

March 2006

Volume 13, Number 1

*In This Issue...*

|  |   |
|--|---|
| <i>Changes to Formulary</i>              | 1 |
| <i>Modifications to Heparin Protocol</i> | 2 |
| <i>Antibiotic Reporting for MRSA</i>     | 2 |
| <i>Once Daily Aminoglycoside Dosing</i>  | 2 |
| <i>Nurse Practitioner Prescribing</i>    | 3 |
| <i>Azithromycin IV</i>                   | 4 |
| <i>Levetiracetam</i>                     | 5 |
| <i>Adverse Drug Reactions 2005</i>       | 6 |
| <i>Pharmacy Awards</i>                   | 6 |

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](http://www.vhpharmsci.com)

*Changes to Formulary*

**Additions**

1. **Azithromycin 500 mg IV (Zithromax<sup>®</sup>)**
  - Once daily macrolide antibiotic (similar class to erythromycin)
  - Indicated for treatment of community acquired pneumonia (CAP) and pelvic inflammatory disease (PID)
  - See page 4 for review
2. **Symbicort<sup>®</sup> 100 and 200 turbuhaler (60 dose)**
3. **Advair<sup>®</sup> 250 and 500 diskus (28 dose)**
4. **Advair<sup>®</sup> 125 and 250 MDI (120 dose)**
  - Combination long-acting beta-2 agonist/steroid inhalation therapy for advanced stages of COPD and asthma
  - Refer to Table 1 for individual products
  - Note: 2 puffs Advair<sup>®</sup> 125 MDI is equivalent to 1 puff Advair<sup>®</sup> 250 diskus (similarly, 2 puffs Advair<sup>®</sup> 250 MDI is equivalent to 1 puff Advair<sup>®</sup> 500 diskus)

**Table 1. Symbicort<sup>®</sup> and Advair<sup>®</sup> Content**

| Product  | VA Cost |
|--|---------|
| Symbicort <sup>®</sup> -100 turbuhaler (Budesonide 100mcg + Formoterol 6mcg) 60 dose | \$30    |
| Symbicort <sup>®</sup> -200 turbuhaler (Budesonide 200mcg + Formoterol 6mcg) 60 dose | \$39    |
| Advair <sup>®</sup> 125 MDI (Fluticasone 125mcg + Salmeterol 25mcg) 120 dose         | \$81    |
| Advair <sup>®</sup> 250 diskus (Fluticasone 250mcg + Salmeterol 50mcg) 28 dose       | \$41    |
| Advair <sup>®</sup> 250 MDI (Fluticasone 250mcg + Salmeterol 25mcg) 120 dose         | \$125   |
| Advair <sup>®</sup> 500 diskus (Fluticasone 500mcg + salmeterol 50mcg) 28 dose       | \$58    |

**5. Levetiracetam 250, 500mg tabs (Keppra<sup>®</sup>)**

- Anticonvulsant indicated for poorly controlled partial seizures with or without generalization in patients who have failed traditional therapy
- Restricted to neurology service
- See page 5 for review

**EDITORIAL STAFF:**

Karen Shalansky, Pharm.D., FCSHP  
 James Kim, Pharm.D., BCPP  
 Barbara Jewesson, B.Sc. (Pharm), Pharmacy Director

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](mailto:karen.shalansky@vch.ca)  
 Find us on the Web at [www.vhpharmsci.com](http://www.vhpharmsci.com)

## 6. Botulinum Toxin 100 units/vial (Botox®)

- Neuromuscular paralytic agent for treatment of focal limb spasticity associated with stroke, traumatic brain injury, spinal cord injury, multiple sclerosis, and cerebral palsy
- Restricted to Rehab Medicine and Spinal Cord Program physicians
- Cost: \$340.00/100 units

## Deletions

### 1. Sodium sulfacetamide eye ointment 10%

- Discontinued by manufacturer

### 2. Dipivefrin 0.1% eye drops (Propine®)

- Discontinued by manufacturer

### 3. Atropine 1% eye ointment

- Discontinued by manufacturer
- Alternative: Atropine 1% eye drops

## Updated Policies

### 1. MODIFICATIONS TO HEPARIN PROTOCOL

There are now **two** heparin protocols available for all in-patients at Vancouver Acute:

#### i) HEPARIN/WARFARIN STANDARDIZED PROTOCOL

- This is the original "heparin-warfarin standardized protocol".
- Due to a laboratory change in reagents for measuring aPTT, the aPTT range for this protocol was recently lowered to 65-90 seconds (corresponding to anti-Xa heparin levels of 0.3-0.7 IU/mL).
- The main indication for this protocol is treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), and peripheral arterial thrombosis.

