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DRUG AND THERAPEUTICS NEWSLETTER

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Vancouver General Hospital, UBC Hospital, GF Strong

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In This Issue...

All formulary changes and policy/procedure updates have been approved by the Drugs and Therapeutics (D&T) Committee and Medical Advisory Council (MAC).

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Changes to Formulary

Additions

1. Fondaparinux 2.5mg/0.5mL (Arixtra®)
- Anticoagulant (direct anti-Xa inhibitor)
- Restricted at VA for the management of NSTEMI, non-PCI patients receiving medical management only.
- See page 3 for review

2. Lanthanum 500mg, 750mg chewable tablets (Fosrenol®)
- Non-calcium based phosphate binder used for control of hyperphosphatemia in patients with end-stage renal disease.
- A lanthanum initiation form must be filled out by Nephrology and approved by the Provincial Renal Agency prior to commencement of therapy.

3. Acetylcholine - electrolytes 20mg/vial (Miochol E®)
- Intraocular preparation used to obtain rapid miosis of the iris post-cataract and other eye surgeries.

4. Bupropion XL 300mg tab (Wellbutrin XL®)
- Once daily long-acting antidepressant agent
- Note that buproprion XL 150mg daily is considered bioequivalent to buproprion SR 150mg; all orders for buproprion XL 150mg will be interchanged to bupropion SR 150mg

Deletions

1. Acetylcholine injection (Miochol®, Miogan®)
- Discontinued by manufacturer
- Replaced with acetylcholine-electrolytes for intraocular use (Miochol E®)

Updated Policies

1. AUTOMATIC STOP ORDER POLICY

The Automatic Stop Order Policy states an automatic stop time of either 3 or 7 days will be applied to a number of medication categories (antibiotics, narcotic and controlled drugs, oral anticoagulants, inhalation solution by nebulizer, TPN, and ophthalmic preparations other than for glaucoma or lubrication). A prescriber may override the autostop date and specify the duration of treatment according to the following:

A) **Acute Care Units**: the duration may not exceed 90 days, except for straight narcotics which may not exceed 6 weeks.
B) **Extended Care Units**: the duration may not exceed 1 year. A specified time frame must be written; "Duration of hospital stay" is not acceptable.

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2. VANCOMYCIN EMPIRIC DOSING GUIDELINES UPDATE

Vancomycin dosing guidelines have been updated to allow for more aggressive dosing when target trough serum levels between 15-20 mg/L are required.

A. Vancomycin Empiric Dosing

Table 1. Initial Vancomycin Dose per Interval

TOTAL BODY WEIGHT	LOADING DOSE (Maximum 2000 mg/ dose)		MAINTENANCE DOSE*
kg	Target pre-level 5-15 mg/L (20 mg/kg)	Target pre-level 15-20 mg/L (25 mg/kg)	(15mg/kg)
40-50	1000 mg	1250 mg	750 mg
51-60	1250 mg	1500 mg	1000 mg
61-70	1250 mg	1750 mg	1000 mg
71-80	1500 mg	2000 mg	1250 mg
81-90	1750 mg	2000 mg	1250 mg
91-100	2000 mg	2000 mg	1500 mg

Table 2. Initial Dosing Interval (hours)*

Serum Creatinine (µmol/L)	Age Group (years)					
	20-29	30-39	40-49	50-59	60-69	70-79
40-60	8	8	12	12	12	18
61-80	8	12	12	12	18	18
81-100	12	12	12	18	18	18
101-120	12	12	18	18	18	24
121-140	12	18	18	18	24	**
141-160	18	24	24	24	**	**
161-180	24	24	**	**	**	**
181-200	24	**	**	**	**	**

*The maintenance dose and interval on Tables 1 and 2 are intended to achieve a pre-vancomycin target level of 5-15 mg/L. To achieve a higher pre-vancomycin serum level of 15-20 mg/L, the dosing interval should be empirically shortened (e.g. Q12H to Q8H). Alternatively, the maintenance dose can be increased to 20 mg/kg.

**Patients with significant renal impairment should receive a loading dose followed by 3 and 24 hours post dose serum levels to determine subsequent dosing.

