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 Advisory Council (MAC).

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

Changes to Formulary

Additions

1. Rofecoxib 12.5mg, 25mg tablets (Vioxx®)
- Cyclooxygenase–2 (COX-2) inhibitor indicated for acute and chronic management of osteoarthritis and rheumatoid arthritis
- To be used in patients at high risk for serious GI events who would otherwise receive a non-steroidal anti-inflammatory drug (NSAID)
- See page 2 for comparison to NSAIDs

2. Alendronate 5mg, 10mg, 70mg tablets (Fosamax®)
- Second generation bisphosphonate indicated for treatment and prevention of osteoporosis
- See page 5 for review

3. Sirolimus 1mg/mL solution (Rapamune®)
- Immunosuppressive agent restricted to islet cell transplantation

4. Busulfan 6mg/mL injection (Busulfex®)
- For use as part of a conditioning regimen prior to hematopoietic progenitor cell transplantation
- Restricted to Division of Hematology

Deletions

1. Sulindac tablets (Clinoril®)
- Alternatives: Ibuprofen, Naproxen

2. Indomethacin suppositories (Indocid®)
- Discontinued by manufacturer
- Alternative: Diclofenac 50mg, 100mg suppository (Voltaren®)

Updated Policies/Procedures

1. Pharmacists To Order Drug and Creatinine Concentrations

Pharmacists have been authorized to order vancomycin, aminoglycoside and creatinine concentrations independently. No pre-approval by a physician is necessary. Pharmacists will continue to interact with physicians regarding any necessary drug regimen modifications.

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2. Closure of Heather Pavilion (HP) Pharmacy Satellite

The last day of operation of the HP Pharmacy Satellite was Friday Sept 12/03. Effective Monday, Sept 15/03, HP/HC/WC Nursing Units were provided pharmacy services as follows:

Nursing Unit	New Pharmacy	Phone/FAX
B2 (Peritoneal Dialysis)	CP-G	Phone: 6-2481 FAX: 54712
B4 (BMT Day Care)	T15	Phone: 5-5717 FAX: 55680
A3 (OPD Clinic)	T15	
C10 (MDCU)	T15	
Eye Care Centre	T15	
Surgical Day Care Unit	CP-G	Phone: 6-2481 FAX: 54712
GTU*	CP-G	
D4*	CP-G	
HC Stat E3	CP-G	
HC E1, W1, E2	BP (PO meds) CP-G (IV meds)	BP Phone: 6-1786 BP FAX E1, W1, TB2: 5-5436
TB2	BP (PO meds) CP-G (IV meds)	
*wards to move to WC3 CP - Centennial Pavilion; T - Tower; BP - Banfield Pavilion		

3. Parenteral Drug Therapy Manual (PDTM) Update

All PDTMs on the nursing units have been updated to the July 2003 version. Of note, there are several new monographs added including argatroban, busulfan IV, darbepoetin, foscarnet, protein C, sumatriptan and zuclopenthixol. Several other monographs have been revised.

If there are any questions regarding the PDTM, please contact Dr. Karen Shalansky at 604-875-4839.

New Drug/Drug Products

1. Rofecoxib (Vioxx®)

Peter Loewen, Pharm.D., Karen Shalansky, Pharm.D.

Rofecoxib is a member of a new class of analgesics called cyclooxygenase-2 (COX-2) inhibitors that selectively inhibit the COX-2 enzyme. It is indicated for acute and chronic treatment of osteoarthritis (OA), rheumatoid arthritis (RA), and primary dysmenorrhea. [1-4]

Pharmacology

COX-2 is responsible for the production of prostaglandins involved in inflammation and is expressed mainly in tissues where inflammation and healing are occurring. Selective inhibition of COX-2 results in anti-inflammatory and analgesic effects. COX-1 is expressed in all cells and is responsible for the production of prostaglandins which maintain normal cell homeostasis and mediate protection of the gastrointestinal (GI) mucosa. Inhibition of COX-1 is thought to result in dysfunction of the normal mechanisms of defense of the gastric mucosa (mucosal blood flow, bicarbonate production, mucus production), resulting in the undesirable toxic GI effects (GI perforation, ulcers and bleeds).[5] Traditional non-steroidal anti-inflammatory drugs (NSAIDs) inhibit both COX-1 and -2 to varying degrees.

