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Pharmacokinetics and pharmacodynamics of fluoroquinolones in the respiratory tract

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ABSTRACT: Pharmacokinetic and pharmacodynamic features are important predictors of the therapeutic efficacy of an antibiotic. In respiratory tract infection, study of the clinical implication of pharmacodynamic features is complicated as infection occurs at several distinct sites. To ensure microbiological efficacy, antibiotics should not only be active against common respiratory pathogens but should also penetrate to the sites of infection.

The newer fluoroquinolones combine good activity against Gram-negative and "atypical" organisms with extended Gram-positive activity, and are unaffected by penicillin susceptibility status and β -lactamase production. Long terminal half-lives allow once- or twice-daily dosing, and a concentration in lung tissue at levels many times higher than is observed in the serum.

Although the benefit of antibiotics in some lower respiratory tract infections has been questioned, they have proved effective in community-acquired pneumonia and acute exacerbations of chronic obstructive pulmonary disease. Early studies of oral fluoroquinolones *versus* intravenous or oral treatment with one or more agents in community-acquired pneumonia have shown promise. Although resistance is a potential problem with increased fluoroquinolone use, its rapid development is not anticipated.

In conclusion, the broad-spectrum antimicrobial activity, tissue distribution and safety profile of fluoroquinolones suggest that they have a place in respiratory tract infection.

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Lower respiratory tract infection is a common condition associated with considerable morbidity and mortality. Chronic bronchitis affects over 1 million individuals in the UK, with an estimated 7 million sufferers in the USA [1]. Community-acquired pneumonia is also common, though data regarding the incidence and associated morbidity and mortality of this nonreportable disease are difficult to assimilate. The management of lower respiratory tract infection is complicated by the increasingly recognized spectrum of pathogens associated with this disease and their antibiotic susceptibility patterns. Disease management guidelines for respiratory tract infection are a relatively recent occurrence [2–4].

Pathogens commonly associated with lower respiratory tract infection include *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*, with atypical organisms playing a significant aetiological role in pneumonia. Increasing antibiotic resistance in these pathogens has led to concerns about the efficacy of currently available antibiotics. *S. pneumoniae* isolates from around the world are displaying increasing resistance to penicillin and other antibiotics [5], while β -lactamase production is seen in >90% of clinical *M. catarrhalis* isolates in the USA and is forecast in ~50% of *H. influenzae* isolates by the year 2000 [6]. In mainland Europe, rates of pneumococcal β -lactam resistance are rising, with the highest

incidences in Spain (~35%), France and Portugal (20%). Macrolide resistance is also increasing, with a correlation being found between the local prevalence of penicillin and macrolide resistance in many countries. For example, in Spain the association between macrolide resistance in penicillin intermediate (~20%) and resistant strains (25%) is marked. For *H. influenzae*, β -lactamase production is again high in Spain (35–50%), with lower rates in France (25–35%), the UK (~20%) and Belgium (15%) [7].

The treatment of lower respiratory tract infection in the community is largely empirical, as identification of the causative pathogen is seldom undertaken. First-line therapies for acute bacterial exacerbations of chronic obstructive pulmonary disease (COPD) commonly include amoxycillin, a cephalosporin or, in some countries, a macrolide. However, as $\leq 25\%$ of patients return within 1 week, the efficacy of such therapy is questionable [8].

Fluoroquinolone antibiotics have a wide spectrum of activity that covers the common respiratory pathogens [9, 10]. However, the perceived limitations of older fluoroquinolones against *S. pneumoniae* have led to a reluctance to use these agents in respiratory tract infection. The newer fluoroquinolones retain the good activity against Gram-negative organisms [11, 12] and "atypical" respiratory pathogens of older agents, while providing extended Gram-positive activity. Of particular interest is their

activity against *S. pneumoniae*, irrespective of penicillin susceptibility, and β -lactamase-positive and -negative strains of *H. influenzae* and *M. catarrhalis* [1, 13, 14].

The investigation of the clinical relevance of an antibiotic's pharmacodynamic interactions in respiratory tract infection is complicated by infections occurring at a number of distinct sites. In acute bronchitis, acute exacerbations of COPD and bronchiectasis, bacteria are found within the lumen of the airways, at the mucosal cell surface and within the bronchial mucosal tissue. In pneumonia, bacteria are mainly found at alveolar locations. However, in all these infections epithelial lining fluid (ELF) and alveolar macrophages also appear to be important sites of infection. While it seems sensible to direct antibiotic therapy against the core pathogens common to most patients, data on antibiotic penetration to these infection sites are relevant.

