Vancouver Coastal Health
Promoting wellness. Ensuring care.

DRUG AND THERAPEUTICS NEWSLETTER

A publication of the CSU Pharmaceutical Sciences
Vancouver General Hospital, UBC Hospital, GF Strong

Sept 2007 *Volume 14, Number 3*

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).

This and other Drug and Therapeutics Newsletters are on the Web at **www.vhpharmsci.com**

Changes to Formulary

Additions

1. Ceftriaxone injection (Rocephin®)
- Third generation cephalosporin
- See Therapeutic Interchange Policy of Cefotaxime to Ceftriaxone page 1

2. Bivalirudin injection (Angiomax®)
- Direct thrombin inhibitor anticoagulant indicated for select patients undergoing percutaneous coronary intervention (PCI)
- See drug review page 3

3. Tenecteplase injection (TNKase®)
- Thrombolytic used for ST elevation myocardial infarction (STEMI) for non-PCI candidates
- Added to replace reteplase as can be given as a single bolus (versus a double bolus injection with reteplase)

Deletions

1. **Reteplase injection (r-PA, Retavase®)**
- Alternative: Tenecteplase

Updated Policies

1. **THERAPEUTIC INTERCHANGE: CEFOTAXIME TO CEFTRIAXONE**

Cefotaxime and ceftriaxone are third generation parenteral cephalosporins that are considered therapeutically equivalent. Ceftriaxone has the advantage of once daily administration compared to 3 times daily for cefotaxime in patients with normal renal function. Generic ceftriaxone is also now available which would result in considerable cost savings.

Since August 13, 2007, all orders for cefotaxime have been automatically interchanged to ceftriaxone by pharmacy using the following conversion (Table 1).

Table 1. Cefotaxime to Ceftriaxone Interchange

Cefotaxime	Interchange to Ceftriaxone
2 g IV Q8H or Q12H	2 g IV Q24H
1 g IV Q8H or Q12H	1 g IV Q24H
1 to 2 g IV Q4H or Q6H (meningitis)	2 g IV Q12H (meningitis)

EDITORIAL STAFF:
Karen Shalansky, Pharm.D., FCSHP
James Kim, Pharm.D., BCPP
Amy Wai, B.Sc.(Pharm)
Nilu Partovi, Pharm.D., FCSHP, Operations Director (acting)

Any comments, questions or concerns with the content of the newsletter should be directed to the editors. Write to CSU Pharmaceutical Sciences Vancouver General Hospital, 855 W12th Ave, Vancouver BC V5Z 1M9, send a FAX to 604-875-5267 or email karen.shalansky@vch.ca

Exceptions to the interchange include orders for outpatients in the hemodialysis unit and those written as “do not substitute”.

Ceftriaxone-Calcium Drug Incompatibility
There have been recent reports of fatalities resulting from the accumulation of calcium-ceftriaxone precipitates in the lungs and kidneys of neonates when these two drugs were given parenterally within 48 hours of each other. These findings are based solely on reports in neonates, and there are no data to suggest a similar risk in adults receiving this combination. However, these two drugs are considered incompatible and should not be mixed via Y-site administration.

2. DELETION OF ORAL AZITHROMYCIN TO CLARITHROMYCIN INTERCHANGE

A therapeutic interchange to convert oral azithromycin orders to oral clarithromycin was developed and approved in January 2007, due to surveillance data suggesting that the use of azithromycin may be associated with a potential increase in *Streptococcus pneumoniae* resistance. Oral azithromycin is currently restricted for *Mycobacterium avium* complex (MAC) prophylaxis and chlamydial infections.

The interchange policy was created to facilitate IV azithromycin step-down to oral clarithromycin. However, an automatic interchange from oral azithromcyin to clarithromycin may result in subtherapeutic dosing for treatment of community acquired pneumonia (CAP) because the typical duration of therapy for azithromycin is shorter (5 days) compared to 7-14 days for clarithromycin, due to the longer half-life of azithromycin.

As such, this interchange has been deleted and pharmacists will contact the prescriber directly to determine the appropriateness of switching oral azithromycin to clarithromycin.

3. DELETION OF VITAMIN B12 1000 MCG INTERCHANGE TO 100 MCG

Vitamin B12 1000 mcg doses have been automatically interchanged to 100 mcg doses (other than if used for Schilling test) since 1993. For patients with uncomplicated vitamin B12 deficiency, doses of 30-100 mcg IM/SC are adequate for repletion. However, in patients with accompanying neurological deficit, vitamin B12 doses of 1000 mcg are recommended for initial treatment. Since there is no toxicity associated with administration of too much vitamin B12 as excess drug would be eliminated renally, and there is no cost difference between the two doses, this therapeutic interchange has been deleted.