Table 1 compares the three COX-2 inhibitors on the Canadian market to a typical NSAID, ibuprofen.[2,6] Unlike rofecoxib and celecoxib, meloxicam exhibits dose-dependent COX-1 inhibition which is incomplete at anti-inflammatory doses.[7] Rofecoxib lacks a sulfonamide moiety, thus is not contraindicated in patients with sulfa allergy. It possesses a long serum elimination half-life allowing once daily dosing for all inflammatory conditions, and lacks effects on the liver cytochrome p450 system, thus resulting in a reduced potential for drug interactions.

Comparison to NSAIDs

Large clinical trials have shown that COX-2 inhibitors are similar in efficacy to traditional NSAIDs (e.g. naproxen, ibuprofen, diclofenac) for OA, RA or pain.[4,8] The most important considerations of the COX-2 inhibitors in comparison with each other and with NSAIDs are safety considerations, including GI toxicity, hypersensitivity reactions, renal effects, cardiovascular effects, and drug interactions.

Table 1. Comparison of COX-2 Inhibitors and Ibuprofen

Drug	Celecoxib (Celebrex®)	Rofecoxib (Vioxx®)	Meloxicam (Mobicox®)	Ibuprofen (Motrin®)
Tmax	2.8 hrs	2-3 hrs	6.5 hrs	2 hrs
Sulfonamide Moiety	Yes	No	No	No
Metabolism	CYP450 2C9	Non-CYP450 enzymes	CYP450 2C9 and 3A4	Non-CYP 450 enzymes
Half-Life	11.2 hrs	17 hrs	20 hrs	2-4 hrs
Dose	OA: 100mg daily RA: 200mg daily-BID	OA: 12.5mg daily RA: 25mg daily	OA: 7.5mg daily RA: 15mg daily	OA/RA: 1200-2400mg/day divided 3-4 times/day
Cost/day	$0.67-2.66	$1.33 (12.5 and 25mg)	$0.83-0.97	$0.12-0.24

Tmax = time to maximum concentration; OA = osteoarthritis; RA = rheumatoid arthritis

1. Gastrointestinal Reactions:
Recently, two randomized, double-blind trials have addressed the critical question of whether celecoxib or rofecoxib are safer than traditional NSAIDs (CLASS trial[8] and VIGOR trial[4]).

In CLASS, 8059 patients (mean age 60) with OA or RA (27%) were randomized to receive celecoxib 400mg twice daily (twice the recommended maximum dose for RA) or diclofenac 150mg/day or ibuprofen 2400mg/day.[8] ASA for cardiovascular or cerebrovascular prophylaxis was permitted and was used by 20% of patients in both groups. Six month interim analysis of 4573 patients revealed no significant difference in the primary composite outcome of ulcer perforation, gastric outlet obstruction or upper GI bleeding (celecoxib 0.76% vs NSAID group 1.45%, p=0.09). When symptomatic gastroduodenal ulcers were included (secondary outcome), the difference became statistically significant in favour of celecoxib (2.08% vs. 3.54%, p=0.02). Of note, any reductions in events were due to fewer GI bleeds (n=10 vs 20) and/or symptomatic gastroduodenal ulcers (n=19 vs 29) in the celecoxib group since no perforations or obstructions were documented in either group.