This review will consider the pharmacokinetic and pharmacodynamic features of the fluoroquinolones ciprofloxacin, ofloxacin, levofloxacin, lomefloxacin, sparfloxacin, gatifloxacin, trovafloxacin, grepafloxacin and moxifloxacin, and their use in respiratory tract infection.

Methodological considerations

While serum antibiotic levels are thought to correlate with therapeutic efficacy, antibiotic penetration at the infection site would seem to be a more relevant feature [15], yet there are few data supporting this hypothesis. In urinary tract infections, clinical cure has been demonstrated in situations where serum antibiotic concentrations were sufficiently low to indicate treatment failure [16].

The advent of modern endoscopic procedures has allowed the investigation of antibiotic concentrations at different sites within the respiratory tree. Sputum is now considered an unsuitable fluid for pharmacokinetic studies, as its lack of homogeneity, dilution by saliva, pooling within the respiratory tract and, in addition, the instability of some antimicrobial agents in sputum lead to methodological and interpretational problems. More commonly, penetration is measured in the bronchial mucosa, ELF and alveolar macrophages. Samples of bronchial mucosa are obtained at endoscopic biopsy, and generally comprise submucosa (53.4%), ciliated epithelium (22.3%), muscle (17.6%) and glandular tissue (7.0%), with a total water content of ~70% [17]. ELF and macrophages are accessible by bronchoalveolar lavage.

Fluoroquinolone pharmacokinetics

Fluoroquinolone antibiotics are rapidly absorbed following oral administration, and generally demonstrate linear kinetics. The pharmacokinetic parameters of the antibiotics studied are shown in table 1 [18–24]. Penetration into body fluids is favourable, as suggested by high volumes of distribution (generally >150 L) and generally low protein binding levels. The absolute bioavailability of fluoroquinolones exceeds 50% and their long terminal half-lives allow once- or twice-daily dosing regimens [25], with peak serum concentrations being reached within 1–3 h of dosing [26].

Antibiotics eliminated by both renal and nonrenal routes offer advantages in patients with fluctuating renal function, while those with primarily renal elimination seem preferable in patients with complete renal failure because of the convenience of infrequent administration. Ofloxacin, ciprofloxacin, levofloxacin and gatifloxacin are mainly excreted in an unchanged form in the urine. There is a linear relationship between levofloxacin clearance and renal function, such that dose adjustment is needed in patients with moderate-to-severe renal impairment. Grepafloxacin is eliminated primarily through metabolism in the liver via the cytochrome P450 system and is excreted mainly in the faeces, either via bile or transmucosally [27]. Sparfloxacin is eliminated mostly by nonrenal processes, but some dosage adjustment is needed in patients with moderate-to-severe renal dysfunction.

A factor contributing to fluoroquinolone activity is the tissue levels that they attain. The main barrier to antibiotic penetration is the nonfenestrated capillary endothelium separating the capillaries from the submucosa [28]. To penetrate the alveolar space the antibiotic must also cross the alveolar membrane, which is rendered relatively impermeable by the presence of many tight junctions or zonulae occludens [29, 30]. There is thus a significant barrier between the ELF and the capillary blood supply. Alveolar macrophages may take up antibiotics from the ELF or serum before migrating into the alveolar space. The activity of the newer macrolides and fluoroquinolones against intracellular respiratory pathogens has led to an increased interest in their penetration into macrophages and polymorphs. The levels of penetration of fluoroquinolones into serum and lung compartments are shown in table 2 [31–35].