4. PARENTERAL DRUG THERAPY MANUAL (PDTM) 2007 UPDATE

All PDTMs at Vancouver Acute have been updated with the June 2007 version. For any questions regarding the PDTM, please contact Dr. Karen Shalansky at 604-875-4839.

The following changes are in the current update:

- **Flumazenil** may be administered direct IV by nurses in the Emergency Department.

- **Propofol** may be administered direct IV by nurses in the Emergency Department as long as an ED physician is at the bedside.

- **Botulinum Toxin** may be administered for treatment of patients with achalasia who are not surgical candidates. This is in addition to its use in patients with focal limb spasticity. This drug is restricted to Rehab Medicine, physicians associated with the Spine Cord Program, and GE clinic.

- **Rituximab** may be prescribed by Renal Transplant Physicians for patients with refractory biopsy-proven antibody-mediated renal allograft rejection. This is in addition to its use for BCCA approved indications.

- **“Administration of Cytotoxic Drugs by the Intrathecal Route via Lumbar Puncture or Ommaya Reservoir”** has been added as Appendix 1 in the PDTM. Reference to this Appendix had been added to cytotoxic drugs (methotrexate and cytarabine) that can be given intrathecally.

5. CRITICAL CARE Y-SITE COMPATIBILITY CHART MAY 2007 UPDATE

These charts (green) have been replaced on all critical care areas. Please contact Dr. Karen Shalansky if you require another chart at 604-875-4839.

6. HEPARIN PROTOCOL ADHERENCE

Diana Tsang, B.Sc. (Pharm), Karen Shalansky Pharm.D., Elaine Lum, Pharm.D.

VGH currently utilizes two heparin protocols, the standard and lower target protocols. A recent evaluation of 100 patients demonstrated that these two protocols were both efficacious and safe in achieving therapeutic anticoagulation. Mean times to achieve PTT above the lower limit of the therapeutic range (includes supratherapeutic levels) in the standard and lower target protocol groups were 8.3 and 9.7 hours, respectively. Mean times for PTT to fall within the therapeutic range were 17.2 and 16.1 hours, respectively (Table 2).

Heparin protocol compliance was evaluated during the first 48 hours of therapy. Complete protocol compliance was attained in 68% of patients using the standard protocol and 74% on the lower target protocol. Twenty errors were identified in 16 patients on the standard protocol, and 18 errors in 13 patients on the lower target. The rate of protocol compliance significantly affected therapeutic outcomes. Patients who had no protocol violations achieved efficacy outcomes significantly faster compared to those with at least one protocol violation (Table 2).

Table 2. Time to Attain Therapeutic Outcomes

Parameter	Standard Heparin Protocol	Lower Target Heparin Protocol
Mean time for PTT > Lower Limit of Therapeutic Range, Hours		
Overall	8.3 ± 6.8	9.7 ± 9.2
No Protocol Violation	7.6 ± 4.9	7.2 ± 2.7[a]
≥ 1 Protocol Violation(s)	10.1 ± 10.2	19.2 ± 16.8[a]
Mean time for PTT to Fall Within Therapeutic Range, Hours		
Overall	17.2 ± 12.5	16.1 ± 10.5
No Protocol Violation	14.9 ± 11.7[b]	14.4 ± 8.4[c]
≥ 1 Protocol Violation s)	22.1 ± 9.6[b]	22.3 ± 14.0[c]

[a]p=0.0001; [b,c]p=0.04

The majority of errors occurred due to incorrect infusion rate adjustment following high or low PTT results, and incorrect initial PTT draw times (Table 3). PTTs should be drawn 6 hours after initiation of heparin or after any infusion rate change. PTTs drawn too early (< 4 hours after a rate change) will not reflect steady state heparin levels and if drawn too late, could result in prolonged over- or under-anticoagulation.

Table 3. Heparin Protocol Violations

Percent and Type of Error	Standard Protocol	Lower Target Protocol
Incorrect Infusion Rate Adjustment	35%	28%
Incorrect Initial PTT Draw Time	15%	39%
Incorrect Bolus Dose Given	15%	0%
Incorrect Infusion Hold Time after High PTT	15%	6%
Omission of PTT Documentation	10%	0%
Omission of PTT Test	5%	22%
Physician not Notified after 3 Consecutive Low or High Values	5%	6%

In conclusion, protocol violations were found to significantly delay the time to achieve therapeutic anticoagulation. Protocol adherence is critical to improve patient outcomes in achieving rapid and safe anticoagulation. Due to individual nuances in heparin disposition, it is important to remember to contact the physician if PTT values remain outside the therapeutic range for 3 consecutive measurements.

