

DRUG AND THERAPEUTICS NEWSLETTER

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

Dec 2004

Volume 11, Number 4a

In This Issue...

<i>Changes to Formulary.....</i>	<i>1</i>
<i>Moxifloxacin Therapeutic Interchange.....</i>	<i>1</i>
<i>Rabeprazole Therapeutic Interchange.....</i>	<i>2</i>
<i>Olanzapine Pre-Printed Order.....</i>	<i>2</i>
<i>Revised Drug Administration Policies.....</i>	<i>2</i>
<i>Moxifloxacin.....</i>	<i>3</i>
<i>Pharmacy Awards.....</i>	<i>5</i>

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 Therapeutic Newsletters are on the Web at www.vhpharmsci.com

Changes to Formulary

Additions

- 1. Moxifloxacin 400mg tablets, injection (Avelox®)**
 - Respiratory fluoroquinolone antibiotic for the treatment of community-acquired pneumonia
 - See page 3 for drug review

Deletions

- 1. Levofloxacin (Levaquin®)**
 - Alternative: Moxifloxacin
- 2. Piperacillin-Tazobactam (Tazocin®)**
 - Alternative: Ticarcillin-Clavulanate (Timentin®)
- 3. TB skin test 250 TU**
 - Discontinued by manufacturer
 - 1TU and 5TU strengths still available

4. Nimodipine Intravenous (Nimotop® IV)

- Discontinued by manufacturer

5. Alfentanyl injection (Alfenta®)

- Discontinued by manufacturer

Updated Policies

1. Drug Cost Containment Strategies

i) Levofloxacin to Moxifloxacin Therapeutic Interchange

In May, 2000, the Drugs and Therapeutics Committee approved the addition of levofloxacin to the formulary, restricted for the treatment of community acquired pneumonia (CAP). In Sept 2004, moxifloxacin was chosen as the Vancouver Coastal Health Region's respiratory fluoroquinolone. Both levofloxacin and moxifloxacin are considered therapeutically equivalent for CAP.

Effective Oct 6, 2004, all orders for levofloxacin were interchanged to either moxifloxacin 400mg PO or IV daily. No dosage adjustment is required for renal or hepatic impairment. The switch to moxifloxacin is anticipated to result in a substantial annual cost savings for the region.

EDITORIAL STAFF:

Karen Shalansky, Pharm.D., FCSHP

Rubina Sunderji, Pharm.D., FCSHP

Peter Loewen, Pharm.D., FCSHP

Luciana Frighetto, B.Sc.(Pharm), MBA, FCSHP

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 kshalans@vanhosp.bc.ca Find us on the Web at www.vhpharmsci.com

ii) Omeprazole to Rabeprazole Oral Therapeutic Interchange

Proton pump inhibitors (PPI) are considered therapeutically equivalent and the choice of formulary agent is based upon the lowest cost alternative. Rabeprazole was recently approved as the low cost PPI for the Vancouver Coastal Health (VCH) Region.

Effective Nov 15, 2004 all orders for oral omeprazole and other PPI were interchanged to rabeprazole 20mg daily. Omeprazole MUPS 40mg daily will be retained for feeding tubes or PO use in patients who are unable to swallow whole tablets as rabeprazole cannot be chewed or crushed. Due the higher cost of omeprazole MUPS, pharmacists have the authority to independently convert patients to rabeprazole PO if a patient is able to eat and swallow other tablets.

iii) Criterion Based Prescribing Policy for Initiation of Olanzapine

There are four atypical antipsychotic (AAP) drugs on formulary at Vancouver Acute (VGH, UBC, GF Strong) including risperidone, olanzapine, quetiapine, and clozapine. Clozapine is reserved for treatment refractory psychosis. In the 2002/03 fiscal year, AAP drug expenditures (excluding clozapine) were approximately \$357,000, of which olanzapine contributed 65%.

There is limited evidence that one AAP (excluding clozapine) is more effective than another in the treatment of schizophrenia or psychotic-related illnesses in either adult or elderly patients. There are however established differences in adverse effects and tolerability. The adverse effects cannot necessarily be predicted prior to initiation of therapy. There are also differences in drug costs. Based on approximate daily doses for schizophrenia and Vancouver Acute drug acquisition costs, olanzapine is the most expensive agent (\$10.13/15mg) followed by quetiapine (\$6.83/450mg) and risperidone (\$3.84/4mg). There is inadequate data from pharmacoeconomic and outcome studies to demonstrate long-term cost saving advantages between AAP agents.

