ASGE guideline: the management of low-molecular-weight heparin and nonaspirin antiplatelet agents for endoscopic procedures

This is one of a series of statements discussing the utilization of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy prepared this text. In preparing this guideline, a MEDLINE literature search was performed, and additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When little or no data exist from well-designed prospective trials, emphasis is given to results from large series and reports from recognized experts.

Guidelines for appropriate use of endoscopy are based on a critical review of the available data and expert consensus. Further controlled clinical studies are needed to clarify aspects of this statement, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance to these recommendations.

INTRODUCTION

Increasingly, patients referred for endoscopic evaluation are taking newer classes of anticoagulant and antiplatelet therapy. This guideline addresses the management of patients undergoing endoscopic procedures who are on either anticoagulation therapy with low-molecular-weight heparin (LMWH) or clopidogrel and other new antiplatelet therapies, including glycoprotein (GP) IIb/IIIa inhibitors. The use of warfarin and unfractionated heparin (UFH) therapy, as well as aspirin and other nonsteroidal anti-inflammatory drugs (NSAID), is addressed in a recently published guideline.[1]

LMWH

The primary indications for the use of LMWH are the prophylaxis and the treatment of thromboembolic complications and cardiac ischemia. LMWHs are fragments of unfractionated heparin produced by a chemical depolymerization process, which yields chains with a mean molecular weight of 5000. The U.S. Food and Drug Administration has approved 4 LMWHs: ardeparin (Normiflo; Wyeth-Ayerst Laboratories, St Davids, Pa), dalteparin (Fragmin; Pfizer, New York, NY), enoxaparin (Lovenox; Aventis Pharmaceuticals Inc, Bridgewater, NJ), and tinzaparin (Innohep; Pharmion Corporation, Boulder, Colo), not all for the same indications.[2]

Pharmacology

Both UFH and LMWH exert their anticoagulant activity by activating antithrombin and inhibiting factor Xa. Unlike UFH, LMWH yields a greater selective activity against factor Xa and has a lower affinity for antithrombin.[3] As a result, LMWHs do not significantly alter the activated partial thromboplastin time, and this test is not useful to monitor their effect.[2]

LMWH produces a more predictable anticoagulant response, has a better bioavailability, has a longer half-life, and has a dose-independent clearance mechanism compared with UFH.[3] In addition, LMWH has been demonstrated to cause less bleeding than UFH, because it binds less avidly to platelets, does not increase microvascular permeability, and is less likely to interfere with the interaction between platelets and the vessel wall.[3] LWMH does not appear to have as high a risk for the development of thrombocytopenia as UFH.[4]

The duration of action of the LMWHs varies, but antifactor Xa activity may persist up to 12 hours after a single subcutaneous injection. LMWHs are either given in standard doses or in weight-adjusted doses, depending on the agent and the indication. The proper dose for patients at the extremes of body weight has not been studied.[2] The best test to monitor activity is an antifactor Xa assay, but assays may differ and may take time to process.[2] In the event of an overdose, intravenous protamine sulfate can be used to reverse the effects of LMWH, as has been used with reversal of UFH. The specific dose varies for each LMWH, and the package insert should be consulted for proper use.

Clinical trials and bleeding complications

Randomized controlled trials have demonstrated the superior efficacy of LMWH compared with warfarin for postoperative prophylaxis to prevent deep venous thrombosis (DVT) in patients undergoing knee[5] and hip[6] arthroplasty. LMWH has demonstrated efficacy in the prevention of thromboembolic complications in cancer patients,[7,8] acutely ill medical patients,[9] and patients with severe congestive heart failure.[10] LWMH also has demonstrated efficacy in treating acute DVT[11,12] and

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pulmonary embolism,[13] and in patients with an acute coronary syndrome.[14-16] Chronic DVT patients also can be managed safely and effectively with outpatient LMWH.[17]