In VIGOR, 8076 patients (mean age 58) were randomized to receive rofecoxib 50mg daily or naproxen 500mg bid.[4] ASA use was not permitted. The primary outcome variable was the composite of symptomatic gastric ulcers, upper GI bleeds, ulcer perforations, or gastric outlet obstructions. After 9 months of follow-up, primary event rates were lower in the rofecoxib arm (2.1% vs. 4.5%, p<0.001). When only serious events (GI bleeds, perforations or obstructions) were included, the rates still favoured rofecoxib (0.6 vs. 1.4%, p=0.005). As with CLASS, these benefits were entirely due to reductions in GI bleeds (n=14 vs. 35) and symptomatic ulcers (n=28 vs. 81).

For meloxicam, two large randomized but short-term (28-day) safety trials in OA patients failed to demonstrate significant differences in serious GI events between meloxicam and either diclofenac[9] or piroxicam[10].

In summary, the evidence indicates that rofecoxib (primary outcome data) and celecoxib (secondary outcome data) are less likely to induce serious GI events than traditional NSAIDs. The absolute risk reduction is very small due to the low baseline event rates and any clinically relevant GI safety benefit may be negated by the concurrent use of even low-dose ASA.

Celecoxib has been further studied in patients with a recent history of ulcer bleeding.[11] This randomized, placebo-controlled trial assessed 287 patients who received either celecoxib 200mg bid alone or diclofenac 75mg bid plus omeprazole 20mg daily. The results showed a similar incidence of recurrent ulcer bleeding (celecoxib 4.9% vs 6.3%) over a 6 month period, suggesting that a COX-2 inhibitor may be used as an alternative to combined therapy with an NSAID plus proton pump inhibitor in patients at high risk for bleeding.

2. Hypersensitivity Reactions:
Celecoxib contains a sulfonamide moiety and is contraindicated in patients with a sulfonamide allergy. Due to the structural similarity between COX-2 inhibitors, NSAIDs and ASA, they are contraindicated in patients with allergic-type reactions to ASA or other NSAIDs, and especially in those who demonstrate the triad of ASA allergy, asthma and nasal polyps.[1,6,12]

3. Renal Effects:
Renal effects of COX-2 inhibitors are similar to those of NSAIDs.[13,14] Both classes of drugs inhibit prostaglandins that regulate blood flow in the kidney, potentially leading to decreased glomerular filtration rate, increased creatinine, and sodium and water retention in susceptible individuals. COX-2 inhibitors and NSAIDs may lessen the effect of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB), and may reduce the natriuretic effect of diuretics. Both classes of drugs should be used with caution in patients with chronic renal insufficiency, congestive heart failure (CHF), or those who are hypovolemic.

3. Cardiovascular Effects:
Due to the selective inhibition of the COX-2 enzyme, COX-2 inhibitors do not have an effect on platelet aggregation. Thus, patients should continue with ASA for cardiovascular (CV) prophylaxis while taking COX-2 inhibitors. Note, however, that the CLASS trial results suggest that concurrent use of ASA with a COX-2 inhibitor mitigates their GI safety advantage.[8]

All three COX-2 inhibitors have been reported to Health Canada for suspected adverse CV outcomes, primarily increased blood pressure, heart rate/rhythm disturbances, and CHF.[7] Please refer to Drug and Therapeutics Newsletter March 2003 for a complete review of this topic.[15] In summary, two large studies, one randomized[4] and one retrospective[16], have implicated that high dose rofecoxib (>25mg daily) is associated with increased CV events.

4. Drug Interactions:
Both celecoxib and rofecoxib may interact with warfarin to increase INR and close monitoring of the antithrombotic effect of warfarin is required with concomitant use.[1,6] Rofecoxib does not inhibit the cytochrome p450 system, thus reducing its drug interaction potential. As with traditional NSAIDs, COX-2 inhibitors may increase lithium concentrations and decrease diuretic and ACE-inhibitor or ARB efficacy.