Due to lack of evidence to support superiority of a single AAP drug and in order to reduce the costs, olanzapine use is restricted to a criterion-based prescribing policy for initiation of olanzapine

therapy. A pre-printed order (PPO) form has been created to ensure that specific criteria (approved diagnosis and either non-response or intolerance to at least one other AAP) are met prior to initiating olanzapine therapy.

Effective Dec 13, 2004, new prescriptions for olanzapine must be prescribed using a PPO.

- A) For patients taking olanzapine prior to hospitalization, physicians should indicate this on the PPO.
- B) For patients not taking olanzapine prior to hospitalization, physicians will be required to select an approved diagnosis and indicate what the patient's past medication response has been to at least one other AAP.

If an adult/geriatric psychiatrist writes a prescription for olanzapine for an indication that is not specified on the PPO, approval must be obtained from the Psychiatry Medical Director. For non-approved indications, all other services outside of the adult/geriatric psychiatry settings will require a psychiatry consult (and subsequent Psychiatry Medical Director approval, if necessary). Once the initial prescription has been written on the PPO and approved, subsequent changes to the olanzapine dose do not require another PPO form to be filled out.

An annual cost savings of approximately \$37,000 is anticipated from this strategy.

2. Revised Drug Administration Policies

- **Potassium Chloride 40mEq/100mL** may be administered via central line in Critical/Special Care Areas and **T11B (Cardiovascular Surgery)**. All other nursing units may only administer a maximum of 20mEq/100mL centrally in emergency situations.
- The **dose of erythromycin** for use as a **prokinetic agent** is 200-250mg IV q6h x 4 doses, then reassess. For post-Whipples' procedure, the dose is 1mg/kg IV q8h for up to 2 weeks.

New Drugs/Drug Products

Moxifloxacin

Tim TY Lau, Pharm.D.

Reviewed by Dr. G. Stiver, Division of Infectious Disease

Moxifloxacin is an extended-spectrum fluoroquinolone (FQ) antibiotic that exhibits coverage against gram-positive cocci, gram-negative bacilli, atypical pathogens, and some anaerobic bacteria.¹ Its antibacterial spectrum covers all major respiratory tract pathogens. In Canada, the oral and intravenous formulations of moxifloxacin are available for the following approved indications: acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and community-acquired pneumonia (CAP).²

On October 6, 2004, moxifloxacin was added to the VH formulary to replace levofloxacin for the treatment of CAP. This was a region-wide initiative within the Vancouver Coastal Health Authority, as significant cost savings were associated with having moxifloxacin on formulary as the sole respiratory fluoroquinolone. The other respiratory FQs include levofloxacin and gatifloxacin.

Efficacy

Moxifloxacin has activity against methicillin-sensitive *Staphylococcus aureus*, *Streptococcus pneumoniae* (penicillin sensitive or resistant), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, Enterobacteriaceae, and *Bacteroides fragilis*.

Types of Infections

Meta-analyses have shown that the respiratory FQs are similar in terms of clinical efficacy.³⁻⁶

Community Acquired Pneumonia/Acute Bacterial Exacerbation of Chronic Bronchitis/Sinusitis

Moxifloxacin has demonstrated similar clinical efficacy to the other respiratory FQs in the treatment of CAP, acute bacterial exacerbation of chronic bronchitis, and acute maxillary sinusitis.³⁻⁶ Moxifloxacin has not been studied in nosocomial pneumonia.

Skin and Skin Structure

Moxifloxacin is effective in the treatment of uncomplicated abscesses, furuncles, cellulitis, impetigo, and other skin infections. In comparison

to cephalexin, moxifloxacin demonstrated equivalent efficacy in the treatment of uncomplicated skin and skin structure infections caused by susceptible bacteria.⁷

Urinary Tract Infection (UTI)

Moxifloxacin is not recommended for the treatment of UTIs because it is minimally excreted unchanged by the kidneys.⁸

Pharmacokinetics/Pharmacodynamics

Moxifloxacin inhibits bacterial DNA gyrase which is vital in controlling DNA replication, transcription, repair and recombination.² FQs exhibit their activity in a concentration-dependent manner as described by the AUC/MIC relationship.⁹ In outpatients with CAP and bronchitis caused by *Streptococcus pneumoniae*, animal and limited clinical data suggest that a free AUC/MIC of ≥ 25 is predictive of bacterial eradication.¹⁰⁻¹² Moxifloxacin, levofloxacin, and gatifloxacin all exhibit a free AUC/MIC of >25 against *Streptococcus pneumoniae* (Table 1).