There have been no clinical trials to assess the efficacy of LMWH to prevent thromboembolic complications in patients with chronic atrial fibrillation (AF). Patients with chronic AF at the highest risk for stroke include those with a history of prior stroke, transient ischemic attack, or systemic embolism; systolic blood pressure greater than 160 mm Hg; left ventricular dysfunction; or women older than 75 years.[18] In support of the need for continued anticoagulation, a retrospective review of AF patients in whom anticoagulation was adjusted before endoscopy or bronchoscopy suggested a higher incidence of thromboembolism compared with patients who had no interruption in their anticoagulation. Overall, the 30-day risk for stroke in AF patients with adjusted anticoagulation was 1.06%, with complex patients with AF having the highest risk at 2.93%.[19]

Overall, major bleeding complications in patients prescribed LMWH range from 0% to 5%, but specific GI bleeding rates have not been reported. Other major bleeding complications include intracranial hemorrhage, hematomas, hemothorax, and bleeding at procedural sites.[20-25]

The use of LMWH for thromboprophylaxis in patients with mechanical prosthetic heart valves is still being evaluated. There have been reports of mechanical prosthetic valvular thromboses in pregnant women treated with enoxaparin, although the true incidence of thrombosis in these patients is not known.[26] In other patients with prosthetic heart valves, short-term use of LMWH appears to be safe.[27]

The role of LMWH in endoscopy

There have been no published studies on the use of LMWH in patients undergoing endoscopy. The use of UFH has been addressed in a recent guideline.[1] Despite this lack of data, the clinical use of these agents in patients undergoing endoscopy probably should follow analyses indicating the most cost-effective approach to managing periprocedure anticoagulation. One approach in a patient on systemic anticoagulation would be to remain on therapy and to perform an initial diagnostic endoscopy, when the need for therapeutic endoscopy (e.g., colonoscopy with polypectomy) is not certain.[28] If a lesion requiring removal is noted on that examination, then the patient can be brought back for another procedure while the anticoagulation has been held or reversed. The next most cost-saving scenario in this analysis is to use LMWH as a ''bridge'' in those patients who will need endoluminal therapy after initial screening endoscopy. An alternative cost-savings strategy is to completely discontinue therapy for a short period of time (i.e., 3-5 days) before the procedure.[29] Some patients may be at too high of a risk to safely stop anticoagulation, in which case, LMWH may be the most appropriate strategy.[29] The dose of LMWH for bridge therapy has not been defined. After a therapeutic procedure, UFH may be restarted 2 to 6 hours later.[1] The optimal time to restart LMWH after endoscopy has not been determined. The benefits of immediate anticoagulation in preventing thromboembolic events should be weighed against the risk of hemorrhage, depending upon the setting (e.g., risk of bleeding after sphincterotomy, polypectomy, EMR).[1] Consultation with the patient's primary care provider, cardiologist, or hematologist may be helpful in managing anticoagulation, particularly in complex patients.

Recommendations

1. Acute GI hemorrhage in the patient taking LMWH. The decision to reverse or to stop this therapy, risking an adverse ischemic event or a thromboembolic complication, must be weighed against the risk of continued bleeding by maintaining continued systemic anticoagulation. Because of the short half-life of the LMWHs, the anticoagulant effect may be reversed within 8 hours of the last dose. If quick reversal is required, intravenous protamine sulfate can be used. Note that the administration of protamine sulfate can cause severe hypotension and anaphylactoid reactions.

2. Elective endoscopic procedures in the patient taking LMWH. A decision regarding discontinuation of therapy before endoscopy has to be weighed against the patient's risk for developing an adverse ischemic event or thromboembolic complication.[30] Endoscopic procedures have been previously categorized as low or high risk for bleeding (Table 1).[1] Low- or high-risk clinical conditions for thromboembolic complications also have been previously defined.[1]

Low-risk procedures. No adjustments in anticoagulation need be made, irrespective of the underlying condition.

High-risk procedures. Discontinue LMWH at least 8 hours before the anticipated therapeutic endoscopy. The decision as to when to restart therapy should be individualized.

