VANCOUVER HOSPITAL & Health Sciences Centre

DRUG AND THERAPEUTICS NEWSLETTER

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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 & Academic Advisory Council (MAAC).

This and other Drug and Therapeutics Newsletters are available on our website at **www.vhpharmsci.com**

Changes to Formulary

Additions

1. Levofloxacin IV/PO (Levaquin®)
- Second generation "respiratory" fluoroquinolone antibiotic for the management of community-acquired pneumonia
- Reserved Antimicrobial Drug
- See page 4 for drug review

Deletions

1. CMI® Multitest skin test
- Discontinued by manufacturer
- Alternative for anergy testing: candida, trichophyton and mumps skin tests

2. Bonney's Blue solution
- Discontinued by manufacturer

3. Indigotindisulfonate (Indigo Carmine®)
- Discontinued by manufacturer

4. Methohexital injection (Brietal®)
- Discontinued by manufacturer

Updated Policies/Procedures

1. Signature Identification

- It is an expectation that all physicians will provide clear identification, including their MSP number or printed last name on all written prescriptions at VHHSC. In the event that the identity of a physician cannot be determined by the Staff of Pharmaceutical Sciences CSU, the prescription will be processed under the name of the attending physician.

2. Parenteral Drug Therapy Manual (PDTM) Update

- All manuals at VHHSC were updated in July 2000. For any questions regarding this manual, contact Dr. Karen Shalansky at (604) 875-4839.
- Also note that the PDTM is available ONLINE at www.vhpharmsci.com for access by hospital staff. See the site for details on obtaining access.

EDITORIAL STAFF:
Karen Shalansky, Pharm.D.
Peter Loewen, Pharm.D.
Rubina Sunderji, Pharm.D.
Peter Jewesson, Ph.D.
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
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3. Revised Drug Administration Policies

- The administration of **midazolam** has been expanded to include all **special care areas**.
- The administration of **bupivacaine** as a Post-operative Infusion of Continuous Regional Analgesia **(PICRA)** has been added under the drug monograph. As well, the nursing policies for monitoring PICRA are addressed in the introduction under policy 2.3.6.6, page 9.
- **Enoxaparin** may be administered for the **management of unstable angina and non-Q-wave myocardial infarction**. See below.

New Drug/Drug Products

1. Enoxaparin for the Treatment Of Acute Coronary Syndromes

Payel Patel, Pharm.D. Student, Rubina Sunderji, Pharm.D., FCSHP

Introduction

Acute coronary syndromes (ACS) include both unstable angina and non-Q wave myocardial infarction (MI).[1] ACS are the result of atherosclerotic plaque rupture and exposure of thrombogenic material resulting in the activation of the coagulation system and platelet pathway.[2,3] Traditional standard therapy has therefore included both aspirin and unfractionated heparin (UFH). Recent clinical trials indicate that low molecular weight heparins (LMWH) provide a therapeutic alternative to UFH in the treatment of ACS.

Enoxaparin is one of four LMWHs available in Canada. It has recently been added to the VHHSC formulary for the treatment of ACS. Compared to UFH, LMWHs are better absorbed after subcutaneous (SC) administration, have reduced protein binding, a longer half-life (3-6 hours compared to 60-90 minutes for UFH), and a more predictable anticoagulant response.[4,5] LMWH has greater affinity for inhibiting factor Xa versus thrombin, although the importance of this difference is unclear.[6,7] Both the predictable anticoagulant response and long half-life of the LMWH allows for once or twice daily SC injections at fixed or weight-adjusted doses.[8] Since LMWHs do not affect the activated partial thromboplastin time (aPTT), routine laboratory monitoring is unnecessary.[7] An antifactor Xa assay is available but due to the lack of a clinically defined therapeutic range and cost of the assay, antifactor Xa assays are not routinely performed. LMWHs also have decreased interactions with platelets, which could account for the reduced microvascular bleeding and lower incidence of heparin-induced thrombocytopenia (HIT).[6,8] Recent clinical trials indicate that the risk of major bleeding secondary to LMWH treatment is similar to UFH[9-11]; however, minor bleeding complications have been higher with LMWHs.[10,11]