Table 1. Fluoroquinolone Free AUC/MIC for *Streptococcus pneumoniae*¹⁰

Fluoroquinolone	Dose	Free AUC/MIC
Moxifloxacin	400mg IV daily	60
Levofloxacin	500mg IV daily	35
Gatifloxacin	400mg IV daily	48

All FQs have good bioavailability of 86-99% and exhibit a post-antibiotic effect against both gram-positive and gram-negative isolates ranging from 1.5-2.5 hours. They also exhibit good penetration characteristics into various tissues and body fluids, including respiratory tissue, skin and soft tissues, gallbladder, bile, and urine (with the exception of moxifloxacin in urine). Moxifloxacin undergoes primarily hepatic metabolism through sulfation and glucuronidation with no significant effects on the cytochrome P450 system. Levofloxacin and gatifloxacin are both excreted renally. Table 2 compares the respiratory FQs.

Potential Risks

Adverse Effects

The FQs have a favourable safety profile and are generally well-tolerated. The most commonly reported adverse events are gastrointestinal disturbances (nausea, vomiting, and diarrhea),

Table 2. Summary of Respiratory Fluoroquinolones

Fluoroquinolone	Moxifloxacin	Levofloxacin	Gatifloxacin
Approved Indications	Acute sinusitis, acute exacerbation of chronic bronchitis, CAP	As for moxifloxacin plus complicated UTI and skin infections	As for moxifloxacin plus complicated UTI, pyelonephritis, gonorrhea
Mechanism of Action	Inhibits bacterial DNA gyrase	As for moxifloxacin	As for moxifloxacin
Pharmacokinetics	Bioavailability: 86% Half-life: 12.1 hours Elimination: Hepatic	Bioavailability: 98.8% Half life: 6.9 hours Elimination: Renal	Bioavailability: 96% Half-life: 8 hours Elimination: Renal
Evidence of Effectiveness	10 RCTs—clinical efficacy 88-97% for acute sinusitis, chronic bronchitis, CAP	8 RCTs—clinical efficacy 82-98% (once daily dosing) for CAP, sinusitis, bronchitis	8 RCTs—clinical efficacy 88-98% for acute sinusitis, chronic bronchitis, CAP, UTI and gonorrhea)
<i>Streptococcus pneumoniae</i> Susceptibility/Intermediate/Resistance	98.8% 1.0% 0.2%	98.8% 0.2% 1.0%	98.8% 0.3% 0.9%
Adverse Events	GI upset, headache, dizziness, QT prolongation	GI upset, headache, dizziness, QT prolongation	GI upset, headache, dizziness, QT prolongation
Dose	400mg PO daily 400mg IV daily	500mg PO daily 500mg IV daily	400mg PO daily 400mg IV daily

CAP = community acquired pneumonia, UTI = urinary tract infection; RCT = randomized controlled trial; VA = Vancouver Acute

central nervous system reactions (headaches and dizziness), and dermatological effects.^{1,13} Less common adverse reactions include sleep disturbances, hallucinations, depression, and seizures.¹³ There is a theoretical concern for the development of tendonitis and tendon rupture in patients receiving FQ, which has rarely been reported. QTc-prolongation has also been associated with FQ administration.¹ In a review comparing the rates of torsades de pointes related to FQ from January 1996 to May 2001, there were 3 cases with moxifloxacin, 14 with levofloxacin, and 8 with gatifloxacin.¹⁴ Note that levofloxacin was released in December 1996, which is 3 years prior to moxifloxacin and gatifloxacin. As such, moxifloxacin should be used with caution in patients with known prolongation of the QTc-interval, patients with hypokalemia, and patients receiving Class 1A (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) antiarrhythmic agents due to the potential increased risk of QTc-prolongation and the lack of studies of moxifloxacin in these populations.

Drug Interactions

Multivalent cation-containing compounds can inhibit the absorption of FQs. The manufacturer suggests that moxifloxacin be taken at least 4 hours before or 8 hours after antacids containing magnesium, aluminum or calcium, or multivitamins containing iron or zinc to avoid this potential interaction.² Moxifloxacin does not seem to have an effect on the hepatic cytochrome P-450 enzyme system.⁸

Susceptibilities/Resistance

There are two mechanisms for the development of FQ resistance: 1) mutations in the subunit of bacterial DNA gyrase, lowering the affinity of the drug; and 2) mutations encoding for drug influx and efflux systems, reducing intracellular drug accumulation.⁹ According to the Canadian Respiratory Organism Susceptibility Study in 2001-2002, the relative susceptibilities of *Streptococcus pneumoniae* to the fluoroquinolones have remained constant (moxifloxacin 98.8%, levofloxacin 98.8%, gatifloxacin 98.8%).¹⁵

