Occasional review

The next generation: fluoroquinolones in the management of acute lower respiratory infection in adults

Peter J Moss, Roger G Finch

Lower respiratory tract infections (LRTI) are the leading infectious cause of death in most developed countries; community acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis (AECB) are responsible for the bulk of the adult morbidity. Until recently quinolone antibiotics were not recommended for the routine treatment of these infections.[1–3] Neither ciprofloxacin nor ofloxacin have adequate activity against *Streptococcus pneumoniae* in vitro, and life threatening invasive pneumococcal disease has been reported in patients treated for respiratory tract infections with these drugs.[4–6] The development of new fluoroquinolone agents with increased activity against Gram positive organisms, combined with concerns about increasing microbial resistance to β-lactam agents, has prompted a re-evaluation of the use of quinolones in LRTI. Sparfloxacin and levofloxacin are now approved for the treatment of community acquired LRTIs in the UK (grepafloxin, which was also approved for this indication, has recently been withdrawn from the market). It is important to define the role of these drugs in the treatment of CAP and AECB.

The most common cause of CAP worldwide is *S pneumoniae* which accounts for 60–75% of pathogens isolated.[7–9] Other less common causes include *Mycoplasma pneumoniae* and *Legionella pneumophila*. Any agent used for the empirical treatment of CAP must cover *S pneumoniae*, and preferably these other organisms as well, especially in severe disease. In AECB the role of bacterial pathogens is less clearly defined; *Haemophilus influenzae*, *S pneumoniae*, and *Moraxella catarrhalis* are most frequently associated. Several of the newer quinolones have MIC_{90} values for *S pneumoniae* that are significantly lower than those reported for ofloxacin and ciprofloxacin, which suggests that they should be effective in clinical use. Clinafloxacin, sitafloxacin, and gemifloxacin have the lowest MIC_{90} values in vitro, followed by trovafloxacin, moxifloxacin, gatifloxacin, grepafloxacin, sparfloxacin, and levofloxacin.[10–14] All have excellent in vitro activity against the other significant bacterial causes of CAP and AECB.[15–18]

Pneumococcal resistance to β-lactams is an increasing problem in many parts of the world, with penicillin resistant pneumococci accounting for up to 40% of isolates in Spain[19] and 33% in the United States.[20] In England and Wales the prevalence is lower; in the first quarter of 1999 6.5% of blood/cerebrospinal fluid isolates were reported to the Public Health Laboratory Service as showing intermediate sensitivity or resistance (D Livermore, personal communication). Pneumococcal resistance to penicillin is not specifically linked to quinolone resistance and, in general, penicillin resistant pneumococci are sensitive to the newer fluoroquinolones.[11 21]

Resistance to ciprofloxacin develops relatively easily in both *S pneumoniae* and *H influenzae*, requiring only a single mutation in the *parC* gene.[22 23] Other quinolones such as sparfloxacin and clinafloxacin require two mutations in the *parC* and *gyrA* genes.[11 23] Despite this, the prevalence of *S pneumoniae* with decreased quinolone sensitivity has increased in parallel with increased prescription of these drugs,[24] and pneumococci with decreased in vitro grepafloxacin sensitivity have been isolated from patients following treatment with this agent.[25] Efflux resistance has been recognised among *S pneumoniae*; some quinolones appear to be more susceptible to this than others.[11 26 27] In the case of *H influenzae*, some isolates from patients with LRTI have developed decreased susceptibility to ciprofloxacin; such isolates remain fully sensitive to clinafloxacin, trovafloxacin, and gatifloxacin but not to moxifloxacin, sparfloxacin, or grepafloxacin.[11]

The pharmacokinetic properties of the new quinolone agents support their use in LRTI. The drugs are extensively distributed, achieving high concentrations in lung tissues and secretions.[28] Those which are available in both oral and intravenous formulations, such as levofloxacin and moxifloxacin, have good absolute bioavailability, allowing early and simple change from intravenous to oral treatment. Most have relatively long terminal elimination half lives and can be administered once daily.

There are few published clinical trials assessing the efficacy of fluoroquinolones in CAP. Three studies have shown intravenous and/or oral levofloxacin to be as good as or better than comparative treatments (ceftriaxone,[29 30] oral cefuroxime,[29] amoxycillin/clavulanic acid[31]) in terms of clinical and

Division of Infectious Diseases and Microbiology, School of Clinical Laboratory Sciences, University of Nottingham, Nottingham City Hospital, Nottingham NG5 1PB, UK
P J Moss
R G Finch

Correspondence to:
Professor R G Finch

bacteriological cure. Sparfloxacin has been compared with erythromycin,[32] roxithromycin,[33] cefaclor,[34] amoxycillin,[35] amoxycillin/clavulanic acid,[32] and amoxycillin/ofloxacin,[36] again showing equivalent clinical and microbiological success rates. Single studies have shown grepafloxacin to be as effective as, and trovafloxacin significantly better than, amoxycillin (by clinical cure rate in evaluable patients) for the treatment of CAP.[37 38] Most patients entered into these comparative trials had mild or moderate rather than severe pneumonia, based on accepted clinical and laboratory indicators. Few have had bacteraemic pneumococcal pneumonia, a more rigorous test of antimicrobial activity in terms of disease severity, and only a very small number of patients were infected with penicillin resistant pneumococci. In most studies the analysis was not performed on an intention-to-treat basis. Comparative clinical data on other new quinolones are limited and generally unpublished.