Conclusions
During chronic therapy, rofecoxib reduces the risk of serious GI events (GI bleeds, symptomatic ulcers) by a small absolute amount compared to traditional NSAIDs. Rofecoxib does not offer any other clinically meaningful advantages over NSAIDs with respect to efficacy or other adverse effects. The same precautions exist for rofecoxib as for NSAIDs in patients with renal disease, CHF, hypertension, and ASA or other NSAID allergy. Rofecoxib doses should not exceed 25mg daily to limit the potential for CV events.

Due to the higher cost of rofecoxib, its use is restricted to those patients at high risk of serious GI events who require chronic therapy, such as:

- Elderly patients
- Previous NSAID-induced upper GI bleed or gastric or duodenal ulcer
- Concurrent use of warfarin or high dose systemic corticosteroid

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2. Alendronate (Fosamax®)

Janice Yeung, Pharm.D., Nilufar Partovi, Pharm.D.

Alendronate is a bisphosphonate that regulates bone metabolism. It is indicated for the treatment and prevention of osteoporosis, glucocorticoid-induced osteoporosis, and Paget's disease.

Pharmacology

Alendronate is a second-generation bisphosphonate (an aminobisphosphonate) with similar antiresorptive action to etidronate (first-generation bisphosphonate). However unlike etidronate, alendronate localizes preferentially to resorption sites of active bone turnover, and bone resorption is inhibited at doses that have minimal or no effect on bone mineralization. Alendronate inhibits osteoclast-mediated bone resorption although the exact mechanism is unclear.[1]

The bioavailability of alendronate after oral administration is less than 1% and is reduced by the presence of food and divalent ions. The drug must be taken on an empty stomach. Elimination of alendronate appears to be exclusively renal; it is estimated to have a 10-year elimination half-life due to its slow release from bone.

Efficacy Trials

Osteoporosis Prevention (No Previous Fractures)

Alendronate has been shown to significantly increase bone mineral density (BMD) in postmenopausal women at lumbar spine, hip and total body compared to placebo.[2,3] An additive effect on BMD was shown in a subset of patients also taking combined estrogen/progestin[2], although additional anti-fracture benefit was not found.[4] While an improvement in BMD is important, a reduction in bone fractures with alendronate would offer more clinical relevance.

A continuation of The Fracture Intervention Trial (FIT) specifically assessed the effect of alendronate in preventing fractures as a primary outcome in 4432 postmenopausal women (age 55-80).[5] After an average follow-up of 4.2 years, alendronate significantly reduced vertebral fractures compared to placebo in only those patients who had baseline T-scores below –2.5 (13.1% vs 19.6%, 95% CI 0.5-0.82).

The Fosamax International Trial Study Group (FOSIT) evaluated the incidence of clinical fractures as a secondary outcome in 1908 postmenopausal women with a baseline lumbar spine BMD T-score of –2.0 or less.[6] After 1 year of alendronate 10mg daily, there was a reduction in non-vertebral fractures (2% vs. 3.9% placebo), although the study was not powered to assess this endpoint.

Osteoporosis Treatment

In 994 postmenopausal women with established osteoporosis, alendronate 10mg daily has been shown to improve BMD in all skeletal sites over a 3-year period.[7] New vertebral fractures (secondary outcome) were experienced in only 2.8% of treated patients compared to 6.2% of patients given placebo (p=0.03).

The FIT trial studied 2027 postmenopausal women (age 55-81) with previous vertebral fractures.[8] Patients initially received alendronate 5mg daily which was then increased to 10mg daily at 24 months. Average follow-up was 2.9 years. The primary endpoint was incidence of new vertebral fractures and the secondary endpoint was incidence of new non-vertebral fractures. Compared to placebo, alendronate significantly reduced the incidence of new vertebral fractures (8% vs. 15%, p<0.001), hip fractures (1.1% vs. 2.2%, p=0.047) and wrist fractures (2.2% vs. 4.1%, p=0.013).