#### ii) LOWER TARGET HEPARIN PROTOCOL: CCU, NEUROSCIENCES, SURGERY (no active DVT, PE, Peripheral Arterial Thrombosis)

- This is the "CCU heparin protocol" which has been adapted to include neurosciences and surgical patients.
- The therapeutic aPTT range for this lower target protocol is 55-75 seconds (corresponding to anti-Xa heparin levels of 0.2-0.5 IU/mL).
- A lower aPTT is targeted for these groups due to their increased risk of bleeding from

administration of anti-thrombotic agents (e.g. fibrinolytics, glycoprotein IIb/IIIa inhibitors, aspirin, clopidogrel), or being post-operative.

- The lower target protocol can be used for CCU, neurosciences and post-operative patients as long as there is no active DVT, PE or peripheral arterial thrombosis.

## 2. ANTIBIOTICS REPORTING FOR MRSA

In the December 2005 newsletter, we indicated that the VGH Medical Microbiology Laboratory reports alternate antibiotics to vancomycin for consideration in the treatment of MRSA infections. In collaboration with the Antibiotic Use Subcommittee, the Laboratory has modified the appended statement to clarify when dual therapy should be considered:

*"These antibiotics are possible alternate therapies if this patient's MRSA is reported to be susceptible. Rifampin should never be used alone. Combination therapy should be considered when using alternates to Vancomycin for infections other than UTIs. For treatment of invasive infections, an Infectious Disease consultation should be considered."*

Please contact Dr. Diane Roscoe (604-875-4547) or the Medical Microbiologist on-call (604-875-5000) if there are any questions.

## 3. ONCE DAILY AMINOGLYCOSIDE DOSING

Tim Lau, Pharm.D.

Once daily aminoglycoside (ODA) dosing has been approved for use at Vancouver Acute in addition to conventional multiple-daily dosing.

### Background

Several clinical studies suggest that ODA dosing is as efficacious with similar toxicity to conventional multiple-daily administration. The rationale for ODA is based on the concentration-dependent kill characteristic of aminoglycosides. At approximately 10 times the minimum concentration necessary for inhibition of bacterial growth, maximal antimicrobial activity is observed. After this exposure, inhibition of bacterial growth continues for hours despite aminoglycoside concentrations falling below the minimum inhibitory concentration. These two factors enable aminoglycosides to be dosed once daily for the treatment of gram negative infections.

*Inclusion*

Patients ordered ODA for prophylactic, empiric, or documented infective treatment. (Pharmacy will continue to process aminoglycoside prescriptions ordered as conventional multiple-daily dosing).

*Exclusions*

- Patients with burns on > 20% of body surface
- Pregnant patients
- Patients on dialysis
- Patients receiving aminoglycosides for synergy against gram positive organisms (e.g. endocarditis)  
(Gentamicin 1mg/kg per dose or streptomycin 7.5mg/kg per dose, adjusted for renal function)
- Cystic fibrosis patients
- Surgical or diagnostic procedure prophylaxis (gentamicin 1.5mg/kg as a single dose)
- Inpatients undergoing Stem Cell Transplantation or receiving chemotherapy for a hematologic malignancy
- Patients in septic shock

*Dosage*

Gentamicin or tobramycin 4.5 to 6mg/kg IV (7mg/kg in critically ill patients)

Amikacin or streptomycin 15mg/kg IV

Dosage is based on ideal body weight (IBW). In morbid obesity (> 125% of the IBW), the dosage is based on the IBW plus 40% of estimated adipose tissue mass [IBW + 0.4 (TBW-IBW)].

IBW (kg) =

Male:  $51.65 + 0.73 (\text{height in cm} - 152.4)$  or  
 $50 + (2.3 \times \text{each inch over 5 ft})$

Female:  $48.67 + 0.65 (\text{height in cm} - 152.4)$  or  
 $45 + (2.3 \times \text{each inch over 5 ft})$

These are administered as a single infusion in 50-100mL of NS or D5W over 30 minutes.