Comparative Studies of LMWH and UFH in ACS

There are no studies directly comparing tinzaparin to UFH for ACS and a comparative trial of dalteparin to UFH showed no difference in outcomes[12]. One small study[13] comparing nadroparin to UFH for ACS showed superior benefits with this LMWH although a subsequent larger comparative trial[14] showed no difference between the treatments. Two large studies[11,15] evaluating enoxaparin demonstrated superior outcomes compared to UFH. Although a recent meta-analysis of studies comparing various LMWHs to UFH for ACS suggested a lack of difference between the treatments[16], some evidence suggests that enoxaparin should still be the preferred agent for this indication.

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group (ESSENCE) was a prospective, double blind, parallel group trial that enrolled 3,171 patients with unstable angina or non-Q-wave MI within 24 hours of onset of chest pain.[11] Patients were randomized to receive enoxaparin (1mg/kg of body weight SC every 12 hours) or UFH (IV bolus 5000 units followed by a continuous infusion at a dose adjusted according to the aPTT) for at least 48 hours and up to 8 days. The primary endpoint was the composite of death, nonfatal MI, or recurrent angina at 14 days. Compared to UFH, the absolute risk reduction (ARR) for enoxaparin was 3.2% (p=0.02). This translates to a number needed to treat (NNT) with enoxaparin of 32 patients for a minimum of 48 hours (maximum 8 days) in order to avoid one event. There were no differences in the individual endpoints of death or myocardial infarction and the majority of the

benefit was accounted for by a reduction in recurrent angina. The benefit in the primary endpoint observed with enoxaparin was sustained at 30 days and at one year.[17] There was no difference between the groups in major bleeding complications. However, there was an absolute risk increase (ARI) in minor bleeding events with enoxaparin of 4.7% ($p<0.001$). The majority of these episodes involved injection site ecchymoses. A criticism of the ESSENCE trial was that the investigators did not use a weight-adjusted UFH nomogram; rather they relied on a fixed dosing system. The clinical significance of weight-adjusted nomograms has yet to be established in patients with angina despite their proven advantage in the treatment of venous thromboembolism.[18,19]

The Thrombolysis in Myocardial Infarction (TIMI) 11B study group compared enoxaparin (1 mg/kg SC every 12 hours) against weight-adjusted UFH in 3,910 patients with ACS presenting within 24 hours of onset of chest pain.[15] This double-blind, randomized trial was divided in two phases to assess the efficacy of enoxaparin in acute (3 to 8 days) and chronic (additional 35 days after discharge) treatment of ACS. After the acute phase, patients who were initially randomized to the UFH arm were treated with placebo injections, while those who received enoxaparin continued to receive a reduced weight-adjusted LMWH regimen of 40-60 mg SC every 12 hours. The primary endpoint was a composite of death, non-fatal MI, or severe recurrent ischemia requiring urgent revascularization at 8 days. This endpoint was also assessed at 43 days to determine if prolonged enoxaparin therapy is of additional benefit. Acute treatment was associated with an ARR of 2.1% in the primary endpoint in favour of enoxaparin (NNT = 48, $p = 0.048$). A significant difference was also recorded in the individual endpoint of MI. The authors noted that the initial benefit in the composite endpoint was maintained at 43 days and that there was no further reduction in events with continued enoxaparin treatment in the chronic phase. Major bleeding was not different between the groups during the acute phase but was higher with enoxaparin during the chronic phase (ARI 1.4%, $p=0.021$). Again, enoxaparin was associated with significantly more minor bleeding in both phases.