3. Elective endoscopic procedure in the patient taking warfarin who may need bridge therapy. LMWH may be useful in extending the period of systemic anticoagulation while the effects of long-acting warfarin are allowed to dissipate. LMWH may replace the previous standard of a ''heparin window'' in high-risk patients. Considerations in favor of LMWH would be the enhanced quality of life for the patient (i.e., no therapeutic monitoring, avoidance of hospitalization, no need for intravenous access) and the possible economic savings of outpatient LMWH compared with a hospital-based ''heparin window.''[31] LMWH should not be used in pregnant women with mechanical prosthetic heart valves. In non-pregnant patients with mechanical valves, short-term use appears to be safe but prospective controlled data are lacking.

Low-risk procedure. No adjustments in anticoagulation need be made, irrespective of the underlying condition.

TABLE 1. Management of low-molecular-weight heparin and nonaspirin antiplatelet agents for endoscopic procedures

Management of LMWH in patients undergoing endoscopic procedures

Procedure risk	Recommendation
High	Consider discontinuation at least 8 h before procedure
Low	No change in therapy

Reinstitution of LMWH should be individualized.

Management of antiplatelet medication (clopidogrel or ticlopidine) in patients undergoing endoscopic procedures

Procedure risk	Recommendation
High	Consider discontinuation 7-10 d before procedure
Low	No change in therapy

Patients on combination therapy (e.g., clopidogrel and aspirin) may be at an additional increased risk of bleeding.

For acute GI hemorrhage in the patient on clopidogrel or ticlopidine, the decision to transfuse platelets should be individualized, usually weighing the risk of an acute cardiovascular event against the risk of continued bleeding.

Reinstitution of clopidogrel or ticlopidine should be individualized.

Procedure risk

High-risk procedures	Low-risk procedures
Polypectomy	Diagnostic
Biliary sphinterotomy	EGD ± biopsy
Pneumatic or bougie dilation	Flexible sphincterotomy ± biopsy
PEG placement	Colonoscopy ± biopsy
EUS-guided FNA	ERCP without endoscopic sphincterotomy
Laser ablation and coagulation	Biliary/pancreatic stent without endoscopic sphincterotomy
Treatment of varices	EUS without FNA
	Enteroscopy

High-risk procedure. Discontinue warfarin 3 to 5 days before the procedure and concomitantly begin administering LMWH. Consider using dose ranges as for the treatment of patients with acute DVT (e.g., enoxaparin 1 mg/kg subcutaneously every 12 hours). Discontinue LMWH for at least 8 hours before the therapeutic endoscopy. The decision as to when to restart therapy should be individualized.

NONASPIRIN ANTIPLATELET AGENTS

Antiplatelet agents are used in the management of coronary artery disease, stroke, and peripheral vascular disease. These are drugs that inhibit platelet activation, adhesion, or aggregation. They include aspirin and nonaspirin NSAIDs, the thienopyridines (clopidogrel and ticlopidine), dipyridamole, and the platelet GP IIb/IIIa receptor inhibitors.[32,33]

There are no published trials primarily designed to assess the effects of newer antiplatelet agents in patients undergoing endoscopy. Aspirin and other NSAIDs may be continued in patients undergoing endoscopy in the absence of a preexisting bleeding disorder.[1] The decision to continue the newer antiplatelet drugs needs to be based on their effect in reducing cardiovascular, ischemic stroke, and peripheral vascular morbidity and mortality vs. their effect on increasing periprocedural bleeding complications.

Pharmacology

Clopidogrel (Plavix; Bristol-Myers Squibb Company, New York, NY) and ticlopidine (Ticlid; Roche Laboratories, Nutley, NJ) selectively inhibit adenosine diphosphate (ADP) induced platelet aggregation,[34,35] They act by inhibiting the binding of ADP to P2 receptors, and the subsequent ADP-mediated activation of the GP IIb/IIIa receptor. Ticlopidine has more significant side effects than clopidogrel (e.g., severe neutropenia, thrombotic thrombocytopenic purpura).[33,35] Platelet inhibition induced by clopidogrel and ticlopidine takes several days to develop