Table 1. — Pharmacokinetic parameters of fluoroquinolone antibiotics in healthy volunteers

Antibiotic	C_{max} mg·L ⁻¹	t_{max} h	$t_{1/2}$ h	AUC mg·h·L ⁻¹	Urinary recovery %	Oral bioavailability %
Ciprofloxacin 500 mg	2.5	2.1	5.0	11.6	30–60	70–80
Ofloxacin 400 mg	4.4	3.5–4.0	5.7	36.8	73	95–100
Levofloxacin 500 mg	5.1	1.3	6.3	47.9	77	99
Lomefloxacin 400 mg*	4.7	—	7.0	32.2	76	—
Sparfloxacin 200 mg	0.56±0.13	3.52±0.98	18.3±3.9	16.4±2.3	5.89±1.4	90
Gatifloxacin 400 mg**	4.2	1.5	7	34.3	96	—
Trovafloxacin 200 mg	2.9	0.75	7.8	24.4	5	60–85
Grepafloxacin 400 mg	1.43	1.86	12.2	14.6	11.3	72
Moxifloxacin 400 mg	1.4	1.0	8–12	39.0	25.0	"High" [#]

Data are presented as mean, range or mean±SD. *: data following a single dose; **: from [86]; +: unpublished data; #: no specific data available. C_{max} : maximum observed plasma concentration; t_{max} : time taken to reach C_{max} ; $t_{1/2}$: terminal elimination half-life; AUC: area under the plasma concentration-time curve. (From [18–24].)

Table 2. – Serum and tissue levels of fluoroquinolone antibiotics following multiple dosing schedules

Antibiotic	Antibiotic concentration			
	Serum mg·L ⁻¹	Bronchial mucosa mg·kg ⁻¹	Epithelial lining fluid mg·L ⁻¹	Alveolar macrophages mg·L ⁻¹
Ciprofloxacin*	1.19±0.16	1.85±0.27	3.0±1.05	13.39±3.53
Levofloxacin**	4.1	6.0	10.9	27.7
Lomefloxacin ⁺	3.34±0.37	5.38±0.57	5.94±0.86	60.62±8.60
Sparfloxacin ⁺⁺	1.2±0.4	4.4±3.0	15.0±8.3	53.7±38.4
Trovafoxacin [‡]	1.47±0.43	1.67±0.70	10.21±12.96	34.3±19.26
Grepafloxacin [#]	1.23±0.14	3.60±0.44	13.87±2.74	209.03±40.98

Data are presented as mean±SD. *: 250 mg *b.d.* for 4 days. Bronchoscopy was performed at a mean of 288.25 min after the final dose. **: 500 mg, single oral dose. Bronchoscopy was performed 4 h after dosing. ⁺: 400 mg *o.d.* for 4 days. No information was given about when bronchoscopy was performed. ⁺⁺: 400 mg loading dose followed by 200 mg·day⁻¹ on days 2 and 3. Bronchoscopy was performed 2.5–5 h after dosing. [‡]: 200 mg daily for 4 days. Bronchoscopy was performed 6 h after the final dose. [#]: 400 mg daily for 4 days. Bronchoscopy was performed ≤13 h after the final dose. Data for gatifloxacin are unpublished and for moxifloxacin are not available. Levels of ofloxacin have not been studied in these tissues. (From [31–35].)

Most studies on tissue antibiotic levels are performed during the steady state, in uninfected individuals. This could result in bias because the pharmacokinetics of antibiotics may be altered in individuals with an infection. It is also possible that tissue penetration at steady state differs from that after a single dose and so several doses may be needed to achieve steady state, which may also affect tissue penetration.

All the study antibiotics penetrate well into the lung tissue, achieving concentrations higher than the corresponding serum levels. Sparfloxacin and grepafloxacin appear to be concentrated avidly by the bronchial mucosa, ELF and alveolar macrophages, with grepafloxacin attaining levels in alveolar macrophages that dramatically exceed serum levels.

Tissue penetration of fluoroquinolones *versus* other agents

Macrolides

The percentage penetration of macrolides into the bronchial mucosa is dependent upon time and the individual drug. Macrolides have been found to concentrate within the ELF, with azithromycin showing a 7-fold and clarithromycin a 5.7-fold increase compared with serum levels. Accumulation within alveolar macrophages is also seen; levels of azithromycin are up to 23-fold and clarithromycin ~70-fold higher than in serum [36]. Although fluoroquinolones have been found to accumulate throughout the cell, macrolides tend to concentrate in the lysosomes. Accumulation is affected by factors such as pH and smoking. Decreasing pH lowers macrolide accumulation [37]. Most agents will rapidly diffuse out of macrophages after removal of the extracellular antibiotic.