Levofloxacin, sparfloxacin, and grepafloxacin have been shown to be as effective clinically as comparative oral treatment (cefuroxime axetil or amoxycillin/clavulanate) for treating AECB.[39–41] However, most acute exacerbations of bronchitis are not due primarily to bacterial infection, and difficulty in defining the role of antibiotics in treatment has made comparative trials problematic.

Safety is paramount if quinolones are to gain wider use in the community as well as in hospital. Most adverse events reported are common to the class, but the frequency and severity varies from drug to drug. Recent reports of hepatotoxicity have led to the product licence for trovafloxacin being suspended in the UK and restricted in the USA.[42] Nausea and other minor gastrointestinal problems are common with all quinolones, as are mild CNS effects such as dizziness, headache, and light headedness. These effects may be more common with grepafloxacin.[43] Photosensitivity is more common and more severe with 8-halogenated quinolones such as sparfloxacin and clinafloxacin.[44] Several quinolones can cause minor prolongation of the electrocardiographic QT interval (as do the macrolides); sparfloxacin has been implicated in an episode of torsades de pointes arrhythmia[45] but the incidence of clinically significant ECG changes is extremely low. In comparative clinical studies the incidence of side effects in the quinolone group has not exceeded that in the comparative group and they are generally better tolerated than macrolides. Some quinolones, notably grepafloxacin, can inhibit hepatic cytochrome P450 leading to increased plasma concentrations of co-administered drugs such as theophylline.

The current guidelines of the Infectious Diseases Society of America list fluoroquinolones as a preferred option for both inpatient and outpatient management of CAP.[46] The European Respiratory Society recommends them as an alternative to aminopenicillins for AECB but not for CAP (except in combination with other agents in very serious infections).[47] New British guidelines are awaited. The antimicrobial spectrum and pharmacokinetic properties of these agents suggest that they are likely to be an effective treatment for respiratory infections due to penicillin resistant pneumococci and other organisms. However, clinical data are limited, particularly in severe and invasive disease. Potential compliance benefits due to once daily dosing must be weighed against increased drug cost; there is little practical evidence to support the suggestion (based on cost analysis models[48]) that quinolones may decrease the cost of treating CAP by reducing the need for hospital admission.

The prevalence of clinically significant pneumococcal resistance to penicillin in the UK is currently low, although it is rising. Beta-lactam antibiotics alone or in combination with a macrolide remain adequate empirical treatment for most cases of CAP. There is no compelling evidence for fluoroquinolones to become the standard first line treatment for CAP. Although there is a need for a safe and effective parenteral/oral agent for treating severe CAP in hospital, it is not yet clear if any of the currently available quinolones can fill this role. Antibiotics are usually not indicated in AECB[49] and there is little evidence to suggest that quinolones offer benefit over other antimicrobial treatments, although they may be used as second line drugs in a few cases where an antibiotic is appropriate.