Alendronate is the only bisphosphonate to be studied in a randomized controlled trial in men with established osteoporosis.[9] A 2-year double-blind trial in 241 men (age 31-87) with osteoporosis, demonstrated that alendronate 10mg daily significantly increased spine, hip and total body BMD and significantly reduced the incidence of vertebral fractures compared to placebo (0.8% vs. 7.1%, p=0.02).

Comparison to Other Bisphosphonates

Currently, there are no head-to-head trials evaluating fracture outcomes between alendronate and either etidronate or risedronate. Intermittent cyclic etidronate has been shown to significantly increase vertebral BMD and decrease the incidence of new vertebral fractures compared to placebo in postmenopausal women with one or more vertebral fractures.[10] The vertebral fracture benefit has been shown to continue for at least 5-7 years.[11,12] There is no data demonstrating benefit of etridronate on non-vertebral or hip fractures.

Risedronate, a second-generation bisphosphonate,

has been shown to significantly increase BMD and decrease the incidence of both vertebral and non-vertebral (including hip) fractures in postmenopausal women with established osteoporosis.[13-15]

Adverse Effects

Common adverse effects (3-7%) include abdominal pain, dyspepsia, constipation, diarrhea and flatulence. Less common adverse effects (1-3%) include esophageal ulcers, abdominal distension, dysphagia and musculoskeletal pain.

Dosage

- Treatment of osteoporosis: 10mg/day or 70mg/week
- Prevention of osteoporosis: 5mg/day
- Treatment and prevention of glucocorticoid-induced osteoporosis: 5mg/day; if postmenopausal and not receiving estrogen, then 10mg/day

Alendronate should be taken in the morning on an empty stomach with a glass of water at least one hour prior to food or beverages. Patients must remain upright for 30 minutes and until their first meal of the day after taking alendronate to decrease the potential for esophageal ulceration.

Cost

Table 1 compares the three bisphosphonates available in Canada.

Table 1. Cost Comparison of Bisphosphonates for Treatment of Osteoporosis

Drug	Treatment Dose	Cost/Week	Pharmacare Benefit
Etidronate* (Didronel®)	400mg/day x 14 days repeated every 90 days	$3.08	Yes
Alendronate* (Fosamax®)	10mg/day or 70mg/week	$13.16** or $8.82	No
Risedronate (Actonel®)	5mg/day or 35mg/week	$12.46 or $8.82	No

*formulary drugs at VHHSC
**generic alendronate 10mg will be available soon , reducing the weekly cost to $8.61

Conclusions

Alendronate significantly increases BMD in postmenopausal women and decreases the incidence of vertebral fractures in both men and women with established osteoporosis (T-score -2.5 or less) or those with one or more existing vertebral fractures. Alendronate has also been shown to significantly decrease the incidence of non-vertebral fractures (hip and wrist) in osteoporotic postmenopausal women. There is no hip or non-vertebral fracture benefit data for etidronate. According to the 2002 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada, bisphosphonates are considered first-line treatment for postmenopausal osteoporosis (alendronate, risedronate (Grade A evidence); etidronate (Grade B evidence)).[16] Alendronate must be taken on an empty stomach and the patient must remain in an upright position for 30 minutes and until their first meal of the day after drug administration.

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LEVOFLOXACIN DAILY VERSUS TWICE DAILY DOSING: Expectorating the Myth

Tim T.Y. Lau, Pharm.D., H. Grant Stiver, M.D.

Levofloxacin is an antibacterial agent belonging to the class of "respiratory" fluoroquinolones, which also include gatifloxacin and moxifloxacin.[1] It exhibits activity against a broad spectrum of gram-positive and gram-negative aerobic, and anaerobic bacteria, commonly encountered in community-acquired respiratory tract infections. These include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, and atypical organisms (*Chlamydia pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*).[1,2] The usual dose of levofloxacin for community-acquired pneumonia (CAP), skin and soft tissue infections, and urinary tract infections is 250-750 mg IV/PO once daily (cost/day: $18.00-54.00 IV/$2.00-6.00 PO).