β-Lactams

β-Lactam antibiotics penetrate poorly into cells, accumulating in the bronchial mucosa to 35–55% of the level attained in serum [36]. This finding correlates well with the expected level for agents confined to extracellular fluids. The hydrophilic nature of β-lactams also leads to

poor penetration into the relatively impermeable alveolar space and the ELF, with levels only reaching 20–50% of serum concentrations [36]. As β-lactams are acidic they generally do not accumulate in eukaryotic cells, though some uptake may occur over time due to endocytosis and localization in the lysosomes. However, their activity at this site is negligible due to the low pH [37]. One study found no detectable levels of most β-lactam agents within alveolar macrophages, the exception being clavulanate [36, 38]. The overall penetration of β-lactams was found to be 30%.

Fluoroquinolone pharmacodynamics

The activities of the fluoroquinolone antibiotics against common respiratory pathogens and intracellular respiratory pathogens (minimum drug concentration inhibitory to 90% of strains tested MIC₉₀) are shown in table 3 [11, 20, 39–45] and table 4, respectively [14, 20, 46–59].

Grepafloxacin is the most active agent against *H. influenzae* (MIC₉₀ 0.008 mg·L⁻¹), with ciprofloxacin, sparfloxacin, trovafoxacin and gatifloxacin showing similar activity (MIC₉₀ 0.015–0.016 mg·L⁻¹), while lomefloxacin, ofloxacin, moxifloxacin and levofloxacin are the least active compounds (MIC₉₀ 0.06–0.12 mg·L⁻¹). Grepafloxacin also shows the greatest activity against *M. catarrhalis* (MIC₉₀ 0.015 mg·L⁻¹), with ciprofloxacin, levofloxacin, sparfloxacin, gatifloxacin, trovafoxacin and moxifloxacin being equally effective against this pathogen (MIC₉₀ 0.03 mg·L⁻¹). The least active agents are ofloxacin and lomefloxacin (MIC₉₀ 0.12 mg·L⁻¹). Against *Staphylococcus aureus*, trovafoxacin and moxifloxacin have the highest activity (MIC₉₀ 0.06 mg·L⁻¹), while sparfloxacin, gatifloxacin and grepafloxacin show similar efficacy (MIC₉₀ 0.12–0.13 mg·L⁻¹). Ciprofloxacin and lomefloxacin are the least active (MIC₉₀ 1.0 mg·L⁻¹).

Although ciprofloxacin resistance in *H. influenzae* is seldom seen [60], resistance in Gram-positive respiratory pathogens, such as *S. pneumoniae* to earlier quinolones, such as ciprofloxacin, has been reported in Europe and the USA [61]. It is possible that the newer fluoroquinolones will be active against these resistant strains, and work is currently being undertaken to assess the significance of these observations. Of the agents discussed

Table 3. – Minimum drug concentration inhibitory to 90% of tested strains (MIC₉₀) values of fluoroquinolone antibiotics against common respiratory pathogens

Antibiotic	MIC range mg·L ⁻¹	MIC ₉₀ mg·L ⁻¹
<i>Streptococcus pneumoniae</i>*		
Ciprofloxacin	0.5–2.0	2.0
Ofloxacin	1.0–2.0	2.0
Levofloxacin	0.25–2.0	2.0
Lomefloxacin	2.0–16.0	8.0
Sparfloxacin	0.5–1.0	0.5
Gatifloxacin	0.06–1.0	1.0
Trovafoxacin	0.03–0.25	0.25
Grepafloxacin	0.12–0.5	0.25
Moxifloxacin	0.03–0.25	0.25
<i>Haemophilus influenzae</i>**		
Ciprofloxacin	0.004–0.03	0.015
Ofloxacin	0.015–0.06	0.06
Levofloxacin	0.008–0.06	0.06
Lomefloxacin	0.06–0.12	0.12
Sparfloxacin	0.004–0.06	0.015
Gatifloxacin	0.004–0.016	0.016
Trovafoxacin	0.004–0.03	0.016
Grepafloxacin	0.001–0.06	0.008
Moxifloxacin	0.008–0.13	0.06
<i>Moraxella catarrhalis</i>***		
Ciprofloxacin	0.008–0.06	0.03
Ofloxacin	0.03–0.12	0.12
Levofloxacin	0.016–0.03	0.03
Lomefloxacin	0.06–0.12	0.12
Sparfloxacin	0.013–0.06	0.03
Gatifloxacin	0.004–0.03	0.03
Trovafoxacin	0.002–0.03	0.03
Grepafloxacin	0.004–0.03	0.015
Moxifloxacin	0.004–0.03	0.03
<i>Staphylococcus aureus</i>⁺		
Ciprofloxacin	0.06–2.0	1.0
Ofloxacin	0.12–1.0	0.5
Levofloxacin	0.06–0.25	0.25
Lomefloxacin	0.5–4.0	1.0
Sparfloxacin	0.06–16.0	0.125
Gatifloxacin	0.03–0.25	0.13
Trovafoxacin	0.008–0.13	0.06
Grepafloxacin	0.03–0.12	0.12
Moxifloxacin	0.016–0.13	0.06