Dosage

The dosage of moxifloxacin is 400 mg orally or intravenously once daily for all indications, independent of meals. No dosage adjustments are required in renal insufficiency or dialysis, or in mild to moderate hepatic impairment. Moxifloxacin is not recommended in severe hepatic insufficiency (Child Pugh Class C) due to no clinical data.²

Conclusions

Based on the similar clinical efficacy and adverse effect profile as compared to other respiratory FQs, and the significant cost savings associated with the addition of moxifloxacin to the region, moxifloxacin has replaced levofloxacin for the treatment of CAP. Due to limited or lack of evidence for the use of moxifloxacin in other indications, including nosocomial pneumonia and urinary tract infections, it is recommended that moxifloxacin be limited to the management of CAP only.

References

1. Barman Balfour JA et al. Moxifloxacin: a review of its clinical potential in the management of community-acquired respiratory tract infections. *Drugs* 2000;59:115-139.
2. Moxifloxacin Product Monograph, CPS 2004.
3. Zhanel G et al. The new fluoroquinolones: a critical review. *Can J Infect Dis* 1999;10:207-39.
4. Mittmann N et al. Oral fluoroquinolones in the treatment of pneumonia, bronchitis and sinusitis. *Can J Infect Dis* 2002;13:293-300.
5. Zhanel G et al. A critical review of the fluoroquinolones. *Drugs* 2002;62:13-59.
6. Slama T. Clinical experience with newer quinolones for community-acquired pneumonia. *Infect Dis Clin Pract* 2002;11:527-33.
7. Keating GM et al. Moxifloxacin. *Drugs* 2004;64:2347-2377.
8. Paladino J. Is more than one quinolone needed in clinical practice? *Ann Pharmacother* 2001;35:1085-95.
9. Blondeau JM. Expanded activity and utility of the new fluoroquinolones: a review. *Clin Ther* 1999;21:3-40.
10. Zhanel G et al. Pharmacokinetics and pharmacodynamics of the new fluoroquinolones: focus on respiratory infections. *Curr Opin Pharmacol* 2001;1:459-63.
11. Aminimanizani A et al. Comparative pharmacokinetics and pharmacodynamics of the newer fluoroquinolone antibacterials. *Clin Pharmacokinet* 2001;40:169-87.
12. Rodvoid K et al. Pharmacokinetics and pharmacodynamics of fluoroquinolones. *Pharmacotherapy* 2001; 21(10 pt 2):233S-252S
13. Bertino J et al. The safety profile of the fluoroquinolones. *Clin Ther* 2000;22:798-817.
14. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. *Pharmacotherapy* 2001;21:1468-72.
15. Zhanel G et al. Canadian Respiratory Organism Susceptibility Study (CROSS) 1997-2002. Personal Communication.

Pharmacy Awards

Several members of Pharmaceutical Sciences CSU have won the following research awards:

Rubina Sunderji Pharm.D. and Karen Shalansky Pharm.D.

- CSHP-BC Branch Publication Award, Original Research Category. Their research paper, co-authored with Dr. K Gin, Dr. C Carter, Dr. K Chambers, C Davies, L Schwartz and Dr. A Fung, is entitled "A randomized trial of patient self-managed versus physician-managed oral anticoagulation". This paper is published in *Can J Cardiol* 2004;20:1117-23.

Richard Slavik Pharm.D. and Peter Zed Pharm.D.

- CSHP-BC Branch Publication Award, Review Article Category. Their research paper is entitled "Intravenous amiodarone for the conversion of atrial fibrillation: misled by meta-analysis". This paper is published in *Pharmacotherapy* 2004;24:792-8.

Chase L, Davidson E, Nicol R, Ferreira B, Tomlinson S, Leong C

- Association of Vascular Access (AVA) Research Poster Award 2nd Place. The poster is entitled "Malposition of peripherally inserted central catheters on insertion: experience of an infusion program team in a major Canadian teaching hospital". This poster was presented at the 18th AVA Annual Conference, Vancouver, BC, Sept 2004.

Leong C, Balen R, Ferreira B, Tomlinson S, Nicol R, Chase L

- Canadian Intravenous Nurses Association (CINA) Research Poster Award 2nd Place. The poster, co-authored with Drs. DL Cecillon and P Jewesson, is entitled "Point of care use of personal data assistants (PDA) for PICC consult management: experience of an infusion program team in a major Canadian teaching hospital". This poster was presented at the 29th CINA Annual Convention, Toronto, ON, Oct 2004.