Formulary Flash

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Heparin vs LMWHs vs Fondaparinux What's the Difference?

Background

For many years, unfractionated heparin (UFH) was the mainstay of anticoagulation therapy for treatment and prevention of thrombosis. Newer agents with more predictable pharmacokinetic profiles such as the low molecular weight heparins (LMWHs) and fondaparinux, have proven to be just as, if not more, effective for the same indications as heparin. The University Health System (UHS) currently has two LMWHs on formulary, dalteparin (Fragmin®) and enoxaparin (Lovenox®), in addition to fondaparinux (Arixtra®), the first in a new class of anticoagulants named factor Xa inhibitors. Although these agents share similarities, differences in their mechanism of action, pharmacokinetic profiles, contraindications and FDA approved indications warrant staff education on their proper use.

Mechanisms of Action

Heparin – Binds to and potentiates the actions of antithrombin (AT) to inactivate factor Xa and prevent the conversion of prothrombin to thrombin, as well as prevent the conversion of fibrinogen to fibrin. Binds non-specifically to various plasma proteins and endothelial cells resulting in an unpredictable dose-response relationship and low bioavailability after subcutaneous (SC) administration. [1]

LMWHs – Also bind and accelerate the activity of AT, but with a preferential, and longer lasting effect on factor Xa. When compared to heparin, LMWHs are less able to inhibit the production of thrombin and bind to plasma proteins and endothelial cells less due to their decreased sized. This accounts for an 85-99% bioavailability when administered SC, more predictable anticoagulant response, less inter-patient variability, and longer duration of action than heparin.[1]

Fondaparinux - Binds and enhances the anti-Xa activity of AT by 300-fold. AT specificity does not allow binding to other plasma proteins. It has no direct effect on thrombin, has excellent bioavailability after SC administration and a long half-life.[1]

Half-life

The difference in half-lives between these agents causes differences in their dosing frequency and duration of action. Consequently, there are different recommendations for timing of treatment doses prior to surgical procedures. The latest edition of the CHEST guidelines has included a new chapter on the Perioperative Management of Antithrombotic Therapy, with recommendations for dose timing prior to surgical procedures.[2]

Timing of Treatment Dose before Surgical Procedure

Agent for Treatment	Half-life	Last dose Before Procedure
IV UFH	45 min.	4 hours (Grade 1C)
SC LMWH	4 – 5 hrs	24 hours (Grade 1C)
SC Fondaparinux	17- 21 hrs	**4-5 days**

Douketis JD et al. Chest 2008;133 (suppl 6):299-339.
Grade 1C- Strong recommendation, low or very-low quality of evidence

Indications

Although these agents are commonly used in similar populations, differences in their approved and off-label indications do exist.

Indications

	UFH	LMWH		Fondaparinux
		Enoxaparin	Fragmin	
Treatment				
DVT/PE	√/√	√/OFF	√*/OFF	√/√
STEMI	OFF	√		
NSTEMI	OFF	OFF	√	OFF
Unstable angina	OFF	√	√	
DVT Prophylaxis				
Medically Ill	√	√	√	OFF
Knee/hip replacement	√	√	√	√
Abdominal Surgery	√	√	√	√
History of HIT				OFF

*FDA approved for treatment in cancer patients
√-FDA approved OFF-Off-label

Comparison of Pharmacokinetic Parameters, Dosing frequencies, and Indications for UFH, LMWHs, and Fondaparinux

	UFH	LMWH		Fondaparinux
		Enoxaparin	Dalteparin	
Mechanism	Enhances AT effects on Factor Xa and thrombin. Binds non-specifically to plasma proteins → unpredictable dose response	Enhances AT effects more selectively on Factor Xa than on thrombin. Less binding to plasma proteins→ more predictable dose response, less inter-patient variability		Enhances anti-Xa activity of AT Specificity for AT → no binding to other plasma proteins, good predictability
Half-life	1 – 2 hours	4.5 – 7 hours	2 – 5 hours	17 - 21 hours
Reversal Agents	**Protamine Sulfate** 1 mg neutralizes 100 units Calculated based on heparin given during the last 3-4 hours	**Protamine Sulfate** (neutralizes 60% of activity) Based on time since LMWH was dosed: < 8 hours – 1 mg protamine per 1 mg LMWH 8 - 12 hours- 0.5 mg protamine per 1 mg LMWH > 12 hours - Protamine not recommended		**Not reversible by Protamine** Factor VII- limited data
Routine Monitoring	aPTT for IV drips	None		None
Dosing frequency	Treatment - Continuous drip	BID or Once daily[a]		Once daily for all indications
Clearance	Hepatic & Reticulo-Endothelial System No renal adjustments	Renal **Adjust** for CrCl < 30 mL/min		Renal **Contraindicated** in CrCl < 30 mL/min
Pregnancy	OK[3]	OK[3]		CI – Insufficient data Case reports available
Breast Feeding	OK (Grade 1A) [3,a] - does not pass into breast milk	OK (Grade 2C) [3,a] - Low bioavailability when ingested orally		Unknown if excreted in breast milk Suggest alternative agent (Grade 2C)[3, a]
Ability to cause HIT	Yes - Well documented	Yes - Well documented		No in vitro cross reactivity to anti-PF4/heparin antibodies Case reports
Use in HIT treatment	NO (Grade 1B) [4,a]	NO (Grade 1B) [4,a]		Yes - CHEST Guidelines (Grade 2C) [4,a] Currently under study Not an FDA approved indication
Use in patient with a history of HIT	If > 100 days since HIT occurrence, some physicians consider a re-trial	If > 100 days since HIT occurrence, some physicians consider a re-trial		A reasonable option – More studies required No in vitro cross reactivity to anti-PF4/heparin antibodies

aPTT - Activated partial thromboplastin time, AT-antithrombin, BID - twice daily, CI - contraindicated, LMWH - Low molecular weight heparin, HIT - Heparin induced thrombocytopenia, TID - three times per day, UFH - Unfractionated heparin

[a] Grade 1A – Strong recommendation, high-quality evidence, Grade 1B - Strong recommendation, moderate-quality evidence, Grade 2C – Weak recommendation, moderate-quality evidence

References

1. Haines ST, Racine E, Aeolla M. In DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach 6th ed. New York (NY): McGraw- Hill;2005.337-373.
2. Douketis JD, Berger PB, Dunn AS, et al. Chest 2008;133 (suppl 6):299-339.
3. Bates SM, Greer IA, Pabinger I, et al. CHEST 2008:133 (suppl 6):844S-886S.
4. Warkentin TE, Greinacher A, Koster A, et al. CHEST 2008:133(suppl 6):340S-380S.

Contributors: Crystal Franco, PharmD; Clinical Pharmacist; Rosa C. Garcia RPh, Manager, Clinical Informatics, Pharmacy Services, Deborah Cardell, MD, Assistant Professor of Medicine, Chair UHS National Patient Safety Goal, Anticoagulation

Editors: Alexander Shepherd MD, PhD, Chairman, P&T Committee; Yolanda Laurel MS,RPh, Director of Pharmacy Services