*: Penicillin=0.06 mg·L⁻¹ for moxifloxacin, gatifloxacin, trovafoxacin and levofloxacin; **: Ampicillin=8.0 mg·L⁻¹ for moxifloxacin, gatifloxacin, trovafoxacin and levofloxacin; ***: β-lactamase-positive *M. catarrhalis* for moxifloxacin, gatifloxacin, trovafoxacin and levofloxacin; ⁺: avoid in Methicillin-resistant *S. aureus* for moxifloxacin, gatifloxacin, trovafoxacin and levofloxacin. MIC: minimum inhibitory concentration. (From [11, 20, 39–45].)

here, trovafoxacin, grepafloxacin and moxifloxacin are equally active against *S. pneumoniae* (MIC₉₀ 0.25 mg·L⁻¹). Ciprofloxacin, levofloxacin and ofloxacin are around 8-fold less effective (MIC₉₀ 2.0 mg·L⁻¹), while lomefloxacin is the least active agent (MIC₉₀ 8.0 mg·L⁻¹).

Antibiotic levels achieved in serum and lung tissues have a bearing on therapeutic outcome, and levels of the study antibiotics are generally above the MIC₉₀ for common respiratory pathogens and atypical organisms (table 2). However, the serum level of ciprofloxacin (1.19±0.16 mg·L⁻¹) is below the MIC₉₀ of *S. pneumoniae* (2.0 mg·L⁻¹) and borderline for *S. aureus* (MIC₉₀ 1.0 mg·L⁻¹).

Table 4. – Minimum drug concentration inhibitory to 90% of tested strains (MIC₉₀) values for fluoroquinolone antibiotics against atypical pathogens

Antibiotic	MIC ₉₀ mg·L ⁻¹
<i>Chlamydia pneumoniae</i>	
Ciprofloxacin	0.25–4.0
Ofloxacin	0.5–2.0
Levofloxacin	0.1
Lomefloxacin	4.0
Sparfloxacin	0.25
Gatifloxacin	0.125
Trovafoxacin	0.006
Grepafloxacin	0.06
Moxifloxacin	1.0
<i>Legionella pneumophila</i>	
Ciprofloxacin	0.002–1.0
Ofloxacin	0.0157–1.0
Levofloxacin	0.1
Lomefloxacin	0.03–12
Sparfloxacin	0.06
Gatifloxacin	–
Trovafoxacin	0.008–0.12
Grepafloxacin	0.004–0.125
Moxifloxacin	0.125
<i>Mycoplasma pneumoniae</i>	
Ciprofloxacin	1.0
Ofloxacin	2.0
Levofloxacin	0.5
Lomefloxacin	2.0
Sparfloxacin	0.06
Gatifloxacin	0.06
Trovafoxacin	0.25
Grepafloxacin	0.125
Moxifloxacin	0.06

*: data for *L. pneumophila* serogroup 1. (From [14, 20, 46–59].)

Lomefloxacin also demonstrates serum levels (3.34±0.37 mg·L⁻¹) that are inadequate against *S. pneumoniae* (MIC₉₀ 8.0 mg·L⁻¹).