B. Vancomycin Drug Monitoring

Vancomycin serum levels should be ordered in the following situations:

1. Pre-vancomycin level on 3rd or 4th dose (within 48 hours) when targeting a higher trough level of 15-20 mg/L (Table 3); repeat weekly to ensure pre-level is within therapeutic range.
2. Pre-vancomycin level after 7 days of therapy if aiming for levels < 15 mg/L and therapy is to continue for 14 days **AND**
   - patient is at risk for accumulation (e.g. Q8H interval) **OR**
   - patient is receiving other nephrotoxic agents
3. Pre-vancomycin level if renal function is changing or uncertain.
4. Pre-vancomycin level if patient is not responding to therapy.
5. Pre-vancomycin level if patient is obese (>90% IBW), pregnant, pediatric, or hypermetabolic (e.g. burn patient, cystic fibrosis).
6. Pre and 3 hour post vancomycin level (target 20-40 mg/L) if calculation of precise kinetic parameters is necessary (e.g. in a case when a target pre-level of 15-20 mg/L cannot be achieved while on prolonged therapy, or in an obese, pregnant, or pediatric patient, especially when aggressive dosing is required).

Table 3. Suggested Target Vancomycin Levels

Vancomycin Pre-Level 5-15 mg/L (goal ~ 10 mg/L)	Vancomycin Pre-Level 15-20 mg/L
• Skin and soft tissue infection not due to MRSA • Uncomplicated catheter-associated bacteremia due to coagulase-negative *Staphylococcus** • Urinary tract infection (catheter-associated; rule out bacteremia)	• CNS infection • Deep-seated or sequestered infection (e.g. abscess) • Endocarditis • Osteomyelitis • MRSA bacteremia, pneumonia or skin and soft tissue infection • MSSA bacteremia (penicillin allergic pt)

*uncomplicated refers to lack of septic thrombosis, tunnel infection, or port abscess for tunnelled or implantable catheters

3. PDTM UPDATES

- **Potassium Chloride & Potassium Acetate infusion pump requirements**:
  For reasons of patient safety and the widespread availability of more pumps, an infusion pump is required for
  i) infusion rates > 10 mEq/h or
  ii) infusion bags containing > 20 mEq/bag.

- The following medications are rarely used in Special Care Areas, and as such have been excluded for administration by nurses via direct IV in these areas: adenosine, ephedrine, epinephrine, lidocaine, phentolamine, and procainamide. These drugs may still be administered direct IV by nurses in Critical Care Areas. The individual monographs and Table B have been updated to reflect this change.

New Drug/Drug Products

Fondaparinux (Arixtra®)

Sarah Stabler, B.Sc. (Pharm), Harjinder Parwana, Pharm.D.

Traditional management of acute coronary syndromes (ACS) has included the use of unfractionated heparin (UFH) and low-molecular weight heparin (LMWH). Recently, interest in the use of a new anticoagulant, fondaparinux, in the setting of ACS has been sparked by the publication of the OASIS-5[1] and OASIS-6[2] trials.

Mechanism of Action

Fondaparinux, a synthetic pentasaccharide, is an inhibitor of factor Xa which acts via selective binding to antithrombin III (ATIII). Once bound, it increases the ability of ATIII to inactivate factor Xa, thereby halting the coagulation cascade.[3] Its mechanism of action is distinct as it is specific to factor Xa and unlike both LMWH and UFH, fondaparinux does not inhibit factor IIa (see Table 1, page 4) .

Vancouver Acute (VA) Restrictions

At VA, fondaparinux is restricted to the management of patients with ACS (unstable angina or non-ST elevation myocardial infarction (NSTEMI)) who are not amenable to percutaneous coronary intervention (PCI), and receiving medical management only. Although fondaparinux is indicated for prophylaxis and treatment of DVT/PE, it will continue to be non-formulary for these indications as it is nearly double the cost of the traditional LMWHs. Fondaparinux can also be used as an alternative anticoagulant for DVT prophylaxis in patients with heparin-induced thrombocytopenia (HIT).[4] Argatroban is the formulary alternative for therapeutic anticoagulation in patients with HIT.

Adverse Events/Contraindications

The most significant adverse effect seen with fondaparinux is bleeding. Thrombocytopenia has been reported in clinical trials, however, its incidence is substantially lower than with UFH and LMWH.

Fondaparinux is contraindicated in patients with a creatinine clearance < 30 mL/min due to the risk of accumulation and subsequent increased risk of bleeding.[3] As well, fondaparinux is contraindicated as sole anticoagulant during PCI, due to high rates of guiding catheter thrombosis.[1,2]

Dosage and Monitoring

The dosage of fondaparinux for management of ACS is 2.5 mg SC daily. CBC and serum creatinine are recommended at baseline, then CBC once to twice weekly to monitor for bleeding and thrombocytopenia.

Literature Review - Role in Therapy

Anticoagulation Recommendations from the 2007 ACC/AHA Guidelines for the Management of UA/NSTEMI[5]

If an invasive strategy is planned, enoxaparin and UFH (Class IA) is preferred over fondaparinux (Class IB). Alternatively, if a conservative approach (medical management) is being followed, enoxaparin (Class IA), UFH (Class IA), or fondaparinux (Class IB) can be used. Fondaparinux may be preferred in patients who are receiving medical management and are at a high risk of bleeding (Class IB).

