak plasma concentrations are achieved in 90 minutes, but anticoagulant effect takes several days), should always be treated with caution.

Unfractionated heparin has two advantages over LMWH: immediate onset and reversibility with protamine. It is the anticoagulant of choice after cardiac, vascular, and neurointerventional procedures. For cardiac cases 300-400 U/kg is normally given, leading to an ACT > 400 seconds (the safe threshold for going on cardiopulmonary bypass). Note that aprotinin artificially shortens the kaolin-activated ACT, thus the ACT must be 600 seconds to come off of bypass if aprotinin/kaolin are used (celite-based ACTs are not affected). In other cases (vascular, neurointerventional), heparin is usually given in simple 3000-5000 U boluses until ACT is 2x baseline. Beware that boluses of heparin can drop SBP due to decreased SVR. Heparin resistance is usually caused by excessive heparin binding proteins or insufficient antithrombin – in the latter case, administration of FFP (which contains AT) will be therapeutic. HIT type 1 occurs in 5-25% of patients (usually 1-2 days after starting heparin), is non-IgG mediated, and self-limited. HIT type 2 is less common (usually 5-10 days after starting heparin), IgG mediated, and fatal in ~ 25% of cases.

LMWH activates antithrombin and inactivates factor Xa, but is unable to inhibit thrombin directly (as UFH does). Its onset is in 20-60 minutes, and is more predictable. In obese, renal failure, or neonatal patients, anti-factor Xa levels have to be monitored.

Fondaparinux is a pentasaccharide that activates antithrombin. It has a longer half-life than LMWH and can be given SQ qday. Risk of bleeding in long term therapy, however, is higher than for LMWH.

Direct thrombin inhibitors (argatroban, melagatran, hirudin, and bivalirudin) are mostly given IV, although ximelagatran is given PO. Key to their use is understanding that all direct thrombin inhibitors significantly

elevate the risk of bleeding and cannot be reversed. Argatroban, uniquely for this class, can be monitored via ACT or PTT (bivalirudin and hirudin cannot).

Tissue plasminogen activators contraindicate surgery or puncture of non-compressible vessels for ten days.

Antiplatelet Drugs

Platelet function normalizes within 3 days of discontinuation of NSAIDs. [Stoelting RK. Basics of Anesthesia, 5th ed. Elsevier: China p. 335, 2007]

Thienopyridine derivatives (namely clopidogrel) inhibit ADP-induced platelet aggregation and prevent fibrin from binding to platelets. Platelets take ~ 7 days to normalize after cessation of clopidogrel, although some believe that normalization can take as many as 10 days (ticlopidine, for instance, requires 14-21 days). GPIIB/IIIA antagonists (abciximab, eptifibatide, and tirofiban) prevent fibrinogen and vWF from binding to the platelet GPIIB/IIIA receptor. Platelets normalize 24-48 hours after discontinuing abciximab.

How To Approach Anticoagulated Patients

Always take into account the reason that patients are on anticoagulant therapy to begin with. Patients who had a thromboembolic event within the last month are at highest risk for thromboembolic complications. Patients undergoing elective surgery should probably wait until at least 3 months of anticoagulant therapy have been completed prior to undergoing an operation. [Stoelting et. al. Basics of Anesthesia, 5th ed. Elsevier – China, p. 342, 2007] Patients who are coming off of coumadin are at risk for thrombosis for several reasons. First, they have some sort of predisposing hypercoagulable state (or they wouldn't be on coumadin to begin with). Second, thrombin formation is abnormally high following cessation of coumadin therapy [Stoelting et. al. Basics of Anesthesia, 5th ed. Elsevier – China, p. 343, 2007]. Third, INR measurements are not entirely representative of the patient's true coagulative state (i.e., there is

some lag). Furthermore, as in all patients, plasminogen activator inhibitor type I levels increase postoperatively.