1 American Thoracic Society. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity and initial antimicrobial therapy. *Am Rev Respir Dis* 1993;**148**:1418–26.
2 Mandell LA, Niederman MS. Antimicrobial treatment of community acquired pneumonia in adults: a conference report. *Can J Infect Dis* 1993;**4**:25–8.
3 British Thoracic Society. Guidelines for the management of community-acquired pneumonia in adults admitted to hospital. *Br J Hosp Med* 1993;**49**:346–50.
4 Frieden TR, Mangi RJ. Inappropriate use of oral ciprofloxacin. *JAMA* 1990;**264**:1438–40.
5 Lee BL, Kimbrough RC, Jones SR, *et al*. Infectious complications with respiratory pathogens despite ciprofloxacin therapy. *N Engl J Med* 1991;**325**:520–1.
6 Korner RJ, Reeves DS, MacGowan AP. Dangers of oral fluoroquinolone treatment in community acquired upper respiratory tract infections. *BMJ* 1994;**308**:191–2.
7 Fine MJ, Smith MA, Carson CA, *et al*. Prognosis and outcomes of patients with community-acquired pneumonia. *JAMA* 1996;**275**:134–41.
8 Macfarlane JT. Treatment of lower respiratory tract infections. *Lancet* 1987;ii:1446–9.
9 Sow O, Frechet M, Diallo AA, *et al*. Community-acquired pneumonia in adults: a study comparing clinical features and outcomes in Africa and Europe. *Thorax* 1996;**51**:385–8.
10 Langtry HD, Lamb HM. Levofloxacin. Its use in infections of the respiratory tract, skin, soft tissues and urinary tract. *Drugs* 1998;**56**:487–515.
11 Piddock LJ, Johnson M, Ricci V, *et al*. Activities of new fluoroquinolones against fluoroquinolone-resistant pathogens of the lower respiratory tract. *Antimicrob Agents Chemother* 1998;**42**:2956–60.
12 Pankuch GA, Jacobs MR, Appelbaum PC. Antipneumococcal activity of grepafloxacin compared to that of other agents by time-kill methodology. *Antimicrob Agents Chemother* 1998;**42**:1263–5.
13 Fuentes F, Marco F, Gimenez MJ, *et al*. Comparative in vitro activity of gemifloxacin against *Strepotococcus pneumoniae* clinical isolates exhibiting high ciprofloxacin MICs (abstract). *21st International Congress of Chemotherapy*. 1999:P385.
14 Milatovic D, Fluit A, Schmitz F-J, *et al*. In vitro activity of sitafloxin and six other fluoroquinolones. Part II: Gram-positive cocci (abstract). *21st International Congress of Chemotherapy*. 1999:P601.
15 Hoogkamp-Korstanje JA. In-vitro activities of ciprofloxacin, levofloxacin, lomefloxacin, ofloxacin, pefloxacin, sparfloxacin and trovafloxacin against gram-positive and gram-negative pathogens from respiratory tract infections. *J Antimicrob Chemother* 1997;**40**:427–31.
16 Hoogkamp-Korstanje JA, Dirks-Go SI, Kabel P, *et al*. Multicentre in-vitro evaluation of the susceptibility of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella*