*Dosing interval*

**Table 2. Dosing Interval for ODA**

| Creatinine Clearance | Dosing Interval  |
|----------------------|--|
| ≥ 60mL/minute        | q24h   |
| 40-59mL/minute       | q36h (pre-dose level recommended) <u>or</u> conventional aminoglycoside dosing suggested             |
| < 40mL/minute        | Use conventional aminoglycoside dosing & take two post-dose levels to determine appropriate interval |

*Monitoring*

The correlation between serum aminoglycoside concentrations with once daily dosing and clinical outcomes has not been intensively studied, and pharmacokinetic monitoring itself has not been shown to improve efficacy or prevent toxicity. Some literature have shown high variability in estimated pharmacokinetic parameters of aminoglycosides with once-daily dosing and other studies have reported that in some patients, nomograms often do not accurately predict the correct dose or dosing interval. Therefore, selective pharmacokinetic monitoring may be required.

- In all patients, twice weekly serum creatinine measurements are recommended to assess renal function.
- For patients with a CrCl < 60mL/min, a pre-dose aminoglycoside level may be warranted to ensure that levels are negligible (< 1mg/L) at the end of the dosing period.
- Baseline and weekly audiometry and the E-test are recommended for patients who require greater than 2 weeks of aminoglycoside therapy. (Please contact Art Mallinson at local 62353, Neuro-otology Unit, for an appointment).

**4. NURSE PRACTITIONER PRESCRIBING**

Nurse Practitioners registered with the College of Registered Nurses of BC (CRNBC) are authorized to prescribe medications as set out in their scope of practice. The CRNBC and individual Nurse Practitioners, not the Pharmacy, are responsible for ensuring appropriate prescribing within their scope of practice. The pharmacy will continue to enforce restrictions established by the Medical Advisory Council on all prescribers. For example, restricted authority for specific medications will be maintained.

## New Drug/Drug Products

### 1. Azithromycin 500mg IV (Zithromax®)

Michelle Paolini, B.Sc. (Pharm), Karen Shalansky, Pharm.D.,  
Tim Lau, Pharm.D.

Azithromycin is a macrolide antibiotic from the same class as erythromycin. It is indicated for the treatment of community-acquired pneumonia (CAP) and pelvic inflammatory disease (PID).

#### Pharmacology

Azithromycin acts by binding the 50s ribosomal subunit of susceptible bacteria and suppressing protein synthesis.<sup>1</sup> It has activity against respiratory pathogens, both typical (*S. pneumoniae*, *H. influenzae*) and atypical (*C. pneumoniae*, *Mycoplasma*, and *Legionella species*) and is effective against pathogens associated with PID (*N. gonorrhoeae*, *C. trachomatis*).<sup>1-3</sup> Azithromycin is usually bacteriostatic, but may be bactericidal in higher concentrations or against susceptible bacteria.<sup>1</sup> Biliary excretion, primarily as unchanged drug, is its main route of elimination.

#### Comparable Parenteral Formulary Agents

Compared to erythromycin, azithromycin provides greater gram-negative coverage (especially against *H. influenzae*) allowing for monotherapy in select patients.<sup>2</sup> Azithromycin also has improved pharmacokinetics and reaches higher intracellular concentrations, thus allowing for once-daily dosing and a shorter course of therapy in out-patients (Table 3).<sup>3</sup>

**Table 3. Comparable Formulary Agents**

| Drug         | Antibiotic Classification | IV dose      | IV Cost/day*    |
|--------------|---------------------------|--------------|-----------------|
| Erythromycin | Macrolide                 | 500mg-1g q6h | \$12.80-\$16.80 |
| Azithromycin | Macrolide                 | 500mg daily  | \$20.40         |
| Moxifloxacin | Fluoroquinolone           | 400mg daily  | \$34.00         |

\*VA acquisition cost

Current guidelines for treatment of hospitalized CAP patients recommend a respiratory fluoroquinolone (e.g. moxifloxacin), or second or third generation cephalosporin plus a macrolide antibiotic for empiric treatment.<sup>4,5</sup> A prospective, randomized trial found azithromycin alone as

effective as the combination of cefuroxime plus erythromycin for empiric therapy of CAP in 145 hospitalized patients, although this trial was likely underpowered to detect significant differences.<sup>2</sup>

#### Adverse Effects

Adverse reactions are generally mild to moderate and include headache, dizziness, nausea, vomiting, abdominal discomfort, and diarrhea. Injection site reactions are fewer than erythromycin and include erythema, pain, rash, and tenderness.<sup>1,6</sup> Unlike erythromycin, azithromycin does not inhibit cytochrome P450 enzymes and thus is not implicated in clinically significant drug-drug interactions (e.g. warfarin, theophylline).<sup>3</sup>

#### Dosage

The dosage of azithromycin for CAP in hospitalized patients is 500mg IV once daily for 7-10 days. Patients should be stepped-down to oral therapy with clarithromycin XL 500-1000mg once daily as soon as indicated. Use with caution in patients with severe hepatic dysfunction.