How to Assess Risk of Perioperative Venous Thrombosis

Orthopaedic surgery patients are at particularly high risk for thromboembolic complications, as are patients coming off of coumadin in order to undergo cardiovascular or abdominal operations. In high risk patients, Stoelting recommends converting to IV heparin perioperatively, and discontinuing UFH 6 hours prior to surgery (or LMWH 12 hours prior to surgery). Heparin can then be restarted 12 hours after surgery. One must always take into account the likelihood of perioperative bleeding. Postoperative heparin is given at maintenance doses only (i.e., no loading doses are used) . Patients at intermediate risk do not require preoperative heparinization. Low risk patients only require SQH or LMWH. In patients who need immediate restoration of vitamin K activity, FFP (10-15 cc/kg IV) can be infused, however FFP is rarely able to normalize or even half-normalize INR below 1.85 [Abdel-Wahab et. al. Transfusion 46: 1279, 2006]. Prothrombin complex concentrate (which is normally dosed at 25-50 IU/kg) has been shown to be more effective [Makris et. al. Br J Haematol 114: 271, 2001] than FFP, but the high risk of perioperative thrombosis must be taken into account.

ii. Enoxaparin: assessment of effect

Definition

Enoxaparin, like any LMWH, is derived by depolymerization of unfractionated heparin and retains UFH's ability to activate antithrombin and thereby provide anticoagulation. Largely secondary to its smaller molecular size, enoxaparin binds less to plasma proteins, macrophages, and endothelial cells, thereby promoting a **more reliable dose-response relationship and longer plasma half-life** compared to UFH.

Compared to UFH, enoxaparin has lower anti-IIa activity relative to anti-Xa activity and this translates into a reduced effect on the aPTT. **The increase in the aPTT observed with UFH is largely due to its anti-IIa activity**. Because of its more predicable pharmacokinetics, enoxaparin is given in fixed doses for thromboprophylaxis and total body weight (TBW)-adjusted doses for full anticoagulation, typically without laboratory monitoring. However, **since LMWHs are renally-cleared, their half-life is prolonged in renal insufficiency**. Additionally, dose-adjustment of enoxaparin can be troublesome in severely obese patients. Based on these observations, laboratory monitoring of LMWH has been advised in such situations, particularly when weight-based regimens are used.

Anti-Xa activity monitoring by a chromogenic assay is the most widely available and the test recommended by the College of American Pathologists for this purpose. Following a therapeutic weight-based dose of enoxaparin given subcutaneously, the anti-Xa activity peaks at 4 hours and this is the advised time to conduct monitoring assays. A conservative therapeutic range for peak effect with BID dosing of enoxaparin is 0.6-1.0 IU/mL for patients being treated for venous thromboembolism. In order to avoid an increased risk of bleeding, levels of >1 IU/mL should be avoided in patients with renal insufficiency or severe obesity.

Since intravascular volume and volume of distribution does not have a linear relationship with TBW, it has been thought that weight based regimens of LMWH for obese patients may lead to overdosing. Interestingly, anti-Xa activity is not significantly increased when LMWH is given to obese patients based on TBW. Additionally, an increased rate of bleeding is not seen with weight-based regimens. However, since few studies have included patients exceeding 150 kg and BMI > 50, it is reasonable to perform anti-Xa monitoring in such patients due to the above theoretical concerns.

The clearance of LMWH is directly proportional to the creatinine clearance (CrCl). The administration of multiple therapeutic doses of

enoxaparin has been shown to result in significantly elevated anti-Xa levels in subjects with CrCl under 30 mL/min. Renal insufficiency has been shown to increase the risk of major bleeding complications following therapeutic anticoagulation with LMWH. In one large study, **a CrCl < 30mL/min was associated with increased incidence of major hemorrhage in patients treated with enoxaparin**. Based on this, **UFH should be the first choice agent for therapeutic anticoagulation for patients with CrCl under 30 mL/min. If enoxaparin must be used, anti-Xa levels should be obtained to guide therapy**.