New Drug/Drug Products

Bivalirudin injection (Angiomax®)

Elaine Lum, Pharm.D.

Bivalirudin is an anticoagulant approved for use in patients undergoing percutaneous coronary intervention (PCI) who i) have a history of heparin-induced thrombocytopenia (HIT) or ii) as an alternative to unfractionated heparin *plus* glycoprotein IIb/IIIa inhibitor (GPI).

Pharmacology

Bivalirudin is a synthetic hirudin analog. Hirudin is a natural anticoagulant found in the saliva of medicinal leeches. It works by specifically and reversibly inhibiting both circulating and clot-bound thrombin.[1] Bivalirudin is eliminated mainly by proteolytic cleavage with some renal clearance. Its elimination half-life is 25 minutes in patients with normal renal function, and is prolonged up to 3.5 hours in patients on dialysis.

The onset of anticoagulation effect is immediate following direct IV injection of bivalirudin. Bivalirudin affects several coagulation assays including activated clotting time (ACT), PTT, thrombin time and INR. Coagulation times return to normal ~1-2 hours after stopping the drug.[2]

Comparable Formulary Agents (Table 4)

Table 4. Comparison of Anticoagulants for HIT

Drug	Bivalirudin	Argatroban	Danaparoid
Mechanism of Action	Direct Thrombin Inhibitor	Direct Thrombin Inhibitor	Inactivates Factors Xa and IIa
Monitoring	ACT	PTT	Anti-Xa (if renal failure)
Half-Life	25 minutes	0.8 hours	25 hours
Peak Onset	Immediate	1-3 hours	4-5 hours
Cross-Reactivity with HIT Antibodies	0%	0%	< 10%
Dose	0.75 mg/kg IV bolus, then 1.75 mg/kg/h[a]	0.5-1 mcg/ kg/min	1500-3750 units, then gradually ↓ to 200 units/hr[a]
Cost/day	***	****	*

[a]adjust dosage in renal impairment

In patients requiring PCI, bivalirudin is the only anticoagulant alternative that has been studied in patients with HIT. In the REPLACE-2 trial, bivalirudin was shown to be non-inferior to heparin *plus* provisional GPI in patients undergoing urgent or elective PCI in terms of the primary composite endpoint at 30 days (death, myocardial infarction [MI], repeat revascularization and major bleeding).[3] Major bleeding and transfusion rates were lower in the bivalirudin group (2.4% vs. 4.1%; p<0.001); however the ACT values in the heparin arm were much higher than those seen in previous trials, which may have contributed to the higher bleeding rate seen with heparin.

In the ACUITY trial, bivalirudin alone was shown to be superior to heparin plus GPI when the 30 day composite endpoint of death, MI, unplanned revascularization and major bleeding was evaluated in moderate to high risk patients undergoing PCI within 72 hours of an acute coronary syndrome (ACS).[4] A lower rate of bleeding was also observed with bivalirudin compared to heparin plus GPI (3% vs. 5.7%; p<0.001).

Adverse Events

The most common adverse effects reported in clinical trials (>10% in either treatment arm) were back pain, pain, nausea, headache and hypotension. Bleeding associated with bivalirudin use during PCI usually occurred at the site of arterial puncture.

Dosage

See Table 4. For patients on heparin prior to PCI, bivalirudin can be initiated 30 minutes after the last dose of heparin or when the ACT is less than 175. For patients on enoxaparin, bivalirudin can be started 8 hours after the last dose of enoxaparin.

Place in Therapy

Bivalirudin is the anticoagulant of choice in patients undergoing PCI with a history of HIT. Bivalirudin may be considered in place of heparin plus GPI in patients undergoing PCI where continuation of an 18 to 24 hour infusion of GPI is not feasible, such as patients who will be transferred to other sites.

References

1. Angiomax AHFS Fact Sheet: http://www.angiomax.com/Files/OtherRef/AHFS.pdf
2. AGIOMAX product monograph. 2004
3. Lincoff AM et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 2003;289:853-63.
4. Stone G et al. Bivalirudin for patients with acute coronary syndrome. NEJM 2006;35:2203-16.

PharmaCare Update

Insulin glargine (Lantus®), the new long-acting insulin, is now covered by PharmaCare under the following circumstances:

A) the patient is over 17 years old and has been diagnosed with Type 1 or Type 2 diabetes and is currently taking insulin NPH and/or pre-mix insulin daily at optimal dosing **AND**

B) Has experienced unexplained nocturnal hypoglycemia at least once a month despite optimal management **OR**

C) Has documented severe or continuing systemic or local allergic reaction to existing insulin

A Special Authority form is required for approval unless written by an endocrinologist.