The newer fluoroquinolones show higher levels of activity against the so-called "atypical" pathogens than older agents. Trovafoxacin (MIC₉₀ 0.006 mg·L⁻¹) and grepafloxacin (MIC₉₀ 0.06 mg·L⁻¹) are the most active agents against *Chlamydia pneumoniae*, with levofloxacin, gatifloxacin and sparfloxacin showing comparable efficacy (MIC₉₀ 0.1–0.25 mg·L⁻¹). Ofloxacin, ciprofloxacin and lomefloxacin are the least active agents. Similarly, the new quinolones are generally more active than the earlier agents of this class against *Mycoplasma pneumoniae*. *Legionella pneumophila* is highly susceptible to most fluoroquinolones.

Area under the curve: minimum inhibitory concentration ratio

While the minimum inhibitory concentration (MIC) is an important measure of a pathogen's antibiotic susceptibility, it is only one of several factors needed to predict the success of therapy. The area under the curve (AUC):MIC ratio (area under the inhibition curve (AUC) describes the relationship between the pharmacokinetics of an antibiotic and its pharmacodynamic interaction with infecting organisms (fig. 1) [62], and can be considered as a surrogate marker for outcomes, including clinical cure. *In vitro* and

Fig. 1. – Pharmacokinetic surrogate relationships. Area under the inhibition curve=area under the plasma concentration-time curve (AUC)/minimum inhibitory concentration (MIC, - - -)=240; maximum observed plasma concentration: MIC=4; time that the serum drug concentration exceeds the MIC ($t > \text{MIC}$)=(10-0.5) h=9.5 h.

clinical studies have been carried out to investigate relationship between antibiotic exposure and bacterial susceptibility to ciprofloxacin [63]. A threshold area under the inhibition curve over a 24-h period (AUC₂₄) of 125 was found to be necessary for effective antibiotic activity in both situations and in a study of ciprofloxacin in nosocomial lower respiratory tract infection [64]. An AUC₂₄ >125 gave a significantly higher rate of microbiological and clinical cure, and at levels <125 the microbiological failure rate was ~70%. At an AUC₂₄ >250, bacterial killing was rapid, with an average eradication of 1.9 days regardless of species. A further study of ciprofloxacin and strains of *S. pneumoniae*, *S. aureus* and *Pseudomonas aeruginosa* with MICs of ~0.5 confirmed that the MIC was predictive of antibacterial activity across bacterial species when an AUC₂₄ of 250 was achieved [65].

Another analysis that correlates well with the efficacy of fluoroquinolone therapy is the maximum concentration (C_{max}):MIC₉₀ ratio. Using ciprofloxacin, enoxacin, norfloxacin, ofloxacin and pefloxacin normalized to a 1-g dose against *Escherichia coli*, *P. aeruginosa* and *S. aureus*, one study predicted efficacy for drugs with a ratio >5:1 [66]. This represents the serum concentration exceeding the MIC₉₀ for most of a 12-h dosing interval. This analysis may be best suited to fluoroquinolones with a half-life ≥ 5 –6 h and a twice-daily dosing regimen.

Time above the minimum inhibitory concentration

There is interdependence between pharmacokinetic surrogate markers, such as AUC, and time above the MIC. With antibiotics that mainly demonstrate time-dependent killing, such as β -lactams, the aggregate time above the MIC is the surrogate marker most often shown to affect bactericidal activity. AUC and the C_{max} :MIC ratio are better predictors of efficacy with fluoroquinolones than time above the MIC [64]. A clinical pharmacodynamics study of ciprofloxacin in lower respiratory tract infection found evidence of a correlation between time above the MIC and time to eradication for 14 pathogens [67]. In

addition, essentially all pathogens with an MIC ≤ 0.25 mg·L⁻¹ were eradicated. In those patients whose pathogens were not eradicated, initial MICs were ≥ 0.5 mg·L⁻¹.

Side-effect profile

Fluoroquinolones are generally well tolerated, with side-effects including upper gastrointestinal disturbances, central nervous system (CNS) reactions and phototoxicity (table 5) [20, 68–84]. Some of these effects may be predicted by structure, such that 8-halogenated derivatives (e.g. lomefloxacin and sparfloxacin) are more likely to cause phototoxicity [81]. The newer fluoroquinolones have demonstrated increased activity against various anaerobes, including *Clostridium difficile*, possibly suggesting a reduced potential for inducing overgrowth of this organism, although this has yet to be demonstrated clinically [85–87].