OASIS-5[1]

OASIS-5 was a non-inferiority trial that compared fondaparinux 2.5 mg SC daily (for 8 days or until hospital discharge) with enoxaparin 1 mg/kg SC twice daily (for 2-8 days or until stable) in 20,078 patients presenting with unstable angina or NSTEMI. The primary outcome of the study was a composite of death, MI, or refractory ischemia at 9 days. Fondaparinux met the criteria for non-inferiority with enoxaparin and had significantly lower bleeding rates (2.2% fondaparinux, 4.1% enoxaparin; $p<0.001$). However, there was no difference in the composite endpoint at 30 or 180 days, or mortality at 180 days ($p=0.05$).

OASIS-6[2]

OASIS-6 was a superiority trial that compared fondaparinux with control (placebo or UFH). Patients presenting with STEMI were randomized to fondaparinux 2.5 mg SC daily (for 8 days or until hospital discharge) or control (UFH 60 units/kg bolus then 12 units/kg/hr or placebo, stratified by indication for anticoagulation). Patients were divided into 2 strata: Stratum 1 = no indication for UFH and patients received either fondaparinux (n=2823) or placebo (n=2835); Strata 2 = indication for UFH and patients received either fondaparinux (n=3213), UHF (n=3221) or placebo (n=2835). Exclusions included patients with contraindications to anticoagulation, including those at high risk of bleeding, those receiving oral anticoagulants, or serum creatinine greater than 265 umol/L. The primary outcome (death or reinfarction at 30 days), in both strata combined, was lower in patients receiving fondaparinux compared to control [9.7% vs. 11.2%, ARR 1.5%, HR 0.86 (0.77-0.96)]. These results were driven by stratum 1 [11.2% fondaparinux vs. 14% placebo, HR 0.79 (0.69-0.92)] whereas no benefit was demonstrated in stratum 2 [8.3% fondaparinux vs. 8.7% UFH, HR 0.96 (0.81-1.13)].

Fondaparinux has not been compared in a head-to-head study against enoxaparin in STEMI patients; further trials are required to prove its superiority or non-inferiority to enoxaparin. In OASIS-6, the benefit of fondaparinux over placebo was restricted to those patients who were not deemed to have an indication for anticoagulation. This stratification was based on the investigator's judgment and the trial did not provide any objective criteria used to determine indication for anticoagulation.

Conclusions

The current available literature supports the use of fondaparinux in the management of ACS (unstable angina or NSTEMI) in patients not undergoing PCI. Although there is literature supporting the use of fondaparinux as an anticoagulant for various other indications (i.e. DVT/PE prophylaxis and treatment, STEMI), it will remain non-formulary for these indications due to its higher cost over traditional LMWH (dalteparin and enoxaparin). Additional benefits of fondaparinux over traditional anticoagulants include the lack of need for monitoring aPTT and a lower incidence of HIT than UFH and LMWH. Fondaparinux may also be used as an alternative anticoagulant for DVT prophylaxis in patients with HIT.

References

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4. Warkentin TE et al. Treatment and prevention of heparin-induced thrombocytopenia. In Irwin RS (ed). Antithrombotic and thrombolytic therapy, 8th ed. Chest 2008;133(Suppl):340S-380S.
5. Anderson J *et al.* ACC/AHA 2007 Guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction. J Am Coll Cardiol 2007;50:1-157.

Table 1. Comparison of Formulary Low Molecular Weight Heparins

Drug	Dalteparin (Fragmin®)	Enoxaparin (Lovenox®)	Fondaparinux (Arixtra®)
ACS[a] Dose	120 units/kg SC Q12H (Max[b] = 10,000 units SC Q12H)	1 mg/kg SC Q12H (Max[b] = 100 mg SC Q12H)	2.5 mg SC daily
Factor Xa:IIa Specificity	2.0-2.7:1	2.7-4.1:1	1:0
Peak Onset (SC)	4 hours	3 hours	2 hours
Plasma Half-Life (anti-Xa activity)	119-139 minutes	3.5-4.2 hours	17-21 hours
Elimination	Renal	Renal	Renal
When to Hold SC Dose Prior to Surgery	12 hours (or 24 hours with once daily dosing)	12 hours (or 24 hours with once daily dosing)	24 hours

[a]ACS = Acute Coronary Syndrome = unstable angina and non-ST elevation myocardial infarction
[b]the manufacturer recommends a maximum dose; however, dosage should be individualized and higher dosages may be administered