The Myth

Recently at VGH, levofloxacin has been prescribed on a twice daily dosing regimen in a select group of patients with respiratory tract infections. This increased frequency in dosing significantly increases the daily drug cost. The aim of this review is to clarify the myth behind daily versus twice daily dosing of levofloxacin.

Pharmacokinetics/Pharmacodynamics (PK/PD)

Myth # 1: "Based on the PK/PD characteristics of levofloxacin, twice daily administration is necessary to provide optimal drug levels to eradicate respiratory pathogens."

The evidence: PK describes the absorption, distribution, metabolism, and excretion of a drug in the body, while PD characterizes the pharmacological activity of the drug in the body over a period of time.[3] In *in vitro* animal and human studies with fluoroquinolones, the PK/PD parameter that best correlates with bacteriological eradication is the "24 hour area under the curve (AUC_{24})" to "minimum inhibitory concentration (MIC)" ratio (AUC_{24}/MIC).[2,3] The "maximum plasma drug concentration" to MIC ratio (Cpmax: MIC) has also been associated with bacteriological eradication and the prevention of bacterial resistance during treatment.[4]

Clinical data suggests that an AUC_{24}/MIC of ≥25-30 correlates with bacterial eradication in the treatment of CAP due to *Streptococcus pneumoniae*. It is unknown whether an AUC_{24}/MIC exceeding 25 provides any additional clinical benefit.[2] In critically ill patients with gram-negative nosocomial respiratory tract infections, an AUC_{24}/MIC of 100-125, and a Cpmax:MIC ratio of ≥10 are associated with maximal bacterial eradication and resistance prevention.[3]

Levofloxacin 500mg daily achieves an AUC_{24}/MIC of 35 against *S. pneumoniae,* 1167 against *H. influenzae*, and 583 against *M. catarrhalis* in young adults.[2] In elderly patients (≥ 65 yrs), an AUC_{24}/MIC of 66.6 against *S. pneumoniae* has been shown due to a more prolonged levofloxacin half-life of 13.4 hours (normal 6.9 hours, compared to ciprofloxacin half-life of ~4 hours).[5] The Cpmax:MIC ratio for levofloxacin for *S. pneumoniae* is 3.6, *H. influenzae* is 120, and *M. catarrhalis* is 60, which is comparable to the other respiratory fluoroquinolones (Table 1).

The Canadian Respiratory Organism Susceptibility Study (CROSS) is a surveillance program that tests all respiratory isolates in Canadian hospitals. A subset analysis of *S. pneumoniae* isolates in British Columbia showed that a levofloxacin 500 mg daily dose yielded an AUC_{24}/MIC of >30 in 97% of patients, with the possible exception of young patients with good renal clearance.[6] In critically ill patients with nosocomial pneumonia, a dose of 750 mg daily would be considered an appropriate regimen.[6]

The respiratory fluoroquinolones also exhibit a post-antibiotic effect (PAE) against gram-positive and gram-negative bacteria. These drugs continue

Table 1. Respiratory Fluoroquinolone PK/PD Parameters[2]

Fluoroquinolone	*Streptococcus pneumoniae*		*Haemophilus influenzae*		*Moraxella catarrhalis*	
	AUC_{24}/MIC	Cpmax:MIC	AUC_{24}/MIC	Cpmax:MIC	AUC_{24}/MIC	Cpmax:MIC
Levofloxacin 500mg PO OD	35	3.6	1167	120	583	60
Gatifloxacin* 400mg PO OD	48	6.2	1600	207	800	103
Moxifloxacin* 400mg PO OD	60	6.8	500	57	250	28

*non-formulary drug at VHHSC

to suppress growth even after the serum concentrations fall below the MIC.[2] The duration of the PAE ranges from 1.5 to 2.5 hours. This property further supports the rationale for once daily dosing of levofloxacin. Thus, based on PK/PD data, once daily levofloxacin should provide adequate levels for optimal bacterial eradication.