#### Conclusions

Azithromycin is an antibiotic similar to erythromycin but with the benefits of once-daily dosing, no clinically significant CYP450-related drug interactions, and improved infusion-related tolerability. As well, azithromycin provides greater gram-negative coverage (especially *H. influenzae*) than erythromycin and reaches higher intracellular concentrations. For hospitalized patients with CAP, azithromycin is recommended to be used in combination with a second or third generation cephalosporin. Parenteral erythromycin will still remain on formulary for its use as a GI motility agent.

#### References

1. Azithromycin Product Monograph. Clinical Pharmacology. 2005.
2. Vergis E et al. Azithromycin vs cefuroxime plus erythromycin for empirical treatment of community-acquired pneumonia in hospitalized patients: a prospective, randomized, multicenter trial. Arch Intern Med 2000;160:1294-1300.
3. Alvarez-Elcoro S et al. The macrolides: erythromycin, clarithromycin, and azithromycin. Mayo Clin Proc 1999;74: 613-34.
4. Mandell LA et al. Canadian guidelines for initial management of community-acquired pneumonia. Clin Infect Dis 2000;31:383-41.
5. Bartlett J et al. Practice guidelines for the management of community-acquired pneumonia in adults. Clin Infect Dis 2000;31:347-82.
6. Erythromycin Product Monograph. Clinical Pharmacology. 2005.

## 2. Levetiracetam (Keppra®)

Karen Tulloch, Pharm.D.

Levetiracetam is an anticonvulsant indicated for the treatment of partial onset seizures with or without secondary generalization in adults and children greater than 4 years of age with epilepsy.<sup>1</sup>

### Pharmacology/Pharmacokinetics

The mechanism of action of levetiracetam is not known. Its antiepileptic effect does not appear to involve known mechanisms relating to inhibitory and excitatory neurotransmission.<sup>1,2</sup> Levetiracetam is rapidly and completely absorbed with peak plasma levels occurring in 1 hour. Food does not affect the bioavailability. The drug is primarily eliminated as unchanged drug in the urine (~66%) with minimal liver metabolism.<sup>1</sup>

### Efficacy

Efficacy data is primarily derived from 3 randomized, double-blind, placebo-controlled trials involving 904 adults with refractory partial-onset seizures over a 3-4 month add-on treatment period.<sup>3-5</sup> Compared to placebo, levetiracetam decreased median weekly seizure frequency by 16-28%, had a 9-30% greater response rate (defined as 50% reduction in seizures), and had a modest impact on a patient's seizure-free status (high-dose only).

The impact of adjunct levetiracetam on the quality

of life has been reported as a secondary endpoint in one trial.<sup>6</sup> Significant improvements over placebo were found for "overall quality of life", "seizure worry", and "cognitive functioning".

### Comparison to Formulary Atypical Agents

Levetiracetam offers a novel mechanism of action distinct from other adjunctive agents. There are no clinically significant drug interactions due to minimal liver metabolism (Table 4). The therapeutic dosing range includes the recommended starting dose as opposed to slow titration required with lamotrigine and topiramate. To date, there are no serious adverse effects reported with levetiracetam as opposed to vigabatrin (visual field disturbances, psychiatric symptoms), lamotrigine (life-threatening skin rashes) and topiramate (psychiatric symptoms, cognitive disturbances).

### Adverse Effects

The most common adverse effects are mild to moderate in severity and include asthenia, dizziness, headache and somnolence. Behavioural disturbances (e.g. emotional lability) have been reported in post-marketing analyses.<sup>7</sup>

### Restrictions

Levetiracetam is restricted to neurology service.

References available upon request.