Prolongation of the QTc interval has been observed with some fluoroquinolones. A very small QTc prolongation of <2 ms has been observed in elderly subjects treated with grepafloxacin. In contrast, subjects receiving sparfloxacin have been reported to have a QTc prolongation of 7–11 ms, with 0.7% of patients having a QTc interval of >500 ms (unpublished data). Additionally, prolongation of the QTc interval with sparfloxacin [83] has been associated with a recent episode of torsades de pointes provoking cardiac arrest that led to pulmonary resuscitation in a female with anterior pituitary deficiency [88]. No data on QTc prolongation have been published for the other quinolones discussed, so no assessment is possible and it is therefore premature to draw any conclusions at this stage. A strong temporal relationship has been noted between macrolide administration and the prolongation of the QTc interval (prolongation of myocardial repolarization). In two patients with bronchopneumonia receiving clarithromycin, QTc intervals of 670 ms and 775 ms were recorded [89], while a retrospective review of records from patients hospitalized with simple pneumonia found intravenous erythromycin use to be associated with a mean QTc prolongation of 46 ms. The mean QTc interval in this group of patients was 468 ms [90].

Some quinolones, such as ofloxacin, are more commonly associated with CNS events than others [80]. Preliminary data with trovafloxacin indicate that it is associated with dose-dependent transient dizziness, with a 200 mg dose being associated with dizziness in up to 11% of patients and light-headedness in 4% [84].

Certain fluoroquinolones are known to raise serum theophylline levels. Patients taking theophylline should be monitored for signs of theophylline toxicity when it is co-administered with ciprofloxacin [91], and it is appropriate to halve the theophylline maintenance dose in patients receiving grepafloxacin [92]. In addition, staggered dosage regimens are recommended to avoid the reduced bioavailability of ciprofloxacin, ofloxacin and sparfloxacin resulting from the concomitant use of compounds containing multivalent cations such as aluminium or magnesium-based antacids, and sucralfate.

Trovafloxacin has been associated with hepatotoxicity including liver enzyme abnormalities and/or symptomatic hepatitis and, rarely, liver failure [84].

Table 5. – Side-effects and drug reactions associated with fluoroquinolone use

Antibiotic	Side-effect	Incidence of phototoxicity	Drug interactions	[Ref.]
Ciprofloxacin	Gastrointestinal effects (5%) CNS effects (1%)	Low	Theophylline Caffeine Compounds containing multivalent cations (e.g. aluminium - and magnesium-based antacids) Sucralfate	[68, 74–78, 80]
Ofloxacin	Gastrointestinal effects (3%) CNS effects (1%) Taste and smell impairment	Low	Slight theophylline interaction Compounds containing multivalent cations (e.g. aluminium - and magnesium-based antacids) Sucralfate	[20, 72, 78, 79]
Levofloxacin	General incidence 1–3% Mostly mild gastrointestinal effects (2%)	–	Compounds containing multivalent cations (e.g. aluminium - and magnesium-based antacids)*	[71, 80]
Lomefloxacin	CNS effects (6%) Gastrointestinal effects (5%) Skin reactions (2%)	Yes	–	[80, 82]
Sparfloxacin	General incidence: high-dose therapy (32%)** low-dose therapy (22%)* Gastrointestinal effects (6–10%) CNS effects (particularly insomnia and other sleep disorders) (>3%) Skin reactions (2%) Prolonged QTc interval (1%)	Yes	Compounds containing multivalent cations (e.g. aluminium - and magnesium-based antacids) Sucralfate Ferrous sulphate	[20, 73, 78, 80, 81, 83]
Trovafloxacin ⁺	Dose-dependent, transient dizziness (11%) Lightheadedness (4%) Nausea (8%) Headache (5%)	No	Caffeine (15% increase in absorption) Cations (e.g. aluminium - and magnesium-based antacids)	[84]
Grepafloxacin ⁺⁺	Nausea (10–12%) Diarrhoea (3%) Taste perversion (4–6%)	Low	Theophylline Caffeine Cations (e.g. aluminium - and magnesium-based antacids)	[69, 70, 77]

*: levofloxacin data sheet; **: 400-mg loading dose then 200 mg·day⁻¹. ***: 200-mg loading dose then 100 mg·day⁻¹. ⁺: 200-mg dose; ⁺⁺: 400-mg dose. CNS: central nervous system; QTc interval: Q–T interval corrected for heart rate.