Economic Implications

Treatment with enoxaparin is associated with a higher drug acquisition cost than UFH. For a 70kg individual, a 5 day course of treatment costs $140 for enoxaparin and approximately $30 for UFH. However, the lack of need for aPTT monitoring and potential for reduction in event rates is reported to result in a more favorable economic outcome. Two Canadian cost-effectiveness analyses have been published to assess the economic impact of using enoxaparin for ACS. O'Brien *et al* performed an economic analysis based on the one-year follow up data from the ESSENCE study.[20] They focused their analysis on the 1,259 Canadian participants (~40% of the study population) enrolled in the trial. Hospital resources were costed with the use of data from a teaching hospital in southern Ontario. The authors found that at one year, the reduced risk and costs of revascularization offset the increased acquisition costs of enoxaparin and resulted in a cost saving per patient of $1485 (95% confidence interval $-93 to $3167; $p = 0.06$). Balen *et al* also concluded from their pharmacoeconomic analysis that enoxaparin is the dominant strategy compared to UFH for ACS.[21]

Conclusions

The current available literature supports the use of enoxaparin in the management of ACS. The recommended dosage is enoxaparin 1 mg/kg SC twice daily for a minimum of 48 hours and a maximum of 8 days. Data from clinical trials and Canadian pharmacoeconomic analyses have shown enoxaparin to be more effective and less costly than UFH for ACS. Additional benefits of enoxaparin include the lack of need for aPTT monitoring and a lower incidence of HIT than UFH. A complete blood count is recommended at baseline and twice weekly for the duration of therapy to monitor for bleeding and thrombocytopenia.

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2. Levofloxacin (LevaquinÒ): A New Formulary Addition for Community-Acquired Pneumonia

Sean Gorman, Pharm.D. Student, Manjoyt Randhawa, Pharm.D. Student (Reviewed by the members of the Antibiotic Use Subcommittee (G Stiver, PJ Jewesson, B Bowie, E Bryce, A Chow, F Marra, T Nevill)

New Canadian Treatment Guidelines for Treatment of Community Acquired Pneumonia (CAP)

New Canadian guidelines for the treatment of CAP have been drafted by a Canadian CAP Working Group and are expected to be published shortly.[1] These guidelines represent an update of previously published recommendations[2] and reflect new information regarding the best management of this common, yet serious infection.[3] As described by the Working Group, these guidelines were derived by the consensus of experts and were not entirely based on evidence from randomized clinical trials. In the creation of the new guidelines, the group considered new mortality risk prediction data, criteria for hospital admission and discharge, and the development of critical pathways for CAP management. Also considered was the need to re-evaluate the choice of empiric first-line agents as a result of changing susceptibility patterns, the availability of newer fluoroquinolones and macrolides, the need to simplify dosing regimens and promote IV-PO sequential therapy, and finally the concern for the development of resistance and toxicity associated with the newer agents.[1]

Adult patients with CAP may be treated as outpatients, in the nursing home setting or they may require acute care hospitalization. Most patients with CAP who do not require hospitalization may be treated with a macrolide (eg. erythromycin, clarithromycin or azithromycin) or doxycycline to cover for pneumococci and atypical organisms including *C. pneumoniae* and *M. pneumonia*. Those patients with chronic obstructive lung disease or macroaspiration should receive a newer macrolide to increase coverage for *H. influenzae.*

Patients with CAP who require hospitalization can be further categorized into those who can be managed on a general medical unit versus those who require support on an intensive care unit.[1] Empiric treatment for general medical unit patients should be aimed at bacteremic pneumococcal pneumonia and therapy should be sufficiently broad to also cover for possible infection with *H. influenzae*, enteric gram-negative bacilli and *Chlamydia* or *Le-*

gionella spp.. Monotherapy with a "respiratory" fluoroquinolone (i.e. a fluoroquinolone such as levofloxacin with good activity against gram-positive cocci, gram-negative bacilli and atypical pathogens), or combination therapy involving a 2nd or 3d generation cephalosporin plus a macrolide is recommended.[1]

Patients admitted to an intensive care unit with CAP not known or suspected to involve *P. aeruginosa* should initially receive combination broad spectrum therapy with a macrolide or a respiratory fluoroquinolone plus a non-pseudomonal 3rd-generation cephalosporin or a beta-lactam/beta-lactamase inhibitor. If *P. aeruginosa* is suspected, combination therapy with an anti-pseudomonal fluoroquinolone (ie. ciprofloxacin) plus an anti-pseudomonal beta-lactam or an aminoglycoside is recommended. Alternatively, triple therapy with an anti-pseudomonal beta-lactam plus an aminoglycoside plus a macrolide can be considered.[1]

Whenever possible, initial therapy should be modified to narrower spectrum antibiotics with activity against the identified pathogens. Treatment is generally continued for 7-14 days and IV-PO stepdown therapy should be considered as soon as clinically feasible to facilitate discharge from hospital, reduce costs and improve the patient's quality of life.