catarrhalis to ciprofloxacin, clarithromycin, co-amoxiclav and sparfloxacin. *J Antimicrob Chemother* 1997;**39**:411–4.
17 Hammerschlag MR, Quemi KK, Roblin PM. In vitro activities of azithromycin, clarithromycin, L-ofloxacin, and other antibiotics against *Chlamydia pneumoniae*. *Antimicrob Agents Chemother* 1992;**36**:1573–4.
18 Kaku M, Ishida K, Irifune K, *et al*. In vitro and in vivo activities of sparfloxacin against *Mycoplasma pneumoniae*. *Antimicrob Agents Chemother* 1994;**38**:738–41.
19 Goldsmith CE, Moore JE, Murphy PG. Pneumococcal resistance in the UK. *J Antimicrob Chemother* 1997; **40**(Suppl A):11–8.
20 Thornsberry C, Ogilvie P, Kahn J, *et al*. Surveillance of antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the United States in 1996–1997 respiratory season. *Diagn Microbiol Infect Dis* 1997;**29**:249–57.
21 Pankuch GA, Jacobs MR, Appelbaum PC. Activity of CP 99,219 compared with DU-6859a, ciprofloxacin, ofloxacin, levofloxacin, lomefloxacin, tosufloxacin, sparfloxacin and grepafloxacin against penicillin-susceptible and -resistant pneumococci. *J Antimicrob Chemother* 1995; **35**:230–1.
22 Vila J, Ruiz J, Sanchez F, *et al*. Increase in quinolone resistance in a *Haemophilus influenzae* strain isolated from a patient with recurrent respiratory infections treated with ofloxacin. *Antimicrob Agents Chemother* 1999;**43**:161–2.
23 Pan XS, Fisher LM. Targetting of DNA gyrase in *Streptococcus pneumoniae* by sparfloxacin: selective targetting of gyrase or topoisomerase Iv by quinolones. *Antimicrob Agents Chemother* 1997;**45**:471–4.
24 Chen DK, McGeer A, De Azavedo JC, *et al*. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. *N Engl J Med* 1999;**341**:233–9.
25 Norrby SR. Grepafloxacin in respiratory tract infections: are we ready to accept a quinolone for empirical treatment? *J Antimicrob Chemother* 1997;**40**(Suppl A):99–101.
26 Zeller V, Fourgeaud M, Moreau NJ. Accumulation of fluoroquinolones by *Streptococcus pneumoniae* and resistance arising from active fluoroquinolone efflux (abstract). *37th Interscience Conference on Antimicrobial Agents and Chemotherapy*. 1997:C57.
27 Broskey J, Coleman K, Gwynn M, *et al*. Quinolone resistance mechanisms in 17 strains of *Streptococcus pneumoniae* and comparative sensitivity to gemifloxacin (abstract). *21st International Congress of Chemotherapy*. 1999:P391.
28 Wise R, Honeybourne D. Pharmacokinetics and pharmacodynamics of fluoroquinolones in the respiratory tract. *Eur Respir J* 1999;**14**:221–9.
29 File TM, Segreti J, Dunbar L, *et al*. A multicenter, randomised study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. *Antimicrob Agents Chemother* 1997;**41**:1965–72.
30 Norrby SR, Petermann W, Willcox PA, *et al*. Levofloxacin versus ceftriaxone in the treatment of pneumonia in hospitalised patients. *Antiinfective Drugs Chemother* 1998;**16**:62.
31 Carbon C. Comparative study of levofloxacin and coamoxiclav in the treatment of community-acquired pneumonia in adults (abstract). *37th Interscience Conference on Antimicrobial Agents and Chemotherapy*. 1997:PLM70.
32 Lode H, Garau J, Grassi C, *et al*. Treatment of community-acquired pneumonia: a randomised comparison of sparfloxacin, amoxycillin/clavulanic acid and erythromycin. *Eur Respir J* 1996;**8**:1999–2007.
33 Ortqvist A, Valtonen M, Cars O, *et al*. A multi-centre, double-blind, randomised study comparing sparfloxacin with roxithromycin. *Chest* 1996;**110**:1499–506.
34 Donowitz GR, Brandon ML, Salisbury JL, *et al*. Sparfloxacin versus cefaclor in the treatment of patients with community-acquired pneumonia: a randomised, double-masked, comparative, multi-center study. *Clin Ther* 1997; **19**:936–53.
35 Aubier M, Verster R, Regamey C, *et al*. Once-daily sparfloxacin versus high-dosage amoxycillin in the treatment of community-acquired, suspected pneumococcal pneumonia in adults. *Clin Infect Dis* 1998;**26**:1312–20.
36 Portier H, May T, Proust A, *et al*. Comparative efficacy of sparfloxacin in comparison with amoxycilin plus ofloxacin in the treatment of community-acquired pneumonia. *J Antimicrob Chemother* 1996;**37**:83–91.
37 Tremolieres F, de Kock F, Pluck N, *et al*. Trovafloxacin versus high-dose amoxicillin (1 g three times daily) in the treatment of community-acquired bacterial pneumonia. *Eur J Clin Microbiol Infect Dis* 1998;**17**:447–53.
38 O'Doherty B, Dutchman DA, Pettit R, *et al*. Randomised, double-blind, comparative study of grepafloxacin and amoxycillin in the treatment of patients with community-acquired pneumonia. *J Antimicrob Chemother* 1997;**40**:73–81.
39 DeAbate CA, Russel M, McElvaine P, *et al*. Multicenter randomised study comparing levofloxacin and cefuroxime axetil in the treatment of acute bacterial exacerbations of chronic bronchitis. *Clin Infect Dis* 1996;**23**:914.
40 Allegra L, Konietzko N, Leophonte P, *et al*. Comparative safety and efficacy of sparfloxacin in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a double-blind, randomised, parallel, multicentre study. *J Antimicrob Chemother* 1996;**37**(Suppl A):93–104.
41 Lode H, Zellweger J, Asmervik J. Short course grepafloxacin therapy for 5 days is as effective as 10 days therapy with co-amoxiclav in acute exacerbations of chronic bronchitis (abstract). *21st International Congress of Chemotherapy*. 1999:P436.
42 European Agency for the Evaluation of Medicinal Products. *Public statement on Trovan/Trovan IV/Turvel/Turvel IV*. 15 June 1999.
43 Glaxo Wellcome. *Raxar: summary of product characteristics 1997*. Glaxo Wellcome, Greenford, UK.
44 Rubinstein E. Safety profile of sparfloxacin in the treatment of respiratory tract infections. *J Antimicrob Chemother* 1996;**37**(Suppl A):145–60.
45 Dupont H, Timsit JF, Souweine B, *et al*. Torsades de pointes probably related to sparfloxacin. *Eur J Clin Microbiol Infect Dis* 1996;**15**:350–1.
46 Bartlett JG, Breiman RF, Mandell LA, *et al*. Community-acquired pneumonia in adults: guidelines for management. *Clin Infect Dis* 1998;**26**:811–38.
47 Huchon G, Woodhead M, Gialdroni-Grassi G, *et al*. Guidelines for management of adult community-acquired lower respiratory infections. *Eur Respir J* 1998;**11**:986–91.
48 Stein GE, Havlichek DH. Sparfloxacin: potential clinical and economic impact in the treatment of respiratory infections. *Pharmacotherapy* 1997;**17**:1139–47.
49 British Thoracic Society. British Thoracic Society guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997;**52**(Suppl 5):S1–28.