Clinical impact

Many physicians in the community do not differentiate between lower respiratory tract infections, treating most patients with antibiotics. Antibiotics have been shown to be more effective than placebo in some patients with acute exacerbations of COPD [93]. There has been some recent work to suggest that quinolones may be useful in reducing the duration and frequency of acute exacerbations of COPD in those patients with ≥ 4 exacerbations per year [68].

There is some evidence that the antibiotic concentration at the site of infection has a bearing on clinical outcome in respiratory tract infection [94], so it seems reasonable to select an agent that attains high concentrations at such sites over one that does not. Fluoroquinolones are concentrated in the respiratory tree, and clinical trials have found them to be effective in the treatment of respiratory tract infection. In community-acquired pneumonia, grepafloxacin has been shown to be clinically equivalent to amoxycillin, with a statistically superior microbiological eradication rate [69]. It has also proved highly effective in the resolution of both typical and atypical pneumonia [70]. In patients with acute bacterial exacerbations of COPD, grepafloxacin also demonstrated clinical equivalence

and microbiological superiority to amoxycillin [95]. A study of acute and chronic lower respiratory tract infection found levofloxacin to have a comparable efficacy to ofloxacin [71, 91]. The uptake and avid concentration of the newer fluoroquinolones by alveolar macrophages also extends their use to atypical pathogens [70]. They may also prove beneficial in reducing the incidence of chronic or recurrent respiratory infections which may result from the survival and multiplication of pathogens, such as *S. aureus* and *H. influenzae*, following ingestion by alveolar macrophages.

In studies of community-acquired pneumonia requiring hospitalization, ofloxacin was as effective as the standard regimen of a β -lactam with or without a macrolide [72], and sparfloxacin has achieved similar outcomes to amoxycillin-clavulanic acid and erythromycin [73]. The use of oral fluoroquinolones in place of intravenous or oral therapy with one or more agents in this setting seems promising. However, further clinical studies are needed. Early studies in hospital-acquired pneumonia have shown that an early switch to oral fluoroquinolone therapy is effective and well-tolerated, possibly because of the high serum and tissue levels achieved [74]. Thus, oral fluoroquinolones may offer the potential to reduce hospital costs [75].

Current treatment guidelines for the management of community-acquired respiratory tract infection in adults recommend the fluoroquinolones for empirical therapy in several patient groups. In the guidelines of the European Respiratory Society [3], the newer fluoroquinolones are suggested as alternatives to the use of aminopenicillin in patients with community-acquired lower respiratory tract infection managed at home, whereas the older quinolones (e.g. ciprofloxacin or ofloxacin) are recommended in these patients managed in the hospital setting. Guidelines from the Infectious Diseases Society of America [4] on the management of community-acquired pneumonia in adults state that fluoroquinolones are among the preferred agents for the empirical treatment of such patients in the community and the hospital, and for pathogen-directed therapy.

Most fluoroquinolones reach concentrations in the serum and lung tissues that exceed the MIC₉₀ for many common respiratory pathogens. Thus, they are present at clinically significant levels at all potential sites of respiratory tract infection. The exceptions are ciprofloxacin and lomefloxacin, which both demonstrated serum levels below the MIC₉₀ of *S. pneumoniae*. This may explain the concern felt by many about the incidences of treatment failure and breakthrough infections seen in patients with pneumonia receiving ciprofloxacin [96].

Subtherapeutic levels of ciprofloxacin may also be implicated in the development of pneumococcal ciprofloxacin resistance. The rapid emergence of resistance to newer fluoroquinolones in respiratory pathogens appears unlikely with recent evidence suggesting that some of them may primarily target the deoxyribonucleic acid gyrase A gene (*gyrA*), rather than *parC* which is the major target for ciprofloxacin and other older quinolones [97]. Of relevance is the fact that the new fluoroquinolones with high activity against *parC* mutants, may suppress the first *parC* mutation, possibly preventing a further mutation leading to high-level resistance [7].

The fluoroquinolones currently available offer major therapeutic advances compared with precursor agents, and the incidence of adverse events is clearly outweighed by their clinical utility. As with other antibiotics the development of resistance is a potential problem associated with their increased use in respiratory tract infection. Rational prescribing and vigilance in monitoring antibiotic resistance levels are needed to perpetuate bacterial susceptibility.

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