In consideration of the publication of the Canadian guidelines, the VHHSC Antibiotic Use Subcommittee (AUS) considered the addition of a respiratory fluoroquinolone at VHHSC. Levofloxacin was considered an acceptable choice over other available respiratory fluoroquinolones (e.g. trovofloxacin, grepafloxacin) based upon its safety record and the published evidence supporting its use in CAP. The AUS was not convinced that there was a need to relax the current restrictions for clarithromycin use (currently restricted for use in *H. pylori*--associated peptic ulcer disease and *Mycobacterium avium* complex infections) nor to add azithromycin to the formulary. Erythromycin and doxycycline are currently on formulary. Doxycycline was considered by the AUS to be a suitable alternative to newer macrolides for outpatient therapy and as an alternative oral antibiotic for patients who cannot tolerate oral erythromycin.

Effective immediately, levofloxacin has been added to the hospital formulary as a reserved antimicrobial drug (RAD). This fluoroquinolone is restricted for use in the management of acute lower respiratory tract infections.

Review of Levofloxacin

Levofloxacin, the l-isomer of ofloxacin, is the first "respiratory" fluoroquinolone to be released in Canada. Compared with the older fluoroquinolones, levofloxacin has enhanced *in vitro* activity against gram-positive bacteria (including *Streptococcus pneumoniae)* as well as possessing good activity against atypical pathogens and gram-negative bacilli.

Pharmacokinetics

Levofloxacin demonstrates excellent oral bioavailability (>95%) that is not significantly affected by co-administration with food.[4] As with other fluoroquinolones, co-administration with aluminum- and magnesium-containing antacids and ferrous sulfate results in significantly decreased levofloxacin absorption.[5] These agents should be administered at least 2 hours before or after levofloxacin administration.

Because the oral absorption of levofloxacin is close to 99%, plasma concentration versus time profiles after either oral or intravenous administration of 500mg are similar. Therefore, both routes of administration can be considered interchangeable in patients with normally functioning gastrointestinal tracts. Maximum serum concentrations (C_{max}) achieved with a single levofloxacin 500mg oral dose (5.19mg/L) are considerably higher than those achieved with ciprofloxacin 750mg (3.4mg/L) or ofloxacin 400mg (4.0mg/L).[6] Minimum plasma concentrations (C_{min}) after repeated oral administration of 500mg once a day are approximately 0.5mg/L.[7]

Levofloxacin penetrates well into most body tissues and fluids including sputum, achieving concentrations that are generally higher than those in plasma.[8] The elimination half-life of levofloxacin (6-8 hours) is comparable to ciprofloxacin and ofloxacin, however the drug is marketed for once daily dosing due to its ability to achieve a high C_{max}.[7] Levofloxacin is primarily eliminated (~80%) in the urine as unchanged drug. Patients with re-

duced renal function (i.e. creatinine clearance < 50mL/min) should receive reduced daily doses.[5] Neither hemodialysis nor CAPD significantly remove levofloxacin.[9] Unlike ciprofloxacin, levofloxacin appears to have only a minor effect on the disposition of theophylline, warfarin, zidovudine, digoxin or cyclosporin. However, patients receiving these drugs concomitantly should be closely monitored for signs of enhanced pharmacological effect or toxicity.