and reaches a maximum of 40% to 60% inhibition of ADP-induced aggregation after 3 to 5 days.[35] Bleeding time is prolonged and reaches a maximum at 3 to 7 days.[35] Recovery of platelet function occurs over 3 to 5 days after the drug is discontinued, but some antiplatelet action may persist for 7 to 10 days, corresponding to the life span of a circulating platelet.[34,35] The active metabolite of clopidogrel has not been identified. Dipyridamole is a phosphodiesterase inhibitor and a weak antiplatelet agent that inhibits uptake of adenosine.[36] A dipyridamole-aspirin combination (Aggrenox; Boehringer Ingelheim Corporation, Ridgefield, Conn) is available.[37]

The final common pathway to platelet aggregation is the GP IIb/IIIa receptor, which binds fibrinogen and other adhesive proteins that bridge adjacent platelets.[38] The GP IIb/IIIa receptor antagonists are intravenously administered drugs given as a bolus followed by a continuous infusion.[33] There are two classes of these drugs, based on molecular size.[33,39] Abciximab (ReoPro; Eli Lilly and Company, Indianapolis, Ind) is a monoclonal antibody, whereas the other drugs are smaller competitive inhibitors of the GP IIb/IIIa receptor: the peptide receptor antagonist eptifibatide (Integrilin; Key Pharmaceuticals, Sydney, Australia) and the nonpeptide receptor antagonist tirofiban (Aggrastat; Merck & Co., Inc., Whitehouse Station, NJ). Estimated duration of action after stopping intravenous infusions are 24 hours for abciximab and 4 hours for eptifibatide and tirofiban. The antiplatelet effects may be partially reversed by platelet infusions or desmopressin (DDAVP; Aventis Pharmaceuticals Inc., Bridgewater, NJ).[39-41]

Clinical trials and bleeding complications

Clopidogrel and ticlopidine. Clopidogrel has indications for use in reducing thrombotic events in patients with recent myocardial infarction, recent stroke, or established peripheral arterial disease, as well as for patients with acute coronary syndrome and for those who undergo percutaneous coronary intervention (PCI), especially stent placement.[42-44]

A major side effect of clopidogrel and ticlopidine is bleeding. Unlike aspirin, which affects the GI mucosa, a short-term endoscopic study in normal volunteers showed no development of mucosal damage.[45] However, the addition of clopidogrel to naproxen treatment increased fecal blood loss.[46] Results from clinical trials provide estimates of the risk of hemorrhage in clinical use. In one clinical trial,[47] hemorrhagic complications occurred in 1.8% of patients who received aspirin alone, 6.2% who received aspirin and warfarin, and 5.5% who received aspirin and ticlopidine. In the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial,[42] the rate of severe GI bleeding was somewhat less with clopidogrel than with aspirin (0.5% vs. 0.7%), while the reported rate of any GI hemorrhage for patients receiving clopidogrel was 2.0% vs. aspirin at 2.7%. In the CURE (Clopidogrel in unstable angina to prevent recurrent events) trial,[43] clopidogrel plus aspirin was associated with an increased risk of major GI bleeding (1.3%) compared with 0.7% for placebo plus aspirin (for ulcers, 0.4% vs. 0.3%). Clopidogrel and ticlopidine should be used with caution in patients who may be at increased risk of bleeding because of underlying GI pathology. Combining therapy with other antiplatelet agents with a different mechanism of action or with standard anticoagulant drugs also may lead to an increased risk of bleeding.

Dipyridamole. The most accepted use for dipyridamole at present is in the secondary prevention of stroke. While somewhat effective as monotherapy, the greatest efficacy is achieved in combination with aspirin.[48,49] Dipyridamole does not appear to increase the risk of bleeding, including in those who are also taking aspirin.[33,48,50]

GP IIb/IIIa inhibitors. The GP IIb/IIIa inhibitors are intravenous drugs approved for use in acute coronary syndrome and PCI.[39] Significant clinical benefits in decreasing the end points of myocardial infarction, death, or the need for target vessel revascularization compared with conventional therapy of heparin and aspirin were seen in patients undergoing PCI and, to a lesser extent, for patients with acute coronary syndrome.[33,51-54] Recent American College of Cardiology/American Heart Association guidelines for the management of unstable angina and non-ST-segment elevation myocardial infarction[55] recommend a GP IIb/IIIa inhibitor (in addition to aspirin and heparin or LMWH) in patients in whom an interventional approach is planned. Current practice frequently also involves the use of clopidogrel (quadruple therapy).