**Table 4. Formulary Adjunctive Antiepileptic Drugs for Refractory Partial-Onset Seizures**

| Drug                    | Indications  | Drug Interactions   | Daily Dose          | VHHC Cost/day |
|-------------------------|--|---|---------------------|---------------|
| Lamotrigine (Lamictal®) | Partial seizures (adjunct and monotherapy)<br>Bipolar disorder   | Oral Contraceptives<br>Valproic Acid ↑ lamotrigine levels<br>Carbamazepine, phenytoin, phenobarb ↓ lamotrigine levels | 300-500mg daily-BID | \$2.37-3.95   |
| Topiramate (Topamax®)   | Partial seizures (adjunct and monotherapy)<br>1° general seizures (TC only)<br>Migraine prophylaxis<br>Neuropathic pain*<br>Bipolar mania* | Oral Contraceptives<br>Topiramate may ↑ phenytoin levels<br>Carbamazepine, phenytoin, phenobarb ↓ topiramate levels   | 200-800mg daily-BID | \$6.21-16.56  |
| Gabapentin (Neurontin®) | Partial Seizures (adjunct)<br>Neuropathic pain<br>Bipolar disorder*, Anxiety*  | Antacids ↓ gabapentin levels  | 600-1800mg TID**    | \$0.58-1.74   |
| Vigabatrin (Sabril®)    | Partial Seizures (adjunct)   | Vigabatrin ↓ levels of phenytoin by 20-30%  | 2000-3000mg BID**   | \$3.56-5.34   |
| Levetiracetam (Keppra®) | Partial Seizures (adjunct)<br>Bipolar mania*   | None  | 1000-3000mg BID**   | \$3.64-10.92  |

\*off-label indication; \*\*reduced dosage in renal dysfunction; TC = tonic-clonic

## *Adverse Drug Reaction Report 2005*

There was a total of 14 suspected adverse drug reactions (ADRs) reported at VGH in 2005 (Table 5). Of note, 6 adverse reactions were considered to have been the cause of hospitalization and 1 resulted in prolonged hospitalization. The continued reporting of all suspected ADRs by nurses, physicians and pharmacists aids in an improved assessment of the magnitude and nature of adverse events. To notify Pharmacy of an ADR, either fill out a yellow ADR alert card, available on all nursing units, and send to Pharmaceutical Sciences CSU, or call local 62481 (VGH site) or local 27249 (UBC site). Pharmacists will complete all ADR report forms and forward copies to the B.C. Regional ADR Centre. This Centre does preliminary analysis of the data and then submits all reports to the Canadian ADR program in Ottawa who then forwards them to the World Health Organization.

**Table 5. Adverse Drug Reactions Reported in 2005**

| Drug   | Suspected Reaction   |
|--|--|
| Allopurinol*                                   | Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) - diffuse maculopapular erythematous rash covering entire body, pruritus, hepatotoxicity (biopsy documented) (1)<br>Excoriations and rash on upper torso, diarrhea (1) |
| Azathioprine*                                  | Acute pancreatitis (1)   |
| Bleomycin*                                     | Acute pneumonitis (1)  |
| Ferrlecit® (Sodium Ferric Gluconate injection) | Back pain (1)  |
| Gemtuzumab*                                    | Hypotension, rigors, fever (1)   |
| Imipenem (high dose 1g IV q8h)                 | Grand mal seizure (1)  |
| Losartan                                       | Confluent itchy, rash on hands, legs, feet and back (1)  |
| Methylprednisolone                             | Hiccoughs (1)  |
| Modafinil (Alertec®)*                          | Acute coronary syndrome (1)  |
| Ramipril*                                      | Laryngospasm (1)   |
| Simvastatin + ramipril**                       | Epigastric pain, elevated lipase, amylase (1)  |
| Ticarcillin-Clavulanate + Gentamicin           | Elevated liver function tests (1)  |
| Vancomycin                                     | Persistent mild rash (1)   |

\*hospitalized due to ADR; \*\*prolonged hospitalization due to ADR

## *Pharmacy Awards*

The Canadian Society of Hospital Pharmacists has honoured several VGH pharmacists with the following awards:

- **Leslie Samoy, Kerry Wilbur, Peter Zed:** Bristol-Myers Squibb Award (Clinical Pharmacy Program). Their research paper, co-authored with Robert Balen is entitled "Drug-related hospitalization to a tertiary care internal medicine service: A prospective study".
- **Nilufar Partovi, Rubina Sunderji:** Novopharm Award (New Programs in Patient Counseling). Their research paper, co-authored with Kiran Sidhu, is entitled "Randomized evaluation of patient medication teaching by videotape in a cardiac unit".
- **Peter Zed:** PharmaScience Award (Patient Care Enhancement). Peter's research paper is entitled "Clinical outcomes and patient satisfaction of a pharmacist-managed emergency department-based outpatient deep vein thrombosis treatment program: 6-year results".
- **Rubina Sunderji:** Sanofi-Aventis Award (Specialty Practice in Cardiology). Her paper, co-authored with Carlo Marra, is entitled "The cost-effectiveness of patient self-managed vs. physician-managed oral anticoagulation: A Bayesian approach".