Spectrum of Activity

Gram-positive organisms: When compared to ciprofloxacin, levofloxacin demonstrates enhanced *in vitro* activity against methicillin-susceptible *S. aureus* and some strains of methicillin-resistant *S. aureus* (MRSA).[10,11] Levofloxacin is also active against most strains of methicillin-susceptible coagulase-negative staphylococci and is similar in activity to ofloxacin and ciprofloxacin for *S. epidermidis*.[12] However, its use clinically for the treatment of MRSA and coagulase negative staphylococci infections has not been established. The *in vitro* activity of levofloxacin against streptococci is slightly greater than ofloxacin and ciprofloxacin.[7] This agent is active against *S. pneumoniae* and the MIC_{90} (1-2mg/L) are similar for strains that are susceptible, intermediate and resistant to penicillin.[11,12] Levofloxacin also retains activity against multi-resistant strains of *S. pneumoniae*, including those that are resistant to third-generation cephalosporins.[11,12] Like other fluoroquinolones, levofloxacin has only modest activity against *Enterococcus faecalis* and *Enterococcus faecium.* Enterococcal strains that are ampicillin and vancomycin resistant (VanA or Van B) are frequently resistant to levofloxacin.[11,12]

Gram-negative organisms: Similar to other fluoroquinolones, levofloxacin has excellent *in vitro* activity against β-lactamase positive and negative *Haemophilus influenzae* and *Moraxella catarrhalis.*[13] Levofloxacin has excellent *in vitro* activity against most enterobacteriaceae and other enteric pathogens, however, its activity tends to be less than that exhibited by ciprofloxacin.[14-16] Levofloxacin has comparable activity to ciprofloxacin against *Serratia marcescens* and *Providencia rettgeri*.[14,15] The agent has only moderate *in vitro* activity against *P. aeruginosa* and this activity is significantly less than that of ciprofloxacin.[17] Most strains of *S. maltophilia* and *B. cepacia* are resistant to levofloxacin and the other currently available fluoroquinolones.[18]

Anaerobic and Other Pathogens: Similar to ciprofloxacin, levofloxacin does not appear to possess clinically useful *in vitro* activity against *B. fragilis*, *C. perfringens*, and *Peptostreptococcus*.[12,14,19] Levofloxacin appears to have improved *in vitro* activity compared to ciprofloxacin and ofloxacin against *L. pneumophilia*, *M. pneumoniae* and *C. pneumoniae*.[20,21] Like ciprofloxacin, levofloxacin is also active against *M. tuberculosis* however it has diminished activity compared to ciprofloxacin against *M. avium* complex.[22,23] Levofloxacin also possesses good *in vitro* activity against most genital pathogens including *N.gonorrhoeae*, *C. trachomatis*, *G. vaginalis* and *U. urealyticum*.[24]

Clinical Studies in CAP

There are two comparative clinical trials evaluating the efficacy of levofloxacin in patients with CAP.[25,26] Both studies were of open-label design and involved comparisons with variable regimens of ceftriaxone or cefuroxime (with or without erythromycin or doxycycline).

File *et al* evaluated 590 adults with CAP in an open-label study comparing levofloxacin with 2nd and 3rd generation cephalosporins.[25] Patients were randomly assigned to receive levofloxacin 500mg daily IV or orally versus ceftriaxone 1g or 2g IV once or twice daily or cefuroxime axetil 500 mg orally twice daily for 7-14 days. Intravenous or oral erythromycin (500-1000mg every 6 hours) or doxycycline was added to cephalosporin therapy in circumstances when atypical respiratory pathogens were suspected or proven. Four hundred and fifty-six patients (226 given levofloxacin and 230 administered ceftriaxone and/or cefuroxime axetil) were evaluated for clinical response to therapy at 5-7 days post-antibiotic therapy.

The analysis revealed clinical success rates at 5-7 days post-antibiotic therapy favouring levofloxacin (96%) versus cephalosporin therapy (90%) (95% CI -10.7 to -1.3). The secondary outcome of bacteriologic eradication also favoured levofloxacin (98%) versus cephalosporin (85%) (95% CI -21.6 to -4.8). Both levofloxacin and ceftriaxone-cefuroxime eradicated 100% of *Streptococcus pneumoniae*. Eradication rates for *Haemophilus influenzae* were 100% for levofloxacin and 79% for ceftriaxone-cefuroxime axetil. Microbiologic success for the atypical pathogens was 99% for

levofloxacin compared to 94% for the cephalosporin arm. It should be noted, however, that only 28% of the comparator group with atypical pathogens received either erythromycin or doxycycline. Clinical response was similar in the cephalosporin-treated patients whether or not they had received erythromycin or doxycycline. Adverse events were reported in 5.8% of patients receiving levofloxacin and 8.5% of patients given the cephalosporins.