All GP IIb/IIIa inhibitors increase the risk of bleeding, most commonly at arterial access sites.[38] Recent trials suggest a modest increase of bleeding from 0.4% to 1.0% for placebo to 1.3% to 1.9% for GP IIb/IIIa inhibitor recipients.[55-56]

Recommendations

There are no published studies regarding the safety of endoscopic procedures in the setting of these antiplatelet agents. The following recommendations are based on their pharmacology and known clinical effects.

1. Acute GI hemorrhage in the patient taking clopidogrel or ticlodipine. Clopidogrel or ticlodipine should be discontinued. The decision to reverse the antiplatelet effect, risking ischemic consequences, must be weighed against the risk of continued bleeding by maintaining the state of impaired platelet aggregation. If quick reversal is required, platelet transfusion may be appropriate.

2. Elective endoscopic procedures in the patient taking clopidogrel or ticlopidine. A decision regarding discontinuation of therapy before endoscopy has to be weighed against the patient's risk for developing an adverse ischemic event, including coronary stent occlusion. Endoscopic procedures previously have been categorized as low risk or high risk for bleeding (Table 1).[1]

Low-risk procedures. No adjustments in the antiplatelet regimen need to be made.

High-risk procedures. Whether to discontinue these agents has not been determined. If discontinued, they should be stopped 7 to 10 days before the procedure. Because of the slow onset of action, it may be appropriate to restart the drug the following day. In patients who receive clopidogrel plus aspirin, consider reversion to a single agent (preferably aspirin) before elective endoscopy.

3. Patients taking dipyridamole. In the absence of a preexisting bleeding disorder, endoscopic procedures may be performed in patients who take dipyridamole or combination dipyridamole-aspirin in standard doses. However, the safety in patients undergoing high-risk procedures is unknown.

4. Patients taking a GP IIb/IIIa inhibitor. Patients being considered for elective endoscopy are not typically exposed to this class of drug. For patients requiring emergency endoscopy for acute GI hemorrhage, the GP IIb/IIIa infusion should be discontinued. Eptifibatide and tirofiban have a relatively short duration, of about 4 hours of action, whereas abciximab may last up to 24 hours. Transfusion of platelets or use of DDAVP may play a role in the setting of major bleeding.

SUMMARY

For the following points: *(A)*, prospective controlled trials; *(B)*, observational studies; *(C)*, expert opinion.

- LMWH and nonaspirin antiplatelet drugs are effective in the prevention and the treatment of thromboembolic disease. *(A)*
- LMWH and nonaspirin antiplatelet drugs are associated with an increased risk of bleeding (except dipyridamole) *(A)*; these should be discontinued in the setting of acute GI bleeding. *(C)*
- The decision to discontinue these drugs must balance the bleeding risk against the risk of a thromboembolic event. *(C)*
- For low-risk procedures, these drugs may be continued. *(C)*
- For high-risk procedures, LMWH should be discontinued at least 8 hours before the procedure. *(C)*
- For clopidogrel or ticlopidine, there are insufficient data, but, if discontinued, the drug should be withheld for 7 to 10 days. *(C)*
- Dipyridamole may be continued. *(C)*
- LMWH may be used as a bridge before endoscopy in patients who require anticoagulation in whom warfarin cannot be safely discontinued. *(C)*
- LMWH should not be used in pregnant women with mechanical prosthetic heart valves. *(B)*
- In nonpregnant patients with mechanical valves, short-term use appears to be safe *(B);* however, prospective controlled data are lacking.

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