Enoxaparin and other Low-Molecular-Weight-Heparins are mainly used for treatment and prophylaxis of DVT and venous thromboembolism. The effect of these agents on standard coagulation tests will vary (minimal for enoxaparin) as will the effect of protamine neutralization, which is incomplete for enoxaparin. Monitoring is usually not required or performed. However, if monitoring is considered necessary (e.g., renal failure, extreme obesity), the anti-Xa activity level is the appropriate test for assessing the level of anticoagulation.

Compared to Unfractionated-Heparin (UFH), enoxaparin has lower anti-IIa activity relative to anti-Xa activity and this translates into a reduced effect on the aPTT. The increase in the aPTT observed with UFH is largely due to its anti-IIa activity.

The Anti-Xa activity level is the most widely available test for monitoring the effect of LMWH (enoxaparin) and this is the test recommended by the College of American Pathologists for this purpose. Following a therapeutic weight-based dose of enoxaparin given subcutaneously, the anti-Xa activity (activity of LMWH) peaks at 4 hours and this is the advised time to conduct monitoring assays. Therapeutic range for treatment of DVT is approximately 0.5-1.0 U/mL and for DVT prophylaxis is 0.1-0.3. However, there may be some variability from laboratory to laboratory and between institutions.

The clearance of LMWH is directly proportional to the creatinine clearance (CrCl). A CrCl < 30mL/min has been shown to be associated

with an increased incidence of major hemorrhage in patients treated with enoxaparin. Based on this, unfractionated-Heparin should be the agent of choice for therapeutic anticoagulation in patients with CrCl under 30 mL/min. If enoxaparin (or LMWH) must be used, then anti-Xa levels should be obtained to guide therapy.

III. Anticoagulants: Effects on PT, PTT

Laboratory testing for coagulation studies are commonly performed in a light blue top tube, which has 3.2% sodium citrate added in a specific amount to prevent coagulation of the blood. The tube should be inverted immediately upon adding the blood sample to mix the sodium citrate with the blood, but the sample should not be shaken in order to avoid hemolysis. Of note, polycythemia may artificially alter coagulation tests unless the amount of sodium citrate is corrected for the polycythemia. In the laboratory, calcium is added back to the sample to overcome the sodium citrate, and then an additional reagent (see below) is added to perform the clotting test.

To obtain the prothrombin time (PT), tissue factor and phospholipid are added to the blood sample. The time (in seconds) are counted until a fibrin clot is formed. The number of seconds is the prothrombin time, and this number can be divided by a lab standard to form the International Normalized Ratio (INR). The PT/INR are valuable for evaluating the common and extrinsic coagulation pathways. Warfarin (vitamin K antagonist) prolongs the PT. Direct-acting anticoagulants also prolong the PT. Examples of these are argatroban (direct thrombin inhibitor), dabigatran (direct thrombin inhibitor), rivaroxaban (factor Xa inhibitor), apixaban (factor Xa inhibitor), and edoxaban (factor Xa inhibitor). While heparins (unfractionated and low-molecular weight) indirectly antagonize factor Xa, they typically do not prolong the PT except in cases of a large heparin bolus (i.e. for cardiopulmonary bypass). Fondaparinux also inhibits Xa, but typically does not alter PT or activated Partial Thromboplastin Time (aPTT) (“Fondaparinux …”).

To obtain the activated Partial Thromboplastin Time (aPTT, PTT), a “thromboplastic material” along with a “negatively charged substance” are added to the sample to activate contact factor for coagulation (Zehnder). Again, the PTT is measured in seconds. The PTT reflects coagulation via the common and intrinsic coagulation pathways. Heparin can cause a prolongation of the PTT along with direct thrombin inhibitors and direct Xa inhibitors. It is important to note that the PTT does not reliably reflect the level of anticoagulation that some oral anticoagulants provide. As previously mentioned, fondaparinux typically does not alter PTT, but it may mildly increase the PTT. Warfarin can increase the PTT in supratherapeutic doses.

Sources

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