The second clinical trial was also an open-label study to evaluate the safety and efficacy of levofloxacin versus ceftriaxone in the treatment of hospitalized patients with either community-acquired or hospital-acquired pneumonia.[26] Patients were randomized to levofloxacin 500mg IV twice daily (N=314) versus ceftriaxone 4g IV once daily (N=305). Patients in the levofloxacin arm were switched to oral therapy on day 3-5 of therapy, and if clinical signs and symptoms of pneumonia had improved. The total duration of therapy was left up to the discretion of the physician but the minimum number of days was five. The primary outcome of efficacy was based on the clinical cure rate determined 2-5 days after the end of treatment.

The diagnosis of CAP was made in 93% of patients, and the median duration of treatment was 9 days for levofloxacin and 8 days for ceftriaxone. At the clinical endpoint, the cure rates for both levofloxacin (76%) and ceftriaxone (75%) were similar (95% CI –5.7 to +7.8). In addition, levofloxacin (83%) was equivalent to ceftriaxone (83%) for bacterial eradication of the organism (95% CI –12.8 to +11.0). However, the eradication rate for levofloxacin was better than ceftriaxone for gram-negative pathogens (96% vs. 88%) but lower for gram-positive pathogens (76% vs. 85%). Adverse events were reported in 22% of patients receiving levofloxacin and 26% of patients on ceftriaxone.

Adverse Effects

Although direct comparisons are lacking, levofloxacin appears to be better tolerated than older fluoroquinolones.[5,27] Gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea, constipation, dyspepsia, taste alteration, and flatulence) are the most commonly observed adverse reactions.[5,27] Reports of central nervous system (CNS) toxicities have been generally limited to headache, dizziness and insomnia. The lower incidence of CNS side effects is thought to be related to a decreased affinity for binding of the drug to GABA receptors. Phototoxicity has also been a concern with several fluoroquinolones, however the incidence of phototoxicity in patients taking levofloxacin has been <0.5%, similar to that of ofloxacin and ciprofloxacin.[5,27] Other adverse events reported in over 3,460 patients are transient elevation in liver function tests <2%, vaginitis 0.8%, rash 0.3% and pruritus 0.3%.[5,27]

Recommended Dosage and Cost

The recommended dosage for the empiric treatment of CAP in adults is 500 mg once daily for 7-14 days depending upon clinical response. This can be given orally or by slow IV infusion (over 60 minutes). The excellent bioavailability of levofloxacin should permit oral administration for the initial management of CAP in select patients. The cost of oral and IV levofloxacin is comparable to the cost of other antibiotics used for CAP (Table 1). The dosage of levofloxacin should be reduced to 250mg daily for patients with a creatinine clearance of less than 50mL/min and 250mg every 48 hours for clearances less than 20mL/min.

Table 1. Cost Comparison of Various CAP Regimens

Drug Regimen	Daily Cost*
Ceftriaxone 1g IV daily PLUS (Erythromycin 500mg po q6h OR Doxycycline 100mg po bid)	$34.00
Ceftriaxone 2g IV daily PLUS Erythromycin 500mg IV q6h	$80.00**
Cefuroxime 750mg IV q8h PLUS (Erythromycin 500mg po q6h or Doxycycline 100mg po bid)	$10.00
Cefuroxime 1.5g IV q8h PLUS Erythromycin 500mg IV q6h	$32.00**
Levofloxacin 500mg po daily	$5.00
Levofloxacin 500mg IV daily	$44.00

*based on VHHSC acquisition costs only
** acquisition cost of erythromycin 500mg IV q6h is $13.00/day

Formulary Status

Levofloxacin, a new "respiratory" fluoroquinolone, has been added to the VHHSC formulary as a reserved antimicrobial drug. A select antimicrobial information notice will be sent with each treatment course and each course will also be monitored by a clinical pharmacist. This agent provides another alternative for the treatment of CAP.

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