Clinical and Bacteriological Efficacy

Myth # 2: "For the treatment of severe pneumonia, twice daily levofloxacin is superior to once daily administration."

The evidence: In a randomized, double blind, multi-centre trial, 500mg twice daily oral levofloxacin failed to show a significant benefit over 500mg once daily levofloxacin in mild to moderate CAP.[7] The clinical response was 94% (137/146) and 95% (138/145), respectively, and microbiological eradication was 100% (53/53) and 98% (44/45). This trial was not powered to determine equivalence. Comparing the respiratory fluoroquinolones, two randomized, blinded trials of gatifloxacin[8] or moxifloxacin[9] vs. levofloxacin 500mg daily showed no difference in response rates for mild to severe CAP.

While there are no head-to-head clinical trials comparing once daily vs. twice daily dosing of levofloxacin in hospitalized patients, both regimens have demonstrated similar clinical and bacteriological efficacy in the treatment of severe pneumonia with or without mechanical ventilation (Table 2). [8-12]

Bacterial Resistance

Myth # 3: "Once daily levofloxacin is associated with the development of bacterial resistance."

The evidence: The concept of maintaining drug levels above a "mutant prevention concentration" to prevent the selecting out of mutants is currently a hypothesis with no supporting epidemiological or clinical data.[2,13] In *in vitro* studies, there is also no clear evidence to suggest that respiratory fluoroquinolones differ in their propensity to develop resistance to *S. pneumoniae*.[2,13] If resistance is observed to one fluoroquinolone, it should be assumed that the pathogen is resistant to all fluoroquinolones as a class.[14]

Susceptibility data from the CROSS has shown that *S. pneumoniae* has remained sensitive to levofloxacin since its introduction: 99.6% in 1997/98, 99.3% in 1998/99, 98.8% in 1999/2000, 99.4% in 2000/01, and 98.8% in 2001/02.[2]

Summary

Based on the current evidence from PK/PD, clinical trials, and concepts in bacterial resistance, levofloxacin 500 mg once daily PO/IV dosing is an appropriate regimen for the treatment of pneumonia. There is no evidence to suggest that a twice daily regimen is superior to once daily dosing.

Table 2. Clinical Trials of Levofloxacin in Severe Pneumonia

Reference (Trial Design)	Sample Size	Dosage Regimen (IV/PO)	Pneumonia Severity	Clinical Response	Bacteriological Response
Sullivan 1999[8] (R, MC, DB)	417	Levo 500mg daily vs. Gatifloxacin 400mg daily x 7-14 days	143 pts (34%) with severe pneumonia	Levo 91% vs. Gati 95% (severe pts)	Levo 93% (106/114) vs. Gati 98% (112/125)
File 2001[9] (R, MC, DB)	507	Trovafloxacin 200mg daily or Levo 500mg daily vs. Moxifloxacin 400mg daily x 7-14d	110 pts (31%) with severe pneumonia	Levo or Trova 80% vs. Moxi 79% (severe pts)	Levo or Trova 90% (69/77) vs. Moxi 85% (64/75)
Fogarty 1998[10] (MC, OL)	264	Levo 500mg daily x 7-14 days	14 pts (15%) with severe pneumonia	94.9% (all pts)	97.1% (severe pts)
Fogarty 2001[11] (MC, OL)	271	Levo 500mg daily x 7-14 days	99 pts (42.1%) with severe pneumonia	97% (severe pts)	91% (10/11)
Norby 1998[12] (MC, R)	619	Levo 500mg BID vs. Ceftriaxone 4g IV daily x minimum 5 days	70% with moderately severe pneumonia 20% severe pneumonia	Levo 76% vs. Ceftriaxone 75% (all pts)	Levo 87% (79/82) vs. Ceftriaxone 87% (92/106)

MC=multicentre; R=randomized; OL=open label; DB=double-blind; Levo=levofloxacin; Gati=gatifloxacin; Trova=